

# **PERIPHERAL AND CENTRAL NERVOUS SYSTEM (PCNS) ADVISORY COMMITTEE**

**FDA White Oak Campus  
10903 New Hampshire Ave.  
Bldg. 31, Conference Center  
Silver Spring, MD  
May 22, 2013**

## **SUVOREXANT (orexin receptor antagonist)**

**For insomnia characterized by difficulties with sleep onset  
and/or maintenance**

### **DISCLAIMER STATEMENT**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought **NDA 204569, SUVOREXANT** (orexin receptor antagonist) oral tablets, submitted by Merck Sharp & Dohme Corp. to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

**FOOD AND DRUG ADMINISTRATION**

Center for Drug Evaluation and Research

***Meeting of the Peripheral and Central Nervous System  
Advisory Committee***

**SUVOREXANT (orexin receptor antagonist)**

**May 22, 2013**

**BRIEFING MATERIALS**

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## **MEMORANDUM**

DATE: April 25, 2013

FROM: Director  
Division of Neurology Products

TO: Members, Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNS AC) and Invited Guests

SUBJECT: Cover Memo for FDA Briefing Package for the May 22, 2013, PCNS AC Meeting to discuss NDA 204569, for the use of Suvorexant in the Treatment of Insomnia characterized by difficulty falling asleep and/or staying asleep

As you know, the PCNS AC will meet on May 22, 2013 to discuss NDA 204569 for the use Suvorexant in the treatment of insomnia. Suvorexant is a selective antagonist of orexin receptors OX1R and OX2R, and blocks binding of orexin A and B to these receptors, presumably inhibiting activation of neurons of the arousal system. It is the first member of this class to be submitted for the treatment of insomnia.

This NDA was submitted by Merck Sharp and Dohme Corp. on [REDACTED], and contains three controlled trials that, by design, could contribute to a finding of substantial evidence of effectiveness for Suvorexant in the treatment of insomnia characterized by difficulty falling asleep (sleep latency) and/or staying asleep (sleep maintenance). In this package of briefing materials, we have included a statistical review of the effectiveness data (performed by Dr. Tristan Massie), a clinical review (performed by Dr. Kachi Illoh), slides (prepared by Dr. Ron Farkas; these slides are not necessarily those that will be presented at the AC meeting), a clinical pharmacology and pharmacometrics review (performed by Drs. Hristina Dimova, Xinning Yang, Joo-Yeon Lee, and Satjit Brar), the agenda for the meeting, and a list of discussion points we would like the Committee to address at the meeting. In this memo, I will briefly describe the relevant effectiveness and safety issues presented in the application. You will also receive the sponsor's briefing materials.

### **Effectiveness**

As noted above, the sponsor has submitted the results of three controlled trials that are relevant for the determination of effectiveness. Studies 28 and 29 were parallel group studies of very similar design; Study 006 was a two-period cross-over study.

## Study 28

This was a parallel group, fixed dose study in which patients with insomnia were randomized to one of two fixed doses of suvorexant or placebo for three months. Specifically, patients were randomized into low dose or high dose (or placebo) in a 2:3:3 ratio in the following manner:

|             | Low dose | High dose |
|-------------|----------|-----------|
| Ages 18-<65 | 20 mg    | 40 mg     |
| Ages >65    | 15 mg    | 30 mg     |

Patients were assessed either with questionnaires only (Q-cohort) or PSG and questionnaires (PQ-cohort). The dose was to be taken right before bedtime.

Patients were assessed at baseline and Night 1, the end of Week 1, and Months 1, 2, and 3. In the PQ-cohort, PSG was performed on Night 1, and Months 1 and 3.

The primary hypothesis compared the high dose on Change from Baseline on mean Subjective Total Sleep Time (sTST) and Change from Baseline on (objective) Wakefulness After Sleep Onset (WASO) (both measures of sleep maintenance) and Change from Baseline in mean Subjective Time to Sleep Onset (sTSO) and Change from Baseline in (objective) Latency to Onset to Persistent Sleep (LPS) (measures of sleep latency), all at Months 1 and 3. High dose secondary hypotheses were sTST and sTSO at Week 1, and WASO and LPS at Night 1.

Because of the multiple time points and outcomes tested, the following approach was taken to protect the experiment-wise Type I error rate at 5%:

### High Dose:

The endpoints for sleep maintenance (sTST and WASO) were tested at a two-sided 2.5% as were the sleep latency endpoints (sTSO and LPS). Within each indication, a sequential testing procedure was used to move from the first set of primary hypotheses (Month 1) to the Month 3 contrasts. At each time point, a Hochberg approach was used to test the subjective (sTST, sTSO) and objective (WASO, LPS) endpoints. To move from Month 1 to Month 3, both subjective and objective outcomes had to be significant. If only one endpoint was significant at Month 1, testing was not done at Month 3. Levels of significance were two sided, alpha of 2.5%

If either hypothesis (sTST or WASO for maintenance and sTSO or LPS for latency) was significant at Month 3, then the secondary hypotheses (Week 1,



Night 1) were tested using the Hochberg approach at a two-sided alpha level of 2.5%.

#### Low Dose:

A similar approach was taken for the Low Dose-placebo comparisons as described above, if the Month 3 outcome was positive for that particular endpoint at the high dose.

#### Results

A total of 1022 patients were randomized at 79 centers in Asia/Eastern Europe/Africa (4%), Europe (35%), Japan (24%), North America (34%), and Central and South America (3%). The following chart displays the disposition of patients:

|                      | Placebo   | LD        | HD        |
|----------------------|-----------|-----------|-----------|
| Randomized           | 385       | 254       | 383       |
| Completed Treatment  | 341 (89%) | 230 (91%) | 345 (90%) |
| Discontinued due to: |           |           |           |
| Adverse event        | 21        | 6         | 15        |
| W/D by Subject       | 12        | 6         | 8         |
| Lack of efficacy     | 9         | 1         | 7         |

Patients ranged from 18-87 years old. A total of 42% (N=429) were greater than 65 years old. A total of 776 were randomized to the PQ-cohort, and 247 to the Q cohort. The entire Q-cohort consisted of patients from Japan.

The following chart displays the results for sTST and WASO (measures of sleep maintenance):

|           | Difference in LS Means<br>(minutes) | P-value  |
|-----------|-------------------------------------|----------|
| sTST      |                                     |          |
| Week 1    |                                     |          |
| HD vs Pbo | 21.4*                               | <0.00001 |
| LD vs Pbo | 13.6*                               | 0.00007  |
| Month 1   |                                     |          |
| HD vs Pbo | 19.6*                               | <0.00001 |
| LD vs Pbo | 16.3*                               | 0.00016  |

Month 3

|           |       |          |
|-----------|-------|----------|
| HD vs Pbo | 19.7* | <0.00001 |
| LD vs Pbo | 10.7* | 0.017    |

\*-statistically significant

|      | Difference in LS Means<br>(minutes) | P-value |
|------|-------------------------------------|---------|
| WASO |                                     |         |

Night 1

|           |        |          |
|-----------|--------|----------|
| HD vs Pbo | -38.4* | <0.00001 |
| LD vs Pbo | -32.5* | <0.00001 |

Month 1

|           |        |          |
|-----------|--------|----------|
| HD vs Pbo | -26.3* | <0.00001 |
| LD vs Pbo | -26.4* | <0.00001 |

Month 3

|           |        |          |
|-----------|--------|----------|
| HD vs Pbo | -22.9* | <0.00001 |
| LD vs Pbo | -16.6* | 0.000009 |

\*-statistically significant

The following chart displays the results of the comparisons on sTSO and LPS (measures of sleep latency):

|  | Difference in LS Means<br>(minutes) | P-value |
|--|-------------------------------------|---------|
|--|-------------------------------------|---------|

sTSO

Week 1

|           |       |        |
|-----------|-------|--------|
| HD vs Pbo | -5.7* | 0.0061 |
| LD vs Pbo | -5.6  | 0.016  |

Month 1

|           |       |         |
|-----------|-------|---------|
| HD vs Pbo | -7.4* | 0.0030. |
| LD vs Pbo | -5.4  | 0.052   |

### Month 3

|           |       |        |
|-----------|-------|--------|
| HD vs Pbo | -8.4* | 0.0002 |
| LD vs Pbo | -5.2  | 0.04   |

\*-statistically significant

|  | Difference in LS Means<br>(minutes) | P-value |
|--|-------------------------------------|---------|
|--|-------------------------------------|---------|

### LPS

#### Night 1

|           |        |         |
|-----------|--------|---------|
| HD vs Pbo | -10.3* | 0.00002 |
| LD vs Pbo | -9.6*  | 0.0004  |

#### Month 1

|           |        |         |
|-----------|--------|---------|
| HD vs Pbo | -11.2* | 0.00002 |
| LD vs Pbo | -10.3* | 0.0004  |

#### Month 3

|           |       |        |
|-----------|-------|--------|
| HD vs Pbo | -9.4* | 0.0004 |
| LD vs Pbo | -8.1* | 0.0061 |

\*-statistically significant

### Study 29

This study had a similar design as Study 28. A total of 1019 patients were randomized at 90 centers in Asia/Central and Eastern Europe (14%), Europe (30%), and North America (48%). The following chart displays patient disposition in this study:

|                      | Placebo   | LD        | HD        |
|----------------------|-----------|-----------|-----------|
| Randomized           | 387       | 240       | 392       |
| Completed Treatment  | 330 (85%) | 205 (85%) | 346 (88%) |
| Discontinued due to: |           |           |           |
| Adverse event        | 17        | 10        | 19        |
| W/D by Subject       | 19        | 8         | 9         |
| Lack of efficacy     | 8         | 7         | 4         |

Patients ranged from 18-86 years old. A total of 41% (N=410) were greater than 65 years old. A total of 753 patients were randomized to the PQ cohort, and 268 to the Q cohort.

The following chart displays the results of the measures of sleep maintenance (sTST and WASO):

|           | Difference in LS Means<br>(minutes) | P-value  |
|-----------|-------------------------------------|----------|
| sTST      |                                     |          |
| Week 1    |                                     |          |
| HD vs Pbo | 26.4*                               | <0.00001 |
| LD vs Pbo | 16.8*                               | 0.00002  |
| Month 1   |                                     |          |
| HD vs Pbo | 26.3*                               | <0.00001 |
| LD vs Pbo | 20.9*                               | <0.00001 |
| Month 3   |                                     |          |
| HD vs Pbo | 25.1*                               | <0.00001 |
| LD vs Pbo | 22.1*                               | 0.00004  |

\*-statistically significant

|           | Difference in LS Means<br>(minutes) | P-value  |
|-----------|-------------------------------------|----------|
| WASO      |                                     |          |
| Night 1   |                                     |          |
| HD vs Pbo | -42.0*                              | <0.00001 |
| LD vs Pbo | -37.0*                              | <0.00001 |
| Month 1   |                                     |          |
| HD vs Pbo | -29.4*                              | <0.00001 |
| LD vs Pbo | -24.1*                              | <0.00001 |
| Month 3   |                                     |          |
| HD vs Pbo | -29.4*                              | <0.00001 |
| LD vs Pbo | -31.1*                              | 0.000009 |

\*-statistically significant

The following chart displays the results of the comparisons on sTSO and LPS (measures of sleep latency):

|           | Difference in LS Means<br>(minutes) | P-value  |
|-----------|-------------------------------------|----------|
| sTSO      |                                     |          |
| Week 1    |                                     |          |
| HD vs Pbo | -13.1*                              | <0.00001 |
| LD vs Pbo | -7.5                                | 0.006    |
| Month 1   |                                     |          |
| HD vs Pbo | -12.8*                              | 0.00003  |
| LD vs Pbo | -6.9                                | 0.05     |
| Month 3   |                                     |          |
| HD vs Pbo | -13.2*                              | 0.00003  |
| LD vs Pbo | -7.6                                | 0.04     |

\*-statistically significant

|           | Difference in LS Means<br>(minutes) | P-value  |
|-----------|-------------------------------------|----------|
| LPS       |                                     |          |
| Night 1   |                                     |          |
| HD vs Pbo | -21.7*                              | <0.00001 |
| LD vs Pbo | -12.4                               | 0.004    |
| Month 1   |                                     |          |
| HD vs Pbo | -12.1*                              | 0.00004  |
| LD vs Pbo | -7.8                                | 0.03     |
| Month 3   |                                     |          |
| HD vs Pbo | -3.6*                               | 0.27     |
| LD vs Pbo | -0.3                                | 0.93     |

\*-statistically significant

## Study 6

This was a two-period counter-balanced cross-over study in which patients received one of 4 doses of Suvorexant (10, 20, 40, or 80 mg) and placebo. Each treatment period was 4 weeks, with a single-blind placebo washout period of at least one week between periods. Patients were assessed with a PSG on Nights 1 and 28 of each period. The primary outcome was Sleep Efficiency (SE), defined as  $100 \times \text{Total Sleep Time} / \text{Time in Bed}$  (in minutes). The Time in Bed was fixed at 8 hours. Secondary outcomes were WASO and LPS.

In order to protect the experiment-wise Type I error of 5%, the highest dose was compared to placebo, and needed to be significant ( $p=0.05$ ) at both time points (Night 1 and Week 4) in order to test the next highest dose in the same way. Doses significant at both time points for SE were then tested for WASO, and doses significant for SE and WASO were tested for LPS.

## Results

A total of 254 patients were randomized at 41 centers; 243 and 249 patients received at least one dose of drug and placebo, respectively, and 228 patients completed the study. Patients ranged in age from 18-64 years old.

The following charts display the results of the primary and secondary outcomes:

### SE

|       | LS Mean Change From Placebo Night 1 | P-value |
|-------|-------------------------------------|---------|
| 10 mg | 5.2                                 | <0.002  |
| 20 mg | 7.6                                 | <0.002  |
| 40 mg | 10.8                                | <0.002  |
| 80 mg | 12.9                                | <0.002  |

|       | LS Mean Change from Placebo at Week 4 | P-value |
|-------|---------------------------------------|---------|
| 10 mg | 4.7                                   | <0.003  |
| 20 mg | 10.4                                  | <0.003  |
| 40 mg | 7.8                                   | <0.003  |
| 80 mg | 7.6                                   | <0.003  |

## WASO

|              | Difference in LS Means at Night 1 | P-value |
|--------------|-----------------------------------|---------|
| 10 mg vs Pbo | -21.2                             | <0.001  |
| 20 mg vs Pbo | -24.7                             | <0.001  |
| 40 mg vs Pbo | -33.9                             | <0.001  |
| 80 mg vs Pbo | -36.8                             | <0.001  |

### Difference in LS Means at Week 4

|              |       |        |
|--------------|-------|--------|
| 10 mg vs Pbo | -21.4 | 0.001  |
| 20 mg vs Pbo | -28.1 | <0.001 |
| 40 mg vs Pbo | -33.2 | <0.001 |
| 80 mg vs Pbo | -28.9 | <0.001 |

## LPS

|              | Difference in LS Means at Night 1 | P-value |
|--------------|-----------------------------------|---------|
| 10 mg vs Pbo | -3.4                              | 0.6     |
| 20 mg vs Pbo | -9.4                              | 0.13    |
| 40 mg vs Pbo | -23.1                             | <0.001  |
| 80 mg vs Pbo | -25.4                             | <0.001  |

### Difference in LS Means at Week 4

|              |       |        |
|--------------|-------|--------|
| 10 mg vs Pbo | -2.3  | 0.6    |
| 20 mg vs Pbo | -22.3 | <0.001 |
| 40 mg vs Pbo | -3.8  | 0.46   |
| 80 mg vs Pbo | -9.5  | 0.07   |

Dr. Massie noted a potential carryover effect for LPS. As he notes (page 51-52 of his review) "Patients who received placebo in Period 1 had further improvement in LPS when they received [drug] in Period 2; however, for patients who received [drug] in Period 1 improvement in LPS did not diminish in Period 2, even though patients received placebo in Period 2.", though there was no carryover effect if only the sequences including 10 mg were examined. The p-value for the interaction between period and treatment was  $p=0.01$ . As result of this effect, he performed several different analyses of first period data.

Analyses of the first period data for only the two sequences that included the 10 mg dose revealed no significant effects on either Night 1 or Week 4 for the 10

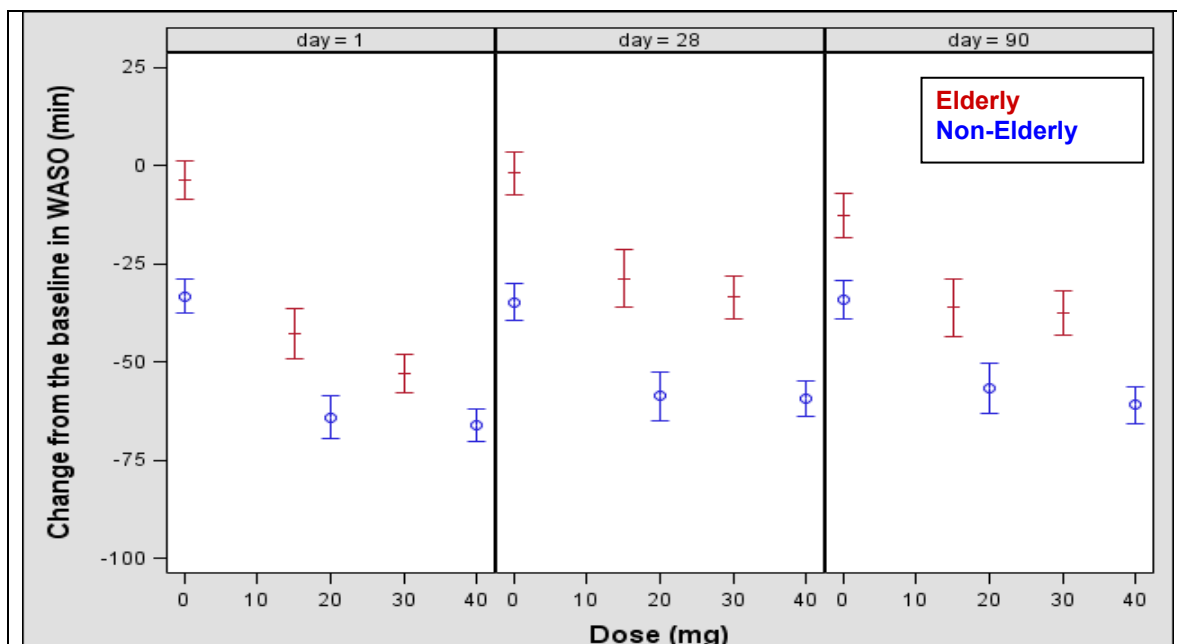
mg dose. The effect of the 10 mg dose on LPS in the first period when pooling all placebo groups was as follows:

#### First Period Effect on LS Mean Change from Placebo for LPS

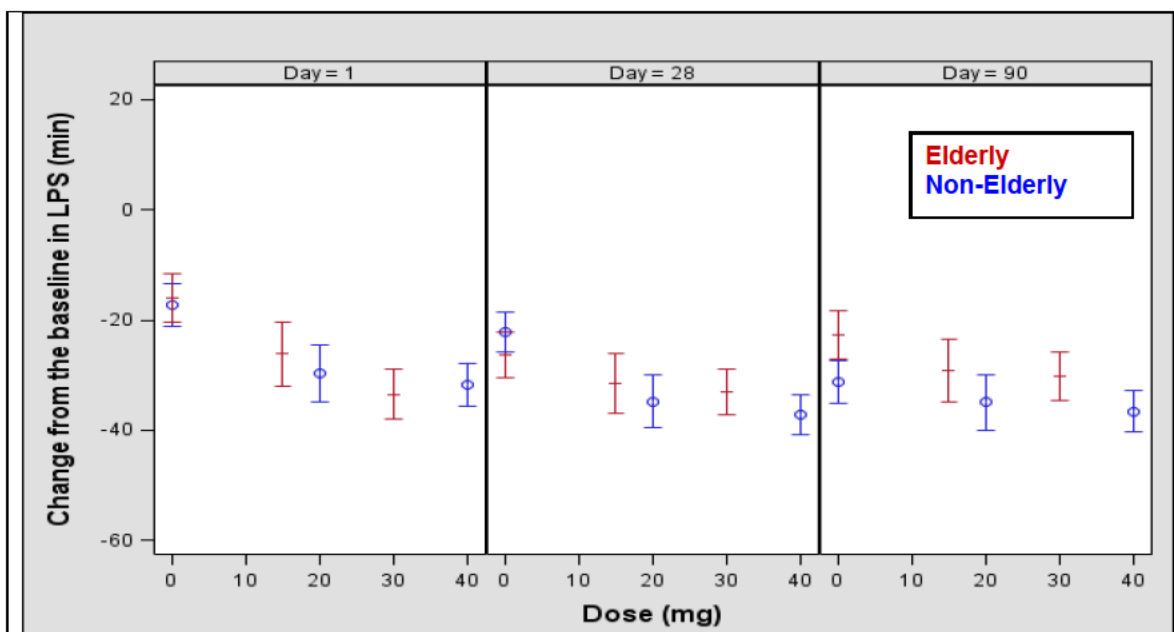
| Night 1      |       | P-value |
|--------------|-------|---------|
| 10 mg vs Pbo | -21.7 | 0.011   |
| Night 28     |       |         |
| 10 mg vs Pbo | -20.6 | 0.013   |

Our Clinical Pharmacology reviewers performed analyses of the objective measures (WASO, LPS) by dose and by plasma levels (the latter divided into “bins”, based on median AUC [not percentiles, despite the labeling of the graphs]). These analyses combined data from Studies 006, 28, and 29, and were divided by age (elderly, non-elderly). The following graphs, taken from the Clinical Pharmacology review) display these analyses:

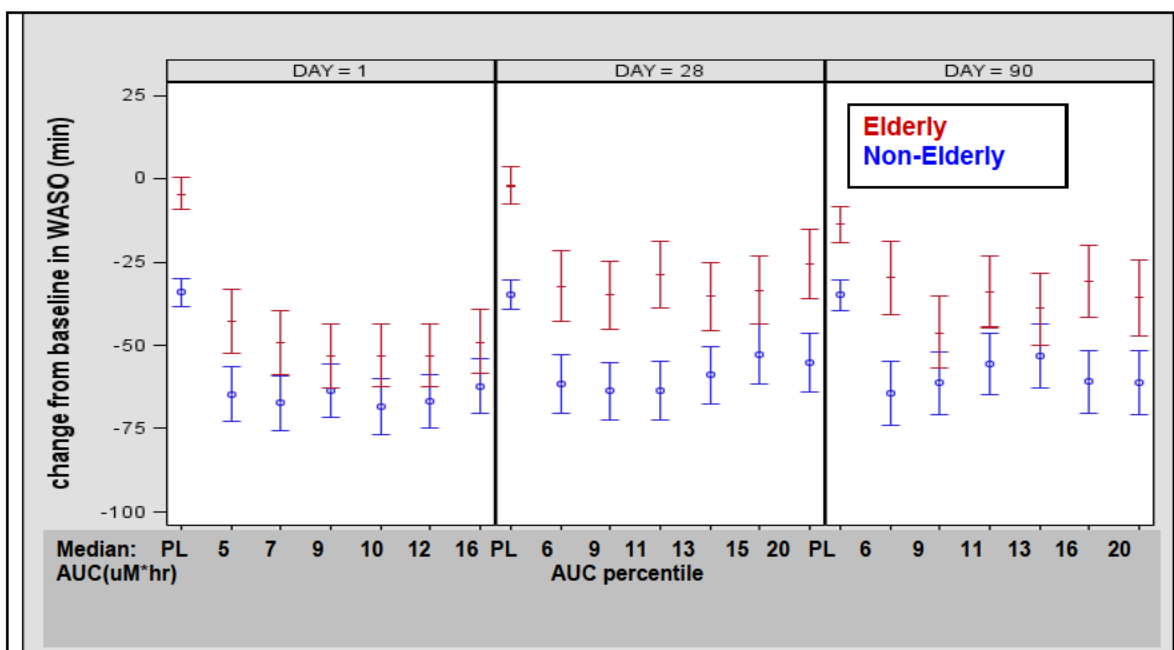
**Figure 1: LS mean with 95% CI for  $\Delta$  WASO (top) and  $\Delta$  LPS (bottom) vs. Dose by day. LS means were adjusted by baseline value, age group, region and gender**

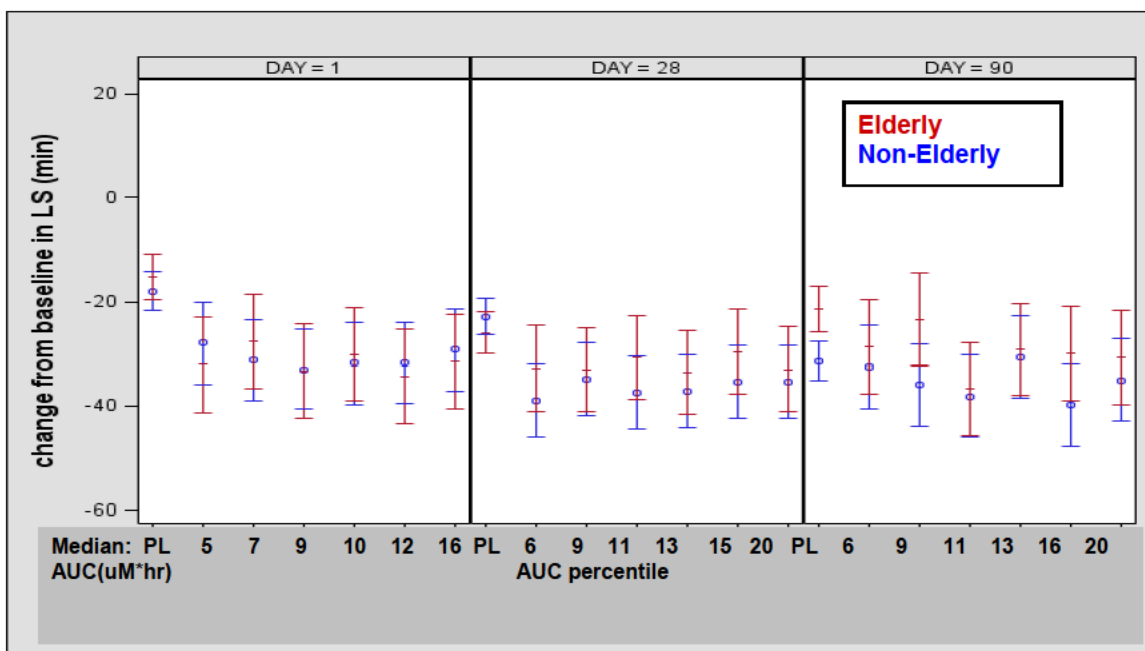




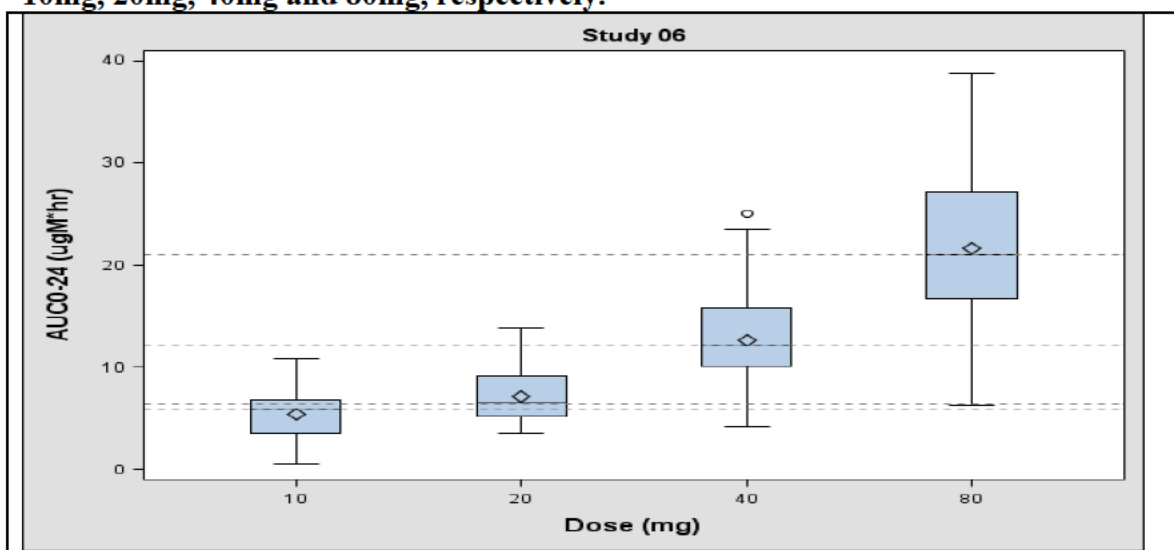


**Figure 2: LS mean with 95% CI for  $\Delta$  WASO (top) and  $\Delta$  LPS (bottom) vs. exposure ( $AUC_{0-24}$ ) by day by elderly and non-elderly patients. LS means were adjusted by baseline value, age group, region and gender to be consistent with dose-response analysis.**





**Figure 3: Distribution of  $AUC_{0-24}$  ( $\mu M \cdot hr$ ) at each dose (data from 1<sup>st</sup> period of Study 006). The dotted horizontal lines on the top indicate the median  $AUC_{0-24}$  at each dose: The median  $AUC_{0-24}$  is 5  $\mu M \cdot hr$ , 6  $\mu M \cdot hr$ , 12  $\mu M \cdot hr$  and 21  $\mu M \cdot hr$  at 10mg, 20mg, 40mg and 80mg, respectively.**



Note that the median suvorexant AUC is 5  $\mu g M \cdot hr$ , and that this is similar to the lowest AUC examined in the previous two graphs, which showed effectiveness at all plasma levels, with no concentration response.

## Safety

In Phase 2 and 3 studies, a total of 2027 patients with insomnia have received at least one dose of suvorexant; 1218 for at least 3 months, 507 for at least 6 months, and 160 for at least one year. Studies 28 and 29 had extension phases in which patients were treated up to 6 months (the Extension Phases only included the LD), and Study 009 was a double-blind safety study in which patients received either placebo or Suvorexant HD.

The following chart displays the numbers of patients in Phase 2 and 3 studies who received the given dose of suvorexant for various durations:

| Dose  | Duration (in Months) |      |     |
|-------|----------------------|------|-----|
|       | 3-<6                 | 6-<9 | >9  |
| 10 mg | 0                    | 0    | 0   |
| 15 mg | 96                   | 22   | 0   |
| 20 mg | 152                  | 20   | 0   |
| 30 mg | 196                  | 54   | 216 |
| 40 mg | 267                  | 73   | 121 |

### Deaths

There were 2 deaths in the development program:

- 1) a 40 year old woman who received 40 mg for 34 days and almost drowned in the ocean the day after her last dose; she was admitted to the ICU and had cardiac arrest
- 2) a 58 year old woman who received placebo and who died of a stroke.

### Serious Adverse Events (SAE)

Over the 12 months of controlled trial data, 2.8% and 3.2% of suvorexant HD (N=1291) and placebo (N=1025) patients, respectively, had a serious adverse event. The only single SAE that occurred more than once in the HD group and more frequently than in the placebo group was diverticulitis (N=2 vs N=1).

Over 6 months of controlled trial data, 0.6% and 2.1% of suvorexant LD (N=493) and placebo (N=767) patients, respectively, experienced a serious adverse event. No single SAE occurred more than once in the suvorexant LD group.

Some SAEs are discussed below under specific adverse events.

## Discontinuations

The following chart displays the percent of patients who discontinued during Phase 3 controlled trials due to an adverse event:

|             | Placebo | LD   | HD   |
|-------------|---------|------|------|
| 0-3 Months  | 4.7%    | 3.2% | 5.4% |
| 0-6 Months  | 5.2%    | 3.2% | NA   |
| 0-12 Months | 6.0%    | NA   | 7.8% |

In the 3 Month controlled trial data, few AEs led to discontinuation in more than one patient. Those of interest are described below:

| Adverse Event     | Pbo (N) | LD (N)  | HD (N)   |
|-------------------|---------|---------|----------|
| N                 | 1025    | 493     | 1291     |
|                   | %       | %       | %        |
| Somnolence        | 0.3 (3) | 0.2 (1) | 1.7 (22) |
| Fatigue           | 0       | 0.2 (1) | 0.7 (9)  |
| Sedation          | 0       | 0       | 0.2 (3)  |
| Lethargy          | 0       | 0       | 0.2 (3)  |
| Nightmare         | 0       | 0.2 (1) | 0.2 (2)  |
| Sleep Paralysis   | 0       | 0       | 0.2 (2)  |
| Memory Impairment | 0       | 0       | 0.2 (3)  |
| Depression        | 0.1 (1) | 0       | 0.2 (2)  |

In general, the adverse events leading to discontinuation of suvorexant in the 3 Month controlled trial cohort were similar to those seen in the 6 and 12 Months controlled trials cohorts. Of interest, the incidence of Somnolence in the 12 Month cohort was 2.2% and 0.4% in the suvorexant HD and placebo groups, respectively.

Some other discontinuations are discussed below under specific adverse events of interest.

## Common Adverse Events

The following chart displays the common adverse events seen in the 3 month controlled trial experience:

| Adverse Event  | Pbo<br>(N=1025) | LD<br>(N=493) | HD<br>(N=1291) |
|----------------|-----------------|---------------|----------------|
| Somnolence     | 3%              | 7%            | 11%            |
| Headache       | 6%              | 7%            | 7%             |
| Fatigue        | 2%              | 2%            | 4%             |
| Dry Mouth      | 1%              | 2%            | 3%             |
| Abnormal Dream | 1%              | 2%            | 2%             |
| URI            | 1%              | 2%            | 2%             |

The following chart displays common adverse events in the 6 Month controlled trial experience:

| Adverse Event   | Pbo<br>(N=767) | LD<br>(N=493) |
|-----------------|----------------|---------------|
| Somnolence      | 3%             | 7%            |
| Headache        | 6%             | 8%            |
| Abnormal Dreams | 1%             | 2%            |
| Diarrhea        | 1%             | 2%            |
| Cough           | 1%             | 2%            |

The following chart displays the common adverse events seen in the 12 Month controlled trial data:

| Adverse Event   | Pbo<br>(N=1025) | HD<br>(N=1291) |
|-----------------|-----------------|----------------|
| Somnolence      | 3%              | 12%            |
| Headache        | 7%              | 8%             |
| Fatigue         | 2%              | 5%             |
| Abnormal Dreams | 1%              | 3%             |
| Nightmares      | 1%              | 2%             |
| Nausea          | 2%              | 3%             |
| Dry Mouth       | 2%              | 3%             |
| URI             | 2%              | 3%             |

Additional adverse events of interest seen in Study 006, the cross-over trial, are listed below:

| AE              | Pbo<br>N=249 | 10 mg<br>N=62 | 20 mg<br>N=61 | 40 mg<br>N=59 | 80 mg<br>N=61 |
|-----------------|--------------|---------------|---------------|---------------|---------------|
| Somnolence      | 0.4%         | 2%            | 5%            | 10%           | 12%           |
| Abnormal Dreams | 1%           | 2%            | 0             | 0             | 5%            |
| Headache        | 2%           | 0             | 2%            | 5%            | 5%            |
| Dizziness       | 0            | 0             | 2%            | 0             | 5%            |

#### Laboratory Findings

##### Mean Changes

There were few differences between suvorexant- and placebo-treated patients in mean changes from baseline in routine laboratory measures. The following chart displays those tests with even minimal between-treatment changes in the 3 Month controlled trial data:

| Measure                             | Mean Change From Baseline |             |              |
|-------------------------------------|---------------------------|-------------|--------------|
|                                     | Pbo<br>N=875              | LD<br>N=424 | HD<br>N=1118 |
| Hematocrit (%)                      | -0.07                     | -0.42       | -0.16        |
| Hemoglobin (g/L)                    | -0.07                     | -0.18       | -0.12        |
| Platelets (10 <sup>3</sup> /microL) | -0.4                      | -1.2        | -2.5         |
| ALT (U/L)                           | 0.5                       | -0.5        | -0.6         |
| AST (U/L)                           | 0.3                       | -0.3        | -0.1         |
| Calcium (mg/dL)                     | -0.06                     | -0.08       | -0.12        |
| Creatine Kinase (mg/dL)             | -0.5                      | -2.4        | -3.0         |
| LDH (U/L)                           | -0.5                      | -2.9        | -1.8         |

The following chart displays the mean change from baseline in serum cholesterol in Study 006:

| Treatment | Mean Change from Baseline (g/dL) |
|-----------|----------------------------------|
| Placebo   | -3.7                             |
| Suv 10 mg | 1.2                              |
| Suv 20 mg | 2.3                              |
| Suv 40 mg | 3.1                              |
| Suv 80 mg | 6.0                              |

#### Outlier Analyses

The following percent of patients met criteria for potentially significant change from baseline in the 3 Month controlled trial data:

| Test                       | Placebo | LD   | HD   |
|----------------------------|---------|------|------|
| Hematocrit<br>(<94.9 LLN)  | 2%      | 0.6% | 3%   |
| Hemoglobin<br>(<90.5% LLN) | 1%      | 0.6% | 2%   |
| Neutrophils<br>(<37% LLN)  | 0.1%    | 1%   | 0.5% |
| Potassium<br>(>111.1% ULN) | 1%      | 1%   | 2%   |

#### EKG

The sponsor performed a Thorough QT study in which they compared single doses of Suvorexant of 60 mg, 160 mg, and 240 mg to Moxifloxacin 400 mg; there were no significant QT effects in the suvorexant-treated subjects. The study did demonstrate the expected QT-prolonging effect of moxifloxacin.

The following chart displays mean changes from baseline for various EKG parameters in the 3 Month controlled trial data:

| Measure                  | Mean Change from Baseline |      |      |
|--------------------------|---------------------------|------|------|
|                          | Placebo                   | LD   | HD   |
| Heart Rate (BPM)         | 0.1                       | -0.5 | -1.1 |
| PR Interval (msec)       | -0.1                      | 0.2  | 1.0  |
| QT Interval (msec)       | 0.4                       | 3.1  | 2.7  |
| QT <sub>c</sub> B (msec) | 0.4                       | 1.2  | -0.5 |
| RR Interval (msec)       | 0.3                       | 7.4  | 17.0 |

There was no difference between treatments in the percent of patients with QT increases of 30-60 msec or greater than 60 msec. There were no meaningful differences in the percent of patients who had a QT interval of >500 msec between treatments.

#### Adverse Events of Special Interest

##### Somnolence

As noted earlier, there was a dose-related increased incidence of next-day somnolence in the 3 Month controlled trial data:

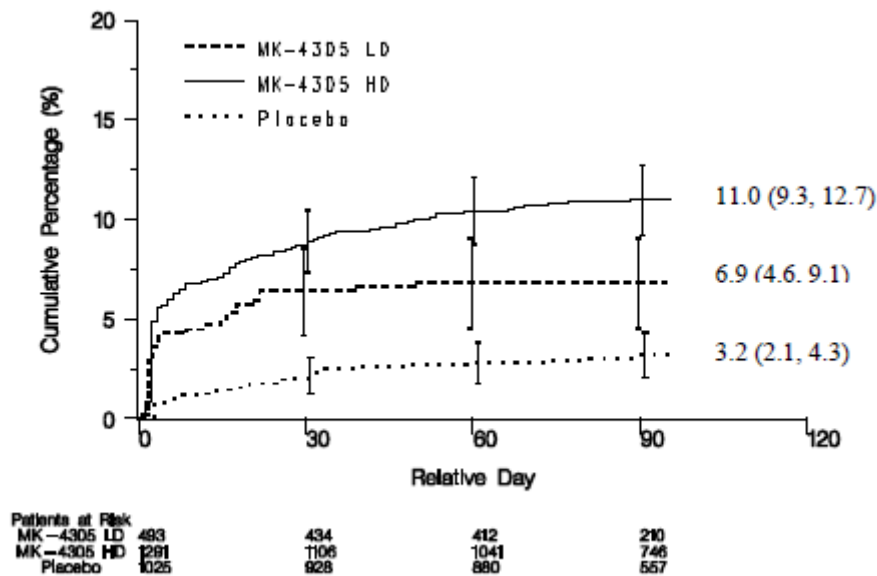
|                                   | Placebo<br>N=1025 | LD<br>N=493 | HD<br>N=1291 |
|-----------------------------------|-------------------|-------------|--------------|
| Somnolence                        | 3%                | 7%          | 11%          |
| Discontinued due to<br>Somnolence | 0.3%              | 0.2%        | 2%           |
| Severe Somnolence                 | 0.1%              | 0.2%        | 0.6%         |
| Somnolence                        |                   |             |              |
| >65 years old                     | 3%                | 5%          | 9%           |
| <65 years old                     | 3%                | 8%          | 12.5%        |

The relationships seen above between age (inverse), dose (direct), and incidence of somnolence persisted in the 6 and 12 Month controlled trials data.

The following chart displays the time course of the onset of somnolence:



**Figure 11: Cumulative Percentage of Subjects Who Reported Somnolence of over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)**



(Source: Sponsor's submission ISS Page 650 Figure 5.3.5.3.3.:5)

Generally speaking, there was little difference in the incidence of somnolence at a given dose of Suvorexant between women and men in the 3 Month controlled trials data:

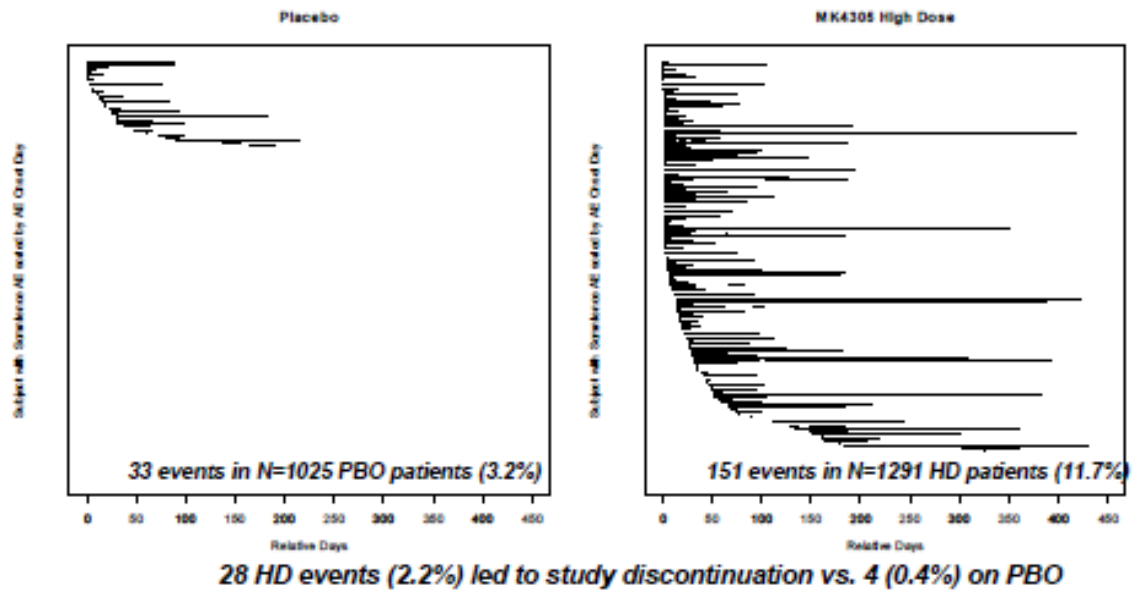
|       | Placebo | LD   | HD  |
|-------|---------|------|-----|
| Men   | 4%      | 3%   | 10% |
| Women | 2%      | 8.5% | 11% |

The difference in incidence of somnolence was also seen in the 6 and 12 month controlled trial data:

|          | Placebo | LD | HD  |
|----------|---------|----|-----|
| 6 Month  | 3%      | 7% | NA  |
| 12 Month | 3%      | NA | 12% |

Patients treated with suvorexant experienced longer durations of somnolence than placebo patients who experienced somnolence. This can be seen in the following plot of the duration of somnolence in individual patients in the 12 Month controlled trials data:

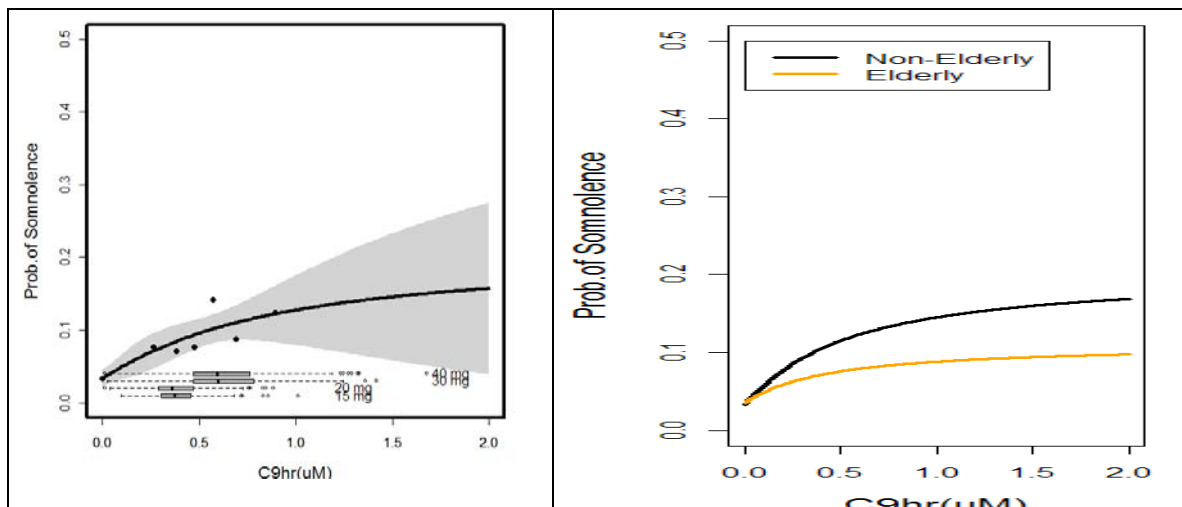
**Figure 13: Subject Plots of Somnolence Events over 0-12 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)**



(Source: Sponsor's submission ISS Page 654 Figure 5.3.5.3.3:7)

The following graphs display a model predicted relationship between somnolence and C<sub>9hr</sub> for the overall population and for elderly vs non-elderly:

**Figure 4: Left: Overall model-predicted relationship for probability of somnolence and suvorexant concentration (C<sub>9hr</sub>). Right: model-predicted relationship for probability of somnolence and suvorexant concentration (C<sub>9hr</sub>) by elderly and non-elderly patients**



## Suicidal Ideation and/or Behavior

The sponsor monitored clinical trials according to a current Agency draft guidance that requires such monitoring and suggests that suicidal ideation/behavior be assessed using the Columbia Suicidality Severity Rating Scale (C-SSRS). Based on these ratings, events are categorized using the Columbia Classification Algorithm for Suicide Assessment (C-CASA), which rates the events as suicidal ideation or suicidal behavior (or not), or indeterminate.

The incidence of events classified as suicidal ideation on clinical grounds (not according to the C-CASA classification) in the 3 Month controlled trial data were:

| Placebo    | LD         | HD         |
|------------|------------|------------|
| 0.1% (N=1) | 0.2% (N=1) | 0.4% (N=5) |

Both the placebo and LD patients had a history of suicidal ideation, as did one of the HD patients. One patient each in the LD and HD dose groups discontinued treatment due to this AE.

According to the C-CASA classification, the following event rate was seen in the 12 Month controlled trials data:

|                   | Placebo<br>(N=1012) | HD<br>(N=1268) |
|-------------------|---------------------|----------------|
| Suicidal Ideation | 0                   | 0.6% (N=8)     |

## Complex Sleep-Related Behaviors

There were 2 patients who reported complex sleep-related behaviors in the 3 Month controlled trial data.

- 1) A 65 year old man with a history of sleep talking experienced sleep talking about 2 ½ hours after a dose of 30 mg (Day 85) and then about 90 minutes later lunged out of bed. Sixteen days later, about 2 weeks off of drug, he had an episode of sleep walking.
- 2) A 58 year old woman experienced sleep walking and sleep paralysis on Day 52 on a dose of 40 mg. The sleep paralysis occurred after a dream, and then hours later found herself standing by a window, unaware of how she got there. Drug was discontinued because of the event

## Excessive Daytime Sleepiness (EDS)

The following chart displays the incidence of EDS in the 3 and 12 Month controlled trial data:

| Duration of Study | Pbo  | LD   | HD          |
|-------------------|------|------|-------------|
| 3 Month           | 0.2% | 0.6% | 1.1% (N=14) |
| 12 Month          | 0.3% | NA   | 1.5% (N=20) |

In the 12 Month, HD patients, 36% of the episodes of EDS were rated as severe; none of those in the other groups were rated as severe. In the 3 Month data, 10/14 (71%) of HD patients discontinued due to EDS. In the 12 Month controlled trial data, 11 Suvorexant HD (0.9%) and 2 placebo (0.2%) patients discontinued due to EDS.

In Study 006, a 63 year old woman experienced EDS after 2 days of 80 mg, and in a Phase 1 study of patients with COPD, a 63 year old woman experienced 5 days of EDS after a dose of 40 mg.

## Hypnagogic and Hypnopompic Hallucinations

Hypnagogic (dreamlike experiences during sleep onset) and hypnopompic (dreamlike experiences upon awakening) hallucinations were seen in the following incidences:

| Duration of Study | Placebo | LD   | HD   |
|-------------------|---------|------|------|
| 3 Month           | 0       | 0.4% | 0.2% |
| 12 Month          | 0       | NA   | 0.4% |

In the 3 Month cohort, two patients (1 LD, 1 HD) experienced sleep paralysis with the event. One HD patient discontinued due to hypnagogic hallucinations (a 73 year old man).

Six subjects in Phase 1 studies also experienced hallucinations after doses of 40-60 mgs.

## Sleep paralysis

The following chart displays the incidence of sleep paralysis in controlled trial data:

| Duration of Study | Placebo | LD   | HD   |
|-------------------|---------|------|------|
| 3 Month           | 0       | 0.2% | 0.3% |
| 12 Month          | 0       | NA   | 0.3% |

In Study 006, one patient on 40 mg and one patient on 80 mg developed sleep paralysis. Each patient experienced multiple episodes.

In Phase 1 studies, 13/662 (2%) of suvorexant and 1/365 (0.3%) of placebo-treated patients experienced sleep paralysis. Of the suvorexant subjects, 6/13 experienced the events at 40 mg. Of the 6, subjects, 4 had multiple events.

## Driving

The sponsor performed two similar studies evaluating highway driving behavior.

Study P039 evaluated driving behavior in 24 healthy subjects >65 years old, and Study P035 evaluated driving in 28 healthy subjects ages 21-64 years old. In these studies, subjects' driving was evaluated in the morning, about 9 hours after nighttime dosing, on Days 2 and 9, after 8 days of dosing. In Study 039, subjects received either 15 mg, 30 mg, or placebo and in Study P035, they received either 20 mg, 40 mg, or placebo. The studies were 4 period cross-over studies, in which all patients received all treatments.

The primary endpoint was the standard deviation of lane position (SDLP), a standard measure in this type of driving study. Zopiclone 7.5 mg was used as an active control; this is also standard in these studies.

A SDLP of 2.4 cm or greater is considered clinically meaningful in these studies (this is the SDLP associated with a blood alcohol level of 0.05%). In addition to examining the mean SDLP, the number of patients with an SDLP of >2.4 (indicating impairment) was compared to the number of patients with an SDLP <-2.4 under each treatment condition (so-called symmetry analysis). The null hypothesis for this measure is that the percent of patients above the 2.4 SDLP and the percent of subjects below -2.4 is symmetric around zero.

## Results

### Study P039

The following chart displays the results of the LS Means of SDLP and the results of the symmetry analyses:

#### LS Mean SDLP

##### Day 2

|           |       |
|-----------|-------|
| Pbo       | 16.67 |
| Zopiclone | 18.56 |
| Suv 15 mg | 16.24 |
| Suv 30 mg | 17.04 |

##### Day 9

|           |       |
|-----------|-------|
| Pbo       | 15.41 |
| Zopiclone | 16.58 |
| Suv 15 mg | 15.50 |
| Suv       | 16.01 |

#### Symmetry Analysis (difference from placebo)

| Day 2        | Zopiclone | 15 mg | 30 mg |
|--------------|-----------|-------|-------|
| # + subjects | 8         | 0     | 3     |
| # - subjects | 0         | 3     | 1     |
| Reject Null  | Yes       | No    | No    |

##### Day 9

|              |     |    |    |
|--------------|-----|----|----|
| # + subjects | 6   | 0  | 5  |
| # - subjects | 1   | 0  | 1  |
| Reject Null  | Yes | No | No |

# Study P035

## LS Mean SDLP

### Day 2

|           |       |
|-----------|-------|
| Pbo       | 15.53 |
| Zopiclone | 17.66 |
| Suv 20 mg | 16.54 |
| Suv 40 mg | 17.19 |

### Day 9

|           |       |
|-----------|-------|
| Pbo       | 15.47 |
| Zopiclone | 16.91 |
| Suv 20 mg | 15.94 |
| Suv 40 mg | 16.77 |

## Symmetry Analysis (difference from placebo)

### Day 2

|  | Zopiclone | 20 mg | 40 mg |
|--|-----------|-------|-------|
|--|-----------|-------|-------|

|              |     |     |     |
|--------------|-----|-----|-----|
| # + subjects | 14  | 6   | 10  |
| # - subjects | 1   | 0   | 2   |
| Reject Null  | Yes | Yes | Yes |

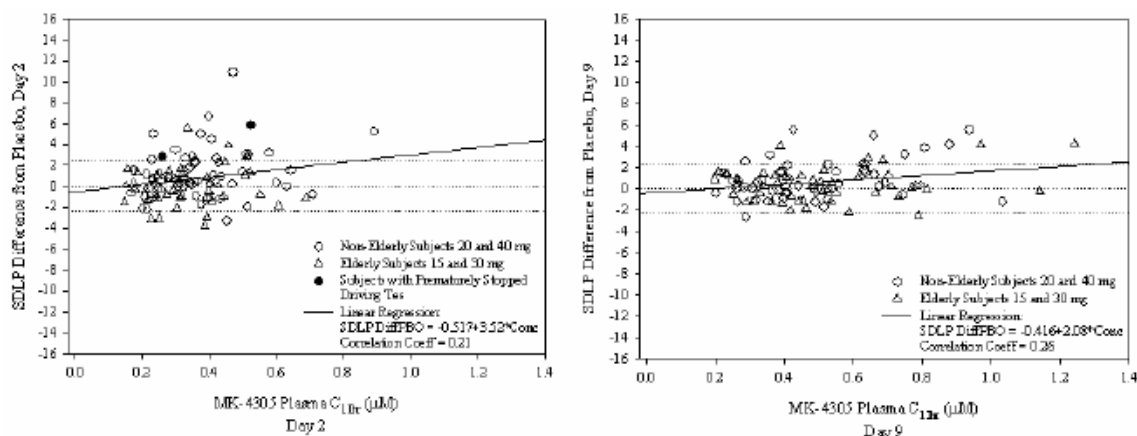
### Day 9

|              |     |    |     |
|--------------|-----|----|-----|
| # + subjects | 8   | 2  | 6   |
| # - subjects | 0   | 1  | 0   |
| Reject Null  | Yes | No | Yes |

Four (4) women stopped 5 driving tests because of somnolence: two after 40 mg on Day 2; one after 20 mg on Day 2, and one woman stopped tests after 40 mg on Day 2 and after 20 mg on Day 9. These tests were stopped between 29 and 57 minutes after the start of the tests.

In these studies, blood levels were measured at 11 hours after drug ingestion. The following graphs display the differences from placebo in C11 plasma levels and SDLP:

**SDLP Differences From Placebo vs Suvorexant Plasma Concentrations ( $C_{11hr}$ ) in Non-Elderly and Elderly Subjects on Day 2 (left panel) and Day 9 (right panel). Subjects whose driving was prematurely stopped due to somnolence were identified (no PK sample was available for AN007, AN016 repeat period data is shown)**



In addition to the formal driving study, the sponsor presented results on reported motor vehicle accidents (MVAs), as well as data derived from questionnaires. There were no more reported MVAs in suvorexant-treated patients compared to placebo-treated patients in controlled trials overall, but in a 12 month-safety study, 5.5% of suvorexant HD patients and 4.1% of placebo-treated patients reported at least one MVA.

In Phase 3 trials, patients were asked about their driving experiences via a specific Motor Vehicle Accidents and Violations (MVAV) Questionnaire. The following chart displays the results of this testing for the various controlled trials cohorts:

| Duration of Study       | Placebo | LD   | HD   |
|-------------------------|---------|------|------|
| 3 Month                 |         |      |      |
| Patients with Accidents | 0.9%    | 1.2% | 1.2% |
| Patients with Citations | 1.3%    | 1.8% | 1.2% |
| 6 Months                |         |      |      |
| Patients with Accidents | 1.3%    | 1.2% | NA   |
| Patients with Citations | 1.5%    | 2.3% | NA   |
| 12 Months               |         |      |      |
| Patients with Accidents | 1.4%    | NA   | 1.5% |
| Patients with Citations | 2%      | NA   | 2.7% |



## Cataplexy

The sponsor constituted an external adjudication committee to review clinical reports of cataplexy, as well as to review the data captured on a Modified Cataplexy Questionnaire that the subject/patient completed after a possible event.

The committee reviewed 45 cases of suspected cataplexy, and determined that none could be defined as cataplexy.

At least one case that could reasonably be considered to be cataplexy is described below:

A 59 year old man reported leg weakness on Day 46 of treatment with 40 mg of suvorexant. On the same day, he also reported EDS, and discontinued the trial secondary to that event.

About 12 hours after his Day 45 dose, he felt increased tiredness and several episodes of leg weakness (lasting about 5-30 seconds) after laughing with co-workers. He continued feeling weak for about 11 hours. About 5 hours after these episodes, he experienced EDS that lasted until bedtime, and occurred several times while driving.

On the questionnaire, this patient responded positively to the event having occurred “when laughing, when excited, surprised, when required to make a quick verbal response in a playful or funny context, when startled, when telling or hearing a joke”.

## Falls

The incidence of falls was essentially the same among all treatment groups in controlled trials. The falls that occurred in the drug-treated patients all appeared to have been related to identifiable, non-drug related, causes.

## Memory, DSST, Balance

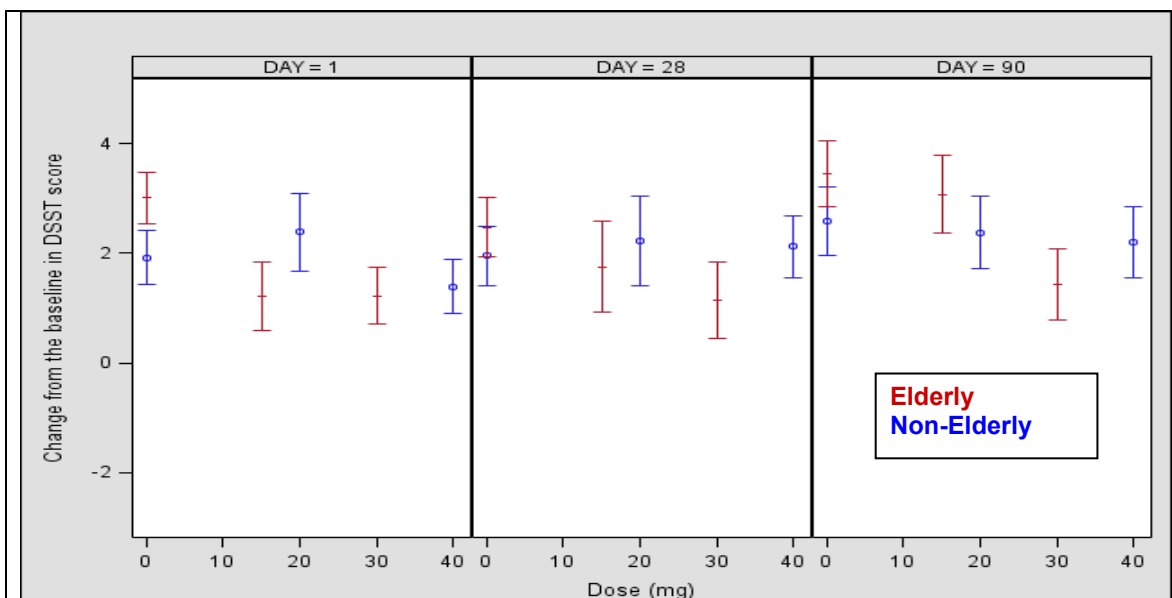
In relatively small studies (the two driving studies, a study in patients with COPD [N=25], a study in patients with Obstructive Sleep Apnea [OSA; N=26]), the sponsor evaluated Delayed Word Recall (IDWR), Digit Symbol Substitution (DSST), and balance (body sway). These studies examined effects at 9 hours after dosing, and included elderly and non-elderly subjects treated up to 9 days; they evaluated various doses: 15 and 30 mg in the elderly, and 20 and 40 mg in non-elderly patients.

Only on the IDWR test in the driving study in non-elderly subjects was a statistically significant worsening on suvorexant (40 mg) seen compared to

placebo seen. In no other study were there significant mean effects on memory or balance that differed between the treatment groups.

The sponsor reports no significant between-group differences on the DSST, including in the Phase 3 trials (in which the DSST was performed in the morning after the overnight PSG recordings), except for Night 1 in elderly patients in the Phase 3 trials, and, in the small studies described above, only in the driving study in non-elderly adults at 11 hours after dosing with suvorexant 40 mg on Day 1, but not after 8 days of dosing. The following graph shows the (lack of) relationship between plasma level and DSST results in both elderly and non-elderly patients in the Phase 3 controlled trials:

**Figure 5: Dose vs.  $\Delta$ DSST (top) and  $C_{9hr}$  vs.  $\Delta$ DSST (bottom) relationship by elderly and non-elderly patients**



## Clinical Pharmacology

Median peak plasma levels of suvorexant occur about 2 hours after ingestion (range ½ to 6 hours). It is extensively metabolized, primarily by CYP3A4, with some contribution from CYP2C19. The major circulating metabolite, M9, is formed by hydroxylation, and further metabolized to a carboxylic acid derivative, M4. M9 appears in the plasma at about equal concentrations to the parent, but it is a substrate of P-gp, and is not expected to enter the brain.

The primary route of metabolism is through the feces (66% recovered in the feces, 23% recovered in the urine). The mean terminal  $T_{1/2}$  is about 12 hours,

and is similar for M9. Accumulation of AUC and Cmax is about 1.2 to 1.6 at steady state.

Suvorexant exposure is higher in women than in men; the female/male ratios of the geometric means for AUC and Cmax were about 1.5 and 1.3, respectively. The apparent oral clearance was about 20% lower in women than in men.

Apparent clearance is inversely related to Body Mass Index (BMI). The concentration of suvorexant at 9 hours after dosing (a critical time point for assessing next day morning effects) is predicted to be about 20% higher in obese patients than in patients with normal BMI. Considering the combination of factors that can affect clearance, some populations may have considerably greater plasma concentrations than others for a given dose. For example, the clearance in obese women is expected to be about 2-3 times lower than in men with a normal BMI.

The concentration at 9 hours post-dose in elderly patients is about 15% greater than that in non-elderly adults.

Based on in vitro studies, suvorexant can inhibit CYP3A4 and intestinal P-gp.

## **Comments**

The sponsor has submitted three controlled trials, examining a range of doses, that could contribute to a finding of substantial evidence of effectiveness for suvorexant for patients with insomnia characterized by difficulty falling asleep (latency) and/or staying asleep (maintenance). In Studies 28 and 29, elderly and non-elderly patients were treated with different doses: 15 and 30 mg in the elderly, and 20 and 40 mg in the non-elderly.

In our view, the data clearly demonstrate that suvorexant is effective for both symptoms (latency and maintenance), based primarily on Studies 28 and 29. Study 006 also clearly shows that suvorexant is effective for sleep maintenance (based on WASO); the results in this study are less impressive for sleep latency (based on LPS).

Given that the data, overall, establish effectiveness, we need to examine the response by dose.

Regarding sleep maintenance, it appears that there is some evidence of dose response in Studies 28 and 29, but that all doses are significantly superior to placebo, based on the subjective endpoint, sTST. However, there appears to be little to no dose response for sleep maintenance based on the objective WASO, where, again, all doses are statistically significantly superior to placebo. In addition, all doses (from 10-80 mg) are statistically superior to placebo on WASO

in Study 006, with very little evidence of a dose response. As we have also shown, analyses of the combined data from all three studies, show little to no dose or concentration response for sleep maintenance, including at concentrations associated with the 10 mg dose, based on objective WASO.

Regarding sleep latency, there appears to be some evidence of dose response in Studies 28 and 29, with the low dose not shown to be statistically superior to placebo, based on the subjective endpoint, sTSO. On the other hand, in Study 28, all doses are significantly superior to placebo, with no evidence of a real dose response, based on the objective measure, LPS, whereas in Study 29, there appears to be somewhat of a dose response, with the low dose not being statistically superior to placebo on LPS. In Study 006, the effects of suvorexant on LPS are unclear; the higher doses (above 20 mg) appear significantly superior to placebo on Night 1, but no doses are significant at Week 4. Some analyses of the first period data suggest that 10 mg may be effective for LPS. However, we have also shown that analyses that combine data from all three studies suggest no dose or concentration response on sleep latency, based on objective LPS. In particular, in those concentration analyses, a median AUC of about 5 microM\*hr was shown to be effective, which is equivalent to the median AUC at the 10 mg dose.

These data, taken together, suggest to us that all doses studied (down to, and including, 10 mg) are effective for both endpoints, and that there is little evidence to suggest that the higher doses are substantially superior to 10-15 mg, at least for sleep maintenance, and likely for sleep latency as well. This conclusion is primarily based on the results of the analyses described above of the objective measures, measures we believe more reliably assess the effects of interest than do the subjective measures.

The question of dose response is particularly important, given the safety data.

Suvorexant clearly causes dose related, next day effects, including sedation, which can be of significant concern. For example, as noted above, there is an 8-fold increase in the incidence of next day somnolence between the low and high doses of suvorexant in the 3 Month controlled trial data that led to discontinuation (0.2 and 1.7%, respectively). The incidence of somnolence continues to increase for at least 60 days after initiation of treatment, and the duration of somnolence in suvorexant patients was longer than the duration of somnolence in placebo patients. There was also a dose-related increase in the incidence of somnolence and severe somnolence, and, interestingly, although this was also true in both age groups, elderly patients had a lower incidence of somnolence at each dose (low and high) than did the non-elderly patients.

Perhaps most importantly, the results of a formal driving study demonstrate that suvorexant can cause significant impairment in driving the morning after dosing.

Specifically, in a study (P035) of non-elderly adults, both 20 and 40 mgs were associated with an increase in patients who had excessive deviation in lane position the morning after a single bedtime dose taken the night before. This next-morning effect clearly persisted after 8 days of continuous dosing of 40 mg. Further, and critically, 4 women had to discontinue the testing due to excessive somnolence.

In Study P039, a similar driving study in elderly adults, there were no statistically significant differences between either dose of suvorexant and placebo in the symmetry analysis, though there were **clear** numerical increases in the number of subjects who met SDLP criteria for impairment at the 30 mg dose.

Suvorexant also seems to increase the risk of suicidal ideation/behavior in a dose related fashion. For example, in the 12 Month controlled trial data, there were 0 placebo patients (N=1012) compared to 8 suvorexant patients (N=1268) who were considered to have had suicidal ideation, when these events were classified formally by protocol.

Suvorexant also seems to be associated with adverse events that can be considered to be elements of a narcolepsy-like syndrome.

Specifically, in controlled trials, suvorexant caused an increase in the incidence of excessive daytime sleepiness, sleep paralysis, and hypnagogic/hypnopompic hallucinations. There were also numerous reports (N=45) of suspected cases of cataplexy. Although an adjudication panel did not consider any of these cases to be cataplexy, our independent review suggests that at least one, and perhaps several more, could reasonably have been cases of actual cataplexy.

Pharmacokinetic considerations are also important in the decision about the appropriate dose(s) to be recommended.

In particular, the clearance of suvorexant in women is lower than in men, and increased BMI is also associated with a slower clearance. As described earlier, populations of patients with a combination of factors that decrease clearance (e.g., obese women) would be expected to have a clearance that is 2-3 times lower than men with a normal BMI. Particularly high plasma concentrations would be expected to be associated with an increased incidence of adverse events, in particular (though certainly not only) impaired driving, and dosing recommendations should take this fact into consideration.

It is also worth noting that plasma levels of suvorexant in elderly adults differ little from those of non-elderly adults, for any given dose.

The sponsor has proposed that the high dose be recommended in product labeling. In our view, the data taken together (both safety and effectiveness, as well as pharmacokinetics) suggest that a lower dose should be recommended, at

least as an initial dose. From the effectiveness point of view, this conclusion is primarily based on our analyses of Studies 28 and 29, as well as on our analyses of Study 006, and the objective measures of both sleep latency and maintenance, as well as our analyses of dose and concentration-response data performed on pooled data by our Clinical Pharmacology team. The lack of significant kinetic differences between elderly and non-elderly patients argues for recommending at most the 15 mg dose (and perhaps the 10 mg dose), at least as a starting dose, though the lowest dose studied in non-elderly patients was 20 mg.

Safety data demonstrate dose related increases in adverse events, in particular impaired driving. Both doses in non-elderly patients were associated with next-morning impairment, and though neither dose in the elderly driving study was significantly different from placebo, the clear increase in 30 mg dose patients who were impaired, in the context of the data described above, also argues for recommending the 10 or 15 mg dose.

Finally, as noted above, women and obese patients have higher plasma levels of suvorexant than men and patients with a normal BMI. Clearly, some populations would be expected to have considerably higher plasma concentrations than others. In some populations (e.g., obese women), even the 15 mg dose may be too high, given the risks of high dose suvorexant. In these patients, a lower dose would presumably be warranted. However, the lowest strength proposed for marketing by the sponsor is 15 mg. It is worth asking, if a dose lower than 15 mg is considered appropriate for these patients, but cannot be attained, whether labeling could be written that would reliably prevent these patients from receiving the drug. Indeed, if a dosage strength lower than 15 mg is unavailable, we would need to consider if the drug could be marketed safely at all, if we believe that a substantial proportion of the indicated population needs a lower dose.

We will be asking the Committee to comment on all of these issues (and, of course, any other issues that the Committee feels are relevant) at the May meeting.

One final point. In this memo, as well as in several of the other documents included in this briefing package, Agency staff has expressed opinions about these issues. Indeed, these views are not necessarily in agreement. However, it is critical for you to know that we have not taken any final positions on any of these issues, and we will not do so, of course, until we have received advice from the Committee in May.

I look forward to seeing you all on the 22<sup>nd</sup>, and look forward to a very productive meeting. Thank you in advance for all of your work on this application.

Russell Katz, M.D.

## **Points to Consider**


The Division has concluded that there is little to no dose-response for effectiveness across the range of doses tested (10 mg – 80 mg).

However, there is a dose-response for significant adverse reactions, including, for example, impaired driving and suicidal ideation.

- We would like the Committee to consider the safety and efficacy data and discuss doses that could be appropriate for marketing.
- We also are interested in any other issues the Committee considers relevant.

## CLINICAL REVIEW

|                       |                |
|-----------------------|----------------|
| Application Type      | NDA 505 (b)(1) |
| Application Number(s) | 204569         |
| Priority or Standard  | Standard       |

|                   |  |
|-------------------|--|
| Submit Date(s)    |  |
| Received Date(s)  |  |
| PDUFA Goal Date   |  |
| Division / Office | DNP/ODE1   |

|                        |                      |
|------------------------|----------------------|
| Reviewer Name(s)       | Kachi Illoh, MD, MPH |
| Review Completion Date | 04/29/2013           |

|                       |                            |
|-----------------------|----------------------------|
| Established Name      | Suvorexant, MK-4305        |
| (Proposed) Trade Name |                            |
| Therapeutic Class     | Orexin Receptor Antagonist |
| Applicant             | Merck Sharp & Dohme Corp.  |

|                        |   |
|------------------------|---|
| Formulation(s)         | 40 mg, 30 mg, 20 mg, and 15 mg tablets                  |
| Dosing Regimen         | 30 mg (elderly adults) or 40 mg orally daily at bedtime |
| Indication(s)          | Sleep maintenance insomnia<br>Sleep onset insomnia      |
| Intended Population(s) | Adults with insomnia                                    |





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# 1 Executive Summary

## 1.1 Brief Overview of the Clinical Development Program

This clinical briefing document provides a review of a New Drug Application (NDA) submitted by Merck for suvorexant, which is formulated as an immediate-release tablet for oral administration. Suvorexant is a new chemical entity that is suggested to act as a highly selective antagonist for orexin receptors OX<sub>1</sub>R and OX<sub>2</sub>R. The proposed indication for suvorexant is for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The dose proposed for non-elderly adults, younger than 65 years, is 40 mg once daily. For elderly adults, 65 years and older, the proposed dose is 30 mg once daily. In addition, Merck recommends allowing for a lower dose of 20 mg in the non-elderly and 15 mg in the elderly based on individual tolerability.

This clinical review focused on three Phase 3 trials (P028, P029, and P009) for assessing the efficacy and safety of suvorexant. Two of these trials, P028 and P029, provided 3-month treatment data for the primary efficacy assessment. The third Phase 3 trial P009 contributed 12-month treatment data and was included with the other two Phase 3 trials in the safety review. This document discusses the individual trials; the efficacy results; and the combined safety data, primarily from the three Phase 3 trials, with supportive data from the Phase 2 trial (P006) and pooled Phase 1 trials (31 trials).

Among the issues for discussion at the advisory committee meeting is to determine whether suvorexant is safe and effective for the proposed indication: to treat insomnia that is associated with either sleep onset or sleep maintenance difficulties, or both sleep onset and sleep maintenance difficulties. Another issue for discussion is the appropriate suvorexant dose for insomnia treatment, given the safety assessment and results of the driving studies that suggest some impairment of driving performance with the tested suvorexant doses.

## 1.2 Efficacy

In trials P028 and P029, suvorexant high dose (HD) showed statistically significant efficacy effect on both sleep maintenance and sleep onset endpoints in adult subjects with primary insomnia. The efficacy effects of suvorexant HD persisted through the entire treatment period and appeared to be clinically meaningful. Suvorexant low dose (LD), which was not primarily evaluated in the trials, appeared to have some efficacy effect on sleep maintenance insomnia. In the trials, suvorexant HD signified 30 mg for elderly subjects and 40 mg for non-elderly subjects, suvorexant LD was 15 mg for elderly subjects and 20 mg for non-elderly subjects.

Trials P028 and P029 were similarly designed to primarily evaluate the efficacy of suvorexant HD compared with placebo in improving sleep maintenance and sleep onset at Months 1 and 3, using subjective and objective polysomnographic (PSG) outcomes.

The trials used multiple endpoints to assess efficacy. For sleep maintenance, Merck compared treatment effects of suvorexant HD and placebo on two primary endpoints and at two time points, as follows: change from baseline in mean subjective total sleep time, sTSTm, at Month 1 and Month 3; and change from baseline in the PSG-derived objective wakefulness after persistent sleep onset, WASO, at Month 1 and Month 3. Likewise for sleep onset, suvorexant HD treatment effects were assessed by the following endpoints: change from baseline in mean subjective time to sleep onset, sTSOm, at Month 1 and Month 3; and change from baseline in objective latency to persistent sleep, LPS, at Month 1 and Month 3.

Key secondary endpoints in trial P028 included change from baseline in sTSTm at Week 1 and WASO at Night 1 for suvorexant HD, and an assessment of suvorexant LD on all the above-stated endpoints and time points for suvorexant HD. Trial P029 assessed suvorexant LD as exploratory analyses.

Merck used a multiplicity testing strategy to assess the primary and secondary endpoints. A longitudinal data analysis (LDA) model was used to perform the statistical analyses for efficacy. The model adjusted for the corresponding baseline value of a response variable, age group (non-elderly versus elderly), region, gender, treatment, time, and the interaction of treatment by time. To control for type 1 error, Merck analyzed the primary and secondary endpoints using a multiplicity testing strategy that included a Bonferroni approach to evaluate two distinct indications – sleep maintenance and sleep onset effects. The strategy also encompassed a fixed sequential testing procedure to move from Month 1 to Month 3 sets of primary hypotheses, and a Hochberg approach within each time point to evaluate the objective and subjective endpoints. As a result, endpoints for sleep maintenance effect (sTSTm and WASO) were tested at the two-sided 2.5% level, while endpoints for sleep onset effect (sTSOm and LPS) were also tested at the two-sided 2.5% level. Overall, the trial's choice of endpoints, blinding procedure, duration, conduct, and statistical analyses appear adequate.

An earlier phase 2 dose finding trial P006 that evaluated multiple suvorexant doses, from 10 mg to 80 mg, in non-elderly subjects informed on the choice of dose to study in the phase 3 trials. The 40 mg dose that was chosen for further assessment appears appropriate, based on its 4-week treatment effect on both objective and subjective endpoints. To treat elderly subjects in the Phase 3 trials, Merck chose a 30 mg dose that was suggested to be comparable to the 40 mg dose based on drug exposure data from prior studies. Both doses for the two age groups are referred to as suvorexant HD. Based on FDA feedback, Merck included a lower dose, suvorexant LD, in the phase 3

program; this dose consisted of 15 mg for elderly subjects and 20 mg for non-elderly subjects.

#### Sleep Maintenance Effects

For sleep maintenance, suvorexant HD treatment in both trials P028 and P029 significantly improved both subjective (sTSTm) and objective (WASO) primary endpoints at Month 1 and Month 3. Based on the pooled data, suvorexant HD compared to placebo treatment at Month 3 added about 22 minutes of sTSTm ( $p < 0.00001$ ), and reduced WASO by 26 minutes ( $p < 0.00001$ ). Supporting efficacy assessments using the subjective endpoint sWASO showed similar significant improvements with suvorexant HD compared to placebo at all time points (all  $p$  values  $< 0.006$ ).

Assessment of secondary endpoints provided additional support of efficacy for suvorexant in treating sleep maintenance insomnia. In the secondary analyses of both trials P028 and P029, suvorexant HD significantly improved sTSTm at Week 1 and WASO at Night 1.

Also in trial P028, suvorexant LD significantly improved the sleep maintenance endpoints sTSTm and WASO at all predefined time points. Trial P029 did not include suvorexant LD for secondary endpoint assessment. Based on the pooled data, suvorexant LD compared to placebo treatment added 16 minutes of sTSTm ( $p < 0.00001$ ), and reduced WASO by 23 minutes at Month 3 ( $p < 0.00001$ ). Importantly, suvorexant LD failed to significantly improve sWASOm, a key sleep maintenance endpoint for FDA, at Months 1 and 3 in trial P028.

Overall, suvorexant HD, and to a less extent suvorexant LD, showed significant improvement in sleep maintenance endpoints. The difference between the treatment effect of suvorexant HD and that of suvorexant LD is about 6 minutes on sTSTm, or 3 minutes on WASO. Whether this difference in treatment effects between the suvorexant doses is sufficient to allow approval of the lower dose for sleep maintenance will be a topic of discussion at the advisory committee meeting. Of note, an acceptance of suvorexant LD as an effective treatment for sleep maintenance will fail to consider the inconsistent effect of the dose on sWASO in trial P028.

#### Sleep Onset Effects

Suvorexant HD improved sleep onset outcomes compared to placebo, though not as consistently as in sleep maintenance. In both trials P028 and P029, suvorexant HD treatment significantly improved the subjective (sTSOm) primary endpoint for sleep onset at Months 1 and 3 (all  $p$  values  $< 0.007$ ). In trial P028, suvorexant HD significantly improved the objective primary endpoint LPS at Months 1 and 3 ( $p$  values  $< 0.0004$ ). However in trial P029, suvorexant HD significantly improved LPS at Month 1 ( $p = 0.00004$ ), but it failed to provide significant LPS improvement at Month 3 ( $p = 0.2651$ ). Based on the pooled data from trials P028 and P029, suvorexant HD compared to

placebo treatment decreased sTSO by about 11 minutes ( $p < 0.00001$ ) and LPS by 6 minutes ( $p = 0.00235$ ) at Month 3.

The secondary efficacy endpoints assessed for sleep onset, sTSOm at Week 1 and LPS at Night 1, showed significant improvements with suvorexant HD compared to placebo treatment in both trials P028 and P029.

Secondary endpoint assessment for suvorexant LD in trial P028 showed inconsistent improvements on sleep onset endpoints at different time points. Suvorexant LD significantly improved sTSOm at Week 1 and LPS at Night 1. The dose improved LPS at Month 1 by 10.3 minutes compared to placebo ( $p = 0.0004$ ), but it did not significantly improve sTSO compared to placebo despite a 5.4-minute decrease in the endpoint ( $p = 0.05191$ ).

Overall, suvorexant HD consistently showed significant improvement in the subjective sleep onset endpoint. The dose showed significant improvement in the objective sleep onset endpoint at all time points, except at Month 3 in one of the two trials. In contrast, suvorexant LD showed inconsistent improvements on sleep onset endpoints at different time points. Whether the inability of suvorexant HD to significantly improve LPS at Month 3 is sufficient to deny approval of the dose for sleep onset will be a topic of discussion at the advisory committee meeting.

#### Clinical Significance of Treatment by Responder Analysis

To further assess the clinical meaningfulness of suvorexant treatment effects, Merck conducted pre-specified responder analyses based on exploratory subjective endpoints. For sleep maintenance, a higher percentage of subjects on suvorexant treatment recorded at least 15% increase from baseline in sTSTm at the different time points in the pooled data. In the pooled data, the percentage of sTST responders in the treatment groups at Month 3 was 54.7% (376/688) for suvorexant HD compared to 41.9% (278/664) for placebo, a treatment difference of 12.8% that yielded a number needed to treat to benefit (NNTB) of 8. For sWASO, the percentage of responders in the treatment groups at Month 3 was 77.5% (529/683) for suvorexant HD compared to 69.4% (458/660) for placebo, a treatment difference of 8.1% and NNTB of 12.

On the sleep onset endpoint, there were more responders in the suvorexant-treated groups than placebo. In the pooled data, the percentage of sTSO responders in the treatment groups at Month 3 was 76.5% (526/688) for suvorexant HD compared to 66.0% (438/664) for placebo, a treatment difference of 10.5% that yielded an NNTB of 10.

The overall data suggest that suvorexant HD has clinically significant efficacy on both sleep maintenance and sleep onset in subjects with primary insomnia. The assessments show that the efficacy of suvorexant HD persisted through the entire treatment period. Suvorexant LD, though not primarily evaluated in the trials, appears to

have some significant but limited efficacy on sleep maintenance insomnia. In addition, point estimates, shown in review section 4.1.7, for the sleep maintenance and sleep onset endpoints from the pooled data suggest that improvements from suvorexant (HD and LD) treatment were generally consistent across the subgroups.

### **1.3 Safety**

This clinical briefing document summarizes analyses of the Phase 3 safety database to characterize overall risk estimates of adverse events (AEs). The most prominent AE from suvorexant treatment was next day sleepiness that occurred at a rate similar to earlier approved insomnia drugs, based on indirect comparison. The suvorexant program also evaluated other known risks associated with sedative hypnotics. Driving trials were conducted to assess for post-treatment next-day impairments in driving performance. Further, suvorexant's mechanism of action warranted scrutiny for the risk of developing narcolepsy. The sponsor provided an extensive safety database that meets the requirements of existing guidance documents.

For the safety assessments, Merck summarized data from 35 clinical trials: two Phase 3 confirmatory efficacy trials; and one Phase 3 long-term safety trial; one Phase 2b dose-finding trial; and 31 Phase 1 clinical pharmacology trials, which were conducted in healthy volunteers and special populations. The Phase 3 trials constituted the primary integrated database that Merck used to assess safety in 2,809 subjects with primary insomnia.

The number of subjects exposed to the proposed treatment doses, 15 to 40mg daily, was adequate. A total of 2027 subjects with chronic insomnia received any suvorexant dose: 1198 non-elderly and 829 elderly subjects. The Phase 3 trials exposed 1784 subjects to suvorexant 15 to 40 mg doses, of which 1218 subjects received treatment for at least 3 months, 507 subjects for at least 6 months, and 160 subjects for at least 12 months.

Two deaths occurred, both in Phase 3 trials. One subject on suvorexant HD experienced a near-drowning event, was hospitalized, went into cardiac arrest, and became brain dead. The other subject was on placebo when she experienced a stroke with brain swelling before she died.

Serious adverse events (SAEs) occurred less frequently in suvorexant treated subjects than in placebo. Over 12 months, SAEs occurred in 2.8% (36/1291) of the subjects who received suvorexant HD and 3.2% (33/1025) who received placebo. Likewise, fewer subjects on suvorexant LD reported SAEs (0.6%, 3/493) compared to placebo (2.1%, 16/767) in the 0-6 months safety population. SAEs in the post-treatment phase included three events of spontaneous abortions, all three received suvorexant treatment: suvorexant HD had two subjects, and suvorexant LD one subject. Two of the three cases had confounding concomitant medications.

Numerically more subjects on suvorexant HD discontinued treatment because of an adverse event compared to those on suvorexant LD or placebo. Discontinuation of treatment because of adverse event in all subjects treated occurred in 5.4% (70/1291) of the HD suvorexant group and 3.2% (16/493) of the LD suvorexant group, compared to 4.7% (48/1025) of the placebo group. Adverse events most commonly associated with treatment discontinuation were somnolence and fatigue in the HD suvorexant group.

Any AEs occurred more frequently among the suvorexant HD subjects with 51.0% (658/1291) compared to suvorexant LD with 46.5% (229/493) or placebo 46.6% (478/1025). Also, subjects on suvorexant HD reported more adverse events in the Nervous system disorders SOC with 21.4% (276/1291) compared to suvorexant LD 16.8% (83/493) or placebo 13.2% (135/1025). Somnolence and fatigue were the most common AEs that had an incidence of 2% or higher in a treatment group and occurred more frequently, in dose-related manner, in the suvorexant group than placebo.

The most significant AE was somnolence. Suvorexant caused a dose-related increase in somnolence within the initial months of treatment. Somnolence within 0-3 months in the combined Phase 3 population occurred in 10.7% (138/1291) of the suvorexant HD group, 6.7% (33/493) of suvorexant LD, and 3.0% (31/1025) of placebo. The incidence of severe somnolence, which was incapacitating with inability to work or do usual activity, was overall low but higher in the suvorexant HD group at 0.6% (8/1291) compared to suvorexant LD at 0.2% (1/493), and placebo at 0.1% (1/1025). As a result, the risk difference for severe somnolence between each suvorexant dose and placebo was small, though higher in the suvorexant HD group: 0.5% with number needed to treat to cause severe somnolence or harm (NNTH) 200 for suvorexant HD, and 0.1% with NNTH 1000 for suvorexant LD.

The rates of somnolence in the suvorexant Phase 3 trials appear to be comparable to those of other approved drugs for the sought indication. For example, zolpidem CR 12.5 mg, which is approved for the same indication, recorded somnolence rates of 15% in the active trial arm of 102 subjects compared to 2% in placebo group of 110 subjects in 3-week trial of non-elderly subjects. In another 3-week trial in elderly subjects, the incidence of somnolence was 6% of 99 subjects on zolpidem CR 6.25 mg compared to 5% of 106 subjects on placebo. Other approved insomnia drugs registered similar rates of somnolence. Overall, information gathered on next-day somnolence may serve as a useful guide in assessing dose-response relationships, especially in future clinical dose titrations.

Merck assessed certain adverse events as Events of Clinical Interest (ECIs). These events included the following: suicidal ideation or behavior, complex sleep-related behaviors, hypnagogic and hypnopompic hallucinations, AEs associated with abuse potential, excessive daytime sleepiness (EDS), cataplexy, falls, sleep paralysis, AEs

associated with a traffic or motor vehicle accident (MVA), and reports of motor vehicle accidents and violations (MVAV) based on MVAV Questionnaire. An independent committee of experts, blinded to treatment assignment and external to Merck, received ECIs of cataplexy, falls, and sleep onset paralysis for adjudication. Events of falls were adjudicated to determine whether they were suggestive of cataplexy. Overall, the incidences of the individual ECIs were low.

In the Phase 3 Population within 0-3 months of treatment, suicidal Ideation occurred in seven subjects; five of them occurred in the suvorexant HD treatment group, an incidence of 0.4% (5/1291); one subject was in the suvorexant LD group, an incidence of 0.2% (1/493); and one subject was in the placebo group, incidence of 0.15 (1/1025). Beyond three months of treatment, the suvorexant HD group recorded another case of suicidal ideation. The C-SSRS assessment identified three additional cases of suicidal ideation that investigators had not considered as AEs and so did not report them as ECIs. All three subjects were on suvorexant HD.

Only two subjects reported complex sleep-related behaviors (CSRBs) in the Phase 3 Population. Both subjects were on suvorexant HD (0.2%, 2/1291). One case, a 65-year-old male with a history of sleep talking reported an event of sleep talking on Trial Day 85 while on suvorexant HD. The same night he lunged out of bed, and hit his head and face against a wall. On Day 101, he had a different CSRB event, sleep walking, after he had received no trial medication for 2 weeks. The second case was a 58-year-old female who reported somnambulism (sleep walking) and severe sleep paralysis on Trial Day 52 while on suvorexant HD.

EDS was expected to occur suddenly during the day in a subject who had an adequate night sleep, so has a safety impact on such activities as driving. In the Phase 3 Population, EDS occurred more frequently in the suvorexant HD group. The EDS incidence was 1.1% (14/1291) in suvorexant HD, 0.6% (3/493) in suvorexant LD, and 0.2% (2/1025) in placebo groups. The EDS risk difference for suvorexant LD compared to placebo was 0.5% (95% CI: -0.2, 1.7); the risk difference for suvorexant HD, with a 95% confidence interval that excluded zero, was 0.8% (95% CI: 0.1, 1.6), NNTH 125.

Five subjects reported hypnagogic and hypnopompic hallucinations within the first three months of treatment: 0.2% (3/1291) in the suvorexant HD group, 0.4% (2/493) in the suvorexant LD group, and none in the placebo group. The event reported for one (0.2%, 1/493) of the two subjects in the suvorexant LD group was a case of hypnagogic hallucination; the other was a hypnopompic hallucination. In contrast, all three subjects (0.2%, 3/1291) in the suvorexant HD group were cases of hypnagogic hallucinations.

Five subjects reported sleep paralysis within the first 3 months; all five received suvorexant treatment. Numerically more subjects reported this ECI while on suvorexant HD (0.3%, 4/1291) compared to suvorexant LD (0.2%, 1/493), and none on placebo.

Three of the four suvorexant HD subjects had confirmed events of sleep onset paralysis on adjudication. One case resulted in treatment discontinuation.

Additional subjects on suvorexant doses of 40 mg and higher reported sleep paralysis in the Phase 2 and Phase 1 trials. In the Phase 2 trial, two subjects on suvorexant 40 mg and 80 mg reported symptoms suggestive of sleep paralysis; these events apparently occurred in the middle of night or on awakening, and not at sleep onset. In the Phase 1 trials, 2% (13/ 662) of subjects on suvorexant alone reported sleep paralysis compared to 0.3% (1/365) on placebo. All 13 subjects in the Phase 1 trial, who reported sleep paralysis on suvorexant, did so while on suvorexant doses of 40 mg to 240 mg; 6 of the 13 subjects were on suvorexant 40 mg.

The suvorexant program had no confirmed cases of narcolepsy with or without cataplexy. The external adjudication committee examined a case of muscle weakness and concluded it was not cataplexy. From the NDA safety submission, no subject among the 2,027 subjects exposed to suvorexant had confirmed cataplexy. If this is accurate, then based on “the rule of threes,” one can be 95% certain that the incidence of cataplexy in suvorexant treated subjects with insomnia is less than 0.0015 (3/2027), or less than 0.0025 (3/1218) for those exposed to at least 3 months of suvorexant treatment. Of note, the external adjudication committee reviewed the fall events, which had comparable incidence across treatment groups, and confirmed that none of the events suggested cataplexy.

Merck assessed the effects of suvorexant treatment on driving performance using AE reports of accident-related injuries, questionnaire responses on motor vehicle accidents or traffic violations (MVAs and MVAVs), and two on-the-road driving trials (P035 and P039). In the Phase 3 trial population within 0-3 months, fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects who drove during the trial within each treatment group was: 0.3% (3/891) on suvorexant HD, 0.3% (1/342) on suvorexant LD, and 0.6% (4/692) on placebo. However with MVAVs, a numerically higher rate occurred in the suvorexant LD group (2.9%, 10/342) compared to suvorexant HD group (2.3%, 13/569) and placebo (2.3%, 12/531).

In the Phase 1 driving trials (P035 and P039), Merck observed no significant impairment of next-day driving performance based on mean standard deviation of lateral position (SDLP) after one night and eight consecutive nights of suvorexant LD or HD in both elderly and non-elderly subjects. In the driving trials some subjects who received suvorexant had increased SDLP beyond the pre-defined threshold, resulting in an imbalance in the SDLP symmetry (secondary endpoint) analyses, especially for the non-elderly subjects. Also, four non-elderly subjects felt sleepy enough to prematurely stop their driving tests. These results suggest that a potential for impairment in driving performance exists with suvorexant treatment. The sponsor provided cautionary language in the proposed label, regarding driving and suvorexant treatment, which seems appropriate.



The incidence of any ECI potentially relevant to abuse potential was comparable across treatment groups: suvorexant HD 2.0% (26/1291), suvorexant LD 3.2% (16/493), and placebo 2.2% (23/1025). One event of derealization occurred in the suvorexant HD group. Other events were of drug maladministration, with an incidence of 1.9% (25/1291) in the suvorexant HD group. Further in Trial P025, Merck evaluated abuse potential of single doses of suvorexant compared to placebo and two doses of zolpidem in healthy male and female recreational polydrug users. Based on the primary outcome, "Drug Liking visual analog score, VAS," suvorexant in all tested doses (40 mg, 80 mg, and 150 mg) showed greater abuse potential than placebo in recreational polydrug users. The mean peak effect difference from placebo for each group was 22.84 for suvorexant 40 mg, 21.99 for suvorexant 80 mg, and 20.44 for suvorexant 100 mg. The suvorexant treatment effect appeared to be similar to, or slightly better than, that of zolpidem 15 mg (24.86) or zolpidem 30 mg (28.08).

A major concern with the use of hypnotic sedatives is next-day residual effects. Merck evaluated AEs associated with residual effects and observed the highest incidence with somnolence, as discussed above. Fatigue occurred less frequently, and like somnolence, it also occurred in a dose-related manner: suvorexant HD 3.8% (49/1291); suvorexant LD 2.2% (11/493); and placebo 1.8% (18/1025).

Merck evaluated another next-day residual effect, impaired psychomotor performance, using the Digit Symbol Substitution Test (DSST) values from 1493 subjects in the Phase 3 trials, P028 and P029. They found no clinically meaningful differences between each of the suvorexant groups and placebo. Four Phase 1 trials (P002, P032, P036, and P039) also failed to show significant treatment effects on DSST (number of correct responses) with suvorexant compared to placebo; a fifth Phase 1 trial P035, which assessed driving in healthy non-elderly subjects, suggested suvorexant 40 mg impairing psychomotor performance after a single dose but not after multiple doses.

Trial P035 also evaluated balance and memory, and showed a statistically significant decrease in word recall 11 hours after single dose of suvorexant 40 mg, and increase on body sway area 11 hrs after single dose of either suvorexant 20 or suvorexant 40 mg. Three other Phase 1 trials (P032, P036, and P039) evaluated balance and memory and found no significant next-day effects following suvorexant treatment.

On abrupt cessation of suvorexant treatment, no clear withdrawal effect occurred, however rebound insomnia was suggested. Merck found no obvious withdrawal effect on sudden discontinuation of suvorexant treatment; this was based on analyses of responses on Tyrer Withdrawal Symptom Questionnaire (WSQ) and reports of prespecified AEs associated with potential withdrawal. Regarding rebound effects, more subjects who switched from suvorexant HD to placebo (48.5%, 233/480) showed a decrease in total sleep time sTST on any of the three nights compared to subjects continued on placebo (37.2%, 295/793). Merck suggested that the effects observed for

some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, the sTST findings for both suvorexant doses, and for the elderly subgroup, support the presence of a rebound effect on abrupt cessation of suvorexant treatment.

Laboratory and vital sign data did not show evidence of suvorexant having deleterious effects. However, serum cholesterol levels increased in a dose-related manner following suvorexant treatment in the Phase 2 trial. Mean serum cholesterol levels increased by 3.0 mg/dL at the suvorexant 40 mg dose level, by 2.1 mg/dL at suvorexant 20 mg dose. Merck suggested that the findings were unlikely to be clinically meaningful.

Overall, the safety data show next-day somnolence as the most prominent AE, incidences of ECIs were low, and highlighted AEs including EDS appeared to occur in a dose-related manner. There was no confirmed case of narcolepsy with or without cataplexy, but there were suggestions of impaired driving performance on assessment of next-day residual effects of both suvorexant doses.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

The proposed drug, suvorexant, is an immediate-release tablet for oral administration. Suvorexant is new molecular entity that is suggested to act as a highly selective antagonist for orexin receptors OX<sub>1</sub>R and OX<sub>2</sub>R. The proposed indication for suvorexant is for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Merck proposes that suvorexant be taken with or without food, immediately before bedtime. The proposed dose in non-elderly adults, younger than 65 years, is 40 mg once daily. Merck suggests that a lower dose of 20 mg once daily may be appropriate for some non-elderly adults based on individual tolerability, but the dose should not exceed 40 mg per day. For elderly adults, 65 years and older, the proposed dose is 30 mg once daily. Again, a lower dose of 15 mg once daily may be appropriate for some elderly adults and the dose should not exceed 30 mg per day.

The suvorexant tablets are film-coated to mask the taste and speckled appearance of the core, and provide color differentiation: the 40 mg tablets are green and oval-shaped, the 30 mg tablets are yellow and round, the 20 mg tablets are white and round, and the 15 mg tablets are white and oval.

## 2.2 Table of Currently Available Treatments for Proposed Indications

Table 1 below lists currently available drug products that are marketed for the treatment of insomnia. The drug products include benzodiazepine receptor agonists that are approved for the treatment of insomnia. Other classes of products approved for insomnia include sedating antidepressants, melatonin receptor agonist, and anti-histamine agents. Short-acting sedatives are approved for insomnia characterized by sleep-onset difficulties, but not for sleep maintenance. Zolpidem tartrate ER (Ambien CR) and eszopiclone are approved for treatment of insomnia with sleep onset and maintenance difficulties.

**Table 1: Marketed Insomnia Drugs**

| Category                  | Product Name             | Comment  |
|---------------------------|--------------------------|--|
| <b>Benzodiazepine</b>     |                          |  |
|                           | Quazepam<br>(Doral)      | Treatment of insomnia associated with sleep onset difficulties and nighttime awakenings<br>Maximum concentration of parent drug within 2 hours, but long duration of action<br>Elimination half-life with active metabolite, 39 hours<br>Efficacy assessed in 5-night and 28-night studies |
|                           | Temazepam<br>(Restoril)  | Short-term insomnia treatment, 7-10 days<br>Half-life of 9 hours<br>Lower dose for the elderly<br>No dose adjustment for liver disease<br>Efficacy assessed in 2-week studies  |
|                           | Triazolam<br>(Halcion)   | Short half-life of parent drug and duration of action<br>Lower dose for the elderly<br>Little residual effects   |
| <b>Non-Benzodiazepine</b> |                          |  |
|                           | Eszopiclone<br>(Lunesta) | Treatment of sleep onset and maintenance insomnia<br>Up to 6 months use for chronic insomnia<br>Half-life 6 hours, duration of action 8 hours<br>Lower dose for the elderly  |
|                           | Ramelteon<br>(Rozerem)   | Sleep onset insomnia<br>Not to use in severe liver disease<br>Not a controlled substance<br>Lower dose for the elderly   |
|                           | Zaleplon<br>(Sonata)     | Sleep onset insomnia only<br>Half-life 1 hour, duration of action 6 hours<br>Does not increase total sleep time<br>Lower dose for the elderly  |
|                           | Zolpidem<br>(Ambien)     | Sleep onset insomnia<br>No effect on sleep architecture  |

|                                 |                            |   |
|---------------------------------|----------------------------|---|
|                                 |                            | Half-life 2.6 hours, duration of action 6 to 8 hours<br>Lower dose for the elderly  |
|                                 | Zolpidem CR<br>(Ambien CR) | Treatment of sleep onset and maintenance insomnia<br>Half-life 2.6 hours, duration of action 7 to 8 hours<br>Lower dose for the elderly   |
| <b>Sedating Anti-Depressant</b> |                            |   |
|                                 | Doxepine<br>(Silenor)      | Sleep maintenance insomnia<br>Clinical trial experience up to 3 month<br>Parent drug half-life 15 hours<br>Not to be taken within 3 hours of a meal<br>Lower dose for the elderly |

Available over-the-counter drugs for insomnia treatment include diphenhydramine products. Other products are used off-label to treat insomnia, for example antidepressants, anxiolytics, antihistamines, melatonin, and herbal supplements. Non-pharmacological therapies include: sleep hygiene, stimulus control, relaxation training, and cognitive therapy. The benzodiazepine drugs estazolam (Prosom) and flurazepam (Dalmane) have been discontinued.

### 2.3 Availability of Proposed Active Ingredient in the United States

Suvorexant is a new chemical entity; it is not currently marketed in the United States.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues associated with approved hypnotic drugs include residual effects such as somnolence, tiredness, psychomotor impairment, and anterograde amnesia; and rebound effects on discontinuation of a hypnotic drug. The rebound effects are more common with the short acting drugs.

Neuropsychiatric adverse events can be problematic with hypnotic drugs. The events include confusion, amnesia, hallucinations, and worsening of psychiatric symptoms. Labeling is often used to address these issues.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Suvorexant was developed under IND 101847. Below is a summary of the key regulatory milestones:

10 April 2008: Initial IND Submission

26 June 2008: Merck responded to FDA comments on 24 June 2008 regarding IND submission and agreed to the following:

- Add serum magnesium to the clinical safety labs and increase the frequency of ECG assessments.
- Conduct a thorough QTc study, P022

5 November 2009: End-of-phase 2 (EOP2) meeting. Discussion led to the following:

- Design of two Phase 3 confirmatory efficacy trials
- Agreed on a 3-month, double-blind treatment period for both trials and including Month 3 as a key efficacy time point
- Trials to include non-elderly and elderly subjects
- Phase 3 trials testing more than one dose
- Trials to include pertinent subjective and objective efficacy endpoints, time points of measurement for a chronic insomnia indication
- FDA recommended monitoring of specific adverse events to evaluate residual effect and abuse liability potential
- Agreed on nature of driving studies to further assess residual effects
- Agreed on collecting PK samples during phase 3 trials to allow for suvorexant exposure assessment
- FDA requested sponsor to provide rationale for choice of sTST over sWASO endpoints for assessing sleep maintenance effects of suvorexant.
- Subsequently on 2 June 2011, Merck agreed to conduct additional sWASOm analyses to assess the efficacy of suvorexant for sleep maintenance using the multiplicity testing strategy as planned for sTSTm.

18 February 2011: FDA Response to Merck's submission on phase 3 trials including integrated Statistical Analysis Plan (iSAP)

- FDA disagreed on use of sTST as endpoint for sleep maintenance and recommended sWASO use instead
- FDA considered the integrated statistical analysis plan (iSAP) acceptable for exploratory efficacy analysis but not primarily for approval purposes, as each confirmatory efficacy trial needed to be convincing on its own

2 June 2011: Teleconference on phase 3 trial protocols and Endpoints

- Merck agreed to provide sWASO data in a similar approach as sTST
- Merck related that another regulatory body opposed amending the protocols to allow sWASO use as co-primary endpoint only for FDA
- FDA to consider sWASO as the co-primary endpoint even if sTST was specified in the protocols, without penalizing Merck for this approach.
- FDA to also consider sTST and other efficacy endpoints in its overall efficacy assessments

26 July 2011: Proposed Pediatric Study Request (PPSR) submission

31 October 2011: FDA Issued FDA 'Inadequate Study Request' letter, denying issuance of pediatric written request (WR)

19 March 2012: Pre-NDA Meeting

- Merck's plans included in protocols and iSAP, analyses of subjective wake time after sleep onset (sWASOm) to be provided in the confirmatory efficacy clinical study reports (CSRs) in the same manner as subjective total sleep time (sTSTm), to provide a supportive analysis for evaluation of sleep maintenance efficacy (as agreed to by FDA on June 2, 2011 per FDA Memorandum of Telephone Conference)
- FDA agreed that the planned organization and presentation of the efficacy and safety results appeared adequate for NDA filing
- Also, FDA agreed to Merck's plan to provide analyses of sWASO in a manner that allowed assessment of sWASOm and objective WASO as co-primary endpoints for sleep maintenance efficacy
- FDA relayed expectation of Merck to include in their analyses of adverse experience information on incidence of complex sleep-related behaviors and sleepwalking, as well as abnormalities of vital signs and laboratory testing that are related to the drug treatment
- FDA agreed with the planned format of the phase 3 CSRs
- FDA agreed with plan to provide financial disclosure information for the phase 2 and 3 trials
- FDA reiterated the need for Merck to submit a pediatric development plan in its NDA package
- FDA stated that the extent and timing of the pediatric studies will be determined upon review of the NDA
- FDA was likely to agree to a waiver for children less than 6 years of age, although a final decision could not be made at the time.
- To Merck's request on the timing of the PPSR revision for FDA review, planned for after approval of the original NDA, FDA responded that the PPSR may be revised following further discussion with the Division and review of the NDA

## **2.6 Other Relevant Background Information**

There is no other relevant background information for this NDA, and there is no information to suggest approval of suvorexant in any other country.

## **3 Sources of Clinical Data**

### 3.1 Tables of Studies/Clinical Trials

Table 2 below summarizes the sources of clinical data used in this review.

**Table 2: Listing of Clinical Trials**

| Trial                                | Objective        | Design            | Population                             | Suvorexant Dose   | Treatment Duration               | Primary Endpoint  |
|--------------------------------------|------------------|-------------------|--|---|----------------------------------|---|
| <b>Phase 3 Confirmatory Efficacy</b> |                  |                   |  |   |                                  |   |
| P028                                 | Safety, Efficacy | R, DB, PC, MC     | Primary Insomnia<br>N=1022             | Suvorexant HD<br>Suvorexant LD<br>Placebo   | 3-month, 3 more months extension | <u>Onset – sTSO, LPS</u><br><u>Maintenance – sTST, WASO</u> |
| P029                                 | Safety, Efficacy | R, DB, PC, MC     | Primary Insomnia<br>N=1019             | Suvorexant HD<br>Suvorexant LD<br>Placebo   | 3-month                          | <u>Onset – sTSO, LPS</u><br><u>Maintenance – sTST, WASO</u> |
| <b>Phase 3 Long-term Safety</b>      |                  |                   |  |   |                                  |   |
| P009                                 | Safety           | R, DB, PC, MC     | Primary Insomnia<br>N=781              | Suvorexant HD<br>Placebo  | 12-month                         | Safety  |
| <b>Phase 2 Dose Finding</b>          |                  |                   |  |   |                                  |   |
| P006                                 | Dose Finding     | R, DB, PC, MC, CO | Primary Insomnia, non-elderly<br>N=254 | Suvorexant 80 mg<br>Suvorexant 40 mg<br>Suvorexant 20 mg<br>Suvorexant 10 mg<br>Placebo | 4-week                           | Sleep Efficiency  |

(Source: Modified from Sponsor's submission ISE Page 71 Table 5.3.5.3.2-Insomnia: 1. R=randomized, DB=double-blind, PC=placebo controlled, AC=active controlled, CO=cross-over, MC=multicenter, Suvorexant LD=15 mg in elderly and 20 mg in non-elderly subjects, Suvorexant HD=30 mg in elderly and 40 mg in non-elderly subjects)

### 3.2 Review Strategy

Overall, this clinical review reflects input from the clinical and other discipline reviewers. Dr. Tristan Massie provided the biometrics review input. Please refer to the biometrics review by Dr. Massie for additional efficacy and statistical details.

The clinical review focused on three Phase 3 trials (P028, P029, and P009) for assessing the efficacy and safety of suvorexant. Two of the three Phase 3 trials, P028 and P029, provided 3-month treatment data for the primary efficacy review. The third Phase 3 trial P009 contributed 12-month treatment data and was included with the other two Phase 3 trials in the safety review. The Phase 2 trial P006 was also reviewed, though it was considered to be supportive in nature. Section 3.3 discusses the individual

trials. Section 4 Review of Efficacy summarizes the efficacy results of the Phase 3 trials, including an overview of the pooled data for efficacy. Section 5 Review of Safety summarizes the combined safety data, primarily from the three Phase 3 trials. Safety data from the Phase 2 trial (P006) and pooled Phase 1 trials (31 trials) were also reviewed.

### **3.3 Discussion of Individual Studies/Clinical Trials**

This section briefly summarizes the Phase 2 dose finding trial P006, and then discusses in more detail the Phase 3 confirmatory efficacy trials and the Phase 3 long-term safety trial P009.

#### **3.3.1 Phase 2 Dose Finding Trial P006**

##### **Administrative Information for Trial P006**

- **Trial Title:** A Phase IIb, Multicenter, Randomized, Double-Blind Placebo-Controlled, 2-period Adaptive Crossover Polysomnography Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia
- **Trial Treatment Dates:** 11/07/2008 to 12/26/2009
- **Trial Sites:** Multicenter (41) in the United States (29) and in Japan (12)
- **Trial Report Date:** 05/09/2011

The primary objectives of P006 were:

- To evaluate the efficacy of suvorexant compared with placebo in improving sleep efficiency (SE) as measured by polysomnography (PSG) on Night 1 and at the end of 4 weeks of treatment, where SE was defined as 100 times total sleep time (minutes) divided by time in bed (minutes).
- To evaluate suvorexant's safety and tolerability.

To achieve the trial's primary objectives, the sponsor tested the hypotheses that at least one dose of suvorexant was superior to placebo in improving SE on Night 1 and at week 4 weeks; and that the drug was well tolerated.

The subjects were non-elderly males and females, aged 18 to 64 years, with primary insomnia. They had reported 6.5 hours or less total sleep time on at least 3 out of 7 nights in a week, 30 minutes or more in sleep latency on at least 3 out of 7 nights in a week, 1 hour or more of wakefulness after sleep onset, and spending 6.5 to 9 hours in bed every night. Also, they had more than 20 minutes of latency to persistent sleep (LPS) and more than 45 minutes of wake after sleep onset (WASO) on PSG measurements. They had both sleep onset and maintenance sleep difficulties, which were subjectively and objectively measurable.

P006 randomized 254 subjects with primary insomnia to receive placebo or suvorexant doses 10, 20, 40, or 80 mg. In the crossover trial, each subject received one of the



suvorexant doses or placebo in each of the two treatment periods. Each treatment period lasted 4 weeks. A single-blind placebo Run-in Phase of 1 to 2-week duration preceded Treatment Period 1; and, a single-blind placebo washout of 1-week duration occurred between the two treatment periods. Then there was a 2-week post-trial follow up.

The primary endpoint was sleep efficiency (SE) as derived from the PSG parameter total sleep time (TST). Secondary endpoints included the PSG parameters of wake after persistent sleep onset (WASO), and latency to persistent sleep (LPS). The trial also assessed exploratory subjective endpoints of sleep, suvorexant's pharmacokinetic (PK) parameters, the Sheehan Disability Scale and the Insomnia Severity Index.

The primary efficacy endpoint (SE) and the secondary efficacy endpoints (WASO and LPS) at Night 1 and at the end of 4 weeks of treatment, were compared between each suvorexant dose and placebo using a mixed effects model with terms for baseline value, region, treatment, sequence, period, time (as a categorical variable), and treatment-by-time and period-by-time interactions. Merck used a fixed sequential multiplicity testing strategy for the primary and secondary efficacy hypotheses to provide strong control of Type I error.

#### Results of Trial P006

On primary endpoint assessment, suvorexant in all tested doses significantly increased sleep efficiency SE compared to placebo at Night 1, with treatment difference in mean SE from placebo of at least 5.2 minutes, and at Week 4, with treatment difference of at least 4.7 minutes (all p values <0.005).

For the secondary endpoint analyses, suvorexant in all tested doses significantly decreased the sleep maintenance measure of WASO compared to placebo at Night 1, with difference in mean WASO from placebo of at least -21.2 minutes, and at Week 4, with difference of at least -21.4 minutes (all p values <0.001).

However, on the secondary endpoint LPS, a measure of sleep onset, no suvorexant dose was statistically significantly better than placebo. Table 3 below is Merck's summary of the efficacy analyses for the primary and secondary endpoints:

**Table 3: Efficacy in Trial P006, Sleep Efficiency (SE), Wakefulness after Persistent Sleep Onset (WASO) and Latency to Onset of Persistent Sleep (LPS)**

| Endpoint | Timepoint | Treatment        | Diff in LS Means<br>versus Placebo (SE) | 95% CI         | p-value |
|----------|-----------|------------------|---|----------------|---------|
| SE       | Night 1   | Suvorexant 10 mg | 5.2 ( 1.71)                             | (1.9, 8.6)     | 0.002   |
|          |           | Suvorexant 20 mg | 7.6 ( 1.72)                             | (4.2, 11.0)    | <0.001  |
|          |           | Suvorexant 40 mg | 10.8 ( 1.72)                            | (7.4, 14.2)    | <0.001  |
|          |           | Suvorexant 80 mg | 12.9 ( 1.73)                            | (9.5, 16.3)    | <0.001  |
|          | Week 4    | Suvorexant 10 mg | 4.7 ( 1.58)                             | (1.6, 7.8)     | 0.003   |
|          |           | Suvorexant 20 mg | 10.4 ( 1.60)                            | (7.2, 13.6)    | <0.001  |
|          |           | Suvorexant 40 mg | 7.8 ( 1.61)                             | (4.6, 10.9)    | <0.001  |
|          |           | Suvorexant 80 mg | 7.6 ( 1.63)                             | (4.4, 10.9)    | <0.001  |
| WASO     | Night 1   | Suvorexant 10 mg | -21.2 ( 6.27)                           | (-33.5, -8.8)  | <0.001  |
|          |           | Suvorexant 20 mg | -24.7 ( 6.31)                           | (-37.1, -12.3) | <0.001  |
|          |           | Suvorexant 40 mg | -33.9 ( 6.33)                           | (-46.4, -21.5) | <0.001  |
|          |           | Suvorexant 80 mg | -36.8 (6.36)                            | (-49.4, -24.3) | <0.001  |
|          | Week 4    | Suvorexant 10 mg | -21.4 ( 6.45)                           | (-34.2, -8.7)  | 0.001   |
|          |           | Suvorexant 20 mg | -28.1 ( 6.58)                           | (-41.0, -15.1) | <0.001  |
|          |           | Suvorexant 40 mg | -33.2 ( 6.61)                           | (-46.3, -20.2) | <0.001  |
|          |           | Suvorexant 80 mg | -28.9 ( 6.70)                           | (-42.1, -15.7) | <0.001  |
| LPS      | Night 1   | Suvorexant 10 mg | -3.4 ( 6.16)                            | (-15.6, 8.7)   | 0.577   |
|          |           | Suvorexant 20 mg | -9.4 ( 6.17)                            | (-21.5, 2.8)   | 0.130   |
|          |           | Suvorexant 40 mg | -23.1 ( 6.20)                           | (-35.3, -10.9) | <0.001  |
|          |           | Suvorexant 80 mg | -25.4 ( 6.23)                           | (-37.7, -13.1) | <0.001  |
|          | Week 4    | Suvorexant 10 mg | -2.3 ( 5.00)                            | (-12.2, 7.5)   | 0.644   |
|          |           | Suvorexant 20 mg | -22.3 ( 5.08)                           | (-32.3, -12.3) | <0.001  |
|          |           | Suvorexant 40 mg | -3.8 ( 5.09)                            | (-13.8, 6.3)   | 0.459   |
|          |           | Suvorexant 80 mg | -9.5 ( 5.17)                            | (-19.7, 0.7)   | 0.068   |

(Source: Modified from Sponsor's submission P006 CSR Page 5. Results were based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by time and period-by-time interactions)

Merck conducted additional post hoc analysis of Period 1 only, on finding evidence of a carryover effect for LPS, and determined the following differences compared to placebo and p-values for Night 1: for suvorexant 10 mg, -19.1 minutes (p-value, 0.020); suvorexant 20 mg, -17.4 minutes (p-value, 0.030); suvorexant 40 mg, -31.0 (p-value, < 0.001); and suvorexant 80 mg, -22.3 minutes (p-value, 0.007). At Week 4 the following differences compared to placebo and p-values were obtained: suvorexant 10 mg, -20.2 minutes (p-value, 0.019); suvorexant 20 mg, -24.6 minutes (p-value, 0.003); suvorexant 40 mg, -15.7 (p-value, 0.063); and suvorexant 80 mg, -19.6 minutes (p-value, 0.024).

### Efficacy on Subjective Endpoints

Merck provided analyses for patient-reported outcomes based on morning and evening e-Diary entries: subjective total sleep time, time to sleep onset, wake after sleep onset, number of awakenings, quality of sleep VAS, freshness of sleep VAS, function VAS, tiredness VAS, energy VAS, and relaxation VAS.

At the end of Trial Week 4, subjects on suvorexant 40 mg and 80 mg doses appeared to have improvements with nominal p-values < 0.05 compared to placebo in the following endpoints: total sleep time, time to sleep onset, wake after sleep onset and subjective sleep quality. The subjects on both suvorexant doses reported fewer awakenings than those on placebo at Week 4.

I reviewed the subjective endpoints that were prominently assessed in the subsequent Phase 3 trials: subjective Total Sleep Time (sTST), Time to Sleep Onset (sTSO), and WASO (sWASO). The subjective total sleep time improved on suvorexant 40 mg and 80 mg doses, as shown in table 4 below.

**Table 4: Subjective Total Sleep Time (sTST) at 4 Weeks in Trial P006**

| <b>Treatment</b> | <b>N</b> | <b>Baseline in minutes (SD)</b> | <b>Mean Change from Baseline in minutes (SD)</b> | <b>Treatment-Placebo Difference in minutes (95% CI)</b> | <b>P value for Difference</b> |
|------------------|----------|---------------------------------|--|---|-------------------------------|
| Placebo          | 211      | 341.4 (60.1)                    | 27.7 (50.31)                                     | -   | -                             |
| Suvorexant 10 mg | 57       | 338.9 (59.6)                    | 38.6 (50.58)                                     | 5.5 (-6.3, 17.3)  | 0.3578                        |
| Suvorexant 20 mg | 53       | 338.4 (55.9)                    | 34.6 (50.23)                                     | -1.8 (-13.9, 10.4)                                      | 0.7741                        |
| Suvorexant 40 mg | 51       | 349.5 (64.0)                    | 38.1 (55.19)                                     | 29.6 (17.1, 42.1)                                       | <0.0001                       |

|                  |    |              |              |                  |        |
|------------------|----|--------------|--------------|------------------|--------|
| Suvorexant 80 mg | 49 | 342.7 (54.9) | 42.3 (42.85) | 19.4 (7.1, 31.7) | 0.0022 |
|------------------|----|--------------|--------------|------------------|--------|

(Source: Modified from Sponsor's submission P006 CSR Page 409 Table 14-72.)

Improvements in time to sleep onset (sTSO) with nominal p values less than 0.05 occurred on suvorexant doses of 40 mg and 80 mg as shown in table 5 below.

**Table 5: Subjective Time to Sleep Onset (sTSO) at 4 Weeks in Trial P006**

| Treatment        | N   | Baseline in minutes (SD) | Mean Change from Baseline in minutes (SD) | Treatment-Placebo Difference in minutes (95% CI) | P value for Difference |
|------------------|-----|--------------------------|---|--|------------------------|
| Placebo          | 211 | 63.0 (31.0)              | -9.8 (29.46)                              | -  | -                      |
| Suvorexant 10 mg | 57  | 67.4 (31.4)              | -16.7 (24.62)                             | -3.0 (-9.3, 3.3)                                 | 0.3523                 |
| Suvorexant 20 mg | 53  | 68.1 (25.7)              | -15.6 (25.59)                             | -4.3 (-10.8, 2.2)                                | 0.1946                 |
| Suvorexant 40 mg | 51  | 56.5 (31.7)              | -19.2 (24.35)                             | -17.4 (-24.1, -10.7)                             | <.0001                 |
| Suvorexant 80 mg | 49  | 59.0 (33.0)              | -18.4 (20.35)                             | -7.7 (-14.3, -1.1)                               | 0.0219                 |

(Source: Modified from Sponsor's submission P006 CSR Page 411 Table 14-73)

Based on revised analyses Merck submitted on 28 February 2013, sWASO improvements from baseline with nominal p values less than 0.05 occurred on suvorexant doses of 40 mg and 80 mg as shown in table 6 below.

**Table 6: Subjective WASO (sWASO) at 4 Weeks in Trial P006**

| Treatment        | N   | Baseline in minutes (SD) | Mean Change from Baseline in minutes (SD) | Treatment-Placebo Difference in minutes (95% CI) | P value for Difference |
|------------------|-----|--------------------------|---|--|------------------------|
| Placebo          | 212 | 68.8 (41.7)              | -16.4 (38.26)                             | -  | -                      |
| Suvorexant 10 mg | 57  | 71.2 (39.1)              | -23.9 (32.61)                             | -3.5 (-11.4, 4.4)                                | 0.3838                 |
| Suvorexant 20 mg | 54  | 72.3 (47.7)              | -18.0 (35.63)                             | 3.2 (-4.9, 11.2)                                 | 0.4405                 |
| Suvorexant 40 mg | 51  | 75.3 (53.6)              | -24.7 (36.26)                             | -18.3 (-26.7, -10.0)                             | <.0001                 |
| Suvorexant 80 mg | 49  | 56.5 (32.9)              | -24.6 (31.77)                             | -13.9 (-22.1, -5.6)                              | 0.0010                 |

(Source: Modified from Sponsor's submission Efficacy Amendment Submitted on 02/28/13 Page 5 for P006 Revised CSR Table 14-74)

#### Safety Results Trial P006

The trial reported no serious adverse events and no deaths. Overall, 10% (26/254) of the subjects discontinued the trial. Discontinuations in each trial treatment were as follows: placebo 5.6% (14/249), suvorexant 10 mg 3.2% (2/62), suvorexant 20 mg 6.6% (4/61), suvorexant 40 mg 0.0% (0/59), and suvorexant 80 mg 9.8% (6/61). The most common AEs by SOC were nervous system disorders. The incidence of somnolence was greater at the higher suvorexant doses compared to placebo as follows: placebo 0.4% (1/243), suvorexant 10 mg 0.0% (0/62), suvorexant 20 mg 4.9% (3/61), suvorexant 40 mg 11.9% (7/59), and suvorexant 80 mg 9.8% (6/61). Other adverse event findings are summarized below and in section 5 Review of Safety.

**Table 7: Adverse Event Categories in Phase 2 Dose Finding Trial P006**

|   | Placebo |         | Suvorexant 10 mg |         | Suvorexant 20 mg |         | Suvorexant 40 mg |         | Suvorexant 80 mg |         | Total Suvorexant |         |
|---|---------|---------|------------------|---------|------------------|---------|------------------|---------|------------------|---------|------------------|---------|
|   | n       | (%)     | n                | (%)     | n                | (%)     | n                | (%)     | n                | (%)     | n                | (%)     |
| Subjects in population  | 249     | (100.0) | 62               | (100.0) | 61               | (100.0) | 59               | (100.0) | 61               | (100.0) | 243              | (100.0) |
| Subjects with one or more adverse events                            | 50      | (20.1)  | 11               | (17.7)  | 12               | (19.7)  | 18               | (30.5)  | 22               | (36.1)  | 63               | (25.9)  |
| Subjects with drug- related adverse events, investigator determined | 17      | (6.8)   | 3                | (4.8)   | 4                | (6.6)   | 12               | (20.3)  | 14               | (23.0)  | 33               | (13.6)  |
| Discontinued due to an adverse event                                | 3       | (1.2)   | 0                | (0.0)   | 0                | (0.0)   | 0                | (0.0)   | 1                | (1.6)   | 1                | (0.4)   |
| Discontinued due to a drug-related adverse event                    | 1       | (0.4)   | 0                | (0.0)   | 0                | (0.0)   | 0                | (0.0)   | 1                | (1.6)   | 1                | (0.4)   |

(Source: Modified from Sponsor's submission P006 CSR Page 6)

One subject discontinued trial treatment on suvorexant 80 mg because of the adverse event of visual hallucinations. Three subjects on placebo discontinued because of elevated hepatic enzymes (n=1), tachycardia (n=1), and difficulty thinking with sedation (n=1). These discontinuations occurred in Period 1 of the trial, so carryover effect was unlikely to have played a role in their occurrence.

There were no dose-related suvorexant effects on vital signs, though decreases of 20 mm Hg or more in systolic blood pressure, both sitting and standing, were greater for suvorexant compared to placebo. Also, ECG data did not demonstrate any clear differences in QT prolongation among treatment groups.

Merck suggested that there were no abnormal laboratory values of clinical relevance. However, suvorexant treatment was associated with a dose-related increase in serum

cholesterol levels with the maximum mean increase of 6.0 mg/dL at suvorexant 80 mg dose by Week 4.

*Reviewer Note: On efficacy at Week 4, all tested suvorexant doses (10 mg, 20 mg, 40 mg and 80 mg) improved the primary efficacy endpoint of sleep efficiency and the objective measure of sleep maintenance, WASO. Only the 40 mg and 80 mg doses appeared to improve the subjective measures of sleep maintenance, sTST and sWASO. None of the doses improved sleep onset that was measured objectively by LPS based on the planned statistical analyses. Suvorexant 40 mg and 80 mg doses appeared to improve the subjective measure of sleep onset, sTSO. There were no deaths and no serious AEs in Trial P006. The most frequent AEs by SOC were nervous system disorders, particularly somnolence. The safety profile and efficacy results at the Phase 2 trial stage suggest that the choice of suvorexant 40 mg for further evaluation in improving both sleep onset and sleep maintenance in the subsequent Phase 3 trials was appropriate.*

### 3.3.2 Phase 3 Confirmatory Efficacy Trial P028

#### **Administrative Information for Trial P028**

- **Trial Title:** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia – Study A
- **Trial Treatment Dates:** 05/25/2010 to 11/22/2011
- **Trial Sites:** Multicenter with 30 United States (US) and 61 Ex-US centers: Australia (2), Brazil (1), Canada (3), Denmark (1), Finland (2), France (3), Germany (6), Japan (26), Peru (1), Russian Federation (2), South Africa (2), Spain (3), Taiwan (4), Sweden (2), and United Kingdom (3)
- **Trial Report Date:** 07/12/2012

#### **Objectives and Rationale**

- To evaluate, in subjects with primary insomnia, efficacy of suvorexant high dose (HD) compared with placebo in improving sleep maintenance and onset at Months 1 and 3, using subjective patient-reported outcomes and objective polysomnographic (PSG) assessments; and to assess the safety and tolerability of suvorexant for up to 3 months of treatment.

#### **Trial Design and Conduct**

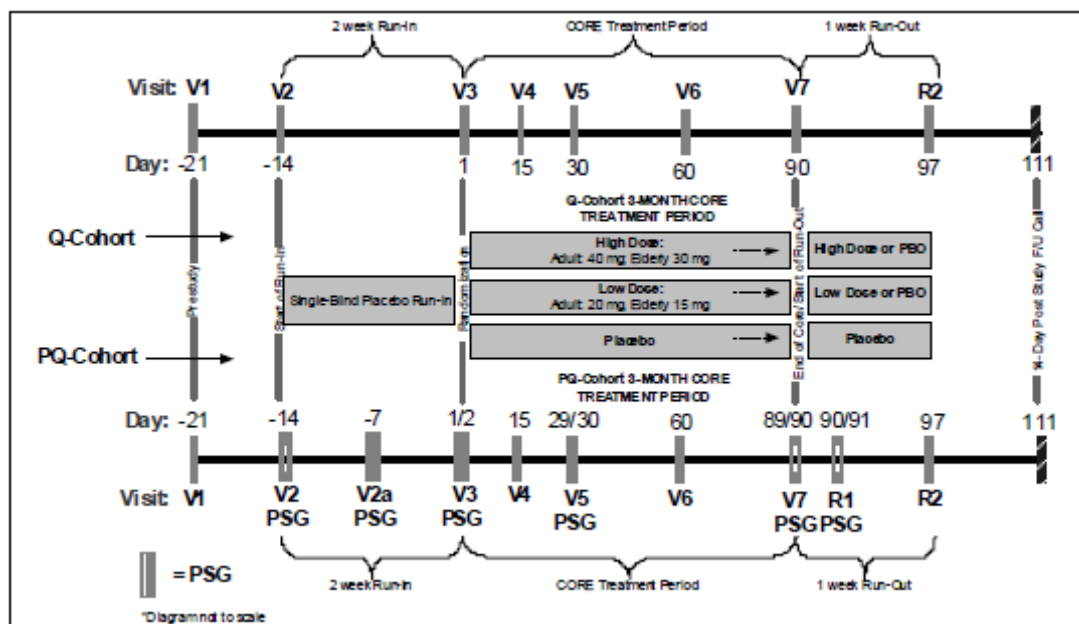
##### *Trial P028 Overview*

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group, questionnaire and PSG trial to assess the safety and efficacy of suvorexant in subjects with primary insomnia. The subjects were males and females 18 years or older, who spent 6.5 to 9 hours nightly in bed but had total sleep time of less than 6.5 hours, sleep latency of 30 minutes or more, and wakefulness after sleep of 1 hour or more. The trial

excluded subjects with narcolepsy, other neurological disorders, and psychiatric disorders requiring ongoing treatment.

The trial had eight visits, V1 to V7 and R2, and two cohorts that had subjects in either the Questionnaire-only cohort (Q-cohort) or the PSG-plus-Questionnaire cohort (PQ-cohort). The screening period commenced at Visit 1. Subjects meeting trial and cohort-specific criteria were evaluated at Visit 2 and commenced on a 2-week single-blind placebo run-in. Subjects in the PQ-cohort underwent PSG assessments during the screening period. At Visit 3, the subjects were randomized in a 3:2:3 ratio to receive suvorexant HD (high dose), suvorexant LD (low dose), or placebo during a 3-month double-blind core treatment period, which ended at Visit 7. During the core treatment period, subjects returned to the clinic after randomization, for Visit 4 at the end of Week 2, and Visits 5-7 end of Months 1, 2, and 3. Overnight PSG assessments occurred at Night 1 and end of Months 1 and 3 visits for PQ cohort subjects, as shown in Figure 1 below.

**Figure 1: Trial Flow Diagram for P028 Core Period without Extension**



(Source: Sponsor's submission SCE Page 138, replicated in P028 Protocol Page 37)

Subjects in both cohorts completed a daily sleep questionnaire via an electronic diary (e-diary). There was an optional 3-month double-blind extension. PQ-cohort subjects who did not enter the extension underwent another PSG assessment at Night 90, the first night of the run-out period, Visit R1-PSG; in effect, these subjects had two consecutive PSG visits, Night 89 (end of Month 3) and Night 90 (beginning of run-out). At the end of core treatment or extension period, there was a 1-week double-blind run-out period.

Table 8 below summarizes the trial schedule and assessments for Q-Cohort.

**Table 8: Trial P028 Flow Chart for Q-Cohort Only – Screening, Core Treatment, and Run-out Periods**

| QUESTIONNAIRE – Q Cohort  | Screening/Placebo Run-In Period |                      | Q-cohort 3-Month Core Treatment Period |               |                |                |                 | Run-Out Period (No extension) |                           | Post-Study Period (No extension)       |
|---|---------------------------------|----------------------|--|---------------|----------------|----------------|-----------------|-------------------------------|---------------------------|--|
| Treatment Period  | Prestudy                        | Screening/Run-In     | Baseline/Randomization                 | End of Week 2 | End of Month 1 | End of Month 2 | End of Month 3  | End of Run-Out                | Discon Visit <sup>1</sup> | Post-study Follow up Call <sup>2</sup> |
| Visit Number:   | 1                               | 2                    | 3                                      | 4             | 5              | 6              | 7               | R2                            |                           |  |
| Target Study Day:   | -21                             | -14                  | 1                                      | 15            | 30             | 60             | 90              | 97                            |                           | 111                                    |
| Visit Window:   |                                 | -3/+21 <sup>13</sup> | -3/+3                                  | -3/+3         | -3/+3          | -3/+3          | -3/+3           | -3/+3                         |                           | -2/+2                                  |
| Procedures/Assessments <sup>3</sup>   |                                 |                      |  |               |                |                |                 |                               |                           |  |
| Informed Consent  | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Provide Participant Identification Card   | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Medical and Psychiatric history   | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Diagnostic Interview/Sleep History/DSM-IV-TR  | X                               |                      |  |               |                |                |                 |                               |                           |  |
| MINI International Neuropsychiatric Interview (MINI)  | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Mini Mental State Examination (MMSE) (elderly only)   | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Quick Inventory of Depressive Symptomatology (QIDS-SR16)  | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Columbia Suicide Severity Rating Scale (C-SSRS)   | X                               | X                    | X                                      | X             | X              | X              | X               | X                             | X                         | X <sup>4</sup>                         |
| Inclusion/Exclusion   | X                               | X                    | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Prior and concomitant therapy   | X                               | X                    | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Physical examination  | X                               |                      |  |               |                |                |                 |                               | X                         |  |
| Vital signs   | X <sup>5</sup>                  | X                    | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| ECG   | X                               |                      | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Hematology, chemistry, urinalysis   | X <sup>6</sup>                  |                      | X                                      | X             | X              |                | X               | X                             | X                         | X                                      |
| Urine drug screen <sup>7</sup>  | X                               |                      | X                                      |               |                |                | X               | X                             | X                         | X                                      |
| Urine pregnancy test <sup>8</sup>   | X                               |                      | X                                      |               | X              | X              | X               | X                             | X                         | X                                      |
| Informed consent for optional Specimens for Genetic and Other Biomedical Research analysis <sup>9</sup> | X                               |                      |  |               |                |                |                 |                               |                           |  |
| Collection of Optional Specimens for genetic and Other Biomedical research <sup>10</sup>                |                                 |                      | X                                      |               |                |                |                 |                               |                           |  |
| Blood sample for HLA DQB1 allele (DNA) <sup>11</sup>  |                                 |                      | X                                      |               |                |                |                 |                               |                           |  |
| Pharmacokinetic (PK) Sampling <sup>12</sup>   |                                 |                      | X                                      | X             | X              |                | X               |                               | X                         |  |
| Visit Number:   | 1                               | 2                    | 3                                      | 4             | 5              | 6              | 7               | R2                            |                           |  |
| Target Study Day:   | -21                             | -14                  | 1                                      | 15            | 30             | 60             | 90              | 97                            |                           | 111                                    |
| Visit Window:   |                                 | -3/+21 <sup>13</sup> | -3/+3                                  | -3/+3         | -3/+3          | -3/+3          | -3/+3           | -3/+3                         |                           | -2/+2                                  |
| Procedures/Assessments <sup>3</sup>   |                                 |                      |  |               |                |                |                 |                               |                           |  |
| Call IVRS   | X                               | X                    | X                                      |               | X              | X              | X               | X                             | X <sup>14</sup>           |  |
| Dispense Study Medication to patient  |                                 | X                    | X                                      | X             | X              | X              | X               | X                             |                           |  |
| Monitor Study Medication Compliance   |                                 | X                    | X                                      | X             | X              | X              | X               | X                             | X                         |  |
| Evening/Morning e-diary <sup>15</sup>   |                                 | X <sup>14</sup>      |  |               |                |                |                 |                               | X                         |  |
| Tyler Withdrawal Symptom Questionnaire (evening e-diary) <sup>15</sup>                                  |                                 |                      | X <sup>15</sup>                        |               |                |                | X <sup>15</sup> |                               |                           |  |
| Clinical Global Impressions-Severity (CGI-S)  |                                 |                      | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Clinical Global Impressions-Improvement (CGI-I)   |                                 |                      | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Patient Global Impressions-Severity (PGI-S)   |                                 |                      | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Patient Global Impressions-Improvement (PGI-I)  |                                 |                      | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Insomnia Severity Index (ISI)   |                                 |                      |  | X             | X              | X              | X               | X                             | X <sup>16</sup>           |  |
| Motor Vehicle, Accidents and Violations   |                                 | X                    | X                                      | X             | X              | X              | X               | X                             | X                         | X                                      |
| Modified Cataplexy Questionnaire (MCQ)  | X                               |                      |  |               |                |                |                 |                               |                           | X                                      |
| Adverse Experiences   | X                               |                      |  |               |                |                |                 |                               |                           | X                                      |

1) For patients who discontinue during the double-blind treatment period or the double-blind run-out period, a discontinuation visit should be performed. (2) Patients who complete the study or prematurely discontinue during the double-blind treatment period or double-blind run-out period will receive a 14-day (from last dose of study medication) follow-up phone call to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken. If patient discontinues due to an AE, a PK sample should be drawn.

2) Patients will be contacted by telephone 14 days after the end of the run-out or premature discontinuation to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken.

3) Study procedures/assessments should be performed at a consistent time of day if possible.

4) Patients will need to be re-consented at Visit 6 for the optional 3-month extension. It should be noted that at ~ 2 weeks prior to Visit 7, sites should call patients to confirm their consent decision. In the event that a patient changes their consent after Visit 6, consent must be updated at Visit 7. Please see protocol details for more specific information.

5) Patients who at any time during the post-study period spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Primary Investigator using the C-SSRS.

6) Body Mass Index (Appendix 6.2) will be calculated only at the Visit 1 from weight and height. Height will only be measured at Visit 1. Weight will be measured at the specified Vital Sign time points. Please refer to Appendix 6.3 for the measurement of weight and Appendix 6.4 for measurement of blood pressure.

7) Hepatitis/HIV screening are additional Visit 1 procedures to be performed at the discretion of the investigator.

8) At Visit 1, urine drug screen test should be sent into central lab vendor for confirmation. At visits thereafter, patients will undergo an on-site drug test. If a patient has a positive urine drug test, a sample must be sent to the central laboratory for confirmation.

9) All female patients of child-bearing potential (< 65 years old) will undergo a serum pregnancy test at Visit 1 which will be sent into the central lab vendor for confirmation. All other pregnancy tests at other visits will be done on-site. If a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation.

10) Signing of the optional pharmacogenomic sample consent form and obtaining the optional genetic sample can be completed at Visit 3 (randomization). This is not necessary to participate in the study. Sample is only collected if patient is randomized.

11) The allele sample is not optional and will be collected at Visit 3 (randomization). Consent for sample is captured within the main informed study consent.

12) Call IVRS to discontinue the patient from the study.

13) The patient will complete an evening and morning e-diary at home every day after satisfactory completion of Visit 1 and up to Visit 3, pending study criteria is met at each consecutive visit.

14) Morning e-diary should be completed at home by the patient after completion of normal morning routine (e.g., using the bathroom, eating breakfast), and preferably within an hour of awakening for the day. E-diary should also be performed on the morning prior to all treatment period visits. Evening e-diaries should be completed by the patient after completion of normal evening routine, and preferably within 30 minutes prior to Lights-Off. Evening e-diary should be completed prior to drug administration.

15) Tyler Questionnaire will be part of the e-diary evening questionnaire and will be completed in the evening; ONLY as indicated; Nights: 2 and 3-post randomization; first 5 nights of run-out (i.e. Nights 90-94); the Tyler will be triggered by the Study Coordinator at the following visits: Visit 3 and Visit 7. Please refer to specific instructions in the e-diary procedures manual.

16) The patient will be asked to mail in a completed ISI to the Investigator site 1 month after completion of their discontin visit.

17) The +21 day visit window prior to Visit 2, is provided to accommodate a 4-week washout period for certain prohibited medications.

18) Samples can be taken at any time during the study visit and will be collected and archived.

(Source: Sponsor's submission P028 Protocol 1.7 Pages 14-16)

Table 9 below summarizes the trial schedule and assessments for PQ-Cohort.



**Table 9: Trial P028 Flow Chart for PQ-Cohort – Screening, Core Treatment, and Run-out Periods**

| PSG plus Questionnaire PQ-Cohort  | Screening/Placebo Run-In Period |                     |              |                           | PQ Cohort 3-Month Core Treatment Period |                    |                |                    |                 |                 |                           |  | Run-Out Period (No extension) |                | Post-Study Period (No extension) |  |
|---|---------------------------------|---------------------|--------------|---------------------------|---|--------------------|----------------|--------------------|-----------------|-----------------|---------------------------|--|-------------------------------|----------------|----------------------------------|--|
|   | Prestudy                        | Screening PSG       | Baseline PSG | Randomization Night 1 PSG | End of Week 2                           | End of Month 1 PSG | End of Month 2 | End of Month 3 PSG | Run-Out PSG     | End of Run-Out  | Discon Visit <sup>1</sup> | Post-study Follow up Call <sup>2</sup> |                               |                |                                  |  |
| PSGs  | 1                               | 2-PSG               | 2a-PSG       | 3-PSG                     | 4                                       | 5-PSG              | 6              | 7-PSG              | PSG 6           | R1-PSG          | R2                        |  |                               |                |                                  |  |
| Visit Number:   | -21                             | -14/-13             | -7/-6        | 1/2                       | 15                                      | 29/30              | 60             | 89/90              | 90/91           | 97              |                           | 111                                    |                               |                |                                  |  |
| Target Study Day:   |                                 | -3/-21 <sup>3</sup> | -3/+3        | -3/+3                     | -3/+3                                   | -3/+3              | -3/+3          | -3/+3              | 0               | -3/+3           |                           | -2/+2                                  |                               |                |                                  |  |
| Visit Window:   |                                 |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Procedures/Assessments <sup>4</sup>   |                                 | PM <sup>5</sup>     | AM           | PM <sup>5</sup>           | AM                                      | PM <sup>5</sup>    | AM             | PM <sup>5</sup>    | AM              | PM <sup>5</sup> | AM                        | PM <sup>5</sup>                        | AM                            |                |                                  |  |
| Informed Consent  | X                               |                     |              |                           |   |                    |                | X <sup>6</sup>     | X <sup>6</sup>  |                 |                           |  |                               |                |                                  |  |
| Provide Participant Identification Card   | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Medical and Psychiatric history   | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Diagnostic Interview/Sleep History/ DSM-IV-TR   | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| MINI International Neuropsychiatric Interview (MINI)  | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Mini Mental State Examination (MMSE) (elderly only)   | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Quick Inventory of Depressive Symptomatology (QIDS-SR16)                                      | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Columbia Suicide Severity Rating Scale (C-SSRS)   | X                               | X                   | X            | X                         | X                                       | X                  | X              | X                  | X               |                 |                           | X                                      | X                             | X <sup>7</sup> |                                  |  |
| Inclusion/Exclusion   | X                               | X                   | X            | X                         | X                                       | X                  | X              | X                  | X               |                 |                           | X                                      | X                             |                |                                  |  |
| Prior and concomitant therapy   | X                               | X                   | X            | X                         | X                                       | X                  | X              | X                  | X               |                 |                           | X                                      | X                             | X              |                                  |  |
| Physical examination  | X                               |                     |              |                           |   |                    |                |                    |                 | X               |                           |  |                               |                |                                  |  |
| Vital signs   | X <sup>8</sup>                  | X                   | X            | X                         | X                                       | X                  | X              | X                  | X               | X               | X                         | X                                      | X                             | X              |                                  |  |
| ECG   | X <sup>9</sup>                  |                     |              | X                         |   | X                  |                | X                  |                 | X               |                           |  |                               |                |                                  |  |
| Hematology, chemistry, urinalysis   | X <sup>9</sup>                  |                     |              | X                         |   | X                  |                | X                  |                 | X               |                           |  |                               |                |                                  |  |
| Urine drug screen <sup>10</sup>   | X                               | X                   | X            | X                         | X                                       | X                  |                | X                  | X               |                 |                           | X                                      |                               |                |                                  |  |
| Urine pregnancy test <sup>11</sup>  | X                               |                     |              | X                         |   | X                  |                | X                  | X               |                 |                           | X                                      |                               |                |                                  |  |
| Informed consent for optional Specimens for Genetic & Other Biomedical Research <sup>12</sup> | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Collection of Optional Specimens for genetic & Other Biomedical research <sup>12</sup>        |                                 |                     |              |                           | X                                       |                    |                |                    |                 |                 |                           |  |                               |                |                                  |  |
| Blood sample for HLA DQB1 allele (DNA) <sup>13</sup>  |                                 |                     |              | X                         | X                                       | X                  | X              | X                  | X               |                 |                           |  |                               |                |                                  |  |
| Pharmacokinetic (PK) Sampling <sup>14</sup>   |                                 | X                   | X            | X                         | X                                       | X                  | X              | X                  | X               | X               |                           |  |                               | X              |                                  |  |
| Alcohol breath test <sup>15</sup>   | X                               | X                   |              | X                         | X                                       |                    | X              | X                  | X               | X <sup>16</sup> |                           | X                                      | X <sup>16</sup>               |                |                                  |  |
| Call IVRS   | X                               | X                   |              | X                         | X                                       |                    | X              | X                  | X               | X <sup>17</sup> |                           | X                                      | X <sup>16</sup>               |                |                                  |  |
| Dispense Study Medication to patient  |                                 | X                   | X            | X                         | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Witnessed Study Medication Dose   |                                 | X                   | X            | X                         | X <sup>18</sup>                         |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Monitor Study Medication Compliance   |                                 | X                   | X            | X                         | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Polysonnography (PSG)   |                                 | X                   | X            | X                         | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Evening/Morning e-diary <sup>19</sup>   | X <sup>19</sup>                 |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               | X              |                                  |  |
| Tyler Withdrawal Symptom Questionnaire (evening e-diary) <sup>20</sup>                        |                                 |                     |              | X <sup>20</sup>           |   |                    |                | X <sup>20</sup>    | X <sup>20</sup> |                 |                           |  |                               |                |                                  |  |
| Digit Symbol Substitution Test (DSST)   |                                 | X                   |              | X                         | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Clinical Global Impressions-Severity (CGI-S)  |                                 |                     | X            |                           | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Clinical Global Impressions-Improvement (CGI-I)   |                                 |                     |              |                           | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Patient Global Impressions-Severity (PGI-S)   |                                 |                     | X            |                           | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Patient Global Impressions-Improvement (PGI-I)  |                                 |                     |              |                           | X                                       |                    | X              | X                  | X               | X               |                           | X                                      | X                             |                |                                  |  |
| Insomnia Severity Index (ISI)   |                                 |                     |              | X                         |   | X                  |                | X                  |                 |                 |                           |  | X <sup>21</sup>               |                |                                  |  |
| Motor Vehicle Accidents and Violations  |                                 | X                   | X            | X                         | X                                       | X                  | X              | X                  | X               |                 |                           | X                                      | X                             |                |                                  |  |
| Modified Cataplexy Questionnaire (MCQ)  | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               | X              |                                  |  |
| Adverse Experiences   | X                               |                     |              |                           |   |                    |                |                    |                 |                 |                           |  |                               | X              |                                  |  |

1) For patients who discontinue during the double-blind treatment period or the double-blind run-out period, a discontinuation visit should be performed. (2) Patients who complete the study or prematurely discontinue during the double-blind treatment period or double-blind run-out period will receive a 14-day (from last dose of study medication) follow-up phone call to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken. If patient discontinues due to an AE, a PK sample should be drawn.

2) Patients will be contacted by telephone 14 days after the end of the run-out or premature discontinuation to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken.

3) The +21 day visit window prior to Visit 2, is provided to accommodate a 4-week washout period for certain prohibited medications. The interval of time between Visits 2, 2a and 3 should be a minimum of 4 days in order to allow for confirmation of PSG results from the centralized PSG reading center.

4) Study procedures/assessments should be performed around consistent time of day if possible.

5) Measurements that are performed in the PM, with the exception of the PSG, will be conducted prior to study drug administration. This applies to all PSG study visits.

6) Patients will need to be re-consented at Visit 6 for the optional 3-month extension. It should be noted that at ~ 2 weeks prior to Visit 7, sites should call patients to confirm their consent decision. In the event that a patient changes their consent after Visit 6, consent must be updated at Visit 7. Please see protocol details for more specific information.

7) Patients who at any time during the post-study period spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Primary Investigator using the C-SSRS.

8) Body Mass Index (Appendix 6.2) will be calculated only at Visit 1 from weight and height. Height will only be measured at the Visit 1. Weight will be measured at the specified Vital Sign time points (for PSG visits weight is measured at AM time points). Please refer to Appendix 6.3 for the measurement of weight and Appendix 6.4 for measurement of blood pressure.

9) Hepatitis/HIV screening are additional Visit 1 procedures to be performed at the discretion of the investigator.

10) At Visit 1, urine drug screen test should be sent into central lab vendor for confirmation. At visits thereafter, patients will undergo an on-site drug test. If a patient has a positive urine drug test, a sample must be sent to the central laboratory for confirmation.

11) All female patients of child-bearing potential (< 65 years old) will undergo a serum pregnancy test at Visit 1 which will be sent into the central lab vendor for confirmation. All other pregnancy tests at other visits will be done on-site. If a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation.

12) Signing of the optional pharmacokinetic sample consent form and obtaining the optional genetic sample can be completed at Visit 3 (randomization). This is not necessary to participate in the study. Sample will only be collected if patient is randomized.

13) The allele sample is not optional and will be collected at Visit 3 (randomization). Consent for sample is captured within the main informed study consent.

14) All PK samples taken on PSG in-clinic visits should be drawn 9 hours ±15 minutes post dosing on AM portions of visit and will be archived. All other non-PSG visit samples can be taken at any time during the study visit and will be collected and archived.

15) Patients should have a negative alcohol breath test on the PSG visit nights. Please refer to the Safety Measurements in Section 3.4.1.5 of this protocol for more details.

16) Call IVRS to discontinue the patient from the study.

17) First dose of randomized blinded study medication will be dispensed.

18) The patient will complete an evening and morning e-diary at home every day after satisfactory completion of Visit 1 and up to Visit 3, pending study criteria is met at each consecutive visit, in order to determine the median habitual bedtime of the patient.

19) Morning e-diary should be completed by the patient after completion of normal morning routine (e.g., using the bathroom, eating breakfast), and preferably within an hour of awakening for the day during the at home period or within 1 hour following Lights-On during PSG days. E-diary should also be performed on the morning prior to all treatment period visits. Evening e-diaries should be completed by the patient after completion of normal evening routine, and preferably within 30 minutes prior to Lights-Off. Evening e-diary on PSG nights should be completed prior to drug administration.

20) Night Questionnaire will be part of the e-diary evening questionnaire and will be completed in the evening; ONLY as indicated: Nights 2 and 3-post randomization; Visit 7-PM (Night 89) and for the next 4 nights (i.e. Nights: 89-93, cumulative). The Tyler will be triggered by the Study Coordinator at the following visits: Visit 3-PSG (Night 1) and Visit 7-PSG (Night 89). Please refer to specific instructions in the e-diary procedure manual.

21) The patient will be asked to mail in a completed ISI to the Investigator site 1 month after completion of their discon visit.

22) On the AM portion of Visit 7, for patients not entering the extension, sites will call into IVRS to log the visit and will obtain run-out study medication. Study medication should only be dispensed to the patient the evening of R1-PSG Day 90. For patients who do enter the extension, sites will call into IVRS on the AM of Visit 7 and extension study medication will be dispensed to the patient at that time."

(Source: Sponsor's submission P028 Protocol 1.8 Pages 17-19)

Table 10 below summarizes the trial schedule and assessments for the 3-Month Extension and Run-Out Periods

**Table 10: Trial P028 Flow Chart for the 3-Month Extension and Run-Out Periods**

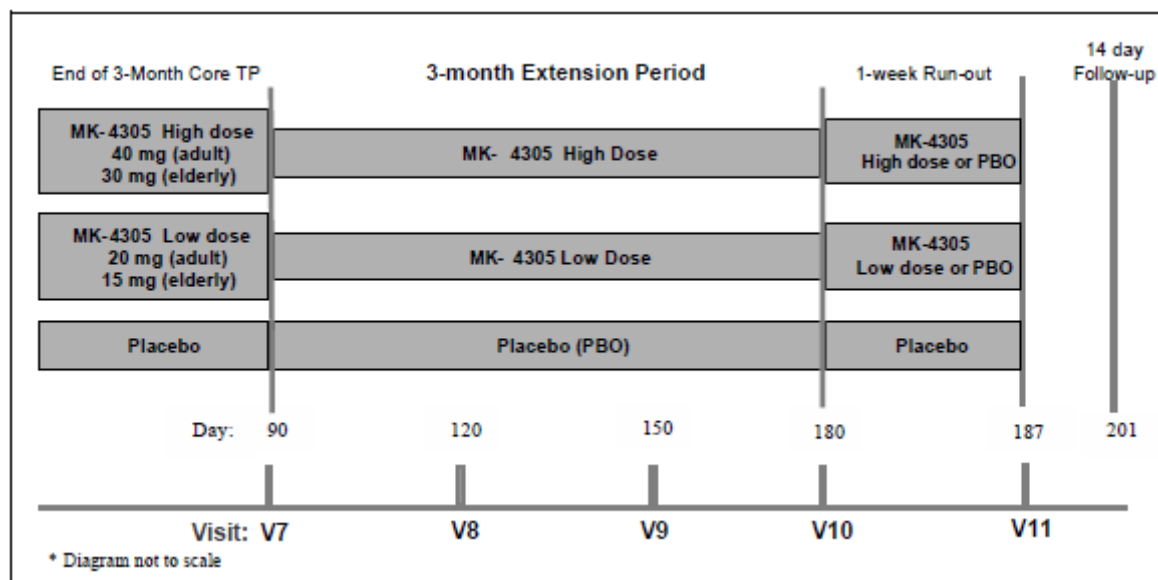
|   | 3-Month Extension Period  |                |                | Run-Out Period |                           | Post-Study Period                      |
|---|---|----------------|----------------|----------------|---------------------------|--|
| Treatment Period  | End of Month 4  | End of Month 5 | End of Month 6 | End of Run-out | Discon Visit <sup>1</sup> | Post-study Follow up Call <sup>2</sup> |
| Visit Number:   | 8   | 9              | 10             | 11             |                           |  |
| Target Study Day:   | 120   | 150            | 180            | 187            |                           | 201                                    |
| Visit Window:   | -3/+3   | -3/+3          | -3/+3          | -3/+3          |                           | -2/+2                                  |
| <b>Procedures/Assessments<sup>3</sup></b>   |   |                |                |                |                           |  |
| Concomitant therapy review  | X   | X              | X              | X              | X                         | X                                      |
| Physical examination  |   |                | X              |                | X                         |  |
| Vital signs   | X   | X              | X              | X              | X                         |  |
| ECG   |   |                | X              |                | X                         |  |
| Hematology, chemistry, urinalysis   |   |                | X              |                | X                         |  |
| Urine drug screen <sup>4</sup>  |   |                |                |                | X                         |  |
| Urine pregnancy test <sup>5</sup>   | X   | X              | X              |                | X                         |  |
| Pharmacokinetic (PK) Sampling   |   |                |                |                | X                         |  |
| Columbia Suicide Severity Rating Scale (C-SSRS)   | X   | X              | X              | X              | X                         | X <sup>6</sup>                         |
| Call IVRS   | X   | X              | X              | X              | X <sup>7</sup>            |  |
| Dispense Study Medication to patient  | X   | X              | X              |                |                           |  |
| Monitor Study Medication Compliance   | X   | X              | X              | X              | X                         |  |
| Evening/Morning e-diary <sup>8</sup>  | X   | X              | X              | X              |                           |  |
| Tyler Withdrawal Symptom Questionnaire (evening e-diary) <sup>9</sup>   |   |                | X <sup>9</sup> |                |                           |  |
| Clinical Global Impressions-Severity (CGI-S)  | X   | X              | X              | X              | X                         |  |
| Clinical Global Impressions-Improvement (CGI-I)   | X   | X              | X              | X              | X                         |  |
| Patient Global Impressions-Severity (PGI-S)   | X   | X              | X              | X              | X                         |  |
| Patient Global Impressions-Improvement (PGI-I)  | X   | X              | X              | X              | X                         |  |
| Insomnia Severity Index (ISI)   |   |                | X              |                | X <sup>10</sup>           |  |
| Motor Vehicle Accidents and Violations  | X   | X              | X              | X              | X                         | X                                      |
| Modified Cataplexy Questionnaire (MCQ)  | X-MCQ will be completed for any report of an adverse experience of cataplexy or falls-X |                |                |                |                           |  |
| Adverse Experiences   | X-----X   |                |                |                |                           |  |
| <sup>1</sup> 1) For patients who discontinue during the double-blind extension period or the double-blind run-out period, a discontinuation visit should be performed. (2) Patients who complete the study or prematurely discontinue during the double-blind treatment period or double-blind run-out period will receive a 14-day (from last dose of study medication) follow-up phone call to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken. If patient discontinues due to an AE, a PK sample should be drawn.   |   |                |                |                |                           |  |
| <sup>2</sup> Patients will be contacted by telephone 14 days after the end of the run-out or premature discontinuation to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken.   |   |                |                |                |                           |  |
| <sup>3</sup> Study procedures/assessments should be performed around consistent time of day if possible.  |   |                |                |                |                           |  |
| <sup>4</sup> All patients will undergo an on-site urine drug test. If any patient has a positive urine drug test, a sample must be sent to the central laboratory for confirmation.   |   |                |                |                |                           |  |
| <sup>5</sup> Female patients of child-bearing potential (< 65 years old) will undergo an on-site urine pregnancy test. If a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation.   |   |                |                |                |                           |  |
| <sup>6</sup> Patients who at any time during the post-study period spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Primary Investigator using the C-SSRS.   |   |                |                |                |                           |  |
| <sup>7</sup> Call IVRS to discontinue the patient from the study.   |   |                |                |                |                           |  |
| <sup>8</sup> E-diary will be completed during the last day of Visit 7 and the first 4 days of the extension. It will also be completed during the 5 days prior Visit 8 on the actual day of Visit 8, plus 5 days following Visit 8 (11 days total). Additionally, the e-diary will be completed 5 days prior to Visit 9 and every day thereafter throughout the end of run-out. Evening e-diary should be completed at home by patient at bedtime prior to taking study medication. Morning e-diary should be completed at home by patient after their normal morning routine (e.g., using the bathroom, eating breakfast) and preferably within an hour of waking for the day. |   |                |                |                |                           |  |
| <sup>9</sup> For patients entering the 3-month extension, the Tyler will be completed on the last day of Visit 7 and the first 4 days of the extension (as noted in Sections 1.7 & 1.8), as well as on the evening of Visit 10 (Night 180) and the following 4 consecutive evenings (i.e Nights 180 to 184, cumulative). The Tyler will be triggered by the Study Coordinator at Visit 7 and Visit 10.  |   |                |                |                |                           |  |
| <sup>10</sup> The patient will be asked to mail in a completed ISI to the Investigator site 1 month after completion of their discon visit.   |   |                |                |                |                           |  |

(Source: Sponsor's submission P028 Protocol 1.9 Page 21)

### Trial P028 Population

The trial plan was to enroll 960 subjects, 60% non-elderly and 40% elderly. The sponsor randomized subjects who provided written informed consent and met the trial inclusion and exclusion criteria, using an interactive voice randomization system (IVRS), in a 3:2:3 ratio to suvorexant HD (40 mg for non-elderly; 30 mg for elderly), suvorexant LD (20 mg for non-elderly; 15 mg for elderly), or placebo. Stratifying randomized subjects according to age group (< 65 years; 65 years and older) and cohort (PQ or Q cohort) yielded four distinct strata. Subjects entering the 3-month extension remained on their assigned core treatment during the extension, as shown in the flow diagram below. For the double-blind run-out period, subjects randomized to suvorexant during the core treatment period were simultaneously randomized in a 1:1 ratio to either continue assigned core treatment at the same suvorexant dose or switch to placebo. At completion, the trial had randomized 1,022 subjects.

**Figure 2: Trial Flow Diagram for P028 Extension and Run-Out Periods**



(Source: Sponsor's submission P028 Protocol Page 37)

### Key Inclusion Criteria (From sponsor's submission - Protocol)

#### Visit 1: Pre-Trial Inclusion

- 1.a. Male or female subject, 18 years of age on the day of signing informed consent.
- 1.b. Subject with DSM-IV-TR diagnosis of Primary Insomnia based on the investigator's judgment and the subject's sleep history as assessed on the Sleep Diagnostic Interview/Sleep History.
- 1.c. For subjects 65 years old: Mini Mental State Examination (MMSE) score of 25.
- 1.d. Subject is in good physical and mental health in the opinion of the investigator.

- 1.e. A female subject, who was of reproductive potential, had a serum  $\beta$ -hCG level consistent with the non-gravid state, and agreed to use acceptable contraception.
- 1.f. Subject reported total sleep time of < 6.5 hours on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.\*
- 1.g. Subject reported sleep latency of 30 minutes on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.\*
- 1.h. Subject reported 1 hour of wakefulness after sleep onset on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.\*

*\*Applied to 1.f to 1.h: For subject chronically using a hypnotic or anxiolytic for treatment of insomnia, defined as use of 4 times/week, a 4-week washout (or 5 half lives, whichever was greater) was required prior to assessment of these Visit 1 criteria.*

- 1.i. Subject reported spending 6.5 to 9 hours nightly in bed on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.
- 1.j. The subject's regular bedtime was between 9 pm (21:00) and 1 AM (01:00).
- 1.k. During the study, the subject was willing to refrain from napping.
- 1.l. Subject understood the trial procedures, alternative treatments available, and risks involved with the trial, and voluntarily agreed to participate by giving written informed consent.
- 1.m. During the trial, subject was willing to limit alcohol to 2 drinks a day and at least 3 hours before going to bed. (A drink was defined as a 12-ounce bottle or can of beer (about 14 grams alcohol) or a 4-ounce glass of wine (about 12 grams alcohol) or 1 ounce of liquor (80 proof or 40% alcohol, about 9 grams alcohol)).
- 1.n. During the trial, the subject was willing to limit caffeine consumption to 5 standard 6-ounce cups of caffeinated beverages a day, or 600 mg caffeine, avoid caffeine after 4 pm (16:00).
- 1.o. Subject was willing to limit nicotine as required by the protocol.
- 1.p. Subject was able to read, understand and complete questionnaires and diaries, including operation of the e-diary.

#### **PQ-Cohort Only: Visit 1- Pre-Trial**

- 1.a. Subject was willing to stay overnight at a sleep laboratory for PSG testing visits as specified in Trial Flow Chart.
- 1.b. Subject was willing to stay in bed for at least 8 hours each night while at the sleep laboratory.
- 1.c. During the trial, subject was willing to refrain from drinking alcohol on all PSG visit days, and at least 24 hours prior to a PSG visit.
- 1.d. During the trial, subject was willing to avoid caffeine after 1 pm (13:00) on PSG visit days.

#### **Visit 2, Visit 2a-PSG: Screening Inclusion**

- 2.a. Subject continued to fulfill all of the Pre-Trial Inclusion Criteria.

#### **PQ-Cohort ONLY: Visit 2-PSG-Screening PSG**

- 2.b. Subject had LPS >20 minutes during the Screening PSG at Visit 2. Note:  
“Persistent sleep” was defined as the first continuous 20 epochs (30 seconds each) of a non-wake state.
- 2.c. Subject had WASO >45 minutes during the Screening PSG at Visit 2.

**PQ-Cohort ONLY: Visit 2a-PSG-Baseline PSG**

- 2.d. Subject continued to fulfill all of the Pre-Trial Inclusion Criteria.
- 2.e. Subject had LPS > 20 minutes on both Screening and Baseline PSG nights.
- 2.f. Subject had a mean WASO of 60 minutes or higher on the combined Screening and Baseline PSG nights, where neither night can be 45 minutes or less.

**Visit 3, Visit 3 PSG Inclusion:**

- 3.a. Subject continued to fulfill all of the Pre-Trial Inclusion Criteria.
- 3.b. Subject demonstrated compliance with the morning and evening e-diary for the period between Visit 2 and 3. E-diary compliance was defined as subject having completed at least 70% (for example, 7 out of 10 days and nights) of both the morning and evening e-diaries.

**Q-Cohort ONLY: Visit 3- Baseline/Randomization**

- 3.c. During the single-blind placebo run-in, subject had a subjective total sleep time (sTST) < 6.5 hours on at least 4 nights for the week prior to baseline, based on the e-diary.
- 3.d. During the single-blind placebo run-in, subject had a subjective time to sleep onset (sTSO) 30 minutes on at least 4 nights for the week prior to baseline, based on the e-diary.

**Visits 6 and 7: Extension Inclusion**

- 4.a. & 5.a. Subject was compliant with trial procedures.

**Key Exclusion Criteria for Trial P028 (From sponsor's submission - Protocol)**

**Visit 1: Pre-Trial Exclusion**

- 1.a If female, subject was pregnant (positive serum pregnancy test at pretrial), breastfeeding, or expecting to conceive within the projected trial duration.
- 1.b Subject was expecting to donate egg or sperm during the trial.
- 1.c Subject had a history or diagnosis of any of the following conditions:
  - Narcolepsy
  - Cataplexy, familial or idiopathic
  - Circadian Rhythm Sleep Disorder
  - Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behavior disorder
  - Sleep-related Breathing Disorder – obstructive or central sleep apnea syndrome or central alveolar hypoventilation syndrome
  - Periodic Limb Movement Disorder

- Restless Legs Syndrome
  - Primary Hypersomnia
  - Excessive Daytime Sleepiness (EDS), not attributable to primary insomnia
- 1.d In the opinion of the investigator, subject had difficulty sleeping due to a confounding medical condition such as chronic pain syndromes, chronic migraine, cardiac disease, nocturia (>3 times/night), asthma, gastroesophageal reflux disease (GERD), or hot flashes.
- 1.e Subject had a history of trans-meridian travel (across >3 time zones or >3 hours time difference) within the previous 2 weeks or expected to travel (across >3 time zones or >3 hours time difference) during the trial. For PQ Cohort only, Transmeridian travel was prohibited 1 week prior to PSG visits.
- 1.f Subject had history of shift work (defined as permanent night shift or rotating day and night shift work) within the previous 2 weeks or anticipated the need to perform shift work during the trial.
- 1.g Subject had any history of a neurological disorder, including but not limited to seizure disorder (other than single episodes of childhood febrile seizures), stroke, transient ischemic attack, multiple sclerosis, cognitive impairment, or significant head trauma with sustained loss of consciousness within the last 10 years.
- 1.h Subject had any of the following:
  - Lifetime history of bipolar disorder, a psychotic disorder, or posttraumatic stress disorder
  - A psychiatric condition requiring treatment with a prohibited medication
  - Other psychiatric condition that, in the investigator's opinion, would interfere with the subject's ability to participate in the trial.
- 1.i Subject had evidence of ongoing major depression (per MINI), significant depressive symptoms (for example, a score 20 on the Quick Inventory of Depressive Symptomatology-Self Report Scale (QIDS-SR16)) or suicidal ideation (that is, a score 2 or more on the QIDS-SR16 item #12) or, in the investigator's opinion, was unable to complete the trial procedures in a safe and appropriate fashion (regardless of QIDS-SR16 score).
- 1.j Subject had a history of substance abuse or dependence, except if subject was in sustained full remission for at least one year or met criteria for early full remission, according to DSM-IV-TR. Substances included alcohol, marijuana, hypnotics, other prescription drugs, and drugs of abuse, but exclude nicotine dependence. A subject who fulfilled DSM-IV-TR criteria for sustained remission could be included if he or she, in the investigator's opinion, was at low risk for further drug dependence or abuse.
- 1.k Subject had either a history within the past 6 months prior to the Pretrial visit or current evidence of an unstable or clinically significant cardiovascular disorder, including but not limited to:
  - Acute coronary syndrome
  - Unstable angina
  - Congestive heart failure
  - Cardiogenic syncope

- Cardiomyopathy
  - Any symptomatic arrhythmia
- 1.l Subject, in the opinion of the investigator, had a history or current evidence of any condition, therapy, lab or ECG abnormality or other circumstances that might confound the results of the trial, or interfere with the subject's participation for the full duration of the trial, such that it was not in the best interest of the subject to participate. Examples of excluded disorders included, but not limited to: HIV or other relevant infections, history of acute or chronic hepatitis, history of gastric bypass or gastric banding surgery, active endocrine disorders. However, subjects with well-controlled insulin-dependent diabetes, type II diabetes, or hypothyroidism were allowed if on stable doses of appropriate therapy for 1 month or more prior to Screening Visit 2.
- 1.m Subject at Visit 1-Pretrial had, by ECG, a clinically significant AV conduction disturbance (for example, second or third degree AV block), sick sinus syndrome, bradycardia (resting pulse <40), or accessory bypass tract (for example, Wolff-Parkinson-White).
- 1.n Subject had abnormal pre-randomization laboratory values per the guidance below or other clinically significant, unexplained laboratory abnormality in the opinion of the investigator:
  - Alanine transaminase (SGPT or ALT) >1.5 x the upper limit of normal (xULN)
  - Aspartate transaminase (SGOT or AST) >1.5 x ULN
  - Total bilirubin >1.5 x ULN
  - Serum creatinine of >2 mg/dL
- 1.o Subject had a positive screening urine drug screen to, for example, benzodiazepines, cannabinoids, cocaine, and other drugs.
- 1.p Subject had a history of hypersensitivity or idiosyncratic reaction to more than two chemical classes of drugs, including prescriptions and over-the-counter medications.
- 1.q Subject was taking, or planned to take, one or more of the medications shown in table 11 below within the specified washout period prior to Visit 2-Screening and throughout the course of the trial. Section on concomitant treatments below contains a detailed list of the prohibited medications.



**Table 11: List of Prohibited Medications and Specified Washout Period**

| Treatment   | Interval*                              |
|---|--|
| Investigational compounds   | 4 weeks or 5 t <sub>1/2</sub> lives    |
| Strong CYP3A4 Inhibitors and Inducers   | 2 weeks or 5 t <sub>1/2</sub> lives    |
| Antihistamines (sedating)   | 2 weeks                                |
| Hypnotics   | 2 weeks or 5 t <sub>1/2</sub> lives ** |
| <b>Other Psychotropics:</b>   |  |
| Antidepressants (other than fluoxetine)   | 2 weeks                                |
| Fluoxetine  | 4 weeks                                |
| Anticonvulsants   | 2 weeks                                |
| Antipsychotics  | 2 weeks or 5 t <sub>1/2</sub> lives    |
| Anxiolytics (benzodiazepines, non-benzodiazepines)  | 2 weeks or 5 t <sub>1/2</sub> lives**  |
| Centrally acting anticholinergics   | 2 weeks                                |
| Any CNS depressants   | 2 weeks                                |
| Mood Stabilizers  | 2 weeks                                |
| Stimulants  | 2 weeks                                |
| Supplements with possible psychotropic effects  | 2 weeks                                |
| <b>Other Medications:</b>   |  |
| Anticoagulants, systemic glucocorticoids, isotretinoin, diet pills  | 2 weeks                                |
| <p>* Interval notes minimum washout period. Washout should occur for 5 half lives or the minimum specified period (2 or 4 weeks), <u>which ever is longer</u> to systemically eliminate the compound.</p> <p>** The indicated hypnotic/anxiolytic washout (prior to Visit 2) applies to intermittent use only (defined as use of &lt; 4 times/week). For those patients chronically using a hypnotic or anxiolytic (defined as use of ≥ 4 times/week) a 4-week washout (or 5 t<sub>1/2</sub> lives, whichever is greater) must occur prior to completion of Visit 1. Please see Section 3.2.1 for more information.</p> |  |

(Source: Sponsor's Submission P028 Protocol Page 34 Table 2-1)

- 1.r Subject consumed the equivalent of >15 cigarettes a day, and the investigator confirmed that the subject's sleep disturbance was in part the result of this consumption.
- 1.s Subject had donated blood products or had had phlebotomy of >300 mL within 8 weeks of signing informed consent, or intended to donate or receive blood products during trial participation.
- 1.t Subject had a history of malignancy 5 years or more prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
- 1.u Subject had a Body Mass Index (BMI) >40 kg/m<sup>2</sup>.
- 1.v Subject was previously randomized in another investigational suvorexant trial.
- 1.w Subject was at the time participating or had participated in a trial with an investigational compound or device within 30 days of signing informed consent or was not willing to refrain from participating in another trial while participating in this trial.
- 1.x Subject was unlikely to adhere to the trial procedures and restrictions, keep appointments or was planning to relocate during the trial.

### Visit 2, Visit 2a-PSG: Screening Exclusion

- 2.a. Subject met any of the Pretrial Exclusion Criteria.



### **PQ-Cohort ONLY: Visit 2-PSG-Screening PSG**

2.b. Subject had a positive alcohol breath test as analyzed by a breathalyzer machine.

2.c. Subject had an underlying pathology of sleep identified during the screening PSG as follows:

- Non-elderly (<65 years of age)
  - An Apnea Hyperpnoea Index >10; or;
  - >10 periodic leg movements associated with an arousal per hour of sleep (PLMAs)
- Elderly (65 years or older)
  - • An Apnea Hyperpnoea Index >15; or;
  - • >15 periodic leg movements associated with an arousal per hour of sleep (PLMAs)

### **Visits 6 and 7: Extension Exclusion**

- Subject had developed a condition that further puts the subject at risk for continuing in the trial.

#### *Reviewer Comment:*

*The overall trial design was typical for a Phase 3 insomnia drug assessment. Also, the inclusion and exclusion criteria appear appropriate for a trial of a new molecular entity in subjects with primary insomnia.*

### **Treatments**

#### *Treatment Groups*

- Suvorexant LD: 15 mg in elderly (65 years and older) and 20 mg in non-elderly subjects (18 to 64 years old)
- Suvorexant HD: 30 mg in elderly and 40 mg in non-elderly subjects
- Placebo

All medications were administered orally, at bedtime or 30 minutes before bedtime during PSG visits.

#### *Concomitant/Restricted Medications:*

The trial required the subjects to discontinue prohibited medications at least 2 weeks prior to the Screening Visit 2, except investigational medications and fluoxetine that had to be withdrawn at least 4 weeks prior to Screening Visit 2. Subjects on chronic hypnotic or anxiolytic treatment, defined as use of 4 times/week, needed a 4-week washout (or 5 t½ lives, whichever was greater) before completing Visit 1. Table 12 below is Merck's summary of the medications that were prohibited or limited during the trial.

**Table 12: Prohibited or Restricted Concomitant Medications in P028**

| Medication Category | Examples*/ Notes<br>(*specific medications listed were examples of class) | Status |
|---------------------|---|--------|
|---------------------|---|--------|

|  |  |        |
|--|--|--------|
|  | compounds and were not limited to those listed)  |        |
| <i>Strong CYP3A4 Inhibitors</i>  | Included atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, refinavir, ritonavir, saquinavir, telithromycin, and voriconazole  | P      |
| <i>Strong CYP3A4 Inducers</i>  | Included barbiturates, carbamazepine, efavirenz, modafinil, nevirapine, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentin, St. John's Wort (hypericum), and systemic glucocorticoids (inhaled steroids were permitted)   | P      |
| <i>Centrally acting analgesics</i>                                       | Could be taken as needed for pain relief (with the documented approval of the Merck clinical monitor), but use may not exceed 3 consecutive days or > 4 days per any week.<br>Note: Use of narcotics for pain relief was to be avoided if there were effective alternative therapies such as non-steroidal anti-inflammatory agents (NSAIDs). Sponsor was notified of any use exceeding 3 consecutive days or > 4 days per any week. | L      |
| <i>Centrally acting anticholinergics</i>                                 |  | P      |
| Other Psychotropic Agents  |  |        |
| <i>Antihistamines:</i><br>Sedating<br>Non-sedating                       | Note: Non-sedating antihistamines were not to be taken more than twice a week.<br>Note: Montelukast sodium (Singulair) and inhaled corticosteroids could be used more than twice weekly as needed for allergic symptoms  | P<br>L |
| <i>Anticonvulsants</i>   |  | P      |
| <i>Antidepressants</i>   |  | P      |
| <i>Antipsychotics</i>  |  | P      |
| <i>Anxiolytics:</i><br>Benzodiazepines<br>Non-benzodiazepine anxiolytics |  | P<br>P |
| <i>Hypnotics:</i><br>Prescription hypnotics<br>OTC hypnotics             | Included Tylenol PM, Nytol PM, Unisom  | P<br>P |
| <i>Mood stabilizers</i>  |  | P      |
| <i>Muscle relaxants (centrally acting with psychotropic effects)</i>     | Included methocarbamol<br>Note: Use of centrally acting muscle relaxants were avoided if there were effective alternative therapies such as NSAIDs.  | L      |
| <i>Stimulants</i>  | Included modafinil, methylphenidate  | P      |

|   |   |        |
|---|---|--------|
| <i>Supplements with possible psychotropic effects</i>                                   | Included melatonin, kava-kava, S-Adenosyl methionine (SAME), St. Johns Wort, tryptophan, and valerian   | P      |
| <b>Other Agents</b>   |   |        |
| <i>Anticoagulants</i>   | Included warfarin, heparin, and ticlopidine. Note: baby aspirin was allowed if taken 4 weeks prior to Visit 2   | P      |
| <i>Diet Pills (prescription and over-the-counter)</i>                                   |   | P      |
| <i>Glucocorticoids</i><br>Systemic glucocorticoids<br>Inhaled corticosteroids           | Included dexamethisone<br>Included beclomethisone<br>Note: Inhaled corticosteroids could be used more than twice weekly as needed for allergic symptoms.  | P<br>L |
| <i>Isotretinoin</i>   | Accutane  | P      |
| <i>Over-the-Counter (OTC), combination products containing caffeine for pain relief</i> | Included Excedrin and Anacin<br>Note: Two tablets were equivalent to a caffeinated beverage and were counted as such toward the maximum of 5 beverages per day. As with any caffeinated beverages, subjects were advised to refrain from using these medications after 4 PM. These medications were not to be taken on days when PSGs were conducted. | L      |
| <i>Pseudoephedrine</i>  | Note: Only to be used before 2 PM, and no more than twice a week.<br>Dosage was limited to 30 mg of active ingredient in each tablet. Extended release formulations were prohibited. These medications were not to be taken on days when PSGs were conducted.   | L      |
| P = Prohibited; L = Limited   |   |        |

(Source: Modified from Sponsor's Submission P028 Protocol Pages 57-58 Table 3-1)

### Primary Endpoints

Overall, Merck performed eight primary endpoints assessments, considering the different endpoints for sleep maintenance and sleep onset, and considering the different time points. The different endpoints for sleep maintenance were sTSTm and WASO, while those for sleep onset were sTSOm and LPS. The time points of assessment for the primary endpoints were Month 1 and Month 3. The endpoints' response at the respective time points was change from baseline.

For sleep maintenance, Merck compared the treatment effects of suvorexant HD and placebo on four primary endpoint assessments, that is, two primary endpoints assessed at two time points, as follows:

### Sleep Maintenance

- Change from baseline in sTSTm at Month 1
- Change from baseline in sTSTm at Month 3
- Change from baseline in WASO at Month 1
- Change from baseline in WASO at Month 3

For sleep onset, Merck also compared suvorexant HD and placebo treatments on four primary endpoint assessments, again, as follows:

#### Sleep Onset

- Change from baseline in sTSOm at Month 1
- Change from baseline in sTSOm at Month 3
- Change from baseline in LPS at Month 1
- Change from baseline in LPS at Month 3

Table 13 below summarizes the sleep terms Merck used to define the endpoints.

**Table 13: Definitions of Sleep Terms for Trial Endpoints**

| Objective PSG Measures |  |   |              |
|------------------------|--|---|--------------|
| A Waking Event         | "awakening"; an awakening                            | A waking event is defined as at least 2 consecutive 30 sec epochs of the PSG scored as waking and bracketed by Stages 1, 2, 3, 4, or REM.   | N            |
| LPS                    | Latency to onset of Persistent Sleep:                | The time from the beginning of the recording (lights off) to the onset of the first continuous 20 epochs of a non wake state (i.e., 10 consecutive minutes of sleep in Stages 1, 2, 3, 4, or REM)   | Min          |
| SE                     | Sleep Efficiency:                                    | Total Sleep Time divided by the total duration of the recording period x 100  | %            |
| TST                    | Total Sleep Time:                                    | The duration of REM and non-REM sleep from lights off to lights on.   | Min          |
| WASO                   | Wakefulness After persistent Sleep Onset:            | Duration of wakefulness after the onset of persistent sleep to lights on. Wakefulness is defined as any epoch of stage 0. Onset of persistent sleep is defined as the first epoch of 10 consecutive minutes of sleep (REM or non-REM (stage 1, 2, 3 or 4)). | Min          |
| Subjective Measures    |  |   |              |
| sWASO                  | Subjective Wakefulness After persistent Sleep Onset: | Patient's reported amount of time spent awake from the time the patient falls asleep to the time the patient wakes up for the day   | Min or hours |
| sTSO                   | Subjective Time to Sleep Onset:                      | Patient's report of the time he or she required to fall asleep  | Min or hours |
| sNAW                   | Subjective Number of Awakenings:                     | Patient's report of the number of times the patient wakes after falling asleep  | N            |
| sTST                   | Subjective Total Sleep Time:                         | Patient's report of the total amount of time spent asleep before waking for the day   | Min or hours |

(Source: Sponsor's Submission P028 Protocol Page 136 Appendix Table 6.6)

A central laboratory performed sleep stage scoring of each 30-second epoch on PSG recordings. Each 30-second epoch received a score of Wake, Stage 1, 2, 3, 4 or REM. The resultant sleep scores were used to derive the PSG parameters for the trial's objective endpoints at Baseline, Night 1 (Day 1), Month 1 (+/-7 days from the target Day 30), and Month 3 (+/-7 days from the target Day 89). Merck defined sleep maintenance parameter WASO as objective or PSG-measured wakefulness after persistent sleep onset. The sleep onset parameter LPS was time to onset of persistent sleep, as defined in Table 13 above. Baseline was defined as PSG parameters obtained at Visit 3 for objective endpoints.

For the subjective endpoints, Merck derived weekly averages, including Months 1 and 3, from the mean of daily measurements that fell within the range of days shown in table 14 below; the derivation included only the weeks with at least 3 days of data, and excluded PSG nights. Merck defined sTSTm as the mean of the subjective or subjects' daily (morning) e-diary report of total sleep time. The sleep onset endpoint sTSOm was defined as the mean of subjects' daily (morning) e-diary report of time to sleep onset total sleep time. Baseline for subjective endpoint assessments was the mean of the last seven (non-missing) measurements obtained from the placebo-run-in period.

**Table 14: Range of Days for Subjective Endpoint Assessments**

| Week/Month       | Day Range |
|------------------|-----------|
| Base Period      |           |
| Week 1           | 2-8       |
| Week 2           | 9-15      |
| Week 3           | 16-22     |
| Month 1          | 23-30     |
| Month 1.5        | 31-45     |
| Month 2          | 46-60     |
| Month 2.5        | 61-75     |
| Month 3          | 76-90     |
| Extension period |           |
| Month 4          | 115-125   |
| Month 5          | 145-155   |
| Month 6          | 166-180   |

(Source: Sponsor's Submission P028 Protocol Page 101)

### *Secondary Endpoints*

The secondary endpoints included the following parameters:

#### Sleep Maintenance:

- Suvorexant HD: Change from baseline sTSTm at Week 1.
- Suvorexant HD: Change from baseline in WASO at Night 1.

- Suvorexant LD: Change from baseline in sTSTm at Week 1, Month 1, and Month 3.
- Suvorexant LD: Change from baseline in WASO at Night 1, Month 1, and Month 3.

Sleep Onset:

- Suvorexant HD: Change from baseline in sTSOm at Week 1.
- Suvorexant HD: Change from baseline in LPS at Night 1.
- Suvorexant LD: Change from baseline in sTSOm at Week 1, Month 1, and Month 3.
- Suvorexant LD: Change from baseline in LPS at Night 1, Month 1, and Month 3.

*Exploratory Endpoints*

The exploratory endpoints included the following:

- Subjective outcomes evaluated at three time points: Week 1, Month 1, and Month 3
  - Number of awakenings (sNAWm)
  - Wake time after sleep onset (sWASOm) in minutes
  - Sleep quality (sQUALm)
  - Refreshed upon awakening (sREFRESHEDm)
- Responder analysis endpoints:
  - Percentage of subjects achieving 6-point or higher improvement from baseline in mean Insomnia Severity Index (ISI) total score
  - Percentage of subjects responding to treatment based on the cumulative frequencies of percent change from baseline in mean subjective total sleep time (sTSTm) on the daily sleep diary (for example, 15% response)
  - Percentage of subjects responding to treatment based on the cumulative frequencies of percent change from baseline in mean subjective time to sleep onset (sTSOm) on the daily sleep diary (for example, 15% response)
- PSG exploratory endpoints evaluated at Night 1, end of Month 1, and end of Month 3 are shown below.
  - Sleep architecture endpoints:
    - Stage 1 duration (S1) in minutes from Lights-Off to Lights-On
    - Stage 1 percent (PS1): defined as S1 divided by TST
    - Stage 2 duration (S2) in minutes from Lights-Off to Lights-On
    - Stage 2 percent (PS2): defined as S2 divided by TST
    - Stage 3 duration (S3) in minutes from Lights-Off to Lights-On
    - Stage 3 percent (PS3): defined as S3 divided by TST
    - Stage 4 duration (S4) in minutes from Lights-Off to Lights-On
    - Stage 4 percent (PS4): defined as S4 divided by TST
    - Rapid Eye Movement sleep (REM) duration in minutes from Lights-Off to Lights-On

- Rapid Eye Movement sleep (REM) percent: defined as REM divided by TST
  - Power spectra: Each 1 Hz bin from 1 to 128 Hz and traditional bands which include Delta, Theta, Alpha, Slow Beta, and Gamma
- Other PSG sleep parameters:
  - Total sleep time (TST) in minutes: defined as duration of REM + NREM (Stages 1+2+3+4) from Lights-Off to Lights-On
  - Number of awakenings (NAW): Counted from persistent sleep onset to Lights-On, an awakening was defined as a PSG recording of at least two consecutive wake epochs and was bracketed by an epoch of Stage 1, 2, 3, or 4 non-REM sleep or REM sleep.
  - Slow wave sleep (SWS) in minutes: defined as duration of Stage 3/4 sleep from Lights-Off to Lights-On
  - Sleep onset latency (SOL) in minutes: defined as the duration of time from Lights-Off to the first epoch of any stage of sleep (sleep onset)
  - Non-REM epoch to REM: Number of non-REM epochs to the first epoch of REM sleep
  - Number of Arousals (NOA): Counted from sleep onset to Lights-On, an arousal was defined as a PSG recording of at least one wake epoch and was bracketed by an epoch of Stage 1, 2, 3, or 4 non-REM sleep or REM sleep.
  - Wakefulness After persistent Sleep Onset (WASO) by hour
- Severity and improvement of insomnia exploratory endpoints included:
  - Clinical Global Impressions – Severity of Illness (CGI-S)
  - Patient Global Impressions – Severity of Illness (PGI-S)
  - ISI total score
  - Clinical Global Impressions – Improvement (CGI-I)
  - Patient Global Impressions – Improvement (PGI-I)
- Additional ISI items evaluated in exploratory analyses included the following:
  - ISI difficulty falling asleep score
  - ISI difficulty staying asleep score
  - ISI waking too early score
  - ISI satisfied/dissatisfied with current sleep score
  - ISI sleep problem interfere with daily functioning score
  - ISI sleep problem impair QOL score
  - ISI worried/distressed about sleep problem score

Insomnia Severity Index (ISI) assessed, on a 7-item subject-reported outcome scale, the severity of a subject's insomnia based on the severity of sleep-onset and sleep maintenance difficulties and any insomnia-related interference with daytime functioning. Each item was rated on a 5-point scale (0-4). An ISI total score in the range of 22 to 28

reflected severe insomnia; a score of 15 to 21 reflected moderate insomnia; and scores less than 10 indicated minimal to no insomnia.

The Clinical Global Impressions (CGI) of Severity of Illness (CGI-S) and of Improvement (CGI-I) were clinician-administered instruments used to assess insomnia severity (CGI-S) and change over time (CGI-I). Each scale was rated from 1 to 7, with lower scores reflecting less illness severity and greater improvement. The CGI-I measured global clinical improvement at a certain time point compared to the subject's baseline.

Patient Global Impressions of Severity Scale (PGI-S) assessed the subjects' description of their insomnia severity in the preceding week based on a response to the question: "How would you describe your insomnia over the past week? Each response was rated 0 (none) to 5 (very severe). For Patient Global Impressions of Improvement Scale (PGI-I), the subjects assessed their insomnia improvement from baseline, with the following question: Compared to when I started the trial, my insomnia is now. Each response ranged from 1 (very much better) to 7 (very much worse).

### **Pharmacokinetic parameters**

Investigators collected PK samples at any time during pre-randomization baseline visit 3, Week 2 visit 3, Month 1 visit 4, Month 3 visit 5, and discontinuation visit. PK samples collected during PSG visits were drawn in the mornings at about 9 hours post-dose.

### **Safety parameters:**

Investigators measured the following to monitor safety:

- Physical examination, vital signs, Electrocardiogram (ECG), and clinical labs were performed according to the trial schedule
- Tyrer Withdrawal Symptom Questionnaire via the evening e-diary questionnaire
- Digit Symbol Substitution Test (PQ-cohort only)
- Columbia Suicide Severity Rating Scale
- Motor Vehicle Accidents and Violations
- Subjective adverse experiences including events of clinical interest (ECIs) as follows:
  - Cataplexy
  - Sleep paralysis; sleep-onset paralysis
  - Hypnagogic or hypnopompic hallucinations
  - Excessive Daytime Sleepiness (EDS)
  - Suicidal ideation and/or behaviors
  - Complex sleep-related behaviors
  - Falls
  - Events associated with potential for abuse
  - Adverse experiences associated with traffic or motor vehicle accidents (when a subject was the driver)



#### Adjudication Procedures

Investigators identified selected adverse experiences for adjudication by an independent expert committee that was external to Merck and was blinded to the subject's treatment assignment. The selected AEs were ECIs that suggest potential intrusion of REM into either wakefulness or initiation of sleep: cataplexy and sleep onset paralysis.

#### Medication Compliance

Compliance was monitored and determined at each trial visit by interviewing subjects, reviewing e-diary data, counting pills.

#### Ethics

This trial was conducted according to the principles of Good Clinical Practice. An institutional review board reviewed and approved the protocol.

#### Statistical Analysis

##### Efficacy Analysis

Merck used a longitudinal data analysis (LDA) model on the Full Analysis Set (FAS) population to perform the efficacy analyses. The analysis model adjusted for baseline value of the response variable, age group (non-elderly versus elderly), region, gender, treatment, time, and the interaction of treatment by time. To control for type 1 error, Merck analyzed the primary and secondary endpoints using a multiplicity strategy, as follows:

- Bonferroni approach to evaluate two distinct indications – sleep maintenance and sleep onset effects
- Fixed sequential testing procedure to move from the Month 1 set of primary hypotheses to the Month 3 set of primary hypotheses
- Hochberg approach within each time point to evaluate the objective and subjective endpoints

As shown in table 15 below, evaluating two indications required a Bonferroni approach to control the overall Type I error among all primary hypotheses at the two-sided 5% significance level. As a result, endpoints for sleep maintenance effect (sTSTm and WASO) were tested at the two-sided 2.5% level and endpoints for sleep onset effect (sTSOm and LPS) were tested at the two-sided 2.5% level.

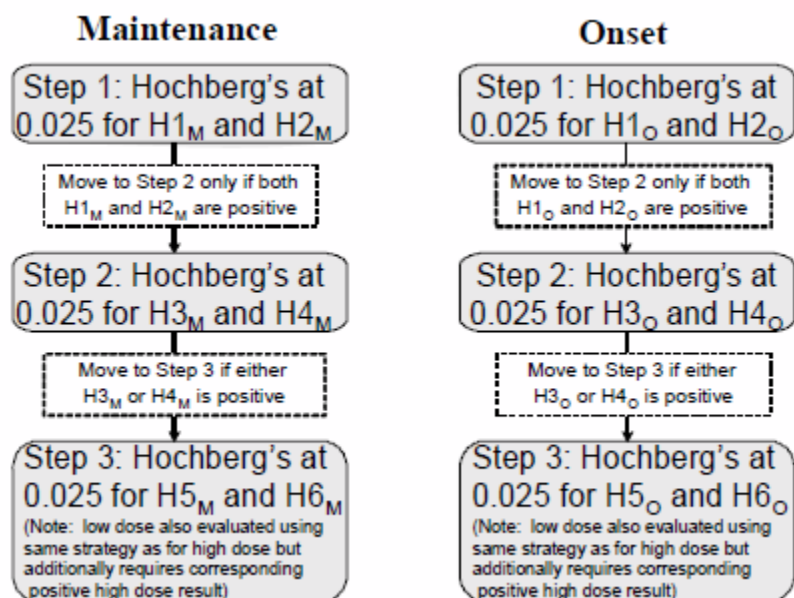
**Table 15: Multiplicity Strategy for Testing Primary and Secondary Hypotheses**

| Dose | Hypotheses | Maintenance ( $\alpha=0.025$ [2-sided]) | Onset ( $\alpha=0.025$ [2-sided])  |
|------|------------|---|------------------------------------|
| High | Primary    | H1 <sub>M</sub> : sTST at Month 1       | H1 <sub>O</sub> : sTSO at Month 1  |
| High | Primary    | H2 <sub>M</sub> : WASO at Month 1       | H2 <sub>O</sub> : LPS at Month 1   |
| High | Primary    | H3 <sub>M</sub> : sTST at Month 3       | H3 <sub>O</sub> : sTSO at Month 3  |
| High | Primary    | H4 <sub>M</sub> : WASO at Month 3       | H4 <sub>O</sub> : LPS at Month 3   |
| High | Secondary  | H5 <sub>M</sub> : sTST at Week 1        | H5 <sub>O</sub> : sTSO at Week 1   |
| High | Secondary  | H6 <sub>M</sub> : WASO at Night 1       | H6 <sub>O</sub> : LPS at Night 1   |
| Low  | Secondary  | H1' <sub>M</sub> : sTST at Month 1      | H1' <sub>O</sub> : sTSO at Month 1 |
| Low  | Secondary  | H2' <sub>M</sub> : WASO at Month 1      | H2' <sub>O</sub> : LPS at Month 1  |
| Low  | Secondary  | H3' <sub>M</sub> : sTST at Month 3      | H3' <sub>O</sub> : sTSO at Month 3 |
| Low  | Secondary  | H4' <sub>M</sub> : WASO at Month 3      | H4' <sub>O</sub> : LPS at Month 3  |
| Low  | Secondary  | H5' <sub>M</sub> : sTST at Week 1       | H5' <sub>O</sub> : sTSO at Week 1  |
| Low  | Secondary  | H6' <sub>M</sub> : WASO at Night 1      | H6' <sub>O</sub> : LPS at Night 1  |

(Source: Sponsor's submission P028 Protocol Page 113 Table 3-6)

Within each indication, a fixed sequential testing procedure was used to move from one time point to the next, for example from the Month 1 set of primary hypotheses to the Month 3 set of primary hypotheses. Then within each time point, a Hochberg approach was used to evaluate the objective and subjective endpoints, as in figure 3 below.

**Figure 3: Hochberg approach for Assessment of Objective and Subjective endpoints**



(Source: Sponsor's submission P028 Protocol Page 113 Figure 3-1)

Note the following:

1. To move sequentially from Month 1 to Month 3, the testing procedure required both the subjective and objective endpoints to be significant. If only one of the endpoints at Month 1 was significant, then that endpoint is declared positive, but the testing procedure for the indication stopped and no further conclusions was made regarding the suvorexant HD effect at Month 3.
2. Statistical significance for suvorexant HD secondary hypotheses within each indication was based on the following: if according to the multiplicity strategy either Month 3 hypothesis was positive, sTSTm or WASO for maintenance indication and sTSOm or LPS for onset indication, then the set of secondary hypotheses (Week 1/Night 1) was tested using a Hochberg approach at the two-sided 2.5% level.
3. Suvorexant LD was compared to placebo within each indication for the primary and secondary endpoints if at least one of the Month 3 endpoints is positive for suvorexant HD. The same multiplicity strategy noted above was used to assess suvorexant LD dose, with the caveat that suvorexant HD was positive for the particular endpoint before suvorexant LD could be declared positive.

Below is a summary of the analyses of the primary and secondary endpoints

**Table 16: Analyses Strategy for Key Efficacy Endpoints**

| Endpoint/Variable<br>(Description, Time Point) | High Dose | Low Dose  |
|--|-----------|-----------|
| <b>Maintenance</b>                             |           |           |
| sTSTm – Change from baseline at Month 1        | Primary   | Secondary |
| WASO – Change from baseline at Month 1         | Primary   | Secondary |
| sTSTm – Change from baseline at Month 3        | Primary   | Secondary |
| WASO – Change from baseline at Month 3         | Primary   | Secondary |
| <b>Onset</b>                                   |           |           |
| sTSOm – Change from baseline at Month 1        | Primary   | Secondary |
| LPS – Change from baseline at Month 1          | Primary   | Secondary |
| sTSOm – Change from baseline at Month 3        | Primary   | Secondary |
| LPS – Change from baseline at Month 3          | Primary   | Secondary |
| <b>Maintenance</b>                             |           |           |
| sTSTm – Change from baseline at Week 1         | Secondary | Secondary |
| WASO – Change from baseline at Night 1         | Secondary | Secondary |
| <b>Onset</b>                                   |           |           |
| sTSOm – Change from baseline at Week 1         | Secondary | Secondary |
| LPS – Change from baseline at Night 1          | Secondary | Secondary |

For all analyses above, the plan was to use the following:  
Statistical Method: Longitudinal data analysis model  
Analysis Population: Full Analysis set  
Missing Data Approach: Model-based

(Source: Sponsor's submission P028 Protocol Page 48 Table 2-3)

The LDA model included region as a covariate, which, in turn, consisted of five groups for the subjective endpoints or four groups for the objective PSG endpoints.

The regions for the subjective endpoints included:

- North America: USA, Canada
- Europe: Denmark, Finland, France, Germany, Spain, Sweden, UK
- Asia, Eastern Europe, Africa: Taiwan, Russia, South Africa
- Japan
- Other: Central and South America: Brazil, Peru

The regions for the objective endpoints included:

- North America: USA, Canada
- Europe: Denmark, Finland, France, Germany, Spain, Sweden, UK
- Asia, Eastern Europe, Africa: Taiwan, Russia, South Africa
- Other: Central and South America: Brazil, Peru

#### Sample Size

Based on the Phase 2 trial P006 experience, Merck determined estimates of standardized effect sizes (SESSs), standard deviation, and deltas for suvorexant HD and suvorexant LD, as shown in table 17 below. Suvorexant LD was assumed to have the same underlying estimates as suvorexant HD.

**Table 17: Underlying Estimates for Suvorexant Compared to Placebo**

| Indication   | Endpoint   | SES <sup>†</sup> | SD <sup>†</sup> | Δ <sup>†</sup> |
|--|------------|------------------|-----------------|----------------|
| Maintenance  | sTSTm (M1) | 0.331            | 42.4            | 14.0           |
|  | WASO (M1)  | 0.421            | 47.9            | 20.2           |
|  | sTSTm (M3) | 0.331            | 42.4            | 14.0           |
|  | WASO (M3)  | 0.421            | 47.9            | 20.2           |
|  | sTSTm (W1) | 0.334            | 39.4            | 13.2           |
|  | WASO (N1)  | 0.757            | 50.1            | 37.9           |
| Onset  | sTSOm (M1) | 0.410            | 26.9            | 11.0           |
|  | LPS (M1)   | 0.285            | 41.5            | 11.8           |
|  | sTSOm (M3) | 0.410            | 26.9            | 11.0           |
|  | LPS (M3)   | 0.285            | 41.5            | 11.8           |
|  | sTSOm (W1) | 0.376            | 19.9            | 7.5            |
|  | LPS (N1)   | 0.501            | 43.9            | 22.0           |
| <sup>†</sup> Standardized Effect Sizes shown are based upon improvement compared to placebo (with respect to change from baseline); SD (adjusted for baseline) and Δ are minutes |            |                  |                 |                |

(Source: Sponsor's submission Trial P028 Protocol 6.10 Page 141 Table 1)

Merck estimated that a total of 960 subjects, 360 subjects in each of the suvorexant HD and placebo groups and 240 in the suvorexant LD group, provided the trial a 91% power to declare all primary maintenance endpoints significant for suvorexant HD compared to placebo, according to the multiplicity strategy. Also, **the trial had a 62% power to declare all primary onset endpoints significant for suvorexant HD compared to placebo**; and, the probability of declaring both Month 1 onset endpoints significant and at least one Month 3 onset endpoint significant was 81%, as shown in table 18 below. Further, to support the PSG endpoints, the power calculations estimated that the PQ cohort include a total of 270 subjects in each of the suvorexant HD and placebo groups, and 180 subjects in the suvorexant LD group.

**Table 18: Power Analyses for Suvorexant HD Primary and Secondary Analyses**

| Indication  | Endpoint   | Standardized effect size <sup>†</sup> | Marginal power <sup>‡</sup> | Multiplicity -adjusted power |                   |
|-------------|------------|---------------------------------------|-----------------------------|------------------------------|-------------------|
|             |            |                                       |                             | Either <sup>§</sup>          | Both <sup>§</sup> |
| Maintenance | sTSTm (M1) | 0.331                                 | 0.976                       |                              |                   |
|             | WASO (M1)  | 0.421                                 | 0.992                       | 0.999                        | 0.969             |
|             | sTSTm (M3) | 0.331                                 | 0.957                       |                              |                   |
|             | WASO (M3)  | 0.421                                 | 0.983                       | 0.967                        | 0.910             |
|             | sTSTm (W1) | 0.334                                 | 0.983                       |                              |                   |
|             | WASO (N1)  | 0.757                                 | 1.000                       | 0.967                        | 0.950             |
| Onset       | sTSOm (M1) | 0.410                                 | 0.999                       |                              |                   |
|             | LPS (M1)   | 0.285                                 | 0.814                       | 0.999                        | 0.813             |
|             | sTSOm (M3) | 0.410                                 | 0.996                       |                              |                   |
|             | LPS (M3)   | 0.285                                 | 0.762                       | 0.811                        | 0.618             |
|             | sTSOm (W1) | 0.376                                 | 0.996                       |                              |                   |
|             | LPS (N1)   | 0.502                                 | 1.000                       | 0.811                        | 0.808             |

<sup>†</sup> SESs shown are based upon improvement compared to placebo (with respect to change from baseline)  
<sup>‡</sup> Based upon a 2.5% (2-sided) t-test for each endpoint within each indication and assuming N=360/270 per group for Questionnaire/PSG endpoints with dropout rates of 5%/1%, 10% and 20% for Week 1/Night 1, Month 1 and Month 3, respectively  
<sup>§</sup> For each indication "Either" refers to either endpoint within a time point declared to be significant according to the multiplicity strategy and "Both" refers to both endpoints within a time point declared to be significant according to the multiplicity strategy (see section 3.5.6 Multiplicity)

(Source: Sponsor's submission Trial P028 Protocol Page 115 Table 3-7)

### Missing Data

Merck used a model-based approach for missing data. The LDA model allowed for the inclusion of subjects with missing data at certain time points. Merck suggested that the LDA model provided valid statistical inference in the presence of possible missing data when the missing data mechanism was missing at random (MAR) or missing completely at random (MCAR). Prior trial results suggested that other reasons for missing data were uncommon. On trial completion, Merck performed no imputation to estimate missing data for evaluation of the primary, secondary and exploratory efficacy endpoints

using the LDA method. The missing data were assumed to be missing at random (MAR).

#### Analysis populations

Merck pre-specified three analyses populations: Full Analysis Set (FAS), the Per-Protocol Populations (PPS), and All-Patients as Treated (APaT) population for safety analysis.

The PSG Full Analysis Set (FAS-PSG) population served as the primary population for the analysis of PSG efficacy data. The FAS-PSG population consisted of all randomized subjects who had the following:

- At least one post-randomization PSG observation after receiving at least one dose of trial treatment
- Baseline data for the analyses that required baseline data

The e-diary Full Analysis Set (FAS–e-diary) population served as the primary population for the analysis of e-diary efficacy data. The FAS–e-diary population consisted of all randomized subjects who had the following:

- At least one post-randomization e-diary observation (i.e., weekly mean) subsequent to administration of at least one dose of study treatment;
- Baseline data for those analyses that require baseline data.

#### Safety Analyses

The APaT population was used for the analysis of safety data. The population consisted of all randomized subjects who received at least one dose of study treatment. Subjects were included in the treatment group based on the actual treatment received.

Further, Merck proposed to evaluate safety using a tiered approach as follows:

Tier 1 safety endpoints were subject to inferential testing for statistical significance with p-values and 95% confidence intervals (CI) to compare treatment groups. The endpoints included: Cataplexy, sleep onset paralysis, suicidal ideation or behaviors, complex sleep-related behaviors, falls, hypnagogic or hypnopompic hallucinations, selected AEs associated with potential for abuse, withdrawal symptoms, residual effect, and rebound insomnia.

Tier 2 safety endpoints were subject to inferential testing for statistical significance with 95% confidence intervals (CI) to compare treatment groups. The endpoints included: Any AE; any serious AE; any drug-related AE; any serious and drug-related AE; discontinuation due to AE; AEs of sleep paralysis or excessive daytime sleepiness; specific AEs, SOC, or pre-defined limit of change (PDLCs) with incidence of four or more subjects in one of the treatment groups; and Tier 1 AEs for the 6 month treatment period.

Tier 3 safety endpoints were subject to descriptive statistics for analysis. The endpoints included: specific AEs, SOCs, or pre-defined limit of change (PDLs) with incidence of fewer than four subjects in all of the treatment groups; and change from baseline results in labs, ECGs, and vital signs.

## **Results:**

### *Protocol Amendments and Changes in Trial Conduct*

Protocol amendments were submitted on 3/31/2010 (Japan-specific protocol), 5/5/2010, and 8/1/2011 (Japan-specific clarification). The amendments included corrections of typographical errors; clarification of the timing of some trial assessments; requirement of informed consent from legal representative such as parents, in addition to subject's, for under 20 years olds in Japan; requirement of 240 Japanese subjects to be randomized in Q-cohort; exclusion of subjects with history of antipsychotics use in Japan; allowed inclusion of subjects on supplement with possible psychotropic effects and on diet pills in Japan; and change of medical expert in Japan. Additional changes in the course of the trial are as follows:

Merck changed the scoring of the PSG endpoints from the conventional Rechtschaffen and Kales scale to the sleep scoring guidelines of the AASM. Consequently, sleep stages N1, N2, N3 sleep were replaced with S1, S2, and SWS (S3/S4), respectively.

Merck performed analysis of sWASOm in a similar fashion as sTSTm to further support the evaluation of sleep maintenance efficacy. With this additional sWASOm analysis, a sleep maintenance efficacy was not attributed completely to improvement in sleep onset.

Prior to treatment unmasking, Merck changed the analyses method for Tier 1 AEs, jettisoning the Cox proportional hazards analysis method for the Miettinen & Nurminen method, because of small numbers of AEs.

When the sum of sTSO, sTST, and sWASO was greater than 24 hours, Merck excluded daily e-diary observations from the calculation of weekly averages.

The Per Protocol analysis excluded subjects recording more than seven days of no sleep during the baseline period or during the Treatment Phase. Also, Merck performed a separate sensitivity analysis that excluded these subjects from the FAS analyses of sTST, sTSO, and sWASO.

Prior to treatment unmasking, Merck changed the day ranges for PSG analysis endpoints from the protocol-specified +/-7 days to +/-10 days from the target Day 30 and Day 89. Merck made this change on observing, during blinded data review, that multiple observations needed to be excluded if these tighter day ranges were retained. To evaluate robustness of results, Merck performed additional analyses on the primary

and secondary hypotheses related to PSG endpoints using the protocol-specified day ranges.

*Reviewer Comment: The changes to the protocol do not appear to affect the overall data interpretation.*

#### *Protocol Violations*

Of 1023 randomized subjects, Merck identified 114 (11.1%) subjects as protocol violators who were subsequently excluded from the per-protocol analysis for efficacy. The protocol violators were identified prior to any treatment unmasking.

Of 1023 subjects randomized to the three treatment groups, one subject, AN 07126, enrolled in more than one suvorexant trial. The subject's data were excluded from all analyses prior to treatment unmasking. Also, the subject reported no AEs.

The most common violation in Trial P028 was from use of prohibited concomitant medication during the core treatment phase (N=33), affecting PSG or e-diary data. In table 19 below, I summarize information on protocol violations in 110 subjects that Merck provided in Protocol Violators Memo Table 1 for Trial P028. Note that multiple violations may have occurred in a subject.

**Table 19: Trial P028 Protocol Violations**

| <b>Protocol Violation</b>   | <b>Action taken for Per Protocol Analysis of efficacy</b>   | <b>Number of Subjects</b> | <b>Data/Time point excluded</b>  |
|---|---|---------------------------|--|
| Incorrect trial medication assignment   | Excluded PSG or e-diary data collected during the period that the subject received the incorrect trial medication   | N=8                       | 2 subjects: PSG and e-diary at Month 3 excluded.<br>6 subjects: Required no exclusion, as medication errors were after Visit 5 |
| Subject randomized more than one suvorexant trial or enrolled multiple times within the same trial                            | In one case with Different-Sequential: "First subject" was included; "Second" subject was excluded.<br><br>In the other case, Different-Overlapping: "Both subjects" are excluded | N=2                       | No exclusion for "First" subject<br><br>All PSG and e-diary entries were excluded.   |
| Exclusion based on high Apnea Hyperpnoea Index or periodic leg movements associated with an arousal per hour of sleep (PLMAs) | Excluded all subject PSG and e-diary data   | N=1                       | All PSG and e-diary entries were excluded  |



|  |  |       |   |
|--|--|-------|---|
| Subjects' e-diary data with >14 consecutive identical e-diary entries based on the morning diary questions related to: sTSO AND sTST | Excluded sTSO, sTST, and sWASO e-diary data corresponding to the primary analysis endpoints<br><br>Excluded entire subject e-diary data if violation occurred at baseline period                         | N=15  | 1 subject: e-diary data at Month 1 excluded.<br>4 subjects: e-diary data at Months 1 and 3 excluded.<br>8 subjects: e-diary data at Month 3 excluded<br><br>2 subjects: all e-diary data excluded |
| Alcohol consumption  | Excluded based on $\geq 6$ drinks per day or $> 20$ drinks per week, or any alcohol on day of PSG visit<br><br>Excluded entire subject e-diary data or PSG data if violation occurred at baseline period | N=24  | 6 subjects: all e-diary data excluded<br><br>5 subjects: all PSG data excluded  |
| Any Caffeine after 6 pm on PSG visits  | Excluded affected subject PSG visit data.<br>Excluded entire subject PSG data if violations on baseline visit.   | N=8   | 5 subjects: all PSG data excluded   |
| Missed trial medication on PSG visit day   | Excluded affected subject PSG visit data   | N=1   | PSG data at Month 3 excluded  |
| Positive urine drug screen at PSG visits   | Excluded affected subject PSG visit data.  | N=1   | PSG data at Month 3 excluded  |
| Trial medication compliance of $< 75\%$ over the first 3 months  | Excluded entire subject PSG and e-diary data   | N=6   | All PSG and e-diary entries were excluded.  |
| Met exclusionary medical history   | Excluded entire subject PSG and e-diary data   | N=3   | All PSG and e-diary entries were excluded.  |
| Insufficient washout phase of prior therapy that may have had an effect on the relief of sleep symptoms                              | Excluded entire subject PSG or e-diary data  | N=6   | All PSG and e-diary entries were excluded.<br><br>Note: 1 subject, AN 7330, had both PSG and e-diary data excluded  |
| Use of prohibited concomitant medication during the core treatment phase of the trial affecting PSG data                             | Excluded affected subject PSG visit data for a prohibited concomitant medication taken within 2 days of or on a PSG visit.<br><br>Excluded entire subject PSG data if violation occurred on              | N= 14 | 3 subjects: all PSG data excluded   |

|  |   |      |  |
|--|---|------|--|
|  | baseline visit  |      |  |
| Use of prohibited concomitant medication during the core treatment phase of the trial affecting e-diary data | Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints  | N=19 | No subject had entire e-diary data excluded. 1 subject had Months 1 and 3 data excluded. |
| No sleep recorded for 7 or more consecutive days   | Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints<br><br>Excluded entire subject e-diary data if violation occurred during baseline period | N=2  | 1 subject had entire e-diary data excluded.  |

(Source: Modified from Sponsor's Submission Trial P028 CSR Appendix 16.2.2.1 Protocol Deviations Memo Page 2)

#### *Disposition in Trial P028*

Trial P028 had 2879 subjects screened for inclusion. A total of 1856 (64.5%) subjects were not randomized mainly because they (92.5%) failed to meet inclusion or exclusion criteria. Of 1023 subjects randomized, one subject was excluded because of multiple trial enrollments as stated above. Exclusion of the subject yielded an All Patients Randomized (APR) set of 1022 subjects: 254 were randomized to suvorexant LD, 383 subjects to suvorexant HD, and 385 to placebo. One subject, AN 07264, who was randomized into placebo group, did not take the assigned treatment. Therefore, 1021 subjects who received at least one dose of trial treatment were evaluated for safety.

Of the randomized 1022 subjects, 916 (89.6%) completed the trial. More subjects discontinued from the placebo group (11.2%) compared to suvorexant LD (9.4%) and suvorexant HD (9.9%). The most common reason for discontinuation in the Treatment Phase, with a similar pattern in both age groups, was because of an AE. Incidences of AEs ranged from 2.4% to 3.9% for suvorexant and 5.5% for placebo. Also, the discontinuation rate among treatment groups was similar for non-elderly and elderly subjects. Table 20 below summarizes subject disposition in Trial P028.

**Table 20: Disposition of Subjects in Trial P028**

|                               | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|-------------------------------|------------------|------------------------|------------------------|----------------|
| <b>Not Randomized</b>         |                  |                        |                        | 1856           |
| <b>Subjects in population</b> | 385              | 254                    | 383                    | 1022           |
| <b>Trial Disposition</b>      |                  |                        |                        |                |
| Not Treated                   | 1 (0.3)          | 0 (0.0)                | 0 (0.0)                | 1 (0.1)        |
| Completed Treatment           | 341 (88.6)       | 230 (90.6)             | 345 (90.1)             | 916 (89.6)     |

|  |            |            |            |            |
|--|------------|------------|------------|------------|
| Discontinued during Treatment            | 43 (11.2)  | 24 (9.4)   | 38 (9.9)   | 105 (10.3) |
| Adverse Event                            | 21 ( 5.5)  | 6 (2.4)    | 15 (3.9)   | 42 ( 4.1)  |
| Withdrawal by Subject                    | 12 ( 3.1)  | 6 (2.4)    | 8 (2.1)    | 26 ( 2.5)  |
| Protocol Violation                       | 1(0.3)     | 5 (2.0)    | 3 (0.8)    | 9 (0.9)    |
| Lost to Follow-up                        | 0 (0.0)    | 1 (0.4)    | 1 (0.3)    | 2 (0.2)    |
| Lack of Efficacy                         | 9 (2.3)    | 1 (0.4)    | 7 (1.8)    | 17 (1.7)   |
| Pregnancy                                | 0 (0.0)    | 1 (0.4)    | 1 (0.3)    | 2 (0.2)    |
| Physician Decision                       | 0 (0.0)    | 4 (1.6)    | 3 (0.8)    | 7 (0.7)    |
| <b>Protocol Milestone</b>                |            |            |            |            |
| Completed Treatment                      | 341 (88.6) | 230 (90.6) | 345 (90.1) | 916 (89.6) |
| Continuing Into Extension                | 151 (39.2) | 100 (39.4) | 172 (44.9) | 423 (41.4) |
| Continuing Into Run-Out                  | 186 (48.3) | 128 (50.4) | 172 (44.9) | 486 (47.6) |
| Not Treated in Run-Out                   | 0 (0.0)    | 0 (0.0)    | 1 (0.3)    | 1 (0.1)    |
| Not Continuing Into Extension Or Run-Out | 4 (1.0)    | 2 (0.8)    | 1 (0.3)    | 7 (0.7)    |
| Discontinued during Treatment            | 43 (11.2)  | 24 (9.4)   | 38 (9.9)   | 105 (10.3) |

(Source: Modified from Sponsor's Submission P028 CSR Page 201 Table 10-3)

Below, I summarize the analysis populations for subjective efficacy endpoints.

**Table 21: Efficacy Analyses Populations All Subjects for Subjective Endpoints**

| Category/Endpoint               | Placebo | Suvorexant LD | Suvorexant HD | Total |
|---------------------------------|---------|---------------|---------------|-------|
| Multiple Enroller               | 0       | 1             | 0             | 1     |
| Number Randomized               | 385     | 254           | 383           | 1022  |
| Number Not Treated              | 1       | 0             | 0             | 1     |
| All Patients Treated Set (APTS) | 384     | 254           | 383           | 1021  |
| <b>sTSTm</b>                    |         |               |               |       |
| Subjects included in FAS        | 382     | 251           | 381           | 1014  |
| <b>sWASOm</b>                   |         |               |               |       |
| Subjects included in FAS        | 381     | 251           | 379           | 1011  |
| <b>sTSOm</b>                    |         |               |               |       |
| Subjects included in FAS        | 382     | 251           | 381           | 1014  |

(Source: Modified from Sponsor's Submission P028 CSR Page 207 Table 10-6)

Below, I summarize the analysis populations for objective efficacy endpoints.

**Table 22: Efficacy Analyses Populations PQ Cohort for Objective Endpoints**

| Category/Endpoint               | Placebo | Suvorexant LD | Suvorexant HD | Total |
|---------------------------------|---------|---------------|---------------|-------|
| Multiple Enroller               | 0       | 1             | 0             | 1     |
| Number Randomized               | 291     | 193           | 291           | 775   |
| Number Not Treated              | 1       | 0             | 0             | 1     |
| All Patients Treated Set (APTS) | 290     | 193           | 291           | 774   |

|                          |     |     |     |     |
|--------------------------|-----|-----|-----|-----|
| <b>WASO</b>              |     |     |     |     |
| Subjects included in FAS | 290 | 193 | 291 | 774 |
| <b>LPS</b>               |     |     |     |     |
| Subjects included in FAS | 290 | 193 | 291 | 774 |

(Source: Modified from Sponsor's Submission P028 CSR Page 211 Table 10-7)

*Reviewer Comment:*

*Overall, close to 90% of subjects completed the trial treatment. Lack of efficacy may have contributed to the small imbalance in discontinuations between the placebo and suvorexant groups. However, the difference in discontinuations does not appear to be large enough to inflate the suvorexant treatment effect.*

*Demographics in Trial P028*

The subject demographics were similar across treatment groups. The subjects' mean age was 56 years, range 18 to 87 years, with 429 (42%) subjects in the elderly age group. About 62% of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race. Below is a summary of subject characteristics in Trial P028.

**Table 23: Subject Characteristics in Trial P028 treatment Phase**

| Category                      | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|-------------------------------|------------------|------------------------|------------------------|----------------|
| <b>Subjects in population</b> | 384              | 254                    | 383                    | 1021           |
| <b>Gender</b>                 |                  |                        |                        |                |
| Male                          | 139 (36.2)       | 92 (36.2)              | 153 (39.9)             | 384 (37.6)     |
| Female                        | 245 (63.8)       | 162 (63.8)             | 230 (60.1)             | 637 (62.4)     |
| <b>Age in years</b>           |                  |                        |                        |                |
| Mean                          | 56               | 55                     | 56                     | 56             |
| SD                            | 15               | 16                     | 15                     | 15             |
| <b>Race</b>                   |                  |                        |                        |                |
| White                         | 244 (63.5)       | 168 (66.1)             | 253 (66.1)             | 665 (65.1)     |
| Black                         | 25 (6.5)         | 15 (5.9)               | 18 (4.7)               | 58 (5.7)       |
| Asian                         | 99 (25.8)        | 66 (26.0)              | 98 (25.6)              | 263 (25.8)     |
| Other                         | 16 (4.2)         | 5 (2.0)                | 14 (3.7)               | 35 (3.4)       |
| <b>Cohort</b>                 |                  |                        |                        |                |
| Q                             | 94 (24.5)        | 61 (24.0)              | 92 (24.0)              | 247 (24.2)     |
| PQ                            | 290 (75.5)       | 193 (76.0)             | 291 (76.0)             | 774 (75.8)     |
| <b>Region</b>                 |                  |                        |                        |                |
| Asia Pacific                  | 2 (0.5)          | 1 (0.4)                | 2 (0.5)                | 5 (0.5)        |
| Central and Eastern Europe    | 0 (0.0)          | 1 (0.4)                | 1 (0.3)                | 2 (0.2)        |
| Central and South America     | 14 (3.6)         | 4 (1.6)                | 15 (3.9)               | 33 (3.2)       |
| Europe                        | 134 (34.9)       | 88 (34.6)              | 135 (35.2)             | 357 (35.0)     |

|                                       |            |            |            |            |
|---------------------------------------|------------|------------|------------|------------|
| Japan                                 | 94 (24.5)  | 61 (24.0)  | 92 (24.0)  | 247 (24.2) |
| Middle East/Africa                    | 15 (3.9)   | 7 (2.8)    | 9 (2.3)    | 31 (3.0)   |
| North America                         | 125 (32.6) | 92 (36.2)  | 129 (33.7) | 346 (33.9) |
| <b>Body Mass Index (BMI) Category</b> |            |            |            |            |
| Underweight (BMI < 18.5)              | 11 (2.9)   | 7 (2.8)    | 14 (3.7)   | 32 (3.1)   |
| Normal range (18.5 ≤ BMI < 25)        | 190 (49.5) | 126 (49.6) | 175 (45.7) | 491 (48.1) |
| Overweight (25 ≤ BMI ≤ 30)            | 132 (34.4) | 91 (35.8)  | 153 (39.9) | 376 (36.8) |
| Obese (BMI > 30)                      | 51 (13.3)  | 30 (11.8)  | 40 (10.4)  | 121 (11.9) |
| Null                                  | 0 (0.0)    | 0 (0.0)    | 1 (0.3)    | 1 (0.1)    |

(Source: Sponsor's Submission P028 CSR Page 215 Table 10-8)

The baseline values of the efficacy endpoints were comparable across treatment groups. Below is a summary of the mean values of the efficacy endpoints at baseline.

**Table 24: Mean Values of Efficacy Endpoints in Minutes at Baseline**

| Endpoint | Placebo | Suvorexant LD | Suvorexant HD |
|----------|---------|---------------|---------------|
| sTSTm    | 315.7   | 322.4         | 316.1         |
| sTSOm    | 66.9    | 63.3          | 68.0          |
| sWASOm   | 78.2    | 73.9          | 78.4          |
| WASO     | 114.9   | 119.2         | 117.7         |
| LPS      | 66.2    | 68.9          | 61.8          |

(Source: Sponsor's Submission P028 CSR Page 231 Table 10-11)

Across treatment groups, subjects had comparable medical history and concomitant medications. Many subjects had history of at least one medical condition: 78.1% (300/384) in placebo, 79.5% (202/254) in suvorexant LD, and 78.6% (301/383) in suvorexant HD groups. Consistent with the medical history, many subjects were on concomitant medications: 60.7% (233/384) in the placebo group, 67.7% (172/254) in the suvorexant LD group, and 64.0% (245/383) in the suvorexant HD group. The most common medications were analgesics, vitamins, and lipid modifying agents.

*Reviewer Comment:*

*Overall, the subjects' demographic and baseline data appear similar across treatment groups. However, there are small numerical differences in baseline values of the efficacy variables across treatment groups. These differences can over time lead to outcome results that give an appearance of meaningful treatment effect.*

*Treatment Compliance in Trial P028*

Measurement of treatment compliance involved pill counts and medication records that were reported in the electronic data capture system (EDC). Compliance was high across treatment groups. About 95% or more of the subjects showed compliance of between 90% and 100% in the percentage of compliant days on therapy, with a mean

compliance rate of at least 98% in all treatment groups. Subjects who showed less than 80% compliance were 0.8 % (3/384) of the placebo group, 0.4% (1/254) of the suvorexant LD group, and 2.1% (8/383) of the suvorexant HD group.

#### *Efficacy*

The efficacy results are reviewed under section 4.1.4 of this report.

#### *Safety*

The results of safety are reviewed as part of the pooled analyses of safety in section 5.

### 3.3.3 Phase 3 Confirmatory Efficacy Trial P029

#### **Administrative Information for Trial P029**

- **Trial Title:** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia – Study B
- **Trial Treatment Dates:** 07/28/2010 to 10/26/2011
- **Trial Sites:** Multicenter with 37 United States (US) and 67 Ex-US centers: Australia (2), Brazil (2), Canada (6), Denmark (2), Finland (2), France (6), Germany (8), India (5), Italy (4), Mexico (3), Peru (5), Poland (5), Republic of Korea (6), Russian Federation (2), South Africa (2), Spain (3), Sweden (3), and United Kingdom (1)
- **Trial Report Date:** 07/10/2012

#### **Objectives and Rationale**

- Similar to Trial P028, Trial P029's objective was to evaluate, in subjects with primary insomnia, efficacy of suvorexant HD compared with placebo in improving sleep maintenance and onset at Months 1 and 3, using subjective patient-reported outcomes and objective PSG assessments; and to assess the safety and tolerability of suvorexant for up to 3 months of treatment.

#### **Trial Design and Conduct**

##### *Trial P029 Overview*

The design of trial P029 was identical to P028, except that P029 reduced its scope of secondary endpoints, and had no extension phase. All secondary endpoints in Trial P029 compared suvorexant HD and placebo, excluding suvorexant LD. Merck compared suvorexant LD and placebo groups, outside the multiplicity strategy, on all efficacy endpoints. Therefore, the secondary endpoints for Trial P029 included the following parameters:

##### Maintenance:

- Suvorexant HD: Change from baseline sTSTm at Week 1.
- Suvorexant HD: Change from baseline in WASO at Night 1.

##### Onset:

- Suvorexant HD: Change from baseline in sTSOm at Week 1.
- Suvorexant HD: Change from baseline in LPS at Night 1.

Other aspects of trial P029 that were identical to P028 include trial conduct, inclusion and exclusion criteria, medication restrictions, endpoints, and statistical analysis plan.

## Results:

### *Protocol Amendments and Changes in Trial Conduct*

In addition to some of the protocol changes made that were similar to trial P028, two trial sites, #58 and #120, were closed because of GCP noncompliance issues. Site 58 screened five subjects but none of them received trial medication. Site 120 screened 32 subjects and randomized 18 subjects. Among the issues detected with Site 120 included alteration of trial records.

Merck performed efficacy analyses using the Full Analysis Set (FAS) excluding Site 120 as the primary population. They also performed a sensitivity analysis on the FAS with Site 120 included. The primary safety population was the All Patients as Treated Set (ApaT) with Site 120 included; a sensitivity analysis on the ApaT excluded Site 120.

### *Protocol Violations in Trial P029*

Of 1021 randomized allocations, Merck identified 116 (11.4%) subjects as protocol violators who were subsequently excluded from the per-protocol analysis for efficacy. The protocol violators were identified prior to any treatment unmasking. Two randomized allocations were excluded because one subject had received 2 allocations, AN 12009 and AN 12299; so the second allocation for this subject, AN 12299, was excluded. The other exclusion was for another subject AN 12060 who was simultaneously enrolled in another suvorexant trial. As a result, Trial P029 randomized 1019 subjects.

The most common violations in Trial P029 were related to alcohol use during the core treatment phase (N=31), affecting PSG or e-diary data. Exclusions of all e-diary data of a subject occurred the most when the subject had more than 14 consecutive identical e-diary entries based on the morning diary questions related to sTSO AND sTST (N=15), or when the subject recorded no sleep for 7 or more consecutive days (N=16). In the table below, I summarize information on protocol violations that Merck provided in Protocol Violators Memo Table 1 for Trial P029. Note that multiple violations may have occurred in a subject.

**Table 25: Trial P029 Protocol Violations**

| Protocol Violation                    | Action taken for Per Protocol Analysis of efficacy            | Number of Subjects | Data/Time point excluded                      |
|---------------------------------------|---|--------------------|---|
| Incorrect trial medication assignment | Excluded PSG or e-diary data collected during the period that | N=5                | 2 subjects: e-diary data at Month 3 excluded. |

|  |   |      |   |
|--|---|------|---|
|  | the subject received the incorrect trial medication   |      | 3 subjects: Required no exclusion, as medication errors were Run-out phase  |
| Subject randomized more than one suvorexant trial or enrolled multiple times within the same trial   | In 2 cases, Same-Sequential entries: "Both subjects" were excluded<br><br>In one case, Different-Sequential: "First subject" was included; "Second" subject was excluded.<br><br>In another case, Different-Overlapping: "Both subjects" are excluded | N=4  | All PSG and e-diary entries were excluded for repeat entries.   |
| The LPS was $\leq 20$ minutes at screening PSG visit 2 or at baseline PSG visit 2a.  | Excluded all PSG records  | N=2  | All PSG entries were excluded   |
| The WASO was $\leq 45$ minutes at screening PSG Visit 2 or at baseline PSG visit 2a or the WASO $< 60$ minutes on the combined screening PGS visits 2 & 2a | Excluded all PSG records  | N=1  | All PSG entries were excluded   |
| Exclusion based on high Apnea Hyperpnoea Index or periodic leg movements associated with an arousal per hour of sleep (PLMAs)                              | Excluded all subject PSG and e-diary data   | N=1  | All PSG and e-diary entries were excluded   |
| Subject had $\text{sTST} \geq 6.5$ hours on $\geq 4$ nights for the week prior to Visit 3, based on morning e-diary  | Excluded all subject e-diary data   | N=2  | All e-diary entries were excluded   |
| Subject had $\text{sTSO} < 30$ minutes on $\geq 4$ nights for the week prior to visit 3, based on morning e-diary  | Excluded all subject e-diary data   | N=3  | All e-diary entries were excluded   |
| Subjects' e-diary data with $> 14$ consecutive identical e-diary entries based on the morning diary questions related to: $\text{sTSO}$ AND $\text{sTST}$  | Excluded $\text{sTSO}$ , $\text{sTST}$ , and $\text{sWASO}$ e-diary data corresponding to the primary analysis endpoints  | N=24 | 3 subjects: e-diary data at Month 1 excluded.<br>4 subjects: e-diary data at Month 3 excluded<br>2 subjects: e-diary data at Months 1 and 3 excluded. |



|  |  |      |  |
|--|--|------|--|
|  | Excluded entire subject e-diary data if violation occurred at baseline period  |      | 15 subjects: all e-diary data excluded   |
| Alcohol consumption  | Excluded based on $\geq 6$ drinks per day or $> 20$ drinks per week, or any alcohol on day of PSG visit<br><br>Excluded entire subject e-diary data or PSG data if violation occurred at baseline period | N=31 | 6 subjects: all e-diary data excluded<br><br>5 subjects: all PSG data excluded     |
| Any Caffeine after 6 pm on PSG visits  | Excluded affected subject PSG visit data.<br>Excluded entire subject PSG data if violations on baseline visit.   | N=13 | 7 subjects: all PSG data excluded  |
| Missed trial medication on PSG visit day   | Excluded affected subject PSG visit data   | N=1  | PSG data at Month 3 excluded.  |
| Positive urine drug screen at PSG visits   | Excluded affected subject PSG visit data.  | N=3  | PSG data at Month 3 excluded   |
| Trial medication compliance of $< 75\%$ over the first 3 months  | Excluded entire subject PSG and e-diary data   | N=6  | All PSG and e-diary entries were excluded.   |
| Met exclusionary medical history   | Excluded entire subject PSG and e-diary data   | N=4  | All PSG and e-diary entries were excluded.   |
| Insufficient washout phase of prior therapy that may have had an effect on the relief of sleep symptoms      | Excluded entire subject PSG or e-diary data  | N=2  | All PSG or all e-diary entries as appropriate were excluded.                       |
| Use of prohibited concomitant medication during the core treatment phase of the trial affecting PSG data     | Excluded affected subject PSG visit data for a prohibited concomitant medication taken within 2 days of or on a PSG visit.   | N= 2 | 1 subject: PSG data at Month 1 excluded<br>1 subject: PSG data at Month 3 excluded |
| Use of prohibited concomitant medication during the core treatment phase of the trial affecting e-diary data | Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints   | N=8  | 4 subjects had Month 1 data excluded.<br>4 subjects had Month 3 data excluded.     |

|  |   |      |   |
|--|---|------|---|
| No sleep recorded for 7 or more consecutive days | Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints<br><br>Excluded entire subject e-diary data if violation occurred during baseline period | N=17 | 1 subject had Month 1 data excluded.<br><br>16 subjects had entire e-diary data excluded. |
|--|---|------|---|

(Source: Modified from Sponsor's Submission Trial P029 CSR Appendix 16.2.2.1 Protocol Deviations Memo Pages 2-8)

### Disposition in Trial P029

Trial P029 had 2876 subjects screened for inclusion. A total of 1856 (64.5%) subjects were not randomized mainly because they (89.4%) failed to meet inclusion or exclusion criteria. Of the remaining, one subject was excluded because of a simultaneous enrollment in another suvorexant trial. Another subject had two allocation numbers, prompting exclusion of one. These exclusions resulted in 1019 randomized subjects: 240 were randomized to suvorexant LD, 392 subjects to suvorexant HD, and 387 to placebo. A total of 1009 subjects received at least one dose of trial treatment were evaluated for safety.

Of the randomized 1019 subjects, 881 (86.4%) completed the trial. Subjects who discontinued were 13.7% (53/387) of the placebo group, 14.2% (34/240) of suvorexant LD, and 10.5% (41/392) of suvorexant HD. The most common reason for discontinuation in the Treatment Phase, with a similar pattern in both non-elderly and elderly age groups, was because of an AE. The discontinuation rate was similar across treatment groups. Table 26 below summarizes subject disposition in Trial P029.

**Table 26: Disposition of Subjects in Trial P029**

|                               | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|-------------------------------|------------------|------------------------|------------------------|----------------|
| <b>Not Randomized</b>         |                  |                        |                        | 1856           |
| <b>Subjects in population</b> | 387              | 240                    | 392                    | 1019           |
| <b>Trial Disposition</b>      |                  |                        |                        |                |
| Not Treated                   | 4 (1.0)          | 1 (0.4)                | 5 (1.3)                | 10 (1.0)       |
| Completed Treatment           | 330 (85.3)       | 205 (85.4)             | 346 (88.3)             | 881 (86.5)     |
| Discontinued during Treatment | 53 (13.7)        | 34 (14.2)              | 41 (10.5)              | 128 (12.6)     |
| Adverse Event                 | 17 (4.4)         | 10 (4.2)               | 19 (4.8)               | 46 (4.5)       |
| Withdrawal by Subject         | 19 (4.9)         | 8 (3.3)                | 9 (2.3)                | 36 (3.5)       |
| Protocol Violation            | 8 (2.1)          | 5 (2.1)                | 4 (1.0)                | 17 (1.7)       |
| Lost to Follow-up             | 1 (0.3)          | 2 (0.8)                | 4 (1.0)                | 7 (0.7)        |

|                               |            |            |            |            |
|-------------------------------|------------|------------|------------|------------|
| Lack of Efficacy              | 8 (2.1)    | 7 (2.9)    | 4 (1.0)    | 19 (1.9)   |
| Physician Decision            | 0 (0.0)    | 2 (0.8)    | 1 (0.3)    | 3 (0.3)    |
| <b>Protocol Milestone</b>     |            |            |            |            |
| Completed Treatment           | 330 (85.3) | 205 (85.4) | 346 (88.3) | 881 (86.5) |
| Continuing Into Run-Out       | 327 (84.5) | 205 (85.4) | 344 (87.8) | 876 (86.0) |
| Not Treated in Run-Out        | 3 (0.8)    | 0 (0.0)    | 2 (0.5)    | 5 (0.5)    |
| Discontinued during Treatment | 53 (13.7)  | 34 (14.2)  | 41 (10.5)  | 128 (12.6) |

(Source: Modified from Sponsor's Submission P029 CSR Page 159 Table 10-3)

Below, I summarize the analysis populations for subjective efficacy endpoints.

**Table 27: Efficacy Analyses Populations All Subjects for Subjective Endpoints**

| Category/Endpoint               | Placebo | Suvorexant LD | Suvorexant HD | Total |
|---------------------------------|---------|---------------|---------------|-------|
| Multiple Enroller               | 2       | 0             | 0             | 2     |
| Number Randomized               | 387     | 240           | 392           | 1019  |
| Number Not Treated              | 4       | 1             | 5             | 10    |
| All Patients Treated Set (APTS) | 383     | 239           | 387           | 1009  |
| <b>sTST</b>                     |         |               |               |       |
| Subjects included in FAS        | 369     | 231           | 379           | 979   |
| <b>sWASOm</b>                   |         |               |               |       |
| Subjects included in FAS        | 361     | 226           | 375           | 962   |
| <b>sTSOm</b>                    |         |               |               |       |
| Subjects included in FAS        | 369     | 231           | 379           | 979   |

(Source: Modified from Sponsor's Submission P029 CSR Page 164 Table 10-6)

Below, I summarize the analysis populations for objective efficacy endpoints.

**Table 28: Efficacy Analyses Populations PQ Cohort for Objective Endpoints**

| Category/Endpoint               | Placebo | Suvorexant LD | Suvorexant HD | Total |
|---------------------------------|---------|---------------|---------------|-------|
| Multiple Enroller               | 2       | 0             | 0             | 2     |
| Number Randomized               | 299     | 150           | 302           | 751   |
| Number Not Treated              | 2       | 0             | 3             | 5     |
| All Patients Treated Set (APTS) | 290     | 193           | 291           | 774   |
| <b>WASO</b>                     |         |               |               |       |
| Subjects included in FAS        | 286     | 145           | 294           | 725   |
| <b>LPS</b>                      |         |               |               |       |
| Subjects included in FAS        | 286     | 145           | 294           | 725   |

(Source: Modified from Sponsor's Submission P029 CSR Page 168 Table 10-7)

*Reviewer Comment:*

*Overall, about 87% of subjects completed the trial treatment. More subjects withdrew from the placebo group compared to the suvorexant groups. The difference in discontinuations is unlikely to inflate the suvorexant treatment effect.*

Demographics

*Demographics in Trial P029*

The subject demographics were similar across treatment groups. The subjects' mean age was 56 years, range 18 to 86 years, with 410 (40.6%) subjects in the elderly age group. About 67% (671/1009) of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race (80.2%, 809/1009). Below is a summary of subject characteristics in Trial P029.

**Table 29: Subject Characteristics in Trial P029 treatment Phase**

| Category                                  | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|---|------------------|------------------------|------------------------|----------------|
| <b>Subjects in population</b>             | 383              | 239                    | 387                    | 1009           |
| <b>Gender</b>                             |                  |                        |                        |                |
| Male                                      | 136 (35.5)       | 82 (34.3)              | 120 (31.0)             | 338 (33.5)     |
| Female                                    | 247 (64.5)       | 157 (65.7)             | 267 (69.0)             | 671 (66.5)     |
| <b>Age in years</b>                       |                  |                        |                        |                |
| Mean                                      | 57               | 56                     | 57                     | 56             |
| SD  | 15               | 16                     | 15                     | 15             |
| <b>Race</b>                               |                  |                        |                        |                |
| White                                     | 309 (80.7)       | 190 (79.5)             | 310 (80.1)             | 809 (80.2)     |
| Black                                     | 21 (5.5)         | 4 (1.7)                | 20 (5.2)               | 45 (4.5)       |
| Asian                                     | 25 (6.5)         | 27 (11.3)              | 26 (6.7)               | 78 (7.7)       |
| Other                                     | 28 (7.3)         | 18 (7.5)               | 31 (8.0)               | 77 (7.6)       |
| <b>Cohort</b>                             |                  |                        |                        |                |
| Q   | 86 (22.5)        | 89 (37.2)              | 88 (22.7)              | 263 (26.1)     |
| PQ  | 297 (77.5)       | 150 (62.8)             | 299 (77.3)             | 746 (73.9)     |
| <b>Region</b>                             |                  |                        |                        |                |
| Asia Pacific                              | 25 (6.5)         | 25 (10.5)              | 25 (6.5)               | 75 (7.4)       |
| Central and Eastern Europe                | 29 (7.6)         | 16 (6.7)               | 16 (4.1)               | 61 (6.0)       |
| Central and South America                 | 28 (7.3)         | 23 (9.6)               | 32 (8.3)               | 83 (8.2)       |
| Europe                                    | 113 (29.5)       | 77 (32.2)              | 115 (29.7)             | 305 (30.2)     |
| North America                             | 188 (49.1)       | 98 (41.0)              | 199 (51.4)             | 485 (48.1)     |
| <b>Body Mass Index (BMI)<br/>Category</b> |                  |                        |                        |                |

|                                 |           |            |           |           |
|---------------------------------|-----------|------------|-----------|-----------|
| Underweight (BMI < 18.5)        | 5(1.3)    | 4 (1.7)    | 4(1.0)    | 13(1.3)   |
| Normal range (18.5 <= BMI < 25) | 161(42.0) | 106 (44.4) | 148(38.2) | 415(41.1) |
| Overweight (25 <= BMI <= 30)    | 157(41.0) | 103 (43.1) | 164(42.4) | 424(42.0) |
| Obese (BMI > 30)                | 59(15.4)  | 26 (10.9)  | 71(18.3)  | 156(15.5) |
| Null                            | 1(0.3)    | 0 (0.0)    | 0(0.0)    | 1(0.1)    |

(Source: Sponsor's Submission P029 CSR Page 172 Table 10-8)

The baseline values of the efficacy endpoints were comparable across treatment groups. Below is a summary of the mean values of the efficacy endpoints at baseline.

**Table 30: Baseline Mean and Range of Values for Efficacy Endpoints in Minutes**

| Endpoint | Placebo              | Suvorexant LD        | Suvorexant HD        |
|----------|----------------------|----------------------|----------------------|
| sTSTm    | 309.7 (0.0 - 483.4)  | 298.3 (0.0 - 512.9)  | 315.3 (0.0 - 502.6)  |
| sTSOm    | 81.3 (5.7 - 480.0)   | 86.0 (10.0 - 480.0)  | 74.4 (5.7 - 480.0)   |
| sWASOm   | 83.3 (0.0 - 343.6)   | 84.8 (0.0 - 303.0)   | 82.1 (0.0 - 279.1)   |
| WASO     | 118.4 (45.5 - 317.0) | 119.6 (46.0 - 332.5) | 119.4 (47.0 - 309.0) |
| LPS      | 68.0 (20.5 - 252.0)  | 65.3 (3.5 - 245.0)   | 67.3 (20.5 - 386.5)  |

(Source: Sponsor's Submission P029 CSR Page 182 Table 10-10)

Age group differences in baseline efficacy measures showed mean WASO values at baseline were about 20 minutes longer and mean sTSOm was 10 to 20 minutes shorter for elderly compared to non-elderly subjects. However, the efficacy measures at baseline were generally comparable across treatment groups within each age group.

Also, there were differences between the PQ- and Q-Cohort in baseline subjective efficacy measures: the mean sTST values at baseline were about 60 minutes shorter, and the mean sTSO values were about 40 to 50 minutes longer in the Q-Cohort compared to the PQ-Cohort.

Across treatment groups, subjects had comparable medical history and concomitant medications. Many subjects had history of at least one medical condition: 79.6% (305/383) in placebo group, 74.1% (177/239) in suvorexant LD group, and 79.8% (309/387) in suvorexant HD group. Subjects on concomitant medications were 64.5% (247/383) in the placebo group, 53.1% (127/239) in suvorexant LD group, and 63.0% (244/387) in suvorexant HD group. The most common medications were analgesics, lipid modifying agents, agents acting on the renin-angiotensin system, anti-inflammatory, and anti-rheumatic products.

*Reviewer Comment:*

*Overall, the subjects' demographic and baseline data appear similar across treatment groups. The small numerical differences in baseline values of the efficacy variables across treatment groups can translate to meaningful effects in the eventual outcome*

*over time. This further justifies the need to account for baseline values in the final outcome analyses.*

#### *Treatment Compliance in Trial P029*

Compliance was high across treatment groups. About 97% or more of the subjects showed compliance of between 90% and 100% in the percentage of compliant days on therapy, with a mean compliance rate of at least 98% in all treatment groups. Subjects who showed compliance rates of 80% or less were 1.0 % (4/383) of the placebo group, 0.8% (2/239) of the suvorexant LD group, and 0.8% (3/387) of the suvorexant HD group.

#### *Efficacy*

The efficacy results are reviewed under section 4.1.4 of this report.

#### *Safety*

The results of safety are reviewed as part of the pooled analyses of safety in section 5.

### 3.3.4 Phase 3 Long-term Safety Trial P009

#### **Administrative Information for Trial P009**

- **Trial Title:** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Long Term Safety Study of MK-4305 in Patients with Primary Insomnia
- **Trial Treatment Dates:** 12/28/2009 to 08/01/2011
- **Trial Sites:** Multicenter (106) in the United States (48), Australia (3), Belgium (4), Canada (4), Colombia (2), Denmark (5), Finland (3), France (4), Germany (3), Hungary (3), Mexico (1), South Africa (9), Spain (6), Sweden (3), and United Kingdom (8)
- **Trial Report Date:** 06/11/2012

#### **Objectives**

The primary objective of P009 was to evaluate safety and tolerability of suvorexant for up to 12 months of treatment.

The secondary objective was to evaluate the efficacy of suvorexant compared with placebo in improving insomnia during the first month of treatment; the improvement was measured by change from baseline in the average of weekly measurements of the subjective variables, sTST and sTSO. To achieve the trial's secondary objectives, the sponsor tested the hypotheses that suvorexant was superior to placebo in improving insomnia during the first month of treatment, using measurements of sTST and sTSO.

Exploratory objectives were to evaluate the following: the efficacy endpoints after 4 to 6 months of trial treatment, other sleep endpoints beyond 1 month of treatment, Clinical Global Impressions-Improvement (CGI-I), Patient Global Impressions-Improvement

(PGI-I), improving symptoms of depression by assessing the Quick Inventory of Depressive Symptomatology (QIDS-SR16) total score after 6 months of treatment, time to trial treatment discontinuation, and relapse of insomnia during the trial's run-out period.

## **Trial Design and Conduct**

### *Trial P009 Overview*

This was a 12-month, randomized, double-blind, placebo-controlled, parallel group, multi-center trial to assess long-term safety of suvorexant HD in subjects with primary insomnia. The trial had a screening phase preceding the 12-month treatment phase. A 2-month, double-blind run-out phase followed the treatment phase.

About 750 subjects were planned to enter the trial. The subjects were males and females, aged 18 years or older. Elderly subjects older than 65 years were included if they scored 25 or higher on the Mini Mental State Examination (MMSE). Women of reproductive potential needed to have a serum hCG level consistent with the non-gravid state at screening visit 1, and agree to use acceptable contraception during the trial.

The trial excluded subjects with narcolepsy, other neurological disorders, and psychiatric disorders requiring ongoing treatment. Also excluded were subjects with history of malignancy within 5 years of trial screening, except if the malignancy was adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer. Other exclusionary criteria were similar to those of the other phase 3 efficacy trials.

The trial had eighteen visits: screening phase Visits 1 to 3, treatment phase visits 4 to 16, and run-out phase Visits 17 to 18. The screening phase included a 1-week single-blind placebo run-in that commenced at Visit 2. At Visit 3, the subjects were randomized in a 2:1 ratio to receive either suvorexant HD (high dose) or placebo once daily at bedtime during the 12-month double-blind treatment phase, which ended at Visit 16. The subjects were stratified by age group, elderly and non-elderly, and by region. The goal was to have 50% of the subjects in each age group.

Subjects randomized to suvorexant were, at the same time, randomized in a 1:1 ratio to receive suvorexant HD or placebo during the run-out phase. Those randomized to placebo at trial beginning continued placebo during the run-out phase. As in other phase 3 trials, suvorexant HD was suvorexant 40 mg in non-elderly subjects and suvorexant 30 mg in elderly subjects.

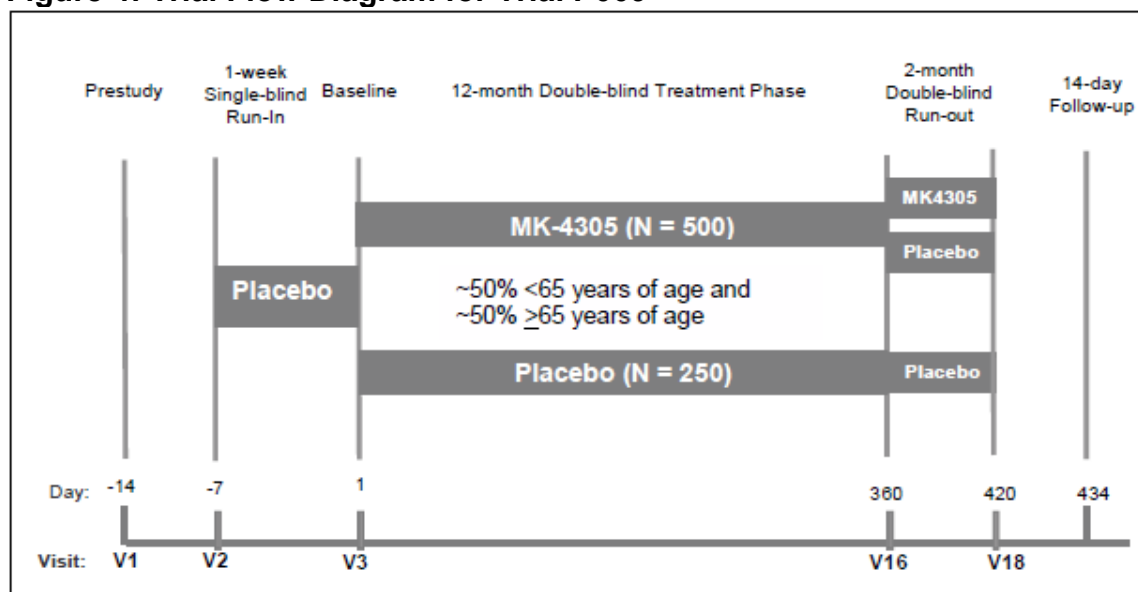
During the treatment phase, subjects returned to the clinic after randomization, at 2-week intervals during the first month, and at Months 3, 6, 9 and 12.

Subjects completed morning and evening questionnaires on e-diary. This was done daily from pre-trial Visit 1 to Visit 5, the end of Month 1. Subsequently, the subjects completed the questionnaire every month for 11 mornings and evenings, that is 5 days before and 5 days after the targeted trial day for a visit or telephone contact, until the

end of month 10 telephone contact. From Month 11, the subjects recommenced daily morning and evening e-diary from 5 days prior to the end of month 11 targeted telephone contact until the end of the trial at Visit 18, the end of run-out phase.

The Tyrer Withdrawal Symptom Questionnaire (WSQ) was administered to subjects, prior to dosing, at Visit 3 and for 3 consecutive evenings. The WSQ was repeated, prior to dosing, for 4 evenings at the targeted end of month 11 telephone contact. Again, it was repeated, prior to dosing, at Visit 16, the evening of the end of Month 12, and for 3 consecutive evenings. Below is the trial flow diagram showing the trial phases and visits.

**Figure 4: Trial Flow Diagram for Trial P009**



(Source: Sponsor's submission P009 Protocol Page 20)

The table below summarizes the trial schedule and assessments for Trial P009.



**Table 31: Trial P009 Schedule of Assessments**

| Treatment Period  | Screening Phase |              |                                    |             | Double-Blind Treatment Phase |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  | Run-Out |  |
|---|-----------------|--------------|------------------------------------|-------------|------------------------------|-----------------------|-------------|------------------------|------------------------|-------------|------------------------|------------------------|-------------|-------------------------|-------------------------|------------------|------------------|--|---------|--|
|   | Prestudy        | Start Run-in | Baseline <sup>10)</sup> /Randomize | End of Wk 2 | End of Mo 1                  | Phone Call End of Mo2 | End of Mo 3 | Phone Call End of Mo 4 | Phone Call End of Mo 5 | End of Mo 6 | Phone Call End of Mo 7 | Phone Call End of Mo 8 | End of Mo 9 | Phone Call End of Mo 10 | Phone Call End of Mo 11 | End of Mo 12     | End of Mo 13     | End of Mo 14 <sup>11)</sup> /Discon <sup>11)</sup> |         |  |
| Visit Number  | 1               | 2            | 3                                  | 4           | 5                            | 6                     | 7           | 8                      | 9                      | 10          | 11                     | 12                     | 13          | 14                      | 15                      | 16               | 17               | 18   |         |  |
| Target Study Day <sup>1)</sup>  | -14             | -7           | 1                                  | 15          | 30                           | 60                    | 90          | 120                    | 150                    | 180         | 210                    | 240                    | 270         | 300                     | 330                     | 360              | 390              | 420  |         |  |
| Allowed Visit Window <sup>12)</sup>   |                 | ±5           | +3/-2                              | ±3          | ±3                           | ±5                    | ±5          | ±5                     | ±5                     | ±5          | ±5                     | ±5                     | ±5          | ±5                      | ±5                      | ±5               | ±5               | ±3   |         |  |
| Informed consent  | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Informed consent for optional Specimens for Genetic & Other Biomedical Research analysis <sup>13)</sup> |                 |              | X                                  |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Medical/psychiatric history   | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Diagnostic Interview/Sleep History/DSM-IV-TR  | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| MDI/Neuropsychiatric interview  | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Reading Assessment <sup>14)</sup>   | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Columbia Suicide Severity Rating Scale (C-SSRS) <sup>15)</sup>  | X               | X            | X                                  | X           | X                            | X                     | X           |                        |                        | X           |                        |                        | X           |                         |                         | X                | X                | X  |         |  |
| Quick Inventory of Depressive Symptomatology (QIDS-SR16)  | X               |              | X                                  |             | X                            |                       | X           |                        |                        | X           |                        |                        | X           |                         |                         | X                | X                | X  |         |  |
| Mini Mental State Examination (MMSE) <sup>17)</sup>   | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Inclusion/exclusion criteria  | X               | X            | X                                  |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Prior/concomitant medications   | X               | X            | X                                  | X           | X                            | X                     | X           | X                      | X                      | X           | X                      | X                      | X           | X                       | X                       | X                | X                | X  |         |  |
| Physical Examination <sup>18)</sup>   | X               |              |                                    |             | X                            |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  | X                | X  |         |  |
| Vital signs <sup>19)</sup> , height <sup>20)</sup> , weight <sup>21)</sup>                              | X               | X            | X                                  | X           | X                            |                       | X           |                        |                        | X           |                        |                        | X           |                         |                         |                  | X                | X  |         |  |
| ECG   | X               |              | X                                  |             | X                            | X                     |             | X                      |                        | X           |                        |                        | X           |                         |                         |                  | X                | X  |         |  |
| Hematology, chemistry and urine pregnancy test <sup>1,21,22)</sup>                                      | X               |              | X <sup>23)</sup>                   | X           | X                            |                       |             |                        |                        | X           |                        |                        | X           |                         |                         |                  | X                | X  |         |  |
| Urine drug screen   | X               | X            | X                                  |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Optional Specimens for Genetic and Other Biomedical Research <sup>13)</sup>                             |                 |              | X                                  |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Blood sample for HLA-DQB1 genotyping (DNA) <sup>14)</sup>   |                 |              | X                                  |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| Pharmacokinetic (PK) Sampling <sup>24)</sup>  | X               |              |                                    | X           | X                            |                       | X           |                        |                        | X           |                        |                        |             |                         |                         |                  |                  | X <sup>25)</sup>                                   |         |  |
| CGI-S & CGI-I <sup>26)</sup>  | X               |              | X                                  | X           | X                            |                       | X           |                        |                        | X           |                        |                        |             |                         |                         | X                | X                | X  |         |  |
| PGI-S & PGI-I <sup>26)</sup>  | X               |              | X                                  | X           | X                            |                       | X           |                        |                        | X           |                        |                        |             |                         |                         | X                | X                | X  |         |  |
| IVRS call   | X               | X            | X                                  | X           | X                            |                       | X           |                        |                        | X           |                        |                        | X           |                         |                         | X                | X                | X  |         |  |
| Dispense Study Medication   |                 | X            | X                                  | X           | X                            |                       | X           |                        |                        | X           |                        |                        | X           |                         |                         | X                | X                | X  |         |  |
| Study Medication Compliance <sup>24)</sup>  |                 |              | X                                  | X           | X                            |                       | X           |                        |                        | X           |                        |                        | X           |                         |                         | X                | X                | X  |         |  |
| Insomnia Severity Index (ISI)   |                 |              | X                                  |             | X                            |                       | X           |                        |                        | X           |                        |                        |             |                         |                         | X <sup>28)</sup> | X <sup>28)</sup> | X <sup>11)</sup>                                   |         |  |
| Motor Vehicle Accidents and Violations (MVA/V)  |                 | X            | X                                  | X           | X                            | X                     | X           | X                      | X                      | X           | X                      | X                      | X           | X                       | X                       | X                | X                | X  |         |  |
| Electronic morning diary <sup>27)</sup>   | X               | X            | X                                  | X           | X                            | X                     | X           | X                      | X                      | X           | X                      | X                      | X           | X                       | X                       | X                | X                | X  |         |  |
| Electronic evening diary <sup>27)</sup>   | X               | X            | X                                  | X           | X                            | X                     | X           | X                      | X                      | X           | X                      | X                      | X           | X                       | X                       | X                | X                | X  |         |  |
| Tyler questionnaire <sup>31)</sup>  |                 |              | X                                  |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         | X                | X                |  |         |  |
| Modified Cataplexy Questionnaire (MCQ)  |                 |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  |  |         |  |
| AE monitoring <sup>32)</sup>  | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  | X  |         |  |
| Procedures (related to AEs)   | X               |              |                                    |             |                              |                       |             |                        |                        |             |                        |                        |             |                         |                         |                  |                  | X  |         |  |

<sup>1)</sup> Target Study Day is relative to the first randomized dosing day (Day 1). There is no Day 0; the day before Day 1 is considered to be Day -1.

<sup>2)</sup> Patients with any secondary education (any formal education beyond 8<sup>th</sup> grade) do not need to conduct a reading assessment. For patients who have no secondary education, the patients will read the first 2 paragraphs of the informed consent.

<sup>3)</sup> Body Mass Index will only be calculated at the Presudy Visit (Visit 1) from weight and height. Height will only be collected at Visit 1 to calculate the BMI. Please refer to appendix 6.14 for the measurements of weight.

<sup>4)</sup> Any female patient of child-bearing potential will undergo a urine pregnancy test and a serum pregnancy test (β-hCG) at Visit 1. At other specified time points, if a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation. Serology testing (Hepatitis A and B and HIV 1 and 2) is optional and is collected at the Investigators discretion.

<sup>5)</sup> Electronic Morning Diary should be completed at home by patient after their normal morning routine (e.g., using the bathroom, eating breakfast) and preferably within an hour of waking for the day.

<sup>6)</sup> Electronic Evening Diary should be completed at home by patient at bedtime prior to taking study medication at the times specified below.

<sup>7)</sup> Electronic diary containing morning and evening questionnaires will be completed every morning and evening starting on the evening of the Presudy (Visit 1) until the End of Month 1 (Visit 5). The questionnaire will then be completed every month for 11 mornings and evenings (5 days before and 5 days after the targeted study day for a visit or telephone contact) until the End of Month 10 telephone contact. The patient will be asked to complete the morning and evening e-diary daily 5 days prior to the End of Month 11 targeted telephone contact until the end of the study (Visit 18). Patients should be instructed to bring the e-diary to the clinic at each visit. Patient compliance should be monitored via vendor website weekly for the first month of the study and monthly thereafter.

<sup>8)</sup> The True Withdrawal Symptom Questionnaire will be administered, prior to dosing, in conjunction with the evening questionnaire on the evening of the Baseline Randomization Visit (Visit 3) and for 3 consecutive evenings. It will be administered again, prior to dosing, for 4 evenings at the targeted End of Month 11 telephone contact on Day 330 until Day 333. It will also be completed, prior to dosing, on the evening of the End of Month 12 Visit (Visit 16) and for 3 consecutive evenings. Please refer to specific instructions in the e-diary procedures manual.

<sup>9)</sup> Please refer to Sections 3.4.1.7, 3.4.1.8, and 3.4.5.2 for the pre-specified ECIs.

<sup>10)</sup> Obtain only if the time between Visit 1 and Visit 3 exceeds 21 days.

<sup>11)</sup> Patients that complete the study or prematurely discontinue will receive a follow-up phone call 14 days after the last dose of study medication or 14 days after the Discontinuation Visit (whichever time point is later). All adverse events, concomitant medications and motor vehicle accidents and violation (MVA/V) since the last study visit will be collected. Patients that discontinue will be asked to complete an ISI at the Discontinuation Visit. Patients that discontinue during the 12 month treatment period will also be sent home with another ISI to complete 1 week after the Discontinuation Visit. The patient will mail the completed ISI to the Investigator site.

<sup>12)</sup> Signing of the optional pharmacogenomic sample consent form and obtaining the optional genetic sample should be completed any time after Visit 2 (randomization). This is not necessary to participate in the study.

<sup>13)</sup> PK samples are mandatory sample collections. Consent for these samples is obtained by the patient signing the main study consent. PK samples should be collected if a patient discontinues due to an adverse event.

<sup>14)</sup> The HLA-DQB1 genotyping sample is a mandatory sample collection. Consent for this sample is obtained by the patient signing the main study consent. This sample should be collected at Visit 3 (randomization).

<sup>15)</sup> CGI-S and PGI-S should not be completed at Visit 1 (Screening Visit) and Visit 3. CGI=Patient Global Impressions (S=Severity, I=Improvement) CGI= Clinical Global Impressions (S=Severity, I=Improvement)

<sup>16)</sup> The allowed visit window is around the Target Study Day and is not cumulative. If four of window, all subsequent visits should be scheduled according to the original Target Study Day.

<sup>17)</sup> To be completed at the Presudy visit for patients ≥65 years of age

<sup>18)</sup> Please refer to Appendix 6.14 for specific weight measurements.

<sup>19)</sup> The first dose of double blind study medication will be on the evening of Visit 3, immediately prior to bed (within 5-10 minutes of bedtime).

<sup>20)</sup> The patient will complete the ISI questionnaire at home at the end of each week after the Month 12 visit, i.e., 1, 2, and 3 weeks after Visit 16, then at the clinic during the Month 1 double-blind run-out visit (Visit 17), and at home during the following 3 weeks (i.e., 1, 2, and 3 weeks after Visit 17), and finally at the clinic during the end of Month 2 double-blind run-out visit (Visit 18).

<sup>21)</sup> The Baseline CSSRS should only be completed at Visit 1. The Since Last Visit CSSRS should be completed at all visits except Visit 1.

<sup>22)</sup> Please refer to Appendix 6.7 for measurement of blood pressure. Vital signs include blood pressure, pulse, respiratory rate and temperature.

<sup>23)</sup> Physical exams must be performed by a physician or a physician assistant depending on state laws. The neurological exam should include muscle strength, deep tendon reflexes, romberg, gait and finger to nose.

<sup>24)</sup> Drug accountability (compliance) will be assessed at each visit by pill count, e-diary data and interview of the patient.

<sup>25)</sup> Randomized patients with ALT and/or AST values elevated > 3x ULN (Upper Limit of Normal) will require additional follow-up. Please refer to the Neuro Hepatic Guidance and FDA Final Guidance – Drug Induced Liver Injury for details.

(Source: Sponsor's submission P009 Protocol Page 17)

#### Endpoints and Analyses Trial P009

Trial P009 had no primary efficacy hypotheses. To examine the secondary efficacy hypotheses, Merck examined the average of Weeks 1, 2, 3, and 4 in sTST, and sTSO.

Merck also used exploratory and other endpoints to primarily assess rebound insomnia at the end of 12 months of treatment, and to secondarily examine efficacy. For these purposes, treatment effects on sTST, sTSO, and sWASO were assessed.

Additional evaluations were performed using the Clinical Global Impressions-Severity (CGI-S) scale, the Clinical Global Impressions-Improvement (CGI-I) scale, the Patient Global Impressions-Severity (PGI-S) scale, the Patient Global Impressions-Improvement (PGI-I) scale, the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16), the Insomnia Severity Index (ISI), and suvorexant's pharmacokinetic (PK) parameters.

For safety assessments, Merck analyzed data from the following:

- Laboratory evaluations (hematology, chemistry, urine drug screen, and urine pregnancy test)
- Physical examination
- Electrocardiogram (ECG)
- Vital Signs
- Motor Vehicle Accident and Violation (MVAV)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Morning questionnaire and Tyrer Withdrawal Symptom Questionnaire via the e-diary

In addition, investigators monitored adverse events (AEs) and the pre-specified ECIs of suicidal ideation or behaviors, events associated with potential for abuse, complex sleep-related behaviors, hypnagogic or hypnopompic hallucinations, excessive daytime sleepiness (EDS), sleep paralysis, cataplexy, falls, and AEs associated with traffic or motor vehicle accidents (when a subject was the driver). The external adjudication committee reviewed events suggestive of cataplexy, falls, and sleep onset paralysis.

#### Statistical Analyses in Trial P009

Merck analyzed the safety data using a tiered approach as in the other phase 3 trials.

According to the P009 protocol, the trial size was largely determined by regulatory safety requirements for duration and number of subjects exposed rather than formal statistical considerations. The estimated sample size was of 750 subjects, 500 on suvorexant and 250 on placebo. These estimates expected dropout rates of about 50% by Month 6 and 60% by Month 12 in each treatment group. Also, the estimates needed to ensure that at least 100 subjects in each of the elderly and non-elderly age-groups completed 12-month treatment, and 250 total subjects completed 6-month treatment.

The planned sample size presented the power to detect differences in hazard rates for Tier 1 AEs as shown in the table below:

**Table 32: Power to Detect Between Treatment Differences in Tier 1 Adverse Events in Trial P009**

| Study Population  | MK-4305 Versus Placebo Hazard Rate | Power <sup>†</sup> |
|---|------------------------------------|--------------------|
| Overall<br>(N=500 for MK-4305 vs.<br>N=250 for Placebo)   | 0.06 vs. 0.01                      | 81%                |
|   | 0.10 vs. 0.01                      | 99%                |
|   | 0.08 vs. 0.02                      | 82%                |
|   | 0.10 vs. 0.02                      | 94%                |
|   | 0.15 vs. 0.05                      | 92%                |
|   | 0.20 vs. 0.05                      | >99%               |
| <sup>†</sup> Based upon Lachin & Foulkes method (two-sided, 5% level test); 60% dropout rate over 1-year treatment phase. |                                    |                    |

(Source: Sponsor's submission P009 Protocol Page 33 Table 2-2)

Based on the same sample size estimates and an LDA ANCOVA model with a 2-sided alpha level of 5%, the power to detect differences in sTSTm and sTSOm, averaged over Weeks 1, 2, 3 and 4, between the treatment groups is shown the table below.

**Table 33: Power to Detect Between Treatment Differences in Efficacy at Month 1 in Trial P009**

| Variable  | Delta (Improvement) | Power <sup>†</sup> |
|---|---------------------|--------------------|
| sTSTm   | 20                  | >99%               |
|   | 15                  | 95%                |
|   | 12                  | 82%                |
| sTSOm   | 12                  | >99%               |
|   | 10                  | 97%                |
|   | 8                   | 87%                |
| <sup>†</sup> Based upon N=500 on MK-4305 and N=250 on Placebo; 2-sided, 5%-level test; estimates of covariance matrix and missing data rates based upon prior in-house studies of MK-0928 (Protocols 003, 014, 10403 and 005) |                     |                    |

(Source: Sponsor's submission P009 CSR Page 102 Table 9-3)

To monitor safety of subjects, an external Data Monitoring Committee (eDMC) conducted two planned interim analyses. The first occurred when 20% of the randomized subjects had completed 3 months of the treatment phase; the second was at the time 40% of the subjects completed the 12-month treatment phase.

## Results:

### *Protocol Amendments and Changes in Trial Conduct*

Merck made amendments and changes during the trial that included the following:

- Changed the dose for non-elderly subjects, younger than 65 years, from 60 mg to 40 mg
- Revised timing of measurements for PK and other laboratory parameters
- Combined elderly and non-elderly subjects to assess trial hypotheses, thereby making the trial analyses consistent with other phase 3 trials
- Added the form for motor vehicle accidents and violations (MVAV) to the trial assessments; this was done after completing trial enrollment, so no baseline values were obtained
- Allowed use of hormonal contraceptives
- Added gender to efficacy analysis model
- Allowed cognitive behavioral therapy (CBT) during the trial if it was initiated at least 4 weeks before visit 1
- Added falls to events for adjudication

### Disposition in Trial P009

Trial P009 had 1076 subjects screened for inclusion. A total of 295 subjects were not randomized. A total of 781 subjects were randomized: 522 subjects to suvorexant HD and 259 subjects to placebo. Two of the randomized subjects, one to each treatment group, received no treatment. Therefore, 779 subjects who received at least one dose of trial treatment were evaluated for safety.

Of the 779 treated subjects, 484 (62%) completed the trial, with similar percentages of completers in each treatment group: 61.7% (322/522) of the suvorexant HD and 62.5% (162/259) of the placebo groups. The most common reason for discontinuation in the Treatment Phase was because of an AE. More subjects discontinued because of an AE in the suvorexant group (11.5%, 60/522) compared to placebo (8.5%, 22/259). Further, in the suvorexant HD group, the discontinuation rate among non-elderly subjects (46.5%, 99/213) was higher than among elderly subjects (32.7%, 101/309). The table below summarizes subject disposition in Trial P009.

**Table 34: Disposition of Subjects in Trial P009**

|                          | Placebo<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|--------------------------|------------------|------------------------|----------------|
| Not Randomized           |                  |                        | 295            |
| Subjects in population   | 259              | 522                    | 781            |
| <b>Study Disposition</b> |                  |                        |                |

|                       |            |            |           |
|-----------------------|------------|------------|-----------|
| Completed             | 162 (62.5) | 322 (61.7) | 484 (62)  |
| Discontinued          | 97 (37.5)  | 200 (38.3) | 297 (38)  |
| Adverse Events        | 22 (8.5)   | 60 (11.5)  | 82 (10.5) |
| Lack of Efficacy      | 28 (10.8)  | 44 (8.4)   | 72 (9.2)  |
| Lost to Follow-up     | 12 (4.6)   | 14 (2.7)   | 26 (3.3)  |
| Physician Decision    | 8 (3.1)    | 17 (3.3)   | 25 (3.2)  |
| Pregnancy             | 0 (0.0)    | 1 (0.2)    | 1 (0.1)   |
| Protocol violation    | 3 (1.2)    | 4 (0.8)    | 7 (0.9)   |
| Withdrawal by Subject | 24 (9.3)   | 60 (11.5)  | 84 (10.8) |

(Source: Modified from Sponsor's Submission P009 CSR Page 113 Table 10-1)

### Baseline Characteristics

The baseline characteristics were similar across the treatment groups. The subjects' mean age was 61.5 years, range 18 to 90 years, with 459 (58.9%) subjects in the elderly age group. About 56% (436/779) of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race. The treatment groups within the non-elderly and elderly age groups showed similar baseline characteristics. Below is a summary of subject characteristics in Trial P009.

**Table 35: Subject Characteristics in Trial P009 Treatment Phase**

|  | <b>Placebo<br/>N (%)</b> | <b>Suvorexant HD<br/>N (%)</b> | <b>Total<br/>N (%)</b> |
|--|--------------------------|--------------------------------|------------------------|
| <b>Subjects in population</b>                | 258                      | 521                            | 779                    |
| <b>Gender</b>                                |                          |                                |                        |
| Male   | 109 (42.2)               | 234 (44.9)                     | 343 (44.0)             |
| Female                                       | 149 (57.8)               | 287 (55.1)                     | 436 (56.0)             |
| <b>Age in years</b>                          |                          |                                |                        |
| Mean   | 62.0                     | 61.3                           | 61.5                   |
| SD   | 14.6                     | 14.5                           | 14.5                   |
| <b>Race</b>                                  |                          |                                |                        |
| White  | 231 (89.5)               | 476 (91.4)                     | 707 (90.8)             |
| Black  | 24 (9.3)                 | 33 (6.3)                       | 57 (7.3)               |
| Asian  | 1 (0.4)                  | 6 (1.2)                        | 7 (0.9)                |
| Multi-Racial                                 | 1 (0.4)                  | 4 (0.8)                        | 5 (0.6)                |
| American Indian Or<br>Alaska Native          | 1 (0.4)                  | 1 (0.2)                        | 2 (0.3)                |
| Native Hawaiian Or<br>Other Pacific Islander | 0 (0.0)                  | 1 (0.2)                        | 1 (0.1)                |
| <b>Region</b>                                |                          |                                |                        |

|                                       |            |            |            |
|---------------------------------------|------------|------------|------------|
| Asia Pacific                          | 5 (1.9)    | 11 (2.1)   | 16 (2.1)   |
| Central and Eastern Europe            | 6 (2.3)    | 14 (2.7)   | 20 (2.6)   |
| Central and South America             | 4 (1.6)    | 8 (1.5)    | 12 (1.5)   |
| Europe                                | 84 (32.6)  | 169 (32.4) | 253 (32.5) |
| North America                         | 159 (61.6) | 319 (61.2) | 478 (61.4) |
| <b>Body Mass Index (BMI) Category</b> |            |            |            |
| Underweight (BMI < 18.5)              | 1 (0.4)    | 3 (0.6)    | 4 (0.5)    |
| Normal range (18.5 <= BMI < 25)       | 81 (31.4)  | 165 (31.7) | 246 (31.6) |
| Overweight (25 <= BMI <= 30)          | 116 (45.0) | 231 (44.3) | 347 (44.5) |
| Obese (BMI > 30)                      | 60 (23.3)  | 121 (23.2) | 181 (23.2) |
| Null                                  | 0 (0.0)    | 1 (0.2)    | 1 (0.1)    |

(Source: Sponsor's Submission P009 CSR Page 118 Table 10-4)

Below, I summarize the analysis populations for the subjective efficacy endpoints.

**Table 36: Efficacy Analyses Populations All Subjects for Subjective Endpoints**

| <b>Category/Endpoint</b>        | <b>Placebo</b> | <b>Suvorexant HD</b> | <b>Total</b> |
|---------------------------------|----------------|----------------------|--------------|
| Number Randomized               | 259            | 522                  | 781          |
| Number Not Treated              | 1              | 1                    | 2            |
| All Patients Treated Set (APTS) | 258            | 521                  | 779          |
| <b>sTST</b>                     |                |                      |              |
| Subjects included in FAS        | 254            | 517                  | 771          |
| <b>sWASOm</b>                   |                |                      |              |
| Subjects included in FAS        | 251            | 512                  | 763          |
| <b>sTSOm</b>                    |                |                      |              |
| Subjects included in FAS        | 254            | 517                  | 771          |

(Source: Modified from Sponsor's Submission P009 CSR Page 116 Table 10-3)

### Efficacy Results

Efficacy analyses were based on a mixed effects model that included the following covariates: baseline value, age category (<65, ≥65 years), region, gender, treatment, time point, and treatment-by-time point interaction.

### Sleep Maintenance

During the first month of treatment, suvorexant HD improved sleep maintenance, as measured by change from baseline in average of weekly sTSTm, compared to placebo. Suvorexant HD showed an increase of 22.7 minutes in average sTSTm from baseline was compared to placebo during the first four weeks of treatment (p-value < 0.0001).

The improvement in sTSTm was observed on each of the first 4 weeks, and continued over the months up to Month 12. Below is a summary of the sTSTm results.

**Table 37: Analyses of Subjective Efficacy of Sleep Maintenance Measured by sTSTm in Trial P009**

| Timepoint | Placebo |                    |        | Suvorexant HD |                    |        |                            |         |
|-----------|---------|--------------------|--------|---------------|--------------------|--------|----------------------------|---------|
|           | N       | Mean Baseline (SD) | LS-MCB | N             | Mean Baseline (SD) | LS-MCB | Diff from Placebo (95% CI) | P value |
| Month 1   | 254     | 329.9 (79.4)       | 16.0   | 517           | 320.4 (76.1)       | 38.7   | 22.7 (16.4, 29.0)          | <0.0001 |
| Month 3   | 186     | 333.7 (78.6)       | 31.9   | 389           | 318.9 (73.7)       | 54.5   | 22.6 (13.6, 31.6)          | <0.0001 |
| Month 6   | 168     | 334.8 (77.1)       | 27.6   | 347           | 317.2 (75.0)       | 54.6   | 27.0 (17.0, 37.0)          | <0.0001 |
| Month 12  | 147     | 336.9 (72.3)       | 33.0   | 298           | 320.6 (76.3)       | 60.5   | 27.5 (16.2, 38.8)          | <0.0001 |

(Source: Modified from Sponsor's submission P009 CSR Pages 141, 149 Tables 11-3, 11-6; LS=Least Square, MCB=Mean change from Baseline; Measurements from 1 month data at Month 1, 11-14 days' data on other months)

#### Sleep Maintenance by sWASO

Merck also evaluated suvorexant's effect on sWASOm as a means of measuring the drug's effect on sleep maintenance. During the first month of treatment, suvorexant HD decreased change from baseline in average of weekly sWASOm by 9.3 minutes compared to placebo during the first four weeks of treatment (p-value < 0.0001). Again, the improvement in sWASOm was observed on each of the first 4 weeks, and continued over the months up to Month 12. I present a summary of the sWASOm results below.

**Table 38: Analyses of Subjective Efficacy of Sleep Maintenance Measured by sWASOm in Trial P009**

| Timepoint | Placebo |                    |        | Suvorexant HD |                    |        |                            |         |
|-----------|---------|--------------------|--------|---------------|--------------------|--------|----------------------------|---------|
|           | N       | Mean Baseline (SD) | LS-MCB | N             | Mean Baseline (SD) | LS-MCB | Diff from Placebo (95% CI) | P value |
| Month 1   | 251     | 71.5 (56.1)        | -12.5  | 512           | 80.1 (57.2)        | -21.7  | -9.3 (-13.5, -5.1)         | <.0001  |

|          |     |                |       |     |                |       |                     |        |
|----------|-----|----------------|-------|-----|----------------|-------|---------------------|--------|
| Month 3  | 184 | 67.9<br>(53.7) | -24.3 | 387 | 79.3<br>(55.9) | -33.3 | -9.0 (-14.7, -3.4)  | 0.0018 |
| Month 6  | 167 | 69.2<br>(56.1) | -21.6 | 344 | 81.1<br>(56.7) | -33.5 | -11.8 (-18.3, -5.3) | 0.0004 |
| Month 12 | 147 | 67.7<br>(55.4) | -23.8 | 295 | 80.1<br>(55.0) | -33.5 | -9.7 (-16.5, -3.0)  | 0.0048 |

(Source: Modified from Sponsor's submission P009 CSR Pages 143, 153 Tables 11-4, 11-7; LS=Least Square, MCB=Mean change from Baseline; Measurements from 1 month data at Month 1, 11-14 days' data on other months)

### Sleep Onset by sTSO

During the first month of treatment, suvorexant HD reduced time to sleep onset, as measured by change from baseline in average of weekly sTSOm, compared to placebo. Suvorexant HD reduced sTSOm from baseline by an average of 9.5 minutes compared to placebo during the first four weeks of treatment (p-value = 0.0002). The improvement in sTSOm was observed on each of the first 4 weeks, and continued over the months up to Month 12. Below is a summary of the sTSTm results.

**Table 39: Analyses of Subjective Efficacy of Sleep Onset as Measured by sTSOm in Trial P009**

| Timepoint | Placebo |                    |        | Suvorexant HD |                    |        |                            |         |
|-----------|---------|--------------------|--------|---------------|--------------------|--------|----------------------------|---------|
|           | N       | Mean Baseline (SD) | LS-MCB | N             | Mean Baseline (SD) | LS-MCB | Diff from Placebo (95% CI) | P value |
| Month 1   | 254     | 65.0<br>(60.6)     | -8.4   | 517           | 65.9<br>(63.8)     | -18.0  | -9.5 (-14.6, -4.5)         | 0.0002  |
| Month 3   | 186     | 60.5<br>(56.0)     | -16.7  | 389           | 66.9<br>(63.0)     | -25.2  | -8.5 (-14.4, -2.6)         | 0.0048  |
| Month 6   | 168     | 59.1<br>(51.3)     | -14.9  | 347           | 68.4<br>(64.9)     | -24.8  | -9.9 (-16.4, -3.4)         | 0.0030  |
| Month 12  | 147     | 55.6<br>(42.2)     | -17.0  | 298           | 64.7<br>(62.2)     | -26.6  | -9.7 (-16.5, -2.9)         | 0.0055  |

(Source: Modified from Sponsor's submission P009 CSR Pages 146, 157 Tables 11-5, 11-8; LS=Least Square, MCB=Mean change from Baseline; Measurements from 1 month data at Month 1, 11-14 days' data on other months)

### Other Endpoints

For most of the 12-month treatment period, the subjective number of awakenings (sNAWm) remained similar between the treatment groups, even increasing slightly at 12 months in the suvorexant group by 0.2 compared to placebo (p=0.0216). Results of other exploratory endpoints shown below include: subjective sleep quality (sQUALm),



subjective refreshed upon awakening (sREFRESHm), Insomnia Severity Index (ISI), CGI-S, CGI-I, PGI-S, and PGI-I.

**Table 40: Additional Efficacy Endpoints in Trial P009**

|           | Placebo<br>Baseline     | Placebo<br>Month 1                 | Suvorexant HD<br>Month 1                  |            | Suvorexant HD<br>Month 3                  |            | Suvorexant HD<br>Month 6                  |            | Suvorexant HD<br>Month 12                 |            |
|-----------|-------------------------|------------------------------------|---|------------|---|------------|---|------------|---|------------|
|           | Baseline<br>(SD)        | Mean<br>Change<br>from<br>Baseline | Difference<br>from<br>Placebo<br>(95% CI) | P<br>value | Difference<br>from<br>Placebo<br>(95% CI) | P<br>value | Difference<br>from<br>Placebo<br>(95% CI) | P<br>value | Difference<br>from<br>Placebo<br>(95% CI) | P<br>value |
| sNAWm     | 2.0 (1.1)               | -0.2                               | 0.1 (-0.0, 0.2)                           | 0.0765     | 0.1 (-0.0, 0.3)                           | 0.1287     | 0.1 (-0.1, 0.3)                           | 0.5522     | 0.2 (0.0, 0.4)                            | 0.0216     |
| sQUALm    | 2.1 (0.5)               | 0.1                                | 0.2 (0.1, 0.2)                            | <.0001     | 0.1 (0.0, 0.2)                            | 0.0226     | 0.1 (0.0, 0.2)                            | 0.0170     | 0.1 (0.0, 0.2)                            | 0.0338     |
| sREFRESHm | 1.4 (0.7)               | 0.2                                | 0.2 (0.1, 0.2)                            | <.0001     | 0.1 (0.0, 0.2)                            | 0.0125     | 0.1 (0.0, 0.3)                            | 0.0137     | 0.2 (0.0, 0.3)                            | 0.0162     |
| ISI       | 13.7<br>(4.6)           | -2.2                               | -1.4 (-2.1, -0.7)                         | <.0001     | -0.9 (-1.7, -0.2)                         | 0.0160     | -1.4 (-2.3, -0.6)                         | 0.0007     | -0.9 (-1.8, -0.0)                         | 0.0390     |
| CGI-S     | 4.3 (0.8)               | -0.5                               | -0.3 (-0.5, -0.2)                         | <.0001     | -0.4 (-0.6, -0.2)                         | <.0001     | -0.4 (-0.6, -0.2)                         | <.0001     | -0.4 (-0.6, -0.2)                         | 0.0003     |
| CGI-I     | 3.3 (1.0)<br>at Month 1 | -                                  | -0.4 (-0.6, -0.3)                         | <.0001     | -0.4 (-0.5, -0.2)                         | <.0001     | -0.5 (-0.7, -0.3)                         | <.0001     | -0.5 (-0.7, -0.3)                         | <.0001     |
| PGI-S     | 3.1 (0.9)               | -0.5                               | -0.3 (-0.4, -0.1)                         | 0.0026     | -0.3 (-0.4, -0.1)                         | 0.0057     | -0.4 (-0.6, -0.2)                         | <.0001     | -0.3 (-0.5, -0.1)                         | 0.0110     |
| PGI-I     | 3.4 (1.2)<br>at Month 1 | -                                  | -0.5 (-0.7, -0.3)                         | <.0001     | -0.5 (-0.7, -0.3)                         | <.0001     | -0.5 (-0.7, -0.3)                         | <.0001     | -0.5 (-0.7, -0.3)                         | <.0001     |

(Source: Modified from Sponsor's submission P009 CSR Pages 651-663, 670-673; Tables 14-57 to 14-66, 14-73 to 14-76)

Time to study discontinuation from any reason, an adverse event, lack of efficacy, or subject withdrawal was comparable between suvorexant HD and placebo groups; all nominal p-values were > 0.0500 for hazard ratios when the treatment groups were compared by reason of discontinuation. For any reason of discontinuation, the discontinuation rates were 38.2% (199/521) for the suvorexant HD group and 37.2% (96/258) for the placebo group; the hazard ratio for time to discontinuation was 1.014 (P=0.9133).

The change from baseline in QIDS-SR16 total score during the double-blind Treatment Phase was comparable between suvorexant HD and placebo groups. However, components of the QIDS-SR16 related to sleep – falling asleep, sleep during night, and waking up too early – improved with suvorexant treatment.

#### Randomized Discontinuation Phase

##### Relapse of Insomnia

The trial categorized subjects with insomnia relapse as those who developed moderate to severe insomnia (ISI total score of 15-28) during the randomized discontinuation phase, but had sub-threshold insomnia or no clinically significant insomnia (ISI total score of 0-14) at the end of Month 12 treatment. More insomnia relapse occurred in

subjects who switched to placebo in the randomized discontinuation phase (MK/PBO group: 27.1%, 38/140) compared to those who remained on suvorexant (MK/MK group: 22.0%, 28/127) or those who remained on placebo (PBO/PBO: 23.2%, 32/138).

When Merck defined insomnia relapse based on sTSTm return to within 5%, 10%, or 20% of baseline, more subjects who switched to placebo developed insomnia relapse. For instance, among subjects with sTSTm returning to within 5% of baseline, insomnia relapse occurred in 38.6% (32/83) of the PBO/PBO group, 32.8% (38/116) of the MK/MK group, and 46.3% (57/123) of the MK/PBO group.

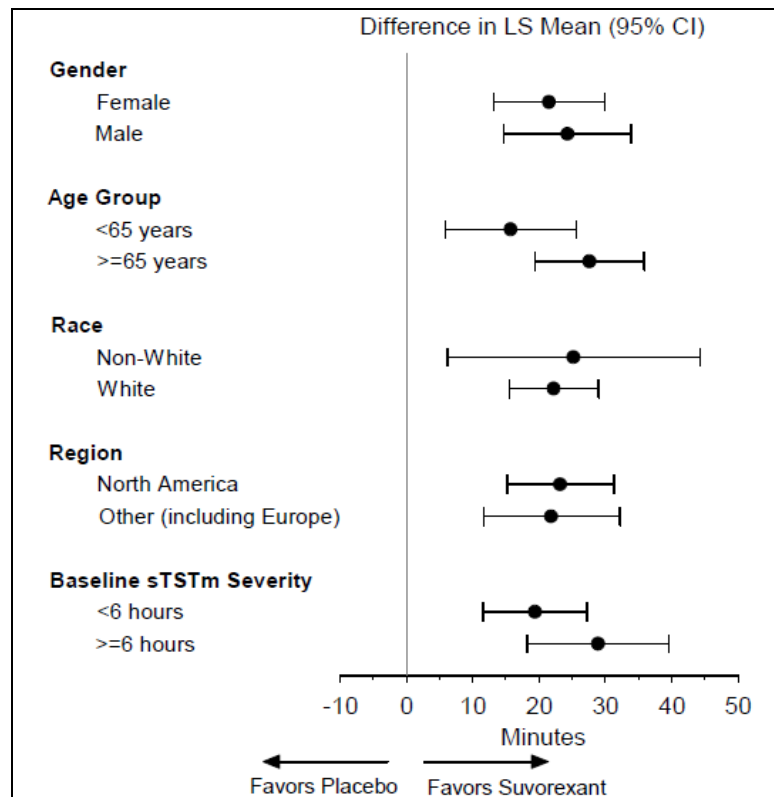
During the randomized discontinuation phase, the average change from Month 12 in sTSTm ranged from 30.3 minutes less per night in the first week to 21.6 minutes less per night in Week 8 for subjects who switched to placebo compared those who remained on suvorexant HD, with nominal p-values < 0.0001. A similar comparison using sWASOm yielded an average change from Month 12 sWASOm ranging from 7.0 minutes to 14.2 minutes more in subjects who switched to placebo compared those who remained on suvorexant HD, with nominal p-values < 0.0200. For sTSOm, the average change ranged from 12.9 minutes to 17.5 minutes more in subjects who switched to placebo compared those who remained on suvorexant HD, with nominal p-values 0.0002 or less.

Further, in the randomized discontinuation phase, subjects who switched to placebo experienced a worsening in their sQUALm, sREFRESHm, ISI total score, CGI-S, CGI-I, PGI-S, PGI-I scores compared those who remained on suvorexant HD. There were no notable differences between the groups on sNAWm.

#### Analyses of Efficacy by Subgroup

Subgroup analyses showed that suvorexant HD improved total sleep time, as measured by sTSTm, with nominal p values <0.0200, in the categories of age group, gender, race, region, and baseline severity. The figure below shows the difference in LS means (95% CI) between suvorexant HD and placebo for sTSTm for each subgroup on average for Month 1.

**Figure 5: Subgroup Analyses of Difference in LS Means (95% CI) between Suvorexant and Placebo for sTSTm Averaged over Month 1**



(Source: Sponsor's submission P009 CSR Page 181 Figure 11-10)

Although the point estimates for sWASOm decreased with suvorexant HD compared to placebo across the subgroups, the effect was less apparent in the non-elderly subjects compared to elderly subjects, with nominal p value of 0.0566 for the non-elderly subjects. Likewise for sleep onset, suvorexant HD decreased sTSOm compared to placebo across the subgroups, but the nominal p values were above 0.05 for the non-elderly age group, non-white race, and baseline sTSOm severity < 45 minutes.

#### Reviewer Comment

*Suvorexant HD showed consistent improvement in sleep onset and sleep maintenance over a treatment period of 12 months. On subgroup analyses, the improvement in sleep onset from suvorexant treatment was less obvious in non-elderly subjects and in subjects with less severe baseline sTSOm.*

#### PK Data

Suvorexant plasma concentration levels were comparable on days 15, 30, and 90 in non-elderly subjects. Similarly, the levels were comparable on same days in the elderly, but on the average about 8% lower than in the non-elderly. Also, suvorexant levels at 24

to 48 hours after last dose were still as high as 70% of the levels at 7 to 13 hour on the different days measured and in each age group.

#### Safety Results

This section provides a summary of the safety findings in Trial P009. Also, this summary is more detailed than the other phase 3 trials because P009 exposed subjects to a longer 12-month treatment period compared to 3-6 months in Trial P028 and P029. For a more extensive review of suvorexant safety, please see safety analyses of pooled phase 3 data in section 5.

#### Exposure

Of 521 subjects treated with suvorexant HD in Trial P009, 378 subjects, including 145 non-elderly and 233 elderly subjects, received a dose of suvorexant HD for at least 6 months. Of these, 160 subjects, including 51 non-elderly and 109 elderly subjects, received a dose of suvorexant HD for at least 12 months. The mean duration of treatment with any suvorexant dose was 282 days.

#### Deaths

Trial P009 recorded no deaths.

#### Serious AEs

As shown in the table below, the treatment groups had comparable incidence of serious AEs: placebo group with 6.6% (17/258) and suvorexant HD with 5.2% (27/521). Treatment discontinuations due to serious AEs were also comparable between the treatment groups: placebo group with 1.9% (5/258) and suvorexant HD with 1.9% (10/521).

**Table 41: Adverse Events in Trial P009**

|  | MK-4305 |        | Placebo |        | Difference in % vs Placebo     |
|--|---------|--------|---------|--------|--------------------------------|
|  | n       | (%)    | n       | (%)    | Estimate (95% CI) <sup>†</sup> |
| Patients in population                                   | 521     |        | 258     |        |                                |
| with one or more adverse events                          | 362     | (69.5) | 164     | (63.6) | 5.9 (-1.1, 13.1)               |
| with no adverse events                                   | 159     | (30.5) | 94      | (36.4) | -5.9 (-13.1, 1.1)              |
| with drug-related <sup>‡</sup> adverse events            | 182     | (34.9) | 53      | (20.5) | 14.4 (7.8, 20.6)               |
| with serious adverse events                              | 27      | (5.2)  | 17      | (6.6)  | -1.4 (-5.5, 1.9)               |
| with serious drug-related adverse events                 | 1       | (0.2)  | 3       | (1.2)  | -1.0 (-3.2, 0.1)               |
| who died   | 0       | (0.0)  | 0       | (0.0)  |                                |
| discontinued <sup>§</sup> due to an adverse event        | 61      | (11.7) | 22      | (8.5)  | 3.2 (-1.5, 7.4)                |
| discontinued due to a drug-related adverse event         | 43      | (8.3)  | 12      | (4.7)  |                                |
| discontinued due to a serious adverse event              | 10      | (1.9)  | 5       | (1.9)  |                                |
| discontinued due to a serious drug-related adverse event | 0       | (0.0)  | 3       | (1.2)  |                                |

<sup>†</sup> Based on Miettinen & Nurminen method.  
<sup>‡</sup> Determined by the investigator to be related to the drug.  
<sup>§</sup> Study medication withdrawn.  
 Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.  
 MK-4305 = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission P009 CSR Page 195 Table 12-3)

In the treatment phase, similar proportions of serious AEs (SAEs) occurred in the treatment groups: 5.2% (27/521) in the suvorexant HD and 6.6% (17/258) in placebo. The most frequent system organ class (SOC), with higher incidence in the suvorexant HD group, was Nervous System Disorders: 0.8% (4/521) in the suvorexant HD group and 0.4% (1/258) in placebo. Although eleven subjects reported the SOC of Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps), fewer subjects were from the suvorexant group; 7 (1.3%) subjects on suvorexant HD compared to 4 (1.6%) subjects on placebo reported this SOC. The table below shows Merck's summary of SAEs with an incidence >0% in a treatment group.

**Table 42: Serious Adverse Events with Incidence >0% in any Treatment Group of Trial P009**

| Adverse Event Category<br>SOC<br>Preferred Term  | Suvorexant HD<br>N (%) | Placebo<br>N (%) |
|--|------------------------|------------------|
| Total Subjects                                   | 521 (100)              | 258 (100)        |
| Subjects with one or more serious adverse events | 27 (5.2)               | 17 (6.6)         |
| <b>Cardiac disorders</b>                         | <b>2 (0.4)</b>         | <b>3 (1.2)</b>   |
| Atrial fibrillation                              | 1 (0.2)                | 3 (1.2)          |
| Coronary artery disease                          | 1 (0.2)                | 0 (0.0)          |
| <b>Ear and labyrinth disorders</b>               | <b>1 (0.2)</b>         | <b>0 (0.0)</b>   |
| Vertigo positional                               | 1 (0.2)                | 0 (0.0)          |

|  |                |                |
|--|----------------|----------------|
| <b>Gastrointestinal disorders</b>  | <b>1 (0.2)</b> | <b>2 (0.8)</b> |
| Gastroesophageal reflux disease  | 1 (0.2)        | 0 (0.0)        |
| Ileus  | 0 (0.0)        | 1 (0.4)        |
| Pancreatitis   | 0 (0.0)        | 1 (0.4)        |
| <b>General disorders and administration site conditions</b>                | <b>1 (0.2)</b> | <b>0 (0.0)</b> |
| Non-cardiac chest pain   | 1 (0.2)        | 0 (0.0)        |
| <b>Infections and infestations</b>   | <b>4 (0.8)</b> | <b>2 (0.8)</b> |
| Abdominal infection  | 0 (0.0)        | 1 (0.4)        |
| Diverticulitis   | 2 (0.4)        | 1 (0.4)        |
| Erysipelas   | 0 (0.0)        | 1 (0.4)        |
| Pneumonia  | 1 (0.2)        | 0 (0.0)        |
| Urinary tract infection  | 1 (0.2)        | 1 (0.4)        |
| <b>Injury, poisoning and procedural complications</b>                      | <b>3 (0.6)</b> | <b>1 (0.4)</b> |
| Clavicle fracture  | 1 (0.2)        | 0 (0.0)        |
| Concussion   | 1 (0.2)        | 0 (0.0)        |
| Joint dislocation  | 0 (0.0)        | 1 (0.4)        |
| Tendon rupture   | 1 (0.2)        | 0 (0.0)        |
| <b>Musculoskeletal and connective tissue disorders</b>                     | <b>3 (0.6)</b> | <b>2 (0.8)</b> |
| Arthralgia   | 1 (0.2)        | 0 (0.0)        |
| Back pain  | 0 (0.0)        | 1 (0.4)        |
| Meniscal degeneration  | 0 (0.0)        | 1 (0.4)        |
| Spinal column stenosis   | 1 (0.2)        | 0 (0.0)        |
| Spondylitis  | 1 (0.2)        | 0 (0.0)        |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> | <b>7 (1.3)</b> | <b>4 (1.6)</b> |
| B-cell lymphoma  | 1 (0.2)        | 0 (0.0)        |
| Basal cell carcinoma   | 2 (0.4)        | 2 (0.8)        |
| Hodgkin's disease  | 1 (0.2)        | 0 (0.0)        |
| Malignant melanoma   | 0 (0.0)        | 1 (0.4)        |
| Neoplasm skin  | 1 (0.2)        | 0 (0.0)        |
| Squamous cell carcinoma  | 1 (0.2)        | 1 (0.4)        |
| Uterine cancer   | 1 (0.2)        | 0 (0.0)        |
| <b>Nervous system disorders</b>  | <b>4 (0.8)</b> | <b>1 (0.4)</b> |
| Cerebral infarction  | 0 (0.0)        | 1 (0.4)        |
| Cervicobrachial syndrome   | 1 (0.2)        | 0 (0.0)        |
| Headache   | 1 (0.2)        | 0 (0.0)        |
| Migraine   | 1 (0.2)        | 0 (0.0)        |
| Transient ischemic attack  | 1 (0.2)        | 0 (0.0)        |
| <b>Psychiatric disorders</b>   | <b>1 (0.2)</b> | <b>0 (0.0)</b> |
| Suicidal ideation  | 1 (0.2)        | 0 (0.0)        |
| <b>Renal and urinary disorders</b>   | <b>0 (0.0)</b> | <b>2 (0.8)</b> |
| Calculus ureteric  | 0 (0.0)        | 1 (0.4)        |
| Renal failure acute  | 0 (0.0)        | 1 (0.4)        |
| <b>Reproductive system and breast disorders</b>                            | <b>0 (0.0)</b> | <b>1 (0.4)</b> |
| Vaginal prolapse   | 0 (0.0)        | 1 (0.4)        |
| <b>Respiratory, thoracic and mediastinal disorders</b>                     | <b>1 (0.2)</b> | <b>0 (0.0)</b> |
| Lung disorder  | 1 (0.2)        | 0 (0.0)        |

(Source: Sponsor's submission P009 CSR Page 208 Table 12-8)

Although more elderly subjects reported SAEs, the incidence of SAEs was comparable between the treatment groups in each of the age groups. In elderly subjects, the incidence of SAEs was 6.8% (21/308) for the suvorexant HD group and 7.9% (12/151) in the placebo group. In the non-elderly subjects, the incidence of SAEs was 2.8% (6/213) for the suvorexant HD group and 4.7% (5/107) in the placebo group. The most

frequently reported SOC was Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps), in five elderly subjects.

During the randomized discontinuation phase, SAEs occurred in five subjects: three subjects (1.9%) who continued suvorexant HD reported one event each of positional vertigo (0.6%), cellulitis (0.6%), and squamous cell carcinoma (0.6%); one subject who switched from suvorexant HD to placebo reported breast cancer in situ; and on subject who remained on placebo reported basal cell carcinoma.

#### Drug-related AEs

In the treatment phase, suvorexant treatment resulted in a higher incidence of drug-related AEs compared to placebo. The incidences of drug-related AEs were 34.9% (182/521) in the suvorexant HD and 20.5% (53/258) in the placebo groups. The most frequent SOC was Nervous System Disorders: 20.3% (106/521) in the suvorexant HD group and 9.7% (25/258) in placebo. Specifically, somnolence occurred most frequently with incidences of 11.7% (61/521) in the suvorexant HD and 1.6% (4/258) in the placebo groups. Table 43 below shows Merck's summary of drug-related AEs with an incidence >2% in a treatment group. Note that the specific AEs (PTs) in table 43, except dizziness, occurred more frequently in suvorexant-treated subjects.

**Table 43: Drug-Related Adverse Events with Incidence >2% in any Treatment Group of Trial P009**

| <b>Adverse Event Category</b><br><b>SOC</b><br>Preferred Term          | <b>Suvorexant HD</b><br><b>N (%)</b>                   | <b>Placebo</b><br><b>N (%)</b>                    |
|--|--|---|
| Total Subjects   | 521 (100)  | 258 (100)   |
| Subjects with one or more drug-related adverse events                  | 182 (34.9)   | 53 (20.5)   |
| <b>Gastrointestinal disorders</b><br>Dry mouth                         | <b>43 (8.3)</b><br>23 (4.4)                            | <b>14 (5.4)</b><br>4 (1.6)                        |
| <b>General disorders and administration site conditions</b><br>Fatigue | <b>30 (5.8)</b><br>22 (4.2)                            | <b>7 (2.7)</b><br>3 (1.2)                         |
| <b>Investigations</b>  | <b>13 (2.5)</b>  | <b>8 (3.1)</b>                                    |
| <b>Musculoskeletal and connective tissue disorders</b>                 | <b>11 (2.1)</b>  | <b>2 (0.8)</b>                                    |
| <b>Nervous system disorders</b><br>Dizziness<br>Headache<br>Somnolence | <b>106 (20.3)</b><br>15 (2.9)<br>18 (3.5)<br>61 (11.7) | <b>25 (9.7)</b><br>10 (3.9)<br>8 (3.1)<br>4 (1.6) |
| <b>Psychiatric disorders</b><br>Abnormal dreams                        | <b>40 (7.7)</b><br>17 (3.3)                            | <b>8 (3.1)</b><br>5 (1.9)                         |

(Source: Sponsor's submission P009 CSR Page 206 Table 12-7)



Age group analyses of trial P009's treatment phase showed a greater proportion of subjects on suvorexant reported drug-related AEs in both elderly and non-elderly subjects. In elderly subjects, the incidence of drug-related AEs was 30.5% (94/308) for the suvorexant HD group and 20.5% (31/151) in the placebo group. In the non-elderly subjects, the incidence of drug-related AEs was 41.3% (88/213) for the suvorexant HD group and 20.6% (22/107) in the placebo group. In both age groups, the most frequently reported SOC was Nervous System Disorders, which in elderly subjects, occurred at an incidence of 16.2% (50/308) in suvorexant HD subjects compared to 11.3% (17/151) in placebo subjects. In non-elderly subjects, Nervous System Disorders SOC occurred at an incidence of 26.3% (56/213) in suvorexant HD subjects compared to 7.5% (8/107) in placebo subjects.

During the randomized discontinuation phase, drug-related AEs occurred in 3.8% (6/156) of subjects who continued suvorexant treatment, 3.7% (6/162) of subjects who remained on placebo, and 1.8% (3/166) of subjects who switched to placebo. Merck reported the following statement on page 206 of trial P009 CSR: "The only specific drug-related AE with incidence  $\geq 2\%$  that occurred during the Randomized Discontinuation Phase was nightmares in the elderly age group (2.0% in MK/MK 0% MK/PBO and PBO/PBO groups)." However, the statement may have been referring to non-elderly subjects instead, as Table 14-223 on pages 974 to 977 lists nightmares with an incidence of 2% (1/51) under non-elderly subjects who remained on suvorexant HD (MK/MK). The table reported no elderly MK/MK subject with nightmares.

#### Discontinuations Because of AEs

AEs leading to treatment discontinuation occurred in 83 subjects and was more frequent in suvorexant-treated subjects with an incidence of 11.7% (61/521) compared to placebo subjects with an incidence of 8.5% (22/258). Also, more subjects discontinued due to a drug-related AE in the suvorexant group compared to the placebo group: 8.3% (43/521) of suvorexant HD group and 4.7% (12/258) of the placebo group.

The most frequent event SOC leading to discontinuation was Nervous System Disorders: 6.5% (34/521) in the suvorexant HD group and 1.9% (5/258) in placebo. Events due to somnolence occurred most frequently with incidences of 3.8% (20/521) in the suvorexant HD and 0.8% (2/258) in the placebo groups. Two (0.4%) additional subjects on suvorexant HD and none (0.0%) on placebo discontinued because of sedation. Discontinuations due to memory impairment occurred in 4 subjects (0.8%) on suvorexant HD and none (0.0%) on placebo. Further, under the SOC of General disorders and administration site conditions, fatigue led to discontinuations in 1.3% (7/521) of suvorexant HD subjects on and 0.4% (1/258) of placebo subjects.



**Table 44: Discontinuations due to Adverse Events with Incidence >0% in any Treatment Group of Trial P009**

| <b>Adverse Event Category</b><br><b>SOC</b><br>Preferred Term | <b>Suvorexant HD</b><br><b>N (%)</b> | <b>Placebo</b><br><b>N (%)</b> |
|---|--------------------------------------|--------------------------------|
| Total Subjects  | 521 (100)                            | 258 (100)                      |
| Subjects with one or more adverse events for discontinuation  | 61 (11.7)                            | 22 (8.5)                       |
| <b>Cardiac disorders</b>                                      | <b>2 (0.4)</b>                       | <b>2 (0.8)</b>                 |
| Atrial fibrillation   | 1 (0.2)                              | 2 (0.8)                        |
| Coronary artery disease                                       | 1 (0.2)                              | 0 (0.0)                        |
| <b>Gastrointestinal disorders</b>                             | <b>0 (0.0)</b>                       | <b>2 (0.8)</b>                 |
| Ileus   | 0 (0.0)                              | 1 (0.4)                        |
| Nausea  | 0 (0.0)                              | 1 (0.4)                        |
| <b>General disorders and administration site conditions</b>   | <b>8 (1.5)</b>                       | <b>3 (1.2)</b>                 |
| Chest pain  | 1 (0.2)                              | 0 (0.0)                        |
| Fatigue   | 7 (1.3)                              | 1 (0.4)                        |
| Feeling abnormal  | 0 (0.0)                              | 1 (0.4)                        |
| Gait disturbance  | 0 (0.0)                              | 1 (0.4)                        |
| <b>Infections and infestations</b>                            | <b>1 (0.2)</b>                       | <b>0 (0.0)</b>                 |
| Diverticulitis  | 1 (0.2)                              | 0 (0.0)                        |
| <b>Injury, poisoning and procedural complications</b>         | <b>1 (0.2)</b>                       | <b>2 (0.8)</b>                 |
| Ankle fracture  | 0 (0.0)                              | 1 (0.4)                        |
| Clavicle fracture   | 1 (0.2)                              | 0 (0.0)                        |
| Joint dislocation   | 0 (0.0)                              | 1 (0.4)                        |
| <b>Investigations</b>   | <b>2 (0.4)</b>                       | <b>3 (1.2)</b>                 |
| Blood amylase increased                                       | 1 (0.2)                              | 0 (0.0)                        |
| Blood calcium increased                                       | 1 (0.2)                              | 0 (0.0)                        |
| Blood creatine phosphokinase increase                         | 0 (0.0)                              | 2 (0.8)                        |
| Blood lactate dehydrogenase decrease                          | 1 (0.2)                              | 0 (0.0)                        |
| Blood magnesium increased                                     | 1 (0.2)                              | 0 (0.0)                        |
| Lipase increased  | 1 (0.2)                              | 1 (0.4)                        |
| <b>Musculoskeletal and connective tissue disorders</b>        | <b>3 (0.6)</b>                       | <b>0 (0.0)</b>                 |
| Myalgia   | 1 (0.2)                              | 0 (0.0)                        |
| Pain in extremity   | 1 (0.2)                              | 0 (0.0)                        |
| Spinal column stenosis  | 1 (0.2)                              | 0 (0.0)                        |

|  |                 |                |
|--|-----------------|----------------|
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> | <b>3 (0.6)</b>  | <b>0 (0.0)</b> |
| B-cell lymphoma  | 1 (0.2)         | 0 (0.0)        |
| Hodgkin's disease  | 1 (0.2)         | 0 (0.0)        |
| Uterine cancer   | 1 (0.2)         | 0 (0.0)        |
| <b>Nervous system disorders</b>  | <b>34 (6.5)</b> | <b>5 (1.9)</b> |
| Balance disorder   | 1 (0.2)         | 0 (0.0)        |
| Dizziness  | 1 (0.2)         | 2 (0.8)        |
| Lethargy   | 1 (0.2)         | 0 (0.0)        |
| Memory impairment  | 4 (0.8)         | 0 (0.0)        |
| Migraine   | 1 (0.2)         | 0 (0.0)        |
| Paraesthesia   | 1 (0.2)         | 1 (0.4)        |
| Parkinson's disease  | 1 (0.2)         | 0 (0.0)        |
| Poor quality sleep   | 1 (0.2)         | 0 (0.0)        |
| Sedation   | 2 (0.4)         | 0 (0.0)        |
| Sleep paralysis  | 1 (0.2)         | 0 (0.0)        |
| Somnolence   | 20 (3.8)        | 2 (0.8)        |
| <b>Psychiatric disorders</b>   | <b>9 (1.7)</b>  | <b>4 (1.6)</b> |
| Abnormal dreams  | 1 (0.2)         | 0 (0.0)        |
| Affective disorder   | 1 (0.2)         | 0 (0.0)        |
| Anxiety  | 0 (0.0)         | 2 (0.8)        |
| Bradyphrenia   | 1 (0.2)         | 0 (0.0)        |
| Depressed mood   | 1 (0.2)         | 0 (0.0)        |
| Depression   | 2 (0.4)         | 0 (0.0)        |
| Hallucination, auditory  | 1 (0.2)         | 0 (0.0)        |
| Hallucination, visual  | 1 (0.2)         | 0 (0.0)        |
| Hypnagogic hallucination   | 1 (0.2)         | 0 (0.0)        |
| Insomnia   | 0 (0.0)         | 2 (0.8)        |
| Somnambulism   | 1 (0.2)         | 0 (0.0)        |
| Suicidal ideation  | 1 (0.2)         | 0 (0.0)        |
| <b>Renal and urinary disorders</b>   | <b>0 (0.0)</b>  | <b>1 (0.4)</b> |
| Renal failure acute  | 0 (0.0)         | 1 (0.4)        |

(Source: Sponsor's submission P009 CSR Page 212 Table 12-10)

In age group analyses of the trial's treatment phase, discontinuations because of AEs were similar between the treatment groups in elderly subjects: 12.0% (37/308) on suvorexant HD and 11.9% (18/151) on placebo. However, in the non-elderly subjects, a greater proportion of subjects on suvorexant discontinued because of AEs: 11.3% (24/213) on suvorexant HD compared to 3.7% (4/107) on placebo. Specifically somnolence led to discontinuations in non-elderly subjects in 3.8% (8/213) on suvorexant HD compared to 0.9% (1/107) on placebo. Similarly in elderly subjects, somnolence led to discontinuations in 3.9% (12/308) on suvorexant HD compared to 0.7% (1/151) on placebo.

During the randomized discontinuation phase, only one subject, a 69 year old female who switched to placebo (MK/PBO group), discontinued because of an AE of breast cancer.

#### Common AEs

The percentage of subjects who reported one or more adverse events on suvorexant HD (69.5%, 362/521) was comparable to placebo (63.6 %, 164/258) during the treatment phase. Similarly, the percentages of elderly and non-elderly subjects who reported one or more adverse events were comparable across treatment groups.

Merck evaluated for AE system organ classes (SOCs) in which suvorexant subjects reported more AEs than placebo subjects, and in which the 95% confidence intervals of the risk difference between treatment groups excluded zero. As show on table below, four SOCs met these conditions: General Disorders and Administration Site Conditions, Immune System Disorders, Nervous System Disorders, and Psychiatric Disorders. The most frequent AEs were nervous system disorders, with incidence in the suvorexant group 29.2% (152/521) compared to placebo 21.3% (55/258).

**Table 45: Adverse Events by System Organ Classes (SOCs) with Higher Incidence in Suvorexant Group and with Significant Risk Difference**

| Dictionary-Derived Term (SOC)                        | Suvorexant HD<br>N=521<br>n (%) | Placebo<br>N=258<br>n (%) | Risk Difference<br>(95% CI) |
|--|---------------------------------|---------------------------|-----------------------------|
| General Disorders and Administration Site Conditions | 64 (12.3)                       | 16 (6.2)                  | 6.1 (1.7, 10.0)             |
| Immune System Disorders                              | 10 (1.9)                        | 0 (0.0)                   | 1.9 (0.4, 3.5)              |
| Nervous System Disorders                             | 152 (29.2)                      | 55 (21.3)                 | 7.9 (1.3, 14.0)             |
| Psychiatric Disorders                                | 58 (11.1)                       | 15 (5.8)                  | 5.3 (1.1, 9.1)              |

(Source: Modified from Sponsor's submission P009 CSR Page 198 Table 12-5)

The AE with the highest incidence during the treatment period was somnolence, which occurred in 13.2% (69/521) of the suvorexant HD group and 2.7% (7/258) of the placebo group. Four other **AEs were more prevalent on suvorexant HD and the 95% confidence interval of the risk difference from placebo excluded zero**. The risk difference (95% CI) for the four AEs were as follows: dry mouth, 3.4 (95% CI: 0.7, 5.9); dyspepsia, 1.9 (95% CI: 0.4, 3.5); fatigue, 4.6 (95% CI: 1.6, 7.4); and peripheral edema, 1.7 (95% CI: 0.3, 3.3). Below I summarize the adverse events by preferred terms (PTs) that occurred at an incidence of at least 2% in a treatment group.

**Table 46: Subjects with Adverse Event Preferred Terms of Incidence >2% in a Treatment Group in Trial P009**

| Dictionary-Derived Term (PT)      | Suvorexant HD<br>N=521 | Placebo<br>N=258 | Total Subjects<br>N=779 |
|-----------------------------------|------------------------|------------------|-------------------------|
| Somnolence                        | 69 (13.24%)            | 7 (2.71%)        | 76 (9.73%)              |
| Headache                          | 44 (8.45%)             | 22 (8.53%)       | 66 (8.45%)              |
| Nasopharyngitis                   | 42 (8.06%)             | 20 (7.75%)       | 62 (7.94%)              |
| Dizziness                         | 24 (4.61%)             | 16 (6.20%)       | 40 (5.12%)              |
| Upper respiratory tract infection | 28 (5.37%)             | 11 (4.26%)       | 39 (4.99%)              |
| Fatigue                           | 34 (6.53%)             | 5 (1.94%)        | 39 (4.99%)              |
| Dry mouth                         | 26 (4.99%)             | 4 (1.55%)        | 30 (3.84%)              |
| Diarrhoea                         | 17 (3.26%)             | 9 (3.49%)        | 26 (3.33%)              |
| Nausea                            | 18 (3.45%)             | 7 (2.71%)        | 25 (3.20%)              |
| Abnormal dreams                   | 19 (3.65%)             | 6 (2.33%)        | 25 (3.20%)              |
| Drug administration error         | 13 (2.50%)             | 12 (4.65%)       | 25 (3.20%)              |
| Arthralgia                        | 16 (3.07%)             | 8 (3.10%)        | 24 (3.07%)              |
| Back pain                         | 15 (2.88%)             | 7 (2.71%)        | 22 (2.82%)              |
| Fall                              | 12 (2.30%)             | 8 (3.10%)        | 20 (2.56%)              |
| Cough                             | 14 (2.69%)             | 5 (1.94%)        | 19 (2.43%)              |
| Urinary tract infection           | 12 (2.30%)             | 6 (2.33%)        | 18 (2.30%)              |
| Influenza                         | 14 (2.69%)             | 4 (1.55%)        | 18 (2.30%)              |
| Sinusitis                         | 9 (1.73%)              | 7 (2.71%)        | 16 (2.05%)              |
| Pain in extremity                 | 10 (1.92%)             | 6 (2.33%)        | 16 (2.05%)              |
| Nightmare                         | 13 (2.50%)             | 2 (0.78%)        | 15 (1.92%)              |
| Hypertension                      | 8 (1.54%)              | 7 (2.71%)        | 15 (1.92%)              |
| Oropharyngeal pain                | 5 (0.96%)              | 6 (2.33%)        | 11 (1.41%)              |
| Lipase increased                  | 5 (0.96%)              | 6 (2.33%)        | 11 (1.41%)              |
| Constipation                      | 3 (0.58%)              | 7 (2.71%)        | 10 (1.28%)              |
| Oropharyngeal pain                | 5 (0.96%)              | 6 (2.33%)        | 11 (1.41%)              |
| Lipase increased                  | 5 (0.96%)              | 6 (2.33%)        | 11 (1.41%)              |
| Constipation                      | 3 (0.58%)              | 7 (2.71%)        | 10 (1.28%)              |

(Source: Reviewer Analyses; Shaded portions show AEs more prevalent in suvorexant group)

*Reviewer Comment:*

*The common AEs observed in trial P009 appear typical for an insomnia drug development program.*

**Adverse Events of Special Interests**

Although the incidences of ECIs were low in Trial P009, most of them occurred more frequently in subjects on suvorexant HD. Merck reported no statistically significant difference in the proportion of subjects with any ECI between the treatment groups during the treatment phase. No event of cataplexy was confirmed by the adjudication

committee. One subject reported both visual and auditory hallucinations on Day 324 of suvorexant HD treatment. The adjudication committee confirmed one case of sleep onset paralysis. Below I summarize the incidences of the ECIs. Section 5 of this review contains additional assessments of ECIs.

**Table 47: Events of Clinical Interest (ECI) in Trial P009 Treatment Phase**

| <b>Events of Clinical Interest (ECIs)</b>   | <b>Suvorexant HD % (n/N)</b> | <b>Placebo % (n/N)</b> | <b>Risk Difference (95% CI)</b> | <b>P value</b>  |
|---|------------------------------|------------------------|---------------------------------|-----------------|
| Total Subjects  | 521                          | 258                    |                                 |                 |
| <b>Suicidal ideation or behaviors</b>   | <b>0.8% (4/521)</b>          | <b>0.0% (0/258)</b>    | <b>0.8 (-0.7, 2.0)</b>          | <b>0.159</b>    |
| <b>Events associated with potential for abuse</b>   | <b>3.5% (18/521)</b>         | <b>3.9% (10/258)</b>   | <b>-0.4 (-3.8, 2.2)</b>         | <b>0.767</b>    |
| Drug maladministration  | 2.3% (12/521)                | 3.9% (10/258)          | -1.6 (-4.8, 0.8)                | 0.213           |
| Derealisation   | 0.2% (1/521)                 | 0.0% (0/258)           | 0.2 (-1.3, 1.1)                 | 0.482           |
| Hallucination, auditory and visual  | 0.2% (1/521)                 | 0.0% (0/258)           | 0.2 (-1.3, 1.1)                 | 0.482           |
| Hypnagogic hallucination  | 0.6% (3/521)                 | 0.0% (0/258)           | 0.6 (-0.9, 1.7)                 | 0.222           |
| Hypnopompic hallucination   | 0.2% (1/521)                 | 0.0% (0/258)           | 0.2 (-1.3, 1.1)                 | 0.482           |
| <b>Complex sleep-related behaviors (Somnambulism)</b>                                     | <b>0.2% (1/521)</b>          | <b>0.0% (0/258)</b>    | <b>0.2 (-1.3, 1.1)</b>          | <b>0.482</b>    |
| <b>Hypnagogic or hypnopompic hallucinations</b>   | <b>0.8% (4/521)</b>          | <b>0.0% (0/258)</b>    | <b>0.8 (-0.7, 2.0)</b>          | <b>0.159</b>    |
| Hypnagogic hallucination  | 0.6% (3/521)                 | 0.0% (0/258)           | 0.6 (-0.9, 1.7)                 | 0.222           |
| Hypnopompic hallucination   | 0.2% (1/521)                 | 0.0% (0/258)           | 0.2 (-1.3, 1.1)                 | 0.482           |
| <b>Excessive daytime sleepiness</b>   | <b>2.5% (13/521)</b>         | <b>0.8% (2/258)</b>    | <b>1.7 (-0.5, 3.6)</b>          | <b>&gt;0.05</b> |
| <b>Sleep paralysis</b>  | <b>0.4% (2/521)</b>          | <b>0.0% (0/258)</b>    | <b>0.4 (-1.1, 1.4)</b>          | <b>&gt;0.05</b> |
| Sleep onset paralysis   | 0.2% (1/521)                 | 0.0% (0/258)           | 0.2 (-1.3, 1.1)                 | 0.482           |
| <b>Cataplexy</b>  | <b>0.0% (0/521)</b>          | <b>0.0% (0/258)</b>    | <b>0.0 (no event)</b>           | <b>&gt;0.05</b> |
| <b>Falls</b>  | <b>2.3% (12/521)</b>         | <b>3.1% (8/258)</b>    | <b>-0.8 (-3.9, 1.5)</b>         | <b>0.508</b>    |
| <b>AEs associated with traffic or motor vehicle accidents, with subject as the driver</b> | <b>0.4% (2/521)</b>          | <b>0.0% (0/258)</b>    | <b>0.4 (95% CI, not stated)</b> | <b>&gt;0.05</b> |

(Source: Modified from Sponsor's submission P009 CSR Pages 217, 224, 226 to 232; Tables 12-11, 12-14 to 12-21)

Merck provided additional information on events that were related to ECIs but not reported as ECIs. Four cases of suicidal ideation were reported as ECIs during the treatment phase, as noted in table 47 above. A fifth case was determined on C-CASA



assessment. During the follow-up period, one additional subject, who had been on suvorexant, reported suicidal ideation.

Using the Motor Vehicle Accidents and Violations (MVAV) Questionnaire, Merck assessed for occurrence of traffic or MVA since the subject's last visit and any related injuries. Although Merck suggests that no association was found between suvorexant administration and occurrence of MVAs, **numerically more subjects on suvorexant HD (5.5%, 22/397) compared to placebo (4.1%, 8/196) had at least one MVAV event.** A similar pattern was observed for number of subjects with accidents. The table below summarizes the MVAV events in Trial P009.

**Table 48: Subjects with Motor Vehicle Accidents or Violations (MVAV) in Trial P009 Treatment Phase**

| MVAV Category  | Suvorexant HD<br>N (%) | Placebo<br>N (%) |
|--|------------------------|------------------|
| Total Subjects   | 397                    | 196              |
| Subjects with one or more MVAV events<br>Number of MVAV events | 22 (5.5)<br>24         | 8 (4.1)<br>11    |
| Subjects with Accidents<br>Number of Accidents                 | 7 (1.8)<br>7           | 3 (1.5)<br>3     |
| Subjects with violations<br>Number of violations               | 15 (3.8)<br>17         | 6 (3.1)<br>8     |

(Source: Modified from Sponsor's submission P009 CSR Page 233 Table 12-22)

No reports of suicidal ideation, complex sleep-related behaviors, hallucinations, or sleep paralysis occurred during the randomized discontinuation phase.

#### Rebound and Withdrawal

Merck compared the sleep parameters of sTST, sTSO, and sWASO between the MK/PBO and PBO/PBO groups on the first 3 nights of run-out to the last baseline values, and determined that no statistically significant differences indicative of clinically meaningful rebound were observed in Trial P009. However, the proportion of subjects with rebound, based on sTST on nights 1, 2, or 3, was numerically higher in subjects who switched to placebo (MK/PBO: 51.0%, 80/157) compared to those who remained on placebo (PBO/PBO: 40.1%, 61/152) with a treatment difference of 10.8 (95% CI, -0.3, 21.7; p value=0.057). The incidence in the MK/MK group was 28.9% (44/152). With regards to withdrawal, the treatment groups were similar in proportion of subjects who reported withdrawal symptoms across nights 1, 2, and 3.

#### Laboratory Values over Time

Merck assessed laboratory measurements using mean values at baseline, treatment period, and change-from-baseline values. Based on the values, no remarkable changes in lab values were noted. During the randomized discontinuation phase, elderly subjects showed increases in creatine kinase mean (SD) values at Month 13 for MK/PBO subjects: MK/PBO, 12.3 (62.8); MK/MK, -2.7 (46.8); and PBO/PBO, 11.7 (48.4). A similar pattern occurred at Month 14: MK/PBO, 7.6 (58.2); MK/MK, -2.4 (61.5); and PBO/PBO, 20.2 (56.9).

*Reviewer Comment:*

*The changes in creatine kinase are unlikely to be clinically significant, especially with a comparable change in subjects who remained on placebo (PBO/PBO).*

Laboratory Values meeting Pre-defined Limits of Change

Also, Merck assessed laboratory measurements using pre-defined limits of change to show changes in laboratory values that are likely to be clinically significant. Based on the pre-defined Tier 2 safety assessment plan, there were no significant differences between the treatment groups in all laboratory parameters, as the 95% confidence intervals for the treatment differences included zero. Although elevated potassium levels ( $\geq 111.1\%$  ULN) occurred more frequently in subjects on suvorexant HD (3.1%, 16/515) compared to placebo (2.0%, 2/254), the confidence interval for the risk difference of 1.1 included zero (-1.6 to 3.4).

Vital Signs

Based on change in mean values, no significant differences occurred between the groups in SBP, DBP, pulse rate, temperature, and weight. Also, no clinically significant differences between the treatment groups, overall or in either age group, were observed based on proportion of subjects meeting the pre-defined limits of change in the vital signs.

ECG

Based on change in mean values or proportion of subjects exceeding pre-defined limits of change from baseline in QTc Interval (Bazett), no significant differences occurred between the treatment groups.

*Reviewer Comment:*

*Trial P009 showed no significant imbalances in laboratory values, vital signs, and ECG data. Further, Trial P009 contributes to the pooled analyses of overall safety of suvorexant that I discuss extensively in Section 5 of this review. Rebound effect and withdrawal of suvorexant are also discussed more extensively in Section 5.*

## 4 Review of Efficacy

### **Efficacy Summary**

The overall data from two confirmatory efficacy trials showed that suvorexant high dose (HD) had statistically significant efficacy effect on both sleep maintenance and sleep onset endpoints in adult subjects with primary insomnia. The efficacy effects of suvorexant HD persisted through the entire treatment period and appeared clinically meaningful. Suvorexant low dose (LD), which was not primarily evaluated in the trials, appeared to have some efficacy effect on sleep maintenance insomnia. In the trials, suvorexant HD signified 30 mg for elderly subjects and 40 mg for non-elderly subjects, suvorexant LD was 15 mg for elderly subjects and 20 mg for non-elderly subjects.

Two parallel-group 3-month Phase 3 trials, P028 and P029, provide the primary support of efficacy for suvorexant treatment of primary insomnia. The two similarly designed trials were conducted in the US and non-US sites. Both trials shared the same primary objective: to evaluate the efficacy of suvorexant HD compared with placebo in improving sleep maintenance and sleep onset at Months 1 and 3, using subjective patient-reported outcomes and objective polysomnographic (PSG) assessments. Suvorexant HD consisted of 30 mg in elderly subjects (65 years and older) and 40 mg in non-elderly subjects (younger than 65 years).

The trials used multiple endpoints to assess the efficacy of suvorexant. For sleep maintenance, Merck compared the treatment effects of suvorexant HD and placebo on two primary endpoints that were assessed at two time points, as follows: change from baseline in mean subjective total sleep time, sTSTm, at Month 1 and Month 3; and change from baseline in the PSG-derived objective wakefulness after persistent sleep onset, WASO, at Month 1 and Month 3. Likewise for sleep onset, suvorexant HD treatment effects were assessed by the following endpoints: change from baseline in mean subjective time to sleep onset, sTSOm, at Month 1 and Month 3; and change from baseline in objective latency to persistent sleep, LPS, at Month 1 and Month 3.

Key secondary endpoints in trial P028 included change from baseline in sTSTm at Week 1 and WASO at Night 1 for suvorexant HD, and an assessment of suvorexant LD on all the above-stated endpoints and time points for suvorexant HD. Trial P029 assessed suvorexant LD as exploratory analyses.

Merck used a multiplicity testing strategy to assess the primary and secondary endpoints. A longitudinal data analysis (LDA) model was used to perform the statistical analyses for efficacy. The analysis model adjusted for baseline values of the response variable, age group (non-elderly versus elderly), region, gender, treatment, time, and the interaction of treatment by time. To control for type 1 error, Merck analyzed the primary and secondary endpoints using a multiplicity testing strategy that included a



Bonferroni approach to evaluate two distinct indications – sleep maintenance and sleep onset effects. The strategy also encompassed a fixed sequential testing procedure to move from Month 1 to Month 3 sets of primary hypotheses, and a Hochberg approach within each time point to evaluate the objective and subjective endpoints. As a result, endpoints for sleep maintenance effect (sTSTm and WASO) were tested at the two-sided 2.5% alpha level, while endpoints for sleep onset effect (sTSOm and LPS) were also tested at the two-sided 2.5% level. Overall, the trial's choice of endpoints, blinding procedure, duration, conduct, and statistical analyses appear adequate.

An earlier phase 2 dose finding trial P006 that evaluated multiple suvorexant doses from 10 mg to 80 mg in non-elderly subjects informed on the choice of dose to study in the phase 3 trials. The 40 mg dose chosen for further assessment appears appropriate based on the 4-week treatment effect on both objective and subjective endpoints. Using drug exposure data from prior clinical pharmacology studies, Merck chose a 30 mg dose to treat elderly subjects in the Phase 3 trials; this dose was considered comparable to the 40 mg dose in non-elderly subjects. Both doses for the two age groups are referred to as suvorexant HD. Based on feedback from regulatory interaction with FDA during the drug development, Merck included a lower dose in the phase 3 program, suvorexant LD, which consisted of 15 mg for elderly subjects and 20 mg for non-elderly subjects.

#### Sleep Maintenance Effects

For sleep maintenance, suvorexant HD treatment, in both confirmatory efficacy trials P028 and P029, resulted in statistically significant improvements on both subjective (sTSTm) and objective (WASO) primary endpoints at Month 1 and Month 3. Based on the pooled data, suvorexant HD compared to placebo treatment added about 22 minutes of subjective total sleep time, and reduced objective wakefulness after persistent sleep by 26 minutes at Month 3. Supporting efficacy assessments using the subjective endpoint sWASO showed similar improvements with suvorexant HD compared to placebo at all time points.

Assessment of secondary endpoints provided additional support for efficacy of suvorexant in treating sleep maintenance insomnia. In the secondary analyses for both trials P028 and P029, suvorexant HD significantly improved sTSTm and WASO at all pre-defined time points.

Also in trial P028, suvorexant LD significantly improved the sleep maintenance endpoints sTSTm and WASO at all predefined time. Trial P029 did not include suvorexant LD for secondary endpoint assessment. Based on the pooled data, suvorexant LD compared to placebo treatment added 16 minutes of sTSTm ( $p < 0.00001$ ), and reduced WASO by 23 minutes at Month 3 ( $p < 0.00001$ ). Importantly, suvorexant LD failed to significantly improve sWASOm at Months 1 and 3 in trial P028. Of note, FDA had previously requested sWASO as a key sleep maintenance endpoint.

Overall, suvorexant HD, and to a less extent suvorexant LD, showed significant improvement in sleep maintenance endpoints. The difference between the treatment effect of suvorexant HD and that of suvorexant LD is about 6 minutes on sTSTm and 3 minutes on WASO. Whether this difference in treatment effects between the suvorexant doses is sufficient to allow approval of the lower dose for sleep maintenance will be a topic of discussion at the advisory committee meeting. Of note, an acceptance of suvorexant LD as an effective treatment for sleep maintenance will ignore the inconsistent effect of the dose on sWASO in trial P028.

#### Sleep Onset Effects

Suvorexant HD treatment improved sleep onset compared to placebo, though not as consistently as in sleep maintenance. In both confirmatory efficacy trials P028 and P029, suvorexant HD treatment resulted in statistically significant improvements on the subjective (sTSOm) primary endpoint for sleep onset at Month 1 and Month 3. In trial P028, suvorexant HD significantly improved the objective primary endpoint LPS at Month 1 and Month 3. However in trial P029, suvorexant HD significantly improved LPS at Month 1 but failed to provide similar LPS improvement at Month 3. Based on the pooled data from trials P028 and P029, suvorexant HD compared to placebo treatment decreased subjective time to sleep onset by about 11 minutes ( $p < 0.00001$ ) and objective LPS by 6 minutes ( $p = 0.00235$ ) at Month 3.

The secondary efficacy endpoints assessed for sleep onset, sTSOm at Week 1 and LPS at Night 1, showed significant improvements with suvorexant HD compared to placebo treatment in both trials P028 and P029.

Secondary endpoint assessment for suvorexant LD in trial P028 showed inconsistent improvements on sleep onset endpoints at different time points. Suvorexant LD significantly improved sTSOm at Week 1 and LPS at Night 1. The dose improved LPS at Month 1 by 10.3 minutes compared to placebo ( $p = 0.0004$ ), but it did not significantly improve sTSO compared to placebo despite a 5.4-minute decrease in the endpoint ( $p = 0.05191$ ).

Overall, suvorexant HD consistently showed significant improvement in the subjective sleep onset endpoint. The dose showed significant improvement in the objective sleep onset endpoint at all time points, except at Month 3 in one of the two trials. In contrast, suvorexant LD showed inconsistent improvements on sleep onset endpoints at different time points. Whether the inability of suvorexant HD to significantly improve LPS at Month 3 is sufficient to deny approval of the dose for sleep onset will be a topic of discussion at the advisory committee meeting.

#### Clinical Significance of Efficacy Based on Responder Analysis

Merck conducted analyses on pre-specified responder analyses based on exploratory subjective endpoints to further assess the clinical meaningfulness of suvorexant treatment effects. For sleep maintenance, a higher percentage of subjects on

suvorexant treatment recorded at least 15% increase from baseline in sTSTm at the different time points in the pooled data. The percentage of sTST responders in the treatment groups at Month 3 was 54.7% (376/688) for suvorexant HD compared to 41.9% (278/664) for placebo, a treatment difference of 12.8% that yielded a number needed to treat to benefit (NNTB) of 8. For sWASO, the percentage of responders in the treatment groups at Month 3 was 77.5% (529/683) for suvorexant HD compared to 69.4% (458/660) for placebo, a treatment difference of 8.1% and NNTB of 12.

For sleep onset, the pooled data from P028 and P029 trials showed that a higher percentage of subjects recorded improvement in subjective sleep onset based on at least 15% decrease from baseline in sTSOm at the different time points with suvorexant treatment. The percentage of sTSO responders in the treatment groups at Month 3 was 76.5% (526/688) for suvorexant HD compared to 66.0% (438/664) for placebo, a treatment difference of 10.5% that yielded an NNTB of 10.

The overall data suggest that suvorexant HD has clinically significant efficacy on both sleep maintenance and sleep onset in subjects with primary insomnia. The assessments showed that the efficacy of suvorexant HD persisted through the entire treatment period. Suvorexant LD, though not primarily evaluated in the trials, appears to have some significant but limited efficacy on sleep maintenance insomnia. In addition, point estimates, shown in review section 4.1.7, for the sleep maintenance and sleep onset endpoints from the pooled data suggest that improvements from suvorexant (HD and LD) treatment were generally consistent across the subgroups.

## **4.1 Indication**

Suvorexant is proposed for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The proposed dose is 40 mg in non-elderly adults, or 30 mg in elderly adults, once daily immediately before bedtime.

### **4.1.1 Methods**

The two similarly designed trials provide primary support for efficacy of suvorexant in treating insomnia for at least three months. The two trials, P028 and P029, had similar primary endpoints to assess improvements in sleep onset, sTSO and LPS, and sleep maintenance, sTST and WASO. In addition, the two 3-arm trials primarily assessed the superiority of suvorexant HD over placebo in improving the sleep parameters during 3 months of treatment. Secondly, the trials assessed benefit of suvorexant LD in treating the sleep parameters. The trials also evaluated the effect of the suvorexant doses on sWASO, an endpoint traditionally used to assess sleep maintenance. Trial P028 further added a 3-month extension phase to evaluate longer treatment effects.

Both trials were adequately designed to evaluate efficacy of suvorexant HD in subjects with primary insomnia. Section 3 provided extensive discussion on the individual trials.

Statistical analysis plans showed that the trials were adequately powered to detect a treatment difference between suvorexant HD and placebo for both sleep maintenance primary endpoints and for at least one sleep onset primary endpoint.

To support the label claims for possible use of lower doses, Merck evaluated the trials, individually and pooled, for efficacy of suvorexant LD. The two confirmatory efficacy trials, P028 and P029, provided pooled data to assess suvorexant LD for efficacy. Merck pooled data from the two trials to provide more precise estimates for treatment differences between suvorexant HD and placebo, and between suvorexant LD and placebo, for the primary and secondary efficacy endpoints. Also, the pooled data enabled Merck to further assess the treatment effects across the subgroups of age, gender, and race.

Merck used similar statistical methods as described in Section 3 of this review for the individual phase 3 trials, and additionally adjusted for the individual trials to analyze the pooled data. Phase 2 trial P006 provided data for suvorexant dose assessment in non-elderly subjects with insomnia treated for four weeks. Section 3 of this review provided additional information on the dose-finding, crossover trial P006.

The primary analyses included all subjects in the full analysis set (FAS) trial population. To be included in the FAS population for any efficacy endpoint, a subject needed to have at least one post-randomization efficacy observation after receiving at least one dose of trial treatment, and if needed, appropriate baseline data. Subjects were analyzed according to the treatment to which they were randomized, suggestive of a modified intention-to-treat approach.

Merck conducted the analyses for the primary, secondary and exploratory efficacy endpoints using the longitudinal data analysis (LDA) method that allowed for an approach of no imputation for missing data. This approach assumed that the missing data were missing at random (MAR) and was used across the trials and pooled (P028 and P029) analyses.

The efficacy assessments for suvorexant HD included non-elderly subjects treated with suvorexant 40 mg and elderly subjects treated with suvorexant 30 mg, while suvorexant LD included non-elderly subjects treated with suvorexant 20 mg and elderly subjects treated with suvorexant 15 mg. Combining the separate doses in each category was based on Merck's earlier studies that matched the respective suvorexant doses with the PK exposures for the age groups.

Merck analyzed the pooled P028 and P029 data to determine consistency of treatment effects across categories of subgroups. A category of Baseline Entry Criteria for subjective endpoints was also included in the subgroup analyses. This subgroup enabled Merck to analyze consistency of response for the key subjective endpoints in the PQ-cohort that included subjects who were enrolled based on PSG criteria. The

analysis compared subjects who met Q-Cohort entrance criteria, by having at least four out of seven pre-randomization nights (excluding PSG nights) where sTST <6.5 hours and sTSO ≥30 minutes, with those who did not meet Q-Cohort entrance criteria. The subgroups analyzed with the pooled P028 and P029 data included the following:

- Age: elderly and non-elderly
- Gender: females and males
- Race: white and other;
- Regions: North America, Europe, and Other
- Cohort: Q-Cohort vs. PQ-Cohort
- Baseline severity of insomnia: dichotomized at median severity for trial population
- Baseline Entry Criteria for subjective endpoints in PQ-cohort: sTSTm<6.5 and sTSOm>=30 compared to sTSTm>=6.5 and sTSOm<30

Also, Merck evaluated efficacy of long-term treatment with suvorexant HD. Phase 3 trial P009 assessed the persistence of suvorexant HD's efficacy in adults with insomnia beyond 3 months and up to 12 months of treatment. The long-term trial was reviewed in detail in Section 3.

#### 4.1.2 Demographics

##### *Pooled Subject Demographics P028 and P029 Trials*

The subject demographics were similar across treatment groups. The subjects' mean age was 56 years (SD, 15 years) with 839 (41.3%) subjects in the elderly age group. About 64% (1308/2030) of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race (72.6%, 1474/2030). Section 3.3 Discussion of Individual Studies/Clinical Trials described subject demographics for the individual trials contributing to efficacy assessments. Trial P028 enrolled more Asian subjects after the Q-cohort enrolled only Japanese subjects. Otherwise, the demographic data from the individual component trials, P028 and P029, were generally similar. Below is a summary of pooled subject characteristics from Trials P028 and P029.

**Table 49: Pooled Subject Characteristics Treatment Phase of Trials P028 and P029**

| Category                      | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|-------------------------------|------------------|------------------------|------------------------|----------------|
| <b>Subjects in population</b> | 767              | 493                    | 770                    | 2,030          |
| <b>Gender</b>                 |                  |                        |                        |                |
| Male                          | 275 (35.9)       | 174 (35.3)             | 273 (35.5)             | 722 (35.6)     |
| Female                        | 492 (64.1)       | 319 (64.7)             | 497 (64.5)             | 1,308 (64.4)   |
| <b>Age in years</b>           |                  |                        |                        |                |

|  |            |            |            |              |
|--|------------|------------|------------|--------------|
| Mean   | 56         | 55         | 56         | 56           |
| SD   | 15         | 16         | 15         | 15           |
| <b>Age Categories</b>                            |            |            |            |              |
| <65 years  | 449 (58.5) | 291 (59.0) | 451 (58.6) | 1,191 (58.7) |
| >=65 years                                       | 318 (41.5) | 202 (41.0) | 319 (41.4) | 839 (41.3)   |
| <b>Race</b>                                      |            |            |            |              |
| White  | 553 (72.1) | 358 (72.6) | 563 (73.1) | 1,474 (72.6) |
| Black  | 46 (6.0)   | 19 (3.9)   | 38 (4.9)   | 103 (5.1)    |
| Asian  | 124 (16.2) | 93 (18.9)  | 124 (16.1) | 341 (16.8)   |
| Other  | 44 (5.7)   | 23 (4.7)   | 45 (5.8)   | 112 (5.5)    |
| <b>Ethnicity</b>                                 |            |            |            |              |
| Hispanic or Latino                               | 123 (16.0) | 90 (18.3)  | 133 (17.3) | 346 (17.0)   |
| Not Hispanic or Latino                           | 644 (84.0) | 403 (81.7) | 637 (82.7) | 1,684 (83.0) |
| <b>Cohort</b>                                    |            |            |            |              |
| Q  | 180 (23.5) | 150 (30.4) | 180 (23.4) | 510 (25.1)   |
| PQ   | 587 (76.5) | 343 (69.6) | 590 (76.6) | 1,520 (74.9) |
| <b>Region</b>                                    |            |            |            |              |
| Asia Pacific                                     | 27 (3.5)   | 26 (5.3)   | 27 (3.5)   | 80 (3.9)     |
| Central and Eastern Europe                       | 29 (3.8)   | 17 (3.4)   | 17 (2.2)   | 63 (3.1)     |
| Central and South America                        | 42 (5.5)   | 27 (5.5)   | 47 (6.1)   | 116 (5.7)    |
| Europe   | 247 (32.2) | 165 (33.5) | 250 (32.5) | 662 (32.6)   |
| Japan  | 94 (12.3)  | 61 (12.4)  | 92 (11.9)  | 247 (12.2)   |
| Middle East/Africa                               | 15 (2.0)   | 7 (1.4)    | 9 (1.2)    | 31 (1.5)     |
| North America                                    | 313 (40.8) | 190 (38.5) | 328 (42.6) | 831 (40.9)   |
| <b>Body Mass Index (BMI) in kg/m<sup>2</sup></b> |            |            |            |              |
| Mean   | 25.6       | 25.4       | 25.7       | 25.6         |
| SD   | 4.2        | 4.1        | 4.3        | 4.2          |
| <b>BMI Category</b>                              |            |            |            |              |
| Underweight (BMI < 18.5)                         | 16 (2.1)   | 11 (2.2)   | 18 (2.3)   | 45 (2.2)     |
| Normal range (18.5 <= BMI < 25)                  | 351 (45.8) | 232 (47.1) | 323 (41.9) | 906 (44.6)   |
| Overweight (25 <= BMI <= 30)                     | 289 (37.7) | 194 (39.4) | 317 (41.2) | 800 (39.4)   |
| Obese (BMI > 30)                                 | 110 (14.3) | 56 (11.4)  | 111 (14.4) | 277 (13.6)   |
| Null   | 1 (0.1)    | 0 (0.0)    | 1 (0.1)    | 2 (0.1)      |

(Source: Modified from Sponsor's Submission ISE Page 281 Table Appendix 5.3.5.3.2-Insomnia: 19)

The mean age for the non-elderly adults was 46 years (SD, 12 years) and for the elderly subjects 71 years (4 years). The pattern of other demographic characteristics was similar between the non-elderly and non-elderly age groups.

As shown in Section 3.3 Discussion of Individual Studies/Clinical Trials, the baseline values of the subjective efficacy endpoints suggested that trial P029 had more severe insomnia symptoms than subjects in P028. However, generally there was remarkable overlap in the ranges of the baseline efficacy endpoint values, particularly with the

objectives endpoint values, WASO and LPS. Below is a summary of the mean values of the efficacy endpoints at baseline for the pooled P028 and P029 trials.

**Table 50: Pooled Subject Baseline Mean and Range of Values for Efficacy Endpoints in Minutes Treatment Phase of Trials P028 and P029**

| Endpoint | Placebo              | Suvorexant LD        | Suvorexant HD        |
|----------|----------------------|----------------------|----------------------|
| sTSTm    | 312.7 (0.0 - 548.4)  | 310.7 (0.0 - 512.9)  | 315.7 (0.0 - 502.6)  |
| sTSOm    | 74.1 (5.7 - 480.0)   | 74.3 (10.0 - 480.0)  | 71.2 (5.7 - 480.0)   |
| sWASOm   | 80.7 (0.0 - 365.0)   | 79.1 (0.0 - 303.0)   | 80.3 (0.0 - 335.1)   |
| WASO     | 116.7 (45.5 - 317.0) | 119.4 (46.0 - 332.5) | 118.6 (46.0 - 343.0) |
| LPS      | 67.1 (20.5 - 347.5)  | 67.3 (3.5 - 335.0)   | 64.6 (20.5 - 386.5)  |

(Source: Modified from Sponsor's Submission ISE Page 303 Table Appendix 5.3.5.3.2-Insonnia: 26)

#### 4.1.3 Subject Disposition

Section 3.3 Discussion of Individual Studies/Clinical Trials described subject disposition for the individual trials. For the pooled P028 and P029 trials, 2041 subjects were randomized; of these, 11 subjects received no treatment, leaving 2030 randomized subjects who received treatment. A total of 1797 (88%) subjects completed 3-month treatment. Discontinuation rates were comparable across treatment groups. More subjects withdrew from the placebo group, in part from lack of efficacy, compared to the suvorexant groups. The table below summarizes the subject disposition during the treatment phase for the pooled trials P028 and P029.

**Table 51: Disposition for Pooled P028 and P029 Trials Treatment Phase**

|                               | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total<br>N (%) |
|-------------------------------|------------------|------------------------|------------------------|----------------|
| <b>Not Randomized</b>         |                  |                        |                        | 3712           |
| Total Subjects                | 772              | 494                    | 775                    | 2041           |
| <b>Study Disposition</b>      |                  |                        |                        |                |
| Not Treated                   | 5 (0.6)          | 1 (0.2)                | 5 (0.6)                | 11 (0.5)       |
| Completed Treatment           | 671 (86.9)       | 435 (88.1)             | 691 (89.2)             | 1797 (88.0)    |
| Discontinued during Treatment | 96 (12.4)        | 58 (11.7)              | 79 (10.2)              | 233 (11.4)     |
| Adverse Event                 | 38 (4.9)         | 16 (3.2)               | 34 (4.4)               | 88 (4.3)       |
| Withdrawal by Subject         | 31 (4.0)         | 14 (2.8)               | 17 (2.2)               | 62 (3.0)       |
| Protocol Violation            | 9 (1.2)          | 10 (2.0)               | 7 (0.9)                | 26 (1.3)       |
| Lost to Follow-up             | 1 (0.1)          | 3 (0.6)                | 5 (0.6)                | 9 (0.4)        |
| Lack of Efficacy              | 17 (2.2)         | 8 (1.6)                | 11 (1.4)               | 36 (1.8)       |

|   |            |            |            |             |
|---|------------|------------|------------|-------------|
| Pregnancy   | 0 (0.0)    | 1 (0.2)    | 1 (0.1)    | 2 (0.1)     |
| Physician Decision                                      | 0 (0.0)    | 6 (1.2)    | 4 (0.5)    | 10 (0.5)    |
| <b>Protocol Milestone</b>                               |            |            |            |             |
| Completed Treatment                                     | 671 (86.9) | 435 (88.1) | 691 (89.2) | 1797 (88.0) |
| Continuing Into Extension                               | 151 (19.6) | 100 (20.2) | 172 (22.2) | 423 (20.7)  |
| Continuing Into Run-Out                                 | 513 (66.5) | 333 (67.4) | 516 (66.6) | 1362 (66.7) |
| Not Treated in Run-Out                                  | 0 (0.0)    | 0 (0.0)    | 1 (0.1)    | 1 (0.0)     |
| Not Continuing Into Extension Or Run-Out                | 7 (0.9)    | 2 (0.4)    | 3 (0.4)    | 12 (0.6)    |
| Discontinued during Treatment (not cont into Ext or RO) | 96 (12.4)  | 58 (11.7)  | 79 (10.2)  | 233 (11.4)  |

(Source: Modified from Sponsor's submission ISE Page 265 Table Appendix 5.3.5.3.2-Insomnia: 4)

*Reviewer Comment:*

*Screen failure and subject withdrawal were the most common reasons for non-randomization of subjects. Overall, about 88% of the randomized subjects completed the trial treatment. More subjects withdrew from the placebo group compared to the suvorexant groups. Also, more subjects withdrew from the placebo group because of lack of efficacy. The difference in discontinuations is unlikely to inflate the suvorexant treatment effect.*

#### 4.1.4 Analysis of Primary Endpoint(s)

A primary objective of trials P028 and P029 was to evaluate, in subjects with primary insomnia, efficacy of suvorexant high dose (HD) compared with placebo in improving sleep maintenance and onset at Months 1 and 3, using subjective patient-reported outcomes and objective polysomnographic (PSG) assessments. This section reviews the results of the primary endpoints for sleep maintenance and sleep onset.

##### Sleep Maintenance

For sleep maintenance, Merck compared the treatment effects of suvorexant HD and placebo on four primary endpoint assessments: two primary endpoints, sTSTm and WASO, assessed at two time points, Months 1 and 3, as follows:

- Change from baseline in sTSTm at Month 1
- Change from baseline in sTSTm at Month 3
- Change from baseline in WASO at Month 1
- Change from baseline in WASO at Month 3

##### Sleep Maintenance by sTSTm



In trial P028, following a multiplicity testing strategy, suvorexant HD significantly increased total sleep time, as measured by sTSTm, compared to placebo, with a treatment difference in mean change from baseline of 19.6 minutes ( $p < 0.00001$ ) at Month 1, and 19.7 minutes ( $p < 0.00001$ ) at Month 3. Although the primary endpoint analysis did not include Week 1, similar improvements in sTST with suvorexant HD occurred at that time point.

Similarly in trial P029, suvorexant HD significantly increased total sleep time, as measured by sTSTm, compared to placebo, with a treatment difference in mean change from baseline of 26.3 minutes ( $p < 0.00001$ ) at Month 1, and 25.1 minutes ( $p < 0.00001$ ) at Month 3. It is not surprising that the same pattern was observed in the pooled P028 and P029 data.

Below I summarize the results for sTSTm at the different time points in the individual trials and pooled data, including results at Week 1 and for suvorexant LD for comparisons.

**Table 52: Primary Efficacy Endpoint for Sleep Maintenance by sTSTm in Trials P028, P029, Pooled P028 and P029**

|                         | Placebo                      | Suvorexant LD                |                    |          | Suvorexant HD                |                    |          |
|-------------------------|------------------------------|------------------------------|--------------------|----------|------------------------------|--------------------|----------|
| Time point              | LS Mean change from baseline | LS Mean change from baseline | Diff. from placebo | P value  | LS Mean change from baseline | Diff. from placebo | P value  |
| <b>P028</b>             |                              |                              |                    |          |                              |                    |          |
| Week 1                  | 14.6                         | 28.2                         | 13.6               | 0.00007  | 36.0                         | 21.4               | <0.00001 |
| Month 1                 | 23.1                         | 39.4                         | 16.3               | 0.00016  | 42.6                         | 19.6               | <0.00001 |
| Month 3                 | 40.6                         | 51.2                         | 10.7               | 0.01711  | 60.3                         | 19.7               | <0.00001 |
| <b>P029</b>             |                              |                              |                    |          |                              |                    |          |
| Week 1                  | 14.0                         | 30.8                         | 16.8               | 0.00002  | 40.4                         | 26.4               | <0.00001 |
| Month 1                 | 22.4                         | 43.4                         | 20.9               | <0.00001 | 48.7                         | 26.3               | <0.00001 |
| Month 3                 | 37.7                         | 59.8                         | 22.1               | 0.00004  | 62.8                         | 25.1               | <0.00001 |
| <b>Pooled P028+P029</b> |                              |                              |                    |          |                              |                    |          |
| Week 1                  | 14.4                         | 29.4                         | 15.0               | <0.00001 | 38.1                         | 23.7               | <0.00001 |
| Month 1                 | 22.9                         | 41.3                         | 18.4               | <0.00001 | 45.6                         | 22.7               | <0.00001 |
| Month 3                 | 39.3                         | 55.3                         | 16.0               | <0.00001 | 61.4                         | 22.1               | <0.00001 |

(Source: Modified from Sponsor's submission ISE Page 315 Table Appendix 5.3.5.3.2-Insomnia: 33; P028 CSR Page 259 Table 11-5; P029 CSR Page 204 Table 11-5; Shaded portions represent primary efficacy analyses)

Sleep Maintenance by WASO

In both trials P028 and P029, suvorexant HD significantly decreased wakefulness after persistent sleep onset WASO, as shown in the table below. The pooled data also mirrored the findings of the individual trials.

**Table 53: Primary Efficacy Endpoint for Sleep Maintenance by WASO in Trials P028, P029, Pooled P028 and P029**

|                         | PBO                          | Suvorexant LD                |                    |          | Suvorexant HD                |                    |          |
|-------------------------|------------------------------|------------------------------|--------------------|----------|------------------------------|--------------------|----------|
| Time point              | LS Mean change from baseline | LS Mean change from baseline | Diff. from placebo | P value  | LS Mean change from baseline | Diff. from placebo | P value  |
| <b>P028</b>             |                              |                              |                    |          |                              |                    |          |
| Night 1                 | -19.6                        | -52.1                        | -32.5              | <0.00001 | -58.0                        | -38.4              | <0.00001 |
| Month 1                 | -18.7                        | -45.0                        | -26.4              | <0.00001 | -45.0                        | -26.3              | <0.00001 |
| Month 3                 | -25.0                        | -41.6                        | -16.6              | 0.00009  | -47.9                        | -22.9              | <0.00001 |
| <b>P029</b>             |                              |                              |                    |          |                              |                    |          |
| Night 1                 | -21.3                        | -58.3                        | -37.0              | <0.00001 | -63.3                        | -42.0              | <0.00001 |
| Month 1                 | -22.5                        | -46.6                        | -24.1              | <0.00001 | -51.9                        | -29.4              | <0.00001 |
| Month 3                 | -24.8                        | -56.0                        | -31.1              | <0.00001 | -54.2                        | -29.4              | <0.00001 |
| <b>Pooled P028+P029</b> |                              |                              |                    |          |                              |                    |          |
| Night 1                 | -20.5                        | -55.1                        | -34.6              | <0.00001 | -60.4                        | -39.9              | <0.00001 |
| Month 1                 | -20.6                        | -46.1                        | -25.4              | <0.00001 | -48.3                        | -27.6              | <0.00001 |
| Month 3                 | -25.0                        | -48.0                        | -23.1              | <0.00001 | -50.9                        | -25.9              | <0.00001 |

(Source: Modified from Sponsor's submission ISE Page 323 Table Appendix 5.3.5.3.2-Insomnia: 39; P028 CSR Page 265 Table 11-7; P029 CSR Page 210 Table 11-7; Shaded portions represent primary efficacy analyses)

#### Sleep Maintenance by sWASOm

To support the results for sleep maintenance, the trials evaluated the effect of suvorexant on the subjective endpoint sWASOm. As with other sleep maintenance endpoints above, suvorexant HD decreased sWASOm at all time points and in both trials, as shown in the table below.

**Table 54: Supporting Efficacy Endpoint for Sleep Maintenance by sWASOm in Trials P028, P029, and Pooled P028 and P029**

|             | Placebo                      | Suvorexant LD                |                    |         | Suvorexant HD                |                    |         |
|-------------|------------------------------|------------------------------|--------------------|---------|------------------------------|--------------------|---------|
| Time point  | LS Mean change from baseline | LS Mean change from baseline | Diff. from placebo | P value | LS Mean change from baseline | Diff. from placebo | P value |
| <b>P028</b> |                              |                              |                    |         |                              |                    |         |

|                         |       |       |      |         |       |       |          |
|-------------------------|-------|-------|------|---------|-------|-------|----------|
| Week 1                  | -10.6 | -17.3 | -6.8 | 0.0033  | -21.1 | -10.5 | <0.00001 |
| Month 1                 | -17.9 | -23.3 | -5.4 | 0.06168 | -27.4 | -9.5  | 0.00025  |
| Month 3                 | -29.6 | -32.0 | -2.4 | 0.38819 | -36.5 | -6.9  | 0.00565  |
| <b>P029</b>             |       |       |      |         |       |       |          |
| Week 1                  | -13.6 | -17.8 | -4.2 | 0.1268  | -22.0 | -8.4  | 0.00046  |
| Month 1                 | -20.8 | -29.2 | -8.4 | 0.00626 | -29.5 | -8.7  | 0.00099  |
| Month 3                 | -29.8 | -37.5 | -7.7 | 0.01885 | -38.7 | -8.9  | 0.00167  |
| <b>Pooled P028+P029</b> |       |       |      |         |       |       |          |
| Week 1                  | -12.1 | -17.4 | -5.3 | 0.00281 | -21.5 | -9.5  | <0.00001 |
| Month 1                 | -19.4 | -26.0 | -6.6 | 0.00159 | -28.5 | -9.1  | <0.00001 |
| Month 3                 | -29.8 | -34.5 | -4.7 | 0.02680 | -37.6 | -7.8  | 0.00003  |

(Source: Modified from Sponsor's submission ISE Page 319 Table Appendix 5.3.5.3.2-Insomnia: 36; P028 CSR Page 262 Table 11-6; P029 CSR Page 207 Table 11-6)

### Sleep Onset

For sleep onset, the treatment effects of suvorexant HD and placebo were compared on the two primary endpoints, sTSOm and WASO, with both assessed at Months 1 and 3, as follows:

- Change from baseline in sTSOm at Month 1
- Change from baseline in sTSOm at Month 3
- Change from baseline in LPS at Month 1
- Change from baseline in LPS at Month 3

### Sleep Onset by sTSOm

In trial P028, following the multiplicity testing strategy, suvorexant HD significantly decreased time to sleep onset, as measured by sTSOm, compared to placebo, with a treatment difference in mean change from baseline of 7.4 minutes ( $p = 0.00298$ ) at Month 1, and 8.4 minutes ( $p = 0.00019$ ) at Month 3. Similar improvements in sTSOm with suvorexant HD treatment occurred at Week 1, with a treatment difference of 5.7 minutes ( $p = 0.00609$ ).

In trial P029, improvements in sleep onset with suvorexant HD were more remarkable than in trial P028, as suvorexant HD in trial P029 significantly decreased sTSOm compared to placebo, with a treatment difference in mean change from baseline of 12.8 minutes ( $p = 0.00003$ ) at Month 1, and 13.2 minutes ( $p = 0.00003$ ) at Month 3. At Week 1, suvorexant HD decreased sTSOm compared to placebo by 13.1 minutes ( $p < 0.00001$ ). The pooled P028 and P029 data showed suvorexant HD decreased sTSOm by 9 to 11 minutes at the different time points.

The table below summarizes the results for sTSOm at the different time points in the individual trials and pooled data, including results at Week 1 and for suvorexant LD for comparisons.

**Table 55: Primary Efficacy Endpoint for Sleep Onset by sTSOm in Trials P028, P029, and Pooled P028 and P029**

| Time point              | PBO                          | Suvorexant LD                |                    |         | Suvorexant HD                |                    |          |
|-------------------------|------------------------------|------------------------------|--------------------|---------|------------------------------|--------------------|----------|
|                         | LS Mean change from baseline | LS Mean change from baseline | Diff. from placebo | P value | LS Mean change from baseline | Diff. from placebo | P value  |
| <b>P028</b>             |                              |                              |                    |         |                              |                    |          |
| Week 1                  | -9.6                         | -15.2                        | -5.6               | 0.01564 | -15.3                        | -5.7               | 0.00609  |
| Month 1                 | -11.7                        | -17.1                        | -5.4               | 0.05191 | -19.1                        | -7.4               | 0.00298  |
| Month 3                 | -17.3                        | -22.5                        | -5.2               | 0.03771 | -25.7                        | -8.4               | 0.00019  |
| <b>P029</b>             |                              |                              |                    |         |                              |                    |          |
| Week 1                  | -6.7                         | -14.2                        | -7.5               | 0.00593 | -19.7                        | -13.1              | <0.00001 |
| Month 1                 | -14.1                        | -21.0                        | -6.9               | 0.04975 | -26.9                        | -12.8              | 0.00003  |
| Month 3                 | -20.5                        | -28.1                        | -7.6               | 0.03894 | -33.7                        | -13.2              | 0.00003  |
| <b>Pooled P028+P029</b> |                              |                              |                    |         |                              |                    |          |
| Week 1                  | -8.3                         | -14.4                        | -6.1               | 0.00081 | -17.6                        | -9.4               | <0.00001 |
| Month 1                 | -13.0                        | -18.6                        | -5.6               | 0.01209 | -23.2                        | -10.1              | <0.00001 |
| Month 3                 | -19.0                        | -24.9                        | -5.9               | 0.00675 | -29.8                        | -10.8              | <0.00001 |

(Source: Modified from Sponsor's submission ISE Page 325 Table Appendix 5.3.5.3.2-Insomnia: 41; P028 CSR Page 268 Table 11-8; P029 CSR Page 213 Table 11-8; Shaded portions represent primary efficacy analyses)

#### Sleep Onset by LPS

In trial P028, suvorexant HD significantly decreased the objective endpoint of latency to persistent sleep LPS compared to placebo, with a treatment difference in mean change from baseline of 11.2 minutes ( $p = 0.00002$ ) at Month 1, and 9.4 minutes ( $p = 0.00037$ ) at Month 3. Similar improvements in LPS with suvorexant HD treatment occurred at Week 1, with a treatment difference of 10.3 minutes ( $p = 0.00002$ ).

However, in trial P029 suvorexant HD failed to significantly decrease LPS at all time points. At Month 1, suvorexant HD significantly decreased LPS, with a treatment difference of 12.1 minutes in mean change from baseline ( $p = 0.00004$ ); but **at Month 3, suvorexant HD treatment produced a non-significant decrease of 3.6 minutes in LPS mean change from baseline compared to placebo ( $p = 0.2651$ )**. In the pooled data, suvorexant HD decreased the LPS endpoint by 6.4 minutes compared to placebo, with a nominal  $p$  value of 0.0024. The table below summarizes the LPS results at the different time points and suvorexant doses.

**Table 56: Primary Efficacy Endpoint for Sleep Onset by LPS in Trials P028, P029, and Pooled P028 and P029**

| Time point              | Placebo                      | Suvorexant LD                |                    |          | Suvorexant HD                |                    |          |
|-------------------------|------------------------------|------------------------------|--------------------|----------|------------------------------|--------------------|----------|
|                         | LS Mean change from baseline | LS Mean change from baseline | Diff. from placebo | P value  | LS Mean change from baseline | Diff. from placebo | P value  |
| <b>P028</b>             |                              |                              |                    |          |                              |                    |          |
| Night 1                 | -20.3                        | -29.9                        | -9.6               | 0.00041  | -30.6                        | -10.3              | 0.00002  |
| Month 1                 | -23.3                        | -33.6                        | -10.3              | 0.0004   | -34.5                        | -11.2              | 0.00002  |
| Month 3                 | -26.6                        | -34.7                        | -8.1               | 0.00606  | -36.0                        | -9.4               | 0.00037  |
| <b>P029</b>             |                              |                              |                    |          |                              |                    |          |
| Night 1                 | -13.0                        | -25.3                        | -12.4              | 0.00392  | -34.7                        | -21.7              | <0.00001 |
| Month 1                 | -24.6                        | -32.5                        | -7.8               | 0.03063  | -36.7                        | -12.1              | 0.00004  |
| Month 3                 | -28.6                        | -28.9                        | -0.3               | 0.93219  | -32.2                        | -3.6               | 0.2651   |
| <b>Pooled P028+P029</b> |                              |                              |                    |          |                              |                    |          |
| Night 1                 | -16.8                        | -28.0                        | -11.2              | <0.00001 | -32.5                        | -15.8              | <0.00001 |
| Month 1                 | -24.1                        | -33.2                        | -9.1               | 0.00007  | -35.5                        | -11.4              | <0.00001 |
| Month 3                 | -27.6                        | -32.2                        | -4.6               | 0.06205  | -34.0                        | -6.4               | 0.00235  |

(Source: Modified from Sponsor's submission ISE Page 329 Table Appendix 5.3.5.3.2-Insonnia: 44; P028 CSR Page 271 Table 11-9; P029 CSR Page 216 Table 11-9; Shaded portions represent primary efficacy analyses, with additional color for non-significant result for primary endpoint)

Sensitivity analyses using nonparametric procedures yielded results that were consistent with the primary analyses for the change from baseline of the endpoints during the treatment phase.

**Reviewer Comment:**

*For sleep maintenance, suvorexant HD treatment resulted in a statistically significant improvement on both subjective (sTSTm) and objective (WASO) primary endpoints at Month 1 and Month 3, and in both confirmatory efficacy trials P028 and P029. Based on the pooled data, treatment with suvorexant HD compared to placebo added about 22 minutes of subjective total sleep time, and reduced objective wakefulness after persistent sleep by 26 minutes at Month 3. Supporting efficacy assessments showed similar improvements with suvorexant HD compared to placebo at Week 1, and on the subjective endpoint sWASO at all time points.*

*For sleep onset, suvorexant HD compared to placebo treatment provided improvements, though not as consistently as in sleep maintenance. In both confirmatory efficacy trials P028 and P029, suvorexant HD treatment resulted in a statistically significant improvement on the subjective (sTSOm) primary endpoint for sleep onset at Month 1 and Month 3. Suvorexant HD significantly improved the objective primary*



*endpoint LPS at all time points only in trial P028. Based on the pooled data, suvorexant HD reduced subjective time to sleep onset (sTSOm) by 11 minutes and the objective endpoint counterpart, LPS, by 6 minutes compared to placebo at Month 3.*

*Of note, suvorexant HD failed to significantly improve LPS response at Month 3 in trial P029. The pre-trial sample size calculations provided for at least 81% power for either of the primary endpoints for sleep onset to be positive at the Month 3 based on the calculated standardized effect size. In Trial P029, sTSOm was positive at Month 3. That LPS is a more clinically relevant endpoint than sTSOm is debatable. Within the limits of recall bias, sTSOm may appear to be more clinically relevant because it is based on the subject's experience rather than on objectively determined biomarker as LPS. Morin and Benca provide the following assessments on these endpoints (reference: Morin CM, Benca R. Chronic insomnia. Lancet. 2012 Mar 24;379:1129-41):*

*"Polysomnographic assessment can show objective sleep impairments (e.g., longer sleep latencies, reduced sleep time), but severity does not always match the patient's complaint of poor sleep. The patient's appraisal of sleep and daytime functioning is crucial since a diagnosis of insomnia is based on clinical symptoms rather than on objective laboratory findings."*

*Although it could be argued that LPS provides a reasonably valid estimate of the time to definitive sleep, the large difference between Month 1 and Month 3 values in trial P029, which was not seen in P028 or with other endpoints, calls into question the reliability of LPS adequately or more completely measuring a subject's feelings of sleep onset changes. Therefore, sTSOm response, which is based on the subject's perception of time to sleep onset, at Month 3 may be adequate in itself to assess improvements in sleep onset. As a result, Suvorexant HD appears to have improved sleep onset at Months 1 and 3 as suggested by the sponsor.*

#### 4.1.5 Analysis of Secondary Endpoints(s)

##### Sleep Maintenance

For sleep maintenance, the secondary endpoints in trial P028 were to further assess the effects of suvorexant HD using change from baseline in sTSTm at Week 1 and in WASO at Night 1; and to assess suvorexant LD effects using the endpoints at the time points as follows:

- Suvorexant LD: Change from baseline in sTSTm at Week 1, Month 1, and Month 3.
- Suvorexant LD: Change from baseline in WASO at Night 1, Month 1, and Month 3.

Trial P029 had secondary endpoints to only assess the effects of suvorexant HD and not suvorexant LD.

##### Suvorexant HD on Sleep Maintenance

Based on the multiplicity strategy for testing endpoints, suvorexant HD significantly improved sTSTm at Week 1 and WASO at Night 1 in both trials P028 and P029, as shown in review section 4.1.4 Primary Endpoint analysis tables 52 and 53.

#### Suvorexant LD on Sleep Maintenance

Again based on the multiplicity strategy for testing endpoints in trial P028, suvorexant LD significantly improved sTSTm at Week 1, Month 1, and Month 3; the dose also significantly improved WASO at Night 1, Month 1, and Month 3 (all p values <0.025). The estimates are summarized in review section 4.1.4 Primary Endpoint analyses tables. Trial P029 showed similar results for the endpoints, though they were not tested as secondary endpoints in that trial. Note that suvorexant LD did not consistently improve sWASO at all time points in both trials (Table 54).

#### Sleep Onset

Suvorexant HD significantly improved sTSOm at Week 1 and LPS at Night 1 in both trials P028 and P029, as shown in review section 4.1.4 Primary Endpoint analysis tables 55 and 56.

Secondary endpoint assessment for suvorexant LD in trial P028 showed inconsistent improvements on sleep onset endpoints at different time points. Suvorexant LD significantly improved sTSOm at Week 1 and LPS at Night 1. The dose improved LPS at Month 1 by 10.3 minutes compared to placebo (p = 0.0004), but it did not significantly improve sTSO despite a 5.4-minute decrease in the endpoint compared to placebo (p = 0.05191).

#### Reviewer Comment:

*The results of the secondary endpoints provide support for the efficacy of suvorexant HD in improving sleep maintenance and sleep onset times in subjects with primary insomnia. Suvorexant HD showed the efficacy effect (all p values <0.025) on subjective endpoints at Week 1 and objective endpoints at Night 1, on both sleep maintenance and sleep onset endpoints, and in both trials P028 and P029. In the pooled P028 and P029 data, endpoint values of mean change from baseline compared to placebo for Week 1 and Night 1 were, in general, comparable or numerically higher than Month 1 and Month 3 values.*

*Suvorexant LD treatment effects provide further support for efficacy of suvorexant on sleep maintenance. The lower suvorexant dose was assessed with secondary endpoints in trial P028. It improved sleep maintenance endpoints sTSTm and WASO at all three time points (all p values <0.025). However, it failed to show similar consistency on sWASOm, a key supporting endpoint for sleep maintenance assessment, in trial P028: 5-minute improvement with suvorexant LD compared to placebo (p = 0.06168) at Month 1 and 2-minute improvement (p = 0.38819) at Month 3.*

*In trial P028, suvorexant LD improved sTSOm and LPS at Week 1; but it did not improve sleep onset endpoints beyond Month 1, when only change from baseline in LPS was positive based on Merck's pre-defined multiplicity testing strategy. As a result, the efficacy of suvorexant LD in treating sleep onset difficulties in primary insomnia subjects remains uncertain based on the NDA data.*

#### 4.1.6 Other Endpoints

In both trials P028 and P029, suvorexant HD and suvorexant LD appeared to improve the following endpoints at Month 1 and Month 3: sQUALm, ISI total score, CGI-S and CGI-I, and PGI-S and PGI-I. The endpoint sREFRESHEDm did not appear to be consistently improved in both trials at Month 3. No improvement in sNAWm occurred with either dose of suvorexant at any time point. The table below summarizes the analyses of the additional endpoints from the pooled P028 and P029 data.

**Table 57: Additional Subjective Efficacy Endpoints in Pooled P028 and P029 Population**

| Endpoints at Different Time Points | Placebo                      | Suvorexant LD   |          | Suvorexant HD   |          |
|------------------------------------|------------------------------|---|----------|---|----------|
|                                    | LS Mean Change from Baseline | Difference from Placebo in LS Mean Change from Baseline | P value  | Difference from Placebo in LS Mean Change from Baseline | P value  |
| <b>sNAWm</b>                       |                              |   |          |   |          |
| Week 1                             | -0.17                        | 0.02  | 0.53667  | -0.01   | 0.70530  |
| Month 1                            | -0.32                        | 0.01  | 0.89316  | -0.01   | 0.70759  |
| Month 3                            | -0.48                        | 0.02  | 0.67356  | 0.03  | 0.46903  |
| <b>sQUALm</b>                      |                              |   |          |   |          |
| Week 1                             | 0.15                         | 0.10  | 0.00008  | 0.14  | <0.00001 |
| Month 1                            | 0.21                         | 0.14  | <0.00001 | 0.16  | <0.00001 |
| Month 3                            | 0.34                         | 0.10  | 0.00090  | 0.11  | 0.00005  |
| <b>sREFRESHEDm</b>                 |                              |   |          |   |          |
| Week 1                             | 0.17                         | 0.10  | 0.00076  | 0.13  | <0.00001 |
| Month 1                            | 0.28                         | 0.16  | 0.00003  | 0.16  | <0.00001 |
| Month 3                            | 0.46                         | 0.13  | 0.00205  | 0.12  | 0.00161  |
| <b>ISI</b>                         |                              |   |          |   |          |
| Month 1                            | -3.0                         | -1.4  | <0.00001 | -1.8  | <0.00001 |
| Month 3                            | -4.9                         | -1.3  | 0.00004  | -1.8  | <0.00001 |
| <b>CGI-S</b>                       |                              |   |          |   |          |
| Month 1                            | -0.6                         | -0.4  | <0.00001 | -0.5  | <0.00001 |
| Month 3                            | -1.0                         | -0.3  | <0.00001 | -0.5  | <0.00001 |
| <b>CGI-I</b>                       |                              |   |          |   |          |
| Month 1                            | 3.3                          | -0.4  | <0.00001 | -0.5  | <0.00001 |
| Month 3                            | 3.0                          | -0.4  | <0.00001 | -0.5  | <0.00001 |



|              |      |      |          |      |          |
|--------------|------|------|----------|------|----------|
| <b>PGI-S</b> |      |      |          |      |          |
| Month 1      | -0.5 | -0.4 | <0.00001 | -0.5 | <0.00001 |
| Month 3      | -0.8 | -0.3 | <0.00001 | -0.4 | <0.00001 |
| <b>PGI-I</b> |      |      |          |      |          |
| Month 1      | 3.2  | -0.4 | <0.00001 | -0.5 | <0.00001 |
| Month 3      | 2.9  | -0.4 | <0.00001 | -0.5 | <0.00001 |

(Source: Modified from Sponsor's submission ISE Pages 331-336, 389, 397, 398, 399, 400 Section 5.3.5.3.2.7.3.4.3 Tables Appendix 5.3.5.3.2-Insomnia: 46, 47, 48, 101, 109, 110, 111, and 112)

## Responder Analyses

Merck conducted analyses on pre-specified responder analyses based on exploratory subjective endpoints to further assess the clinical meaningfulness of suvorexant treatment effects. Based on 6-point or greater improvement at Month 3 from baseline in the ISI total score, the proportion of responders was higher with either suvorexant HD (51.1%, 168/329) or suvorexant LD (52.0%, 115/221) treatment compared to placebo (39.3%, 129/328) in trial P028. Similarly in trial P029, the proportion of responders was higher with either suvorexant HD (58.7%, 192/327) or suvorexant LD (59.5%, 113/190) treatment compared to placebo (45.2%, 140/310).

From the pooled P028 and P029 analyses, the proportion of ISI total score responders at Month 3, was higher with either suvorexant HD or suvorexant LD. The proportions of responders in the treatment were as follows: 42.2% (269/638) for placebo; 54.9% (360/656) for suvorexant HD, with a treatment difference from placebo of 12.7%; and 55.5% (228/411) for suvorexant LD, with a treatment difference from placebo of 13.3%. The table below summarizes the responder analysis based on ISI total score in the pooled data from trials P028 and P029.

**Table 58: Responder Analyses by  $\geq 6$  point improvement in Insomnia Severity Index (ISI) Total Score in Pooled Trials P028 and P029**

| Treatment  | N   | n   | (%)    | Treatment vs. Placebo at Time Point        |                      |
|--|-----|-----|--------|--|----------------------|
|  |     |     |        | Estimated odds ratio (95% CI) <sup>†</sup> | p-Value <sup>†</sup> |
| Month 1  |     |     |        |  |                      |
| MK-4305 LD   | 440 | 149 | (33.9) | 1.8 ( 1.4, 2.4)                            | 0.00004              |
| MK-4305 HD   | 699 | 279 | (39.9) | 2.4 ( 1.9, 3.1)                            | <0.00001             |
| Placebo  | 685 | 157 | (22.9) |  |                      |
| Month 3  |     |     |        |  |                      |
| MK-4305 LD   | 411 | 228 | (55.5) | 1.8 ( 1.4, 2.3)                            | 0.00002              |
| MK-4305 HD   | 656 | 360 | (54.9) | 1.8 ( 1.4, 2.2)                            | <0.00001             |
| Placebo  | 638 | 269 | (42.2) |  |                      |
| <sup>†</sup> Based on a generalized linear mixed model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), cohort (PQ, Q), gender, treatment, time point, and treatment-by-time point interaction as covariates.<br>MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.<br>MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years. |     |     |        |  |                      |

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 278 Table 5.3.5.3.4.7:211)

Suvorexant treatment also resulted in higher proportion of responders based on 15% or greater improvement in sTSTm or sWASOm at different time points in both trials P028 and P029. For the sleep onset endpoint sTSO, suvorexant treatment had more responders than placebo at various time points, except for suvorexant LD at Month 3 in trial P028.

In the pooled data from P028 and P029 trials, a higher percentage of subjects recorded improvement in subjective sleep onset based on at least 15% decrease from baseline in sTSOm at the different time points with suvorexant treatment. **The percentage of responders in the treatment groups at Month 3 was 76.5% (526/688) for suvorexant HD compared to 66.0% (438/664) for placebo, a treatment difference of 10.5% (OR, 1.6; 95% CI: 1.3, 2.1; p value = 0.00004).** Below is a summary of the responder analysis based on sTSOm in the pooled data from trials P028 and P029.

**Table 59: Responder Analyses by  $\geq 15\%$  improvement in sTSOm in Pooled Trials P028 and P029**

| Treatment  | N   | n   | (%)    | Treatment vs. Placebo at Time Point        |                      |
|--|-----|-----|--------|--|----------------------|
|  |     |     |        | Estimated odds ratio (95% CI) <sup>†</sup> | p-Value <sup>†</sup> |
| Week 1   |     |     |        |  |                      |
| MK-4305 LD   | 479 | 267 | (55.7) | 1.7 ( 1.4, 2.2)                            | <0.00001             |
| MK-4305 HD   | 752 | 451 | (60.0) | 2.0 ( 1.7, 2.5)                            | <0.00001             |
| Placebo  | 740 | 316 | (42.7) |  |                      |
| Month 1  |     |     |        |  |                      |
| MK-4305 LD   | 463 | 289 | (62.4) | 1.5 ( 1.1, 1.9)                            | 0.00210              |
| MK-4305 HD   | 728 | 508 | (69.8) | 2.0 ( 1.6, 2.5)                            | <0.00001             |
| Placebo  | 715 | 384 | (53.7) |  |                      |
| Month 3  |     |     |        |  |                      |
| MK-4305 LD   | 425 | 297 | (69.9) | 1.2 ( 0.9, 1.5)                            | 0.19823              |
| MK-4305 HD   | 688 | 526 | (76.5) | 1.6 ( 1.3, 2.1)                            | 0.00004              |
| Placebo  | 664 | 438 | (66.0) |  |                      |
| <sup>†</sup> Based on a generalized linear mixed model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), cohort (PQ, Q), gender, treatment, time point, and treatment-by-time point interaction as covariates.<br>MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.<br>MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years. |     |     |        |  |                      |

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 279 Table 5.3.5.3.4.7:212)

Similarly for sleep maintenance, a higher percentage of subjects on suvorexant treatment recorded at least 15% increase from baseline in sTSTm at the different time points in the pooled data. **The percentage of responders in the treatment groups at Month 3 was 54.7% (376/688) for suvorexant HD compared to 41.9% (278/664) for placebo, a treatment difference of 12.8% (OR, 1.8; 95% CI: 1.4, 2.3; p value <0.00001).** Below is a summary of the responder analysis based on sTSTm in the pooled data from trials P028 and P029.

**Table 60: Responder Analyses by  $\geq 15\%$  improvement in sTSTm in Pooled Trials P028 and P029**

| Treatment  | N   | n   | (%)    | Treatment vs. Placebo at Time Point        |                      |
|--|-----|-----|--------|--|----------------------|
|  |     |     |        | Estimated odds ratio (95% CI) <sup>†</sup> | p-Value <sup>†</sup> |
| Week 1   |     |     |        |  |                      |
| MK-4305 LD   | 479 | 150 | (31.3) | 2.1 ( 1.6, 2.8)                            | <0.00001             |
| MK-4305 HD   | 752 | 262 | (34.8) | 2.5 ( 2.0, 3.3)                            | <0.00001             |
| Placebo  | 740 | 145 | (19.6) |  |                      |
| Month 1  |     |     |        |  |                      |
| MK-4305 LD   | 463 | 197 | (42.5) | 2.0 ( 1.5, 2.5)                            | <0.00001             |
| MK-4305 HD   | 728 | 316 | (43.4) | 2.1 ( 1.6, 2.6)                            | <0.00001             |
| Placebo  | 715 | 210 | (29.4) |  |                      |
| Month 3  |     |     |        |  |                      |
| MK-4305 LD   | 425 | 213 | (50.1) | 1.5 ( 1.2, 2.0)                            | 0.00158              |
| MK-4305 HD   | 688 | 376 | (54.7) | 1.8 ( 1.4, 2.3)                            | <0.00001             |
| Placebo  | 664 | 278 | (41.9) |  |                      |
| <sup>†</sup> Based on a generalized linear mixed model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), cohort (PQ, Q), gender, treatment, time point, and treatment-by-time point interaction as covariates.<br>MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.<br>MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years. |     |     |        |  |                      |

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 280 Table 5.3.5.3.4.7:213)

Similar results were obtained for responders based on sWASOm improvement. As shown in the table below for the pooled data, the percentage of responders in the treatment groups at Month 3 was 77.5% (529/683) for suvorexant HD compared to 69.4% (458/660) for placebo, a treatment difference of 8.1% (OR, 1.5; 95% CI: 1.2, 1.9; p value <0.00077).

**Table 61: Responder Analyses by  $\geq 15\%$  improvement in sWASOm in Pooled Trials P028 and P029**

| Treatment      | N   | n   | (%)    | Treatment vs. Placebo at Time Point        |                      |
|----------------|-----|-----|--------|--|----------------------|
|                |     |     |        | Estimated odds ratio (95% CI) <sup>†</sup> | p-Value <sup>†</sup> |
| <b>Week 1</b>  |     |     |        |  |                      |
| MK-4305 LD     | 474 | 267 | (56.3) | 1.5 ( 1.1, 1.8)                            | 0.00179              |
| MK-4305 HD     | 746 | 486 | (65.1) | 2.0 ( 1.6, 2.5)                            | <0.00001             |
| Placebo        | 729 | 350 | (48.0) |  |                      |
| <b>Month 1</b> |     |     |        |  |                      |
| MK-4305 LD     | 457 | 307 | (67.2) | 1.5 ( 1.2, 1.9)                            | 0.00193              |
| MK-4305 HD     | 723 | 512 | (70.8) | 1.7 ( 1.4, 2.1)                            | <0.00001             |
| Placebo        | 704 | 414 | (58.8) |  |                      |
| <b>Month 3</b> |     |     |        |  |                      |
| MK-4305 LD     | 425 | 322 | (75.8) | 1.4 ( 1.1, 1.9)                            | 0.00923              |
| MK-4305 HD     | 683 | 529 | (77.5) | 1.5 ( 1.2, 1.9)                            | 0.00077              |
| Placebo        | 660 | 458 | (69.4) |  |                      |

<sup>†</sup> Based on a generalized linear mixed model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), cohort (PQ, Q), gender, treatment, time point, and treatment-by-time point interaction as covariates.

MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.

MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 281 Table 5.3.5.3.4.7:214)

In all the responder analyses from the pooled data, there appeared to be a dose-related improvement of the insomnia endpoints from suvorexant treatment.

#### 4.1.7 Subpopulations

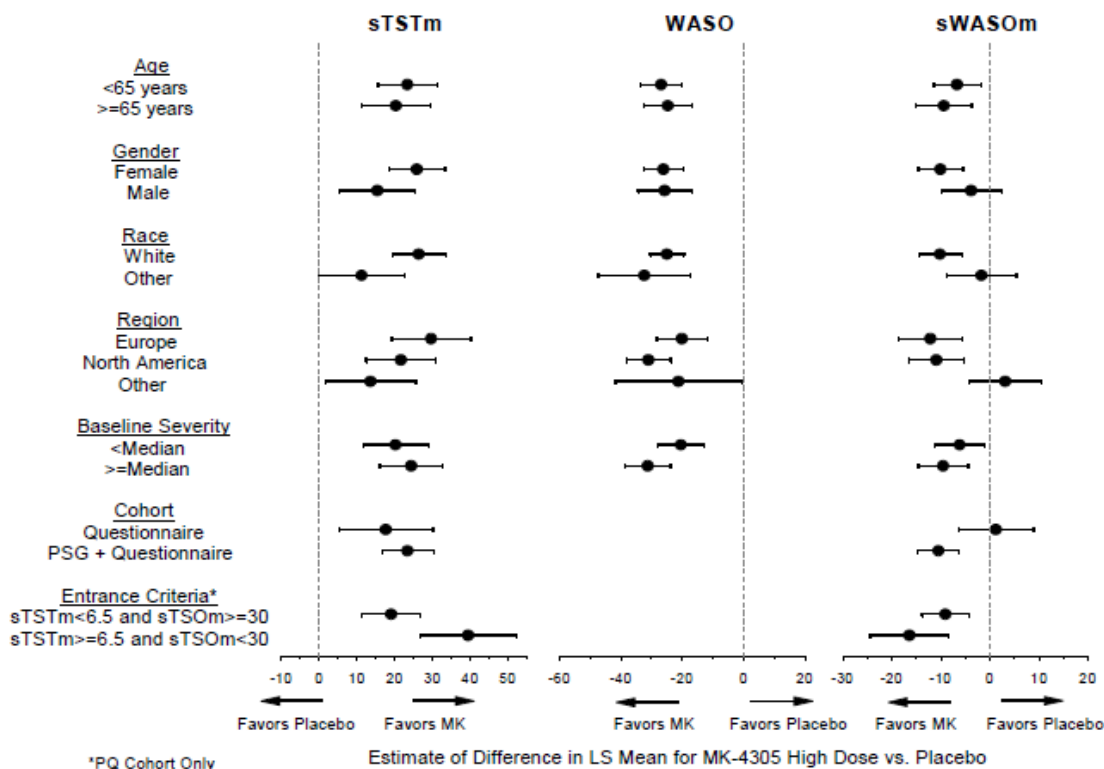
##### Subgroup Analyses

Merck analyzed the pooled P028 and P029 data to determine consistency of treatment effects across categories of subgroups: age; gender; race; regions; cohort; baseline severity; and for the PQ-cohort, base entry criteria.

##### Subgroup Analyses for Sleep Maintenance

Points estimates from the pooled data that suggest improvements from suvorexant (HD and LD) treatment in sleep maintenance endpoints, sTSTm and WASO, were consistent across the subgroups. However for sWASOm, "Other" race, "Other" region, and Q-Cohort did not appear to have such improvements as other subgroups. The figure below summarizes the subgroup analyses of endpoint estimates with 95% confidence intervals at Month 3 for suvorexant HD treatment.

**Figure 6: Subgroup Analyses of Change from Baseline in Sleep Maintenance Efficacy Endpoints at Month 3 for Suvorexant HD Compared to Placebo in Pooled P028 and P029 Data**

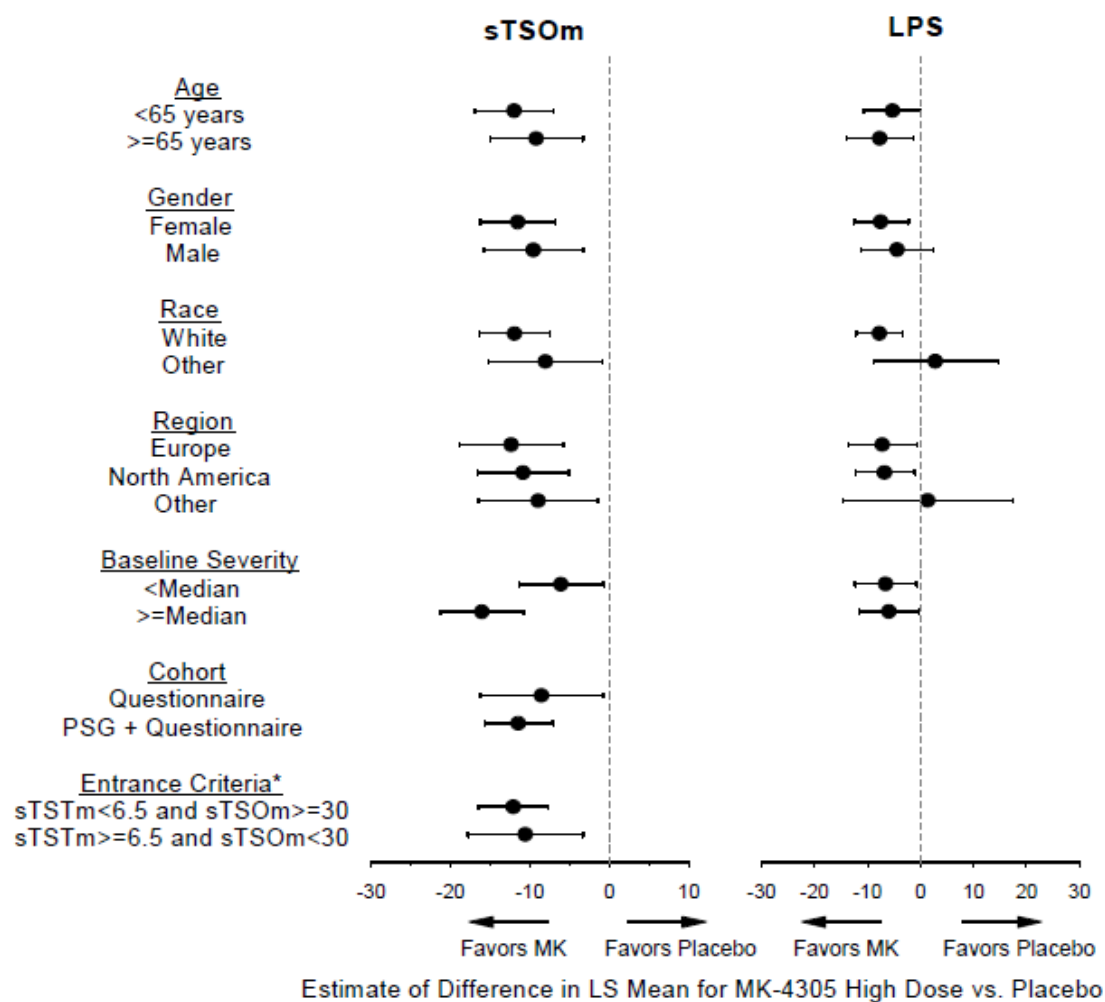


(Source: Sponsor's submission ISE Page 215 Figure 5.3.5.3.2-Insomnia: 26)

### Subgroup Analyses for Sleep Onset

Point estimates from the pooled data that suggest treatment improvements from suvorexant HD and suvorexant LD were consistent across the subgroups in the sleep onset endpoint sTSTOm. However for LPS, the subgroups of "Other" race and "Other" region did not appear to be similarly improved with either suvorexant LD or suvorexant HD at Month 3. The confidence intervals for these subgroup point estimates were wide, suggesting sample size may have played a role in the results. The figure below summarizes the subgroup analyses of endpoint estimates with 95% confidence intervals at Month 3 for suvorexant HD treatment.

**Figure 7: Subgroup Analyses of Change from Baseline in Sleep Onset Efficacy Endpoints at Month 3 for Suvorexant HD Compared to Placebo in Pooled P028 and P029 Data**



\*PQ Cohort Only  
(Source: Sponsor's submission ISE Page 220 Figure 5.3.5.3.2-Insomnia: 20)

FDA Biometrics review team conducted extensive subgroup analyses on the individual and pooled data from trials P028 and P029. Please see Dr. Massie's review for details, including tables of analyses. I note the following observations from Dr. Massie's review:

Gender:

- With suvorexant LD or suvorexant HD treatment, there was no compelling evidence of differential efficacy by gender based on LPS, WASO, sTST, or sTSO results from trials P028 and P029 pooled data.

Race:

- The subgroup assessment of suvorexant HD treatment effects on sTSO showed no evidence suggestive of an interaction in either trial P028 or P029.
- However for sTST in trial P028, the differential efficacy of suvorexant HD between “Whites” and “Others” ( $p = 0.0162$ ) at Month 1 suggested an interaction. Trial P029 had no such interaction for sTST.
- For LPS in trial P028, again the differential efficacy of suvorexant HD between “Whites” and “Others” ( $p = 0.0016$ ) at Month 1 suggested an interaction. Trial P029 had no such interaction for LPS.
- For suvorexant HD treatment effects on WASO in both trials P028 and P029, no remarkable interaction was evident.

Age:

- With suvorexant LD or suvorexant HD treatment, there was no compelling evidence of differential efficacy by age group, based on WASO, sTST, or sTSO results from trials P028 and P029 pooled data.
- Suvorexant HD treatment showed lower effects on LPS for the elderly compared to the non-elderly at 1 month in the pooled analysis. However, the LPS effect on in the elderly subgroup was still numerically in the right direction.

Regions (North America compared to Non-North America):

- With suvorexant LD or suvorexant HD treatment, there was no compelling evidence of differential efficacy by region based on LPS, WASO, sTST, or sTSO results from either trial P028 or trial P029.

Site:

- In trial P028, excluding any site had no effect on the significance of suvorexant HD treatment effects compared to placebo for the LPS endpoint at Month 1, Month 3, or Night 1. In trial P029, excluding any site had no effect on the significance of suvorexant HD treatment effects compared to placebo for the LPS endpoint at Month 1. However, exclusion of site 0004 resulted in a loss of nominal significance for suvorexant LD treatment effects compared to placebo for the LPS endpoint at Month 1.

Cohort:

- With suvorexant HD treatment, there was no compelling evidence of substantial differential efficacy by cohort based on sTST or sTSO results from either trial P028 or trial P029.

#### 4.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Merck proposes to market multiple dose strengths for suvorexant to enable non-elderly subjects to be treated with a dose of 40 mg once daily and elderly subjects with a dose of 30 mg once daily. The proposed drug label suggests that a lower dose of 20 mg once



daily for some of the non-elderly or 15 mg once daily for some of the elderly may be appropriate based on individual tolerability.

A dose-finding phase 2 trial, P006, evaluated multiple suvorexant doses from 10 mg to 80 mg in non-elderly subjects. This trial was reviewed in section 3.3 Discussion of Individual Clinical Trials, and FDA Biometrics report by Dr. Massie. In trial P006, suvorexant in all tested doses significantly improved sleep efficiency (SE) and WASO compared to placebo at Night 1 and at Week 4. However, only the 40 mg and 80 mg doses appeared to improve the subjective measures of sleep maintenance and onset, sTST, sWASO, and sTSO.

Merck chose to further evaluate the suvorexant 40 mg dose in the subsequent Phase 3 trials. This dose improved sleep onset and sleep maintenance insomnia, as measured by objective and subjective endpoints after 4 weeks of suvorexant treatment. The dose choice for further Phase 3 trial evaluation appears appropriate. Based on drug exposure data from clinical pharmacology studies, Merck chose the suvorexant 30 mg dose for elderly subjects as being comparable to the 40 mg dose in the non-elderly. This decision also appears appropriate. Of note, it appears that limiting the indication to only sleep maintenance insomnia, suvorexant doses from 10 mg to 40 mg were appropriate for subsequent Phase 3 trial evaluation.

In the phase 3 trials, the sponsor evaluated primarily suvorexant HD, consisting of 30 mg in elderly subjects and 40 mg dose in the non-elderly. The trials evaluated suvorexant LD, which consisted of 15 mg in elderly subjects and 20 mg in the non-elderly, in secondary or exploratory analysis. The estimates from the pooled analyses suggest that suvorexant produced dose-related treatment effects on all endpoints, subjective and objective, at all time points (Week 1 or Night 1, Month 1, and Month 3). Further, suvorexant LD appeared to have significantly improved sleep maintenance endpoints at the different time points. However, only the suvorexant HD appeared to provide better assurance of improving sleep onset endpoints at the different time points, especially with the subjective sTSO endpoint. As a result, the proposed dose of suvorexant HD for sleep onset and sleep maintenance insomnia appears appropriate. Merck did not explore dose titration, based on efficacy or tolerability, in individual subjects during the phase 3 trials.

#### 4.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Suvorexant HD treatment showed persistent efficacy during the 3-month treatment phase of trials P028 and P029. As reviewed in section 3, trial P009 showed suvorexant HD's persisting efficacy up to 12 months of treatment.

##### Persistence of Effects during 3-month Treatment

For almost all endpoints, the estimates for suvorexant HD's treatment difference from placebo at Month 1 were similar to those of Month 3 in trials P028 and P029. Except for

LPS endpoints at Month 3 in trial P029, suvorexant HD showed significant positive effects on all endpoints tested in the primary analyses at Months 1 and 3. The pooled data results shown on section 4.1.4 support the evidence for persistence of efficacy for suvorexant HD. Below is a summary of the efficacy results for suvorexant HD during the treatment phase of trials P028 and P029.

**Table 62: Efficacy of Suvorexant HD compared to Placebo in Trials P028 and P029 - Summary of LS Mean Differences in Change from Baseline of Endpoints**

| Timepoint   | Maintenance |        |        | Onset  |        |
|---|-------------|--------|--------|--------|--------|
|   | sTSTm       | sWASOm | WASO   | sTSOm  | LPS    |
| <b>P028</b>   |             |        |        |        |        |
| Week 1/Night 1  | 21.4*       | -10.5* | -38.4* | -5.7*  | -10.3* |
| Week 2  | 19.3        | -9.7   |        | -6.5   |        |
| Week 3  | 19.1        | -7.9   |        | -7.3   |        |
| Month 1   | 19.6*       | -9.5*  | -26.3* | -7.4*  | -11.2* |
| Month 1.5   | 17.5        | -7.3   |        | -7.5   |        |
| Month 2   | 18.9        | -6.4   |        | -7.2   |        |
| Month 2.5   | 18.4        | -7.5   |        | -8.5   |        |
| Month 3   | 19.7*       | -6.9*  | -22.9* | -8.4*  | -9.4*  |
| <b>P029</b>   |             |        |        |        |        |
| Week 1/Night 1  | 26.4*       | -8.4*  | -42.0* | -13.1* | -21.7* |
| Week 2  | 23.5        | -7.4   |        | -13.6  |        |
| Week 3  | 28.1        | -8.3   |        | -14.2  |        |
| Month 1   | 26.3*       | -8.7*  | -29.4* | -12.8* | -12.1* |
| Month 1.5   | 26.5        | -11.0  |        | -14.1  |        |
| Month 2   | 25.6        | -11.3  |        | -13.9  |        |
| Month 2.5   | 23.3        | -9.3   |        | -12.3  |        |
| Month 3   | 25.1*       | -8.9*  | -29.4* | -13.2* | -3.6   |
| Note: All timepoints' results are included in this table; however, shaded cells represent primary or secondary time points that were included as part of the multiplicity strategy, and thus assessed for statistical significance (*)<br>*Statistically significant based upon the protocol-specified multiplicity strategy (or for the sWASOm supportive analysis, statistically significant after substituting sWASOm for sTSTm in the protocol-specified multiplicity strategy) |             |        |        |        |        |

(Source: Sponsor's submission ISE Page 241 Table 5.3.5.3.2-Insomnia: 51)

For suvorexant LD, the pooled data results shown in review section 4.1.4 support the evidence for persistence of the magnitude of suvorexant LD effects during the 3 months of treatment. Below is a summary of the efficacy results for suvorexant LD during the treatment phase of trials P028 and P029.

**Table 63: Efficacy of Suvorexant LD compared to Placebo in Trials P028 and P029 - Summary of LS Mean Differences in Change from Baseline of Endpoints**

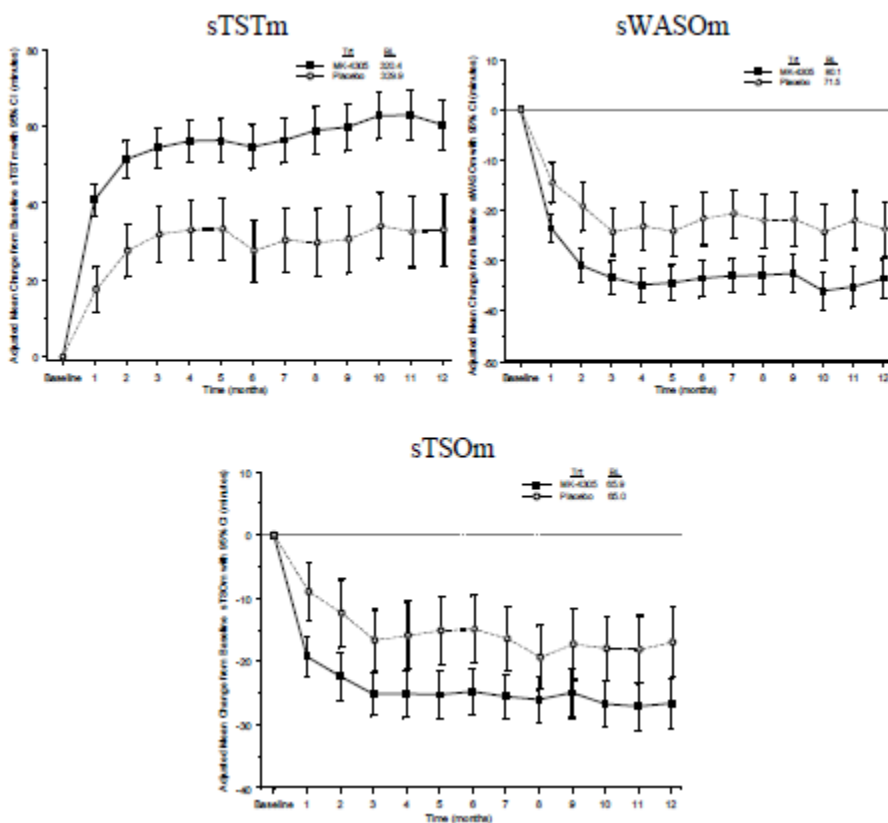
| Timepoint  | Maintenance |        |                   | Onset |        |
|--|-------------|--------|-------------------|-------|--------|
|  | sTSTm       | sWASOm | WASO <sup>†</sup> | sTSOm | LPS    |
| <b>P028</b>  |             |        |                   |       |        |
| Week 1/Night 1   | 13.6*       | -6.8   | -32.5*            | -5.6  | -9.6   |
| Week 2   | 12.7        | -5.5   |                   | -2.7  |        |
| Week 3   | 12.1        | -3.2   |                   | -3.8  |        |
| Month 1  | 16.3*       | -5.4   | -26.4*            | -5.4  | -10.3* |
| Month 1.5  | 13.6        | -2.6   |                   | -5.1  |        |
| Month 2  | 15.9        | -4.2   |                   | -4.3  |        |
| Month 2.5  | 12.3        | -2.8   |                   | -6.0  |        |
| Month 3  | 10.7*       | -2.4   | -16.6*            | -5.2  | -8.1   |
| <b>P029<sup>‡</sup></b>  |             |        |                   |       |        |
| Week 1/Night 1   | 16.8        | -4.2   | -37.0             | -7.5  | -12.4  |
| Week 2   | 18.9        | -8.8   |                   | -9.7  |        |
| Week 3   | 18.1        | -7.0   |                   | -5.8  |        |
| Month 1  | 20.9        | -8.4   | -24.1             | -6.9  | -7.8   |
| Month 1.5  | 18.6        | -7.5   |                   | -8.6  |        |
| Month 2  | 21.9        | -11.7  |                   | -8.7  |        |
| Month 2.5  | 20.1        | -8.5   |                   | -6.5  |        |
| Month 3  | 22.1        | -7.7   | -31.1             | -7.6  | -0.3   |
| Note: All timepoints' results are included in this table; however, shaded cells represent primary or secondary time points that were included as part of the multiplicity strategy, and thus assessed for statistical significance (*)<br>*Statistically significant based upon the protocol-specified multiplicity strategy (or for the sWASOm supportive analysis, statistically significant after substituting sWASOm for sTSTm in the protocol-specified multiplicity strategy)<br>‡LD vs. placebo comparisons were not primary or secondary objectives of P029; therefore, statistical significance (*) was not assessed for this treatment comparison in P029<br>†Asterisks represent statistical significance based on protocol-specified primary analysis (i.e. sTSTm and WASO as primary variables for assessment of efficacy on sleep maintenance) |             |        |                   |       |        |

(Source: Sponsor's submission ISE Page 242 Table 5.3.5.3.2-Insomnia: 52)

#### Persistence of Effects during 12-month Treatment

The efficacy of suvorexant persisting through 12 months of treatment was demonstrated by the results of trial P009. The figure below shows the trend of the change from baseline in mean sTSTm, sTSOm, and sWASOm for the suvorexant HD and placebo groups during the 12 months of treatment.

**Figure 8: Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean sTSTm, sTSOm, and sWASOm (in minutes) during 12-Month Treatment of Suvorexant HD and Placebo in Trial P009**



Source: Sponsor's submission ISE Page 245 Figure 5.3.5.3.2-Insomnia: 32)

**Reviewer Comment:**

*In general, the magnitude of suvorexant treatment effects appears to be sustained in the 3-month or 12-month treatment period.*

#### 4.1.10 Additional Efficacy Issues/Analyses

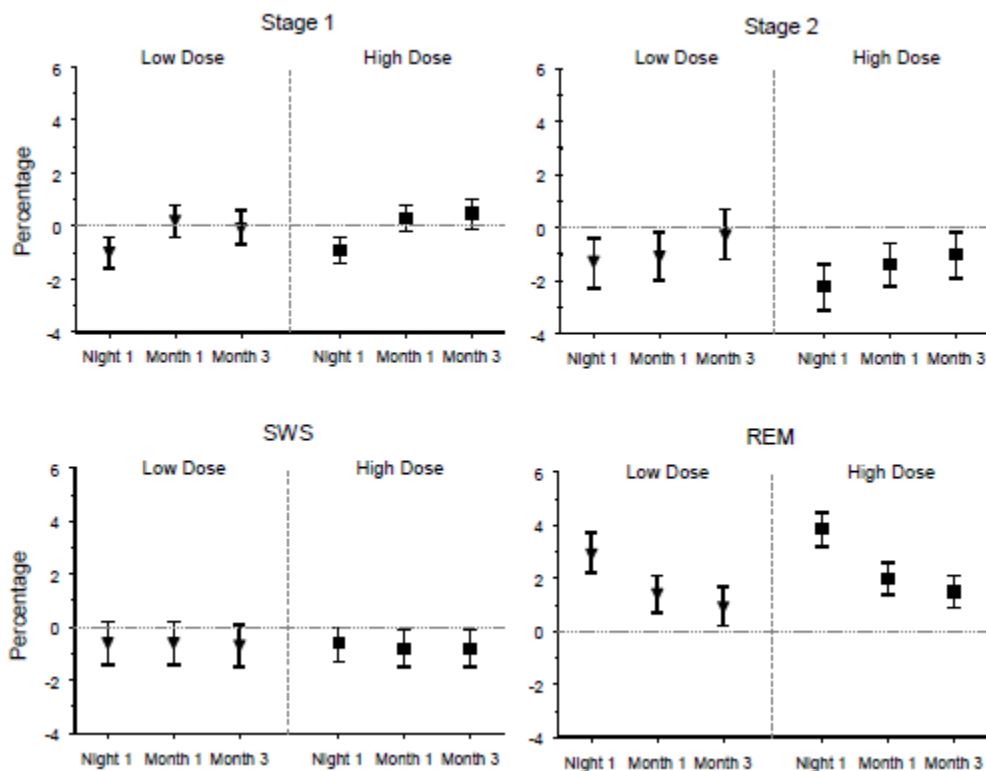
##### Additional Endpoints

##### Sleep Architecture Endpoints

In trials P028 and P029, suvorexant HD and suvorexant LD caused an increase in the duration of all sleep stages. However, when the duration of the sleep stages were corrected for the overall increase in TST, only stage REM was increased in the suvorexant dose groups compared to placebo. Consistent with the mechanism of action of orexin receptor antagonists (ORAs), the REM stage increase from suvorexant treatment appears to account for most increase in total sleep time. The figure below

shows results of the differences in LS Means for the sleep architecture endpoints, expressed as percentages of TST, from the pooled P028 and P029 data.

**Figure 9: Differences from Placebo in Least Squares Means (95% CI) for Sleep Architecture Endpoints: Stages 1, 2, SWS and REM (percent of TST) from Pooled P028 and P029 Data**



Source: Sponsor's submission ISE Page 346 Figure Appendix 5.3.5.3.2-Insomnia: 58)

### REM Sleep Latency

In the pooled P028 and P029 analysis, suvorexant treatment reduced REM Sleep Latency. Compared to placebo, suvorexant HD reduced REM sleep latency by 46.1 minutes at Night 1 ( $p < 0.00001$ ) and by 21.4 minutes at Month 3 ( $p < 0.00001$ ). Similarly, suvorexant LD reduced the REM sleep latency by 40.3 minutes at Night 1 ( $p < 0.00001$ ) and by 15.9 minutes at Month 3 ( $p = 0.00123$ ).

### Other Polysomnographic Sleep Endpoints

#### TST

In the pooled P028 and P029 analysis, suvorexant HD increased TST by 54.4 minutes more than placebo at Night 1 ( $p < 0.00001$ ) and 33.3 minutes more at Month 3 ( $p < 0.00001$ ).

Similarly, suvorexant LD increased TST by 44.8 minutes more than placebo at Night 1 ( $<0.00001$ ) and 27.5 minutes more at Month 3 ( $<0.00001$ ).

#### NAW as a Ratio of TST

To account for the longer sleep duration of suvorexant-treated subjects, the results of NAW after persistent sleep (NAWPS2E) were adjusted for TST duration. In the pooled analysis of trials P028 and P029, with NAWPS2E adjusted for TST, both doses of suvorexant showed lower rates of awakenings on Night 1 (all p-values  $<0.002$ ). At Month 1 and Month 3 both suvorexant doses showed comparable rates of awakenings as placebo.

#### Sleep Onset Latency

Analysis of change from baseline in SOL provides additional insight on the effect of suvorexant treatment on objective sleep onset. While LPS is duration from lights off to the first epoch of the first twenty consecutive epochs of non-wake, SOL is the duration of time in minutes from lights off to the first epoch of three consecutive epochs of Stage S1 or any single epoch of Stage S2, SWS, or Stage R. As shown in the table below, suvorexant HD and suvorexant LD decreased SOL change from baseline in a dose-dependent manner at Night 1, Month 1 and Month 3.

**Table 64: Sleep Onset Latency (SOL 1; minutes) Change from Baseline at All Time Points during the Treatment Phase from Pooled P028 and P029 data**

| Treatment   | N   | Baseline<br>Mean (SD)                        | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                               |
|---|-----|--|-------------------------|------------------------------------|-------------------------------|
|   |     |  |                         | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Night 1   |     |  |                         |                                    |                               |
| MK-4305 LD  | 336 | 50.8 (40.7)                                  | 28.2 (24.6)             | -22.6 (36.6)                       | -20.0 (-22.7, -17.3)          |
| MK-4305 HD  | 576 | 46.1 (38.0)                                  | 23.2 (19.4)             | -22.9 (36.3)                       | -24.0 (-26.1, -21.9)          |
| Placebo   | 570 | 46.6 (35.7)                                  | 33.1 (34.8)             | -13.5 (37.9)                       | -14.2 (-16.3, -12.1)          |
| Month 1   |     |  |                         |                                    |                               |
| MK-4305 LD  | 317 | 50.3 (38.0)                                  | 22.5 (21.4)             | -27.8 (37.1)                       | -25.6 (-28.3, -22.9)          |
| MK-4305 HD  | 550 | 46.5 (38.5)                                  | 19.1 (19.3)             | -27.4 (38.0)                       | -28.2 (-30.2, -26.1)          |
| Placebo   | 542 | 47.1 (36.0)                                  | 28.8 (32.8)             | -18.3 (40.3)                       | -18.7 (-20.7, -16.6)          |
| Month 3   |     |  |                         |                                    |                               |
| MK-4305 LD  | 299 | 49.2 (36.8)                                  | 22.7 (23.3)             | -26.4 (35.2)                       | -25.1 (-27.7, -22.5)          |
| MK-4305 HD  | 511 | 46.3 (38.9)                                  | 18.3 (17.9)             | -27.9 (37.5)                       | -28.8 (-30.8, -26.9)          |
| Placebo   | 503 | 47.6 (35.6)                                  | 26.2 (29.7)             | -21.4 (38.7)                       | -21.3 (-23.3, -19.3)          |
| Pairwise Comparison   |     | Difference in LS Means (95% CI) <sup>†</sup> |                         | p-Value <sup>†</sup>               |                               |
| Night 1   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -9.8 (-12.7, -6.9)                           |                         | <.00001                            |                               |
| MK-4305 LD vs. Placebo  |     | -5.8 (-9.3, -2.4)                            |                         | 0.00082                            |                               |
| Month 1   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -9.5 (-12.4, -6.6)                           |                         | <.00001                            |                               |
| MK-4305 LD vs. Placebo  |     | -7.0 (-10.4, -3.6)                           |                         | 0.00006                            |                               |
| Month 3   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -7.6 (-10.4, -4.8)                           |                         | <.00001                            |                               |
| MK-4305 LD vs. Placebo  |     | -3.8 (-7.1, -0.5)                            |                         | 0.02306                            |                               |
| <sup>†</sup> Based on a mixed effects model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |  |                         |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.   |     |  |                         |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.   |     |  |                         |                                    |                               |

(Source: Sponsor's submission ISE Page 373 Table Appendix 5.3.5.3.2-Insomnia: 85)

#### Number of Arousals (NOAs)

Arousals were defined as a shift from deeper stages of sleep to S1 or Wake.

Suvorexant HD and suvorexant LD treatments increased number of arousals compared with placebo in trials P006, P028, and P029, at all time points. In the pooled P028 and P029 analysis, suvorexant HD increased LS Mean change from baseline in NOAs by 3.8 compared to placebo at Night 1 and Month 3 (each p<0.00001). Similarly, suvorexant LD increased the endpoint by 3.9 at Night 1 (p<0.00001) and by 2.4 at Month 3 (p = 0.00050).

#### WASO by Segments of the Night

Merck analyzed WASO by hour of the night and showed that suvorexant HD and suvorexant LD had greater WASO reductions from baseline compared to placebo in the pooled P028 and P029 data. The reductions appeared from the second hour of Night 1 through Hour 8.

#### Power Spectra

Merck analyzed treatment to baseline ratio of spectral power (microvolts<sup>2</sup>/Hz) for the gamma, beta, sigma, alpha, theta, and delta bands, during NREM all night.

In the pooled P028 and P029 analysis, suvorexant HD and suvorexant LD treatment was associated with a 3%-6% decrease in power in the Gamma, Beta, and Alpha bands at Night 1 only. Simultaneously, the suvorexant treatments compared to placebo were associated with 4%-8% increase in power in the Delta band and  $\leq 3\%$  increase in power in the Theta band also at Night 1.

## 5 Review of Safety

### Safety Summary

This review considers the safety data for suvorexant (MK-4305) as presented in Merck's NDA 204569. Merck's overall goal with this submission is to gain approval for suvorexant for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. In the NDA submission, suvorexant is associated with next day sleepiness at a rate that appears similar, by indirect comparison, to the earlier approved insomnia drugs. The suvorexant program also evaluated other known risks associated with sedative hypnotics. Further, suvorexant's mechanism of action warranted scrutiny for the risk of developing narcolepsy. The sponsor provided an extensive safety database that meets the requirements of existing guidance documents.

Suvorexant is an orally administered selective antagonist for orexin receptors OX<sub>1</sub>R and OX<sub>2</sub>R. It blocks the binding of orexin A and orexin B to orexin receptors OX<sub>1</sub>R and OX<sub>2</sub>R, thereby inhibiting wakefulness and promoting sleep. Suvorexant has no pharmacological affinity for receptors that bind to gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine, or opiates. No drug of this pharmacologic class has been approved for clinical use.

For this NDA, Merck summarized data from 35 clinical trials: two Phase 3 confirmatory efficacy trials; and one Phase 3 long-term safety trial; one Phase 2b dose-finding trial; and 31 Phase 1 clinical pharmacology trials, which were conducted in healthy volunteers and special populations. The Phase 3 trials constituted the primary integrated database that Merck used to assess safety in 2,809 subjects with primary insomnia. On 7 December 2012, Merck provided a Safety Update that included information on the 32<sup>nd</sup> Phase 1 trial, which compared bioavailability of four doses of suvorexant under fasting condition in 120 subjects.



This safety review summary depended on analyses of the Phase 3 safety database to characterize overall risk estimates of adverse events (AEs). I examined the safety pools from the Phase 2 and Phase 1 trials to further characterize the AE risks.

The number of subjects exposed to suvorexant exceeds the target recommended in the ICH guidelines. Adequate numbers of subjects were exposed to the proposed treatment doses, 15 to 40mg daily. A total of 2,027 subjects with chronic insomnia received any suvorexant dose: 1,198 non-elderly and 829 elderly subjects. The Phase 3 trials exposed 1,784 subjects to suvorexant 15 to 40 mg doses, of which 1,218 subjects received treatment for at least 3 months, 507 subjects for at least 6 months, and 160 subjects for at least 12 months.

My review revealed no major deficiencies in the safety aspects of the NDA. I found all necessary summaries and supporting data for the major risk events that the sponsor had identified. Also, I observed no major inconsistencies between the data sources. The routine safety assessments appeared capable of detecting major safety signals from suvorexant treatment.

As stated earlier, in the Phase 3 trials, suvorexant 15 mg in elderly subjects and suvorexant 20 in non-elderly subjects constituted suvorexant LD, while suvorexant 30 mg in elderly subjects and suvorexant 40 mg in the non-elderly constituted suvorexant HD.

Deaths were infrequent in the suvorexant development program. Two deaths occurred, both in Phase 3 trials. One subject, a 40-year old female on suvorexant HD, was on a leisure ocean swim when she was caught in a rip current. She nearly drowned but was rescued and then hospitalized. Later she went into cardiac arrest, and developed a serious adverse event (SAE), hypoxic-ischemic encephalopathy, before she was declared brain dead. The other subject, a 58-year-old white female with a history of coronary artery disease, status post myocardial infarction and coronary stent placement, was on placebo when she experienced a stroke with brain swelling before she died.

SAEs occurred less frequently in suvorexant treated subjects than in placebo. Over 12 months, SAEs occurred in 2.8% (36/1291) of the subjects who received suvorexant HD and 3.2% (33/1025) who received placebo. Likewise, fewer subjects on suvorexant LD reported SAEs (0.6%, 3/493) compared to placebo (2.1%, 16/767) in the 0-6 months safety population. SAEs in the post-treatment phase included three events of spontaneous abortions, all three received suvorexant treatment: suvorexant HD had two subjects, and suvorexant LD one subject. Two of the three cases had confounding concomitant medications.

Numerically more subjects on suvorexant HD discontinued treatment because of an adverse event compared to those on suvorexant LD or placebo. Discontinuation of treatment because of adverse event in all subjects treated occurred in 5.4% (70/1291) of the HD suvorexant group and 3.2% (16/493) of the LD suvorexant group, compared to 4.7% (48/1025) of the placebo group. Adverse events most commonly associated with treatment discontinuation were somnolence and fatigue in the HD suvorexant group.

Merck reported a higher incidence of any AEs in suvorexant HD subjects with 51.0% (658/1291) compared to suvorexant LD with 46.5% (229/493) or placebo 46.6% (478/1025). Also, subjects on suvorexant HD reported more adverse events in the Nervous system disorders SOC with 21.4% (276/1291) compared to suvorexant LD 16.8% (83/493) or placebo 13.2% (135/1025). The most common AEs had incidences of 2% or more and occurred more frequently, in dose-related manner, in the suvorexant group than placebo were somnolence and fatigue.

The most significant AE was somnolence. Suvorexant caused a dose-related increase in somnolence within the initial months of treatment. Somnolence within 0-3 months in the combined Phase 3 population occurred in 10.7% (138/1291) of the suvorexant HD group, 6.7% (33/493) of suvorexant LD, and 3.0% (31/1025) of placebo. Severe somnolence was incapacitating sleepiness that made an affected subject unable to work or do usual activity. The incidence of severe somnolence was overall low but higher in the suvorexant HD group at 0.6% (8/1291) compared to suvorexant LD at 0.2% (1/493), and placebo at 0.1% (1/1025). As a result, the risk difference for severe somnolence between each suvorexant dose and placebo was small, though higher in the suvorexant HD group: 0.5% with number needed to treat to cause severe somnolence or harm (NNTH) 200 for suvorexant HD, and 0.1% with NNTH 1000 for suvorexant LD. If harm is considered as moderate or severe somnolence, the risk difference will be 3.0% (NNTH 33) for suvorexant HD, and 0.8% (NNTH 125) for suvorexant LD.

More subjects on either suvorexant dose reported somnolence within one week of starting treatment compared to any other period in the first 3 months of treatment. Assessing adverse events by age showed that fewer elderly subjects on suvorexant treatment reported somnolence compared to non-elderly subjects. For example, among 1291 subjects treated with suvorexant HD, somnolence occurred in 12.5% (83/664) of the elderly subjects and 8.8% (55/627) of the non-elderly subjects. Likewise among the subjects on suvorexant LD, elderly subjects reported lower somnolence rates than the non-elderly. This pattern of lower somnolence reports in elderly subjects compared to non-elderly adults was consistent across treatment periods. This may be attributed to the lower dose that the elderly subjects received at each suvorexant dose level.

The rates of somnolence in the suvorexant Phase 3 trials appear to be comparable to those of other approved drugs for the sought indication. For example, zolpidem CR 12.5

mg, which is approved for the same sought indication, recorded somnolence rates of 15% in the active trial arm of 102 subjects compared to 2% in placebo group of 110 subjects in 3-week trial of non-elderly subjects. In another 3-week trial in elderly subjects, the incidence of somnolence was 6% of 99 subjects on zolpidem CR 6.25 mg compared to 5% of 106 subjects on placebo. Other approved insomnia drugs registered similar rates of somnolence. Overall, information gathered on next-day somnolence may serve as a useful guide in assessing dose-response relationships, especially in future clinical dose titrations.

Merck assessed certain adverse events as Events of Clinical Interest (ECIs). These events were selected based on safety concerns associated with other marketed sedative hypnotic drugs, and on safety concerns related to suvorexant's mechanism of action. The ECIs included the following: suicidal ideation or behavior, complex sleep-related behaviors, hypnagogic and hypnopompic hallucinations, AEs associated with abuse potential, excessive daytime sleepiness (EDS), cataplexy, falls, sleep paralysis, AEs associated with a traffic or motor vehicle accident (MVA), and reports of motor vehicle accidents and violations (MVAV) based on MVAV Questionnaire. An independent committee of experts, blinded to treatment assignment and external to Merck, received ECIs of cataplexy, falls, and sleep onset paralysis for adjudication. Adjudication for events of fall was to determine whether falls were suggestive of cataplexy. Overall, the incidences of the individual ECIs were low.

In the Phase 3 Population within 0-3 months, suicidal Ideation occurred in seven subjects; five of them occurred in the suvorexant HD treatment group, an incidence of 0.4% (5/1291); one subject was in the suvorexant LD group, an incidence of 0.2% (1/493); and one subject was in the placebo group, incidence of 0.15 (1/1025). Beyond three months of treatment, the suvorexant HD group recorded another case of suicidal ideation. The C-SSRS assessment identified three additional cases of suicidal ideation that investigators had not considered as AEs and so did not report them as ECIs. All three subjects were on suvorexant HD.

Only two subjects reported complex sleep-related behaviors (CSRBs) in the Phase 3 Population. Both subjects were on suvorexant HD (0.2%, 2/1291). One case, a 65-year-old male with a history of sleep talking reported an event of sleep talking on Trial Day 85 while on suvorexant HD. The same night he lunged out of bed, and hit his head and face against a wall. On Day 101, he had a different CSR event, sleep walking, after he had received no trial medication for 2 weeks. The second case was a 58-year-old female who reported somnambulism (sleep walking) and severe sleep paralysis on Trial Day 52 while on suvorexant HD. No additional CSRBs were reported in the Phase 1 and Phase 2 trials.

EDS, as defined in the suvorexant development program, was expected to occur with a sudden onset during the day, in a subject who had adequate night sleep. EDS occurrence has safety implications, especially when it occurs while individuals are going

about their usual duties such as driving. In the Phase 3 Population, EDS occurred more frequently in the suvorexant HD group. The EDS incidence in each treatment group was as follows: 1.1% (14/1291) suvorexant HD, 0.6% (3/493) suvorexant LD, and 0.2% (2/1025) placebo. The EDS risk difference for suvorexant LD compared to placebo was 0.5% (95% CI: -0.2, 1.7); the risk difference for suvorexant HD, with a 95% confidence interval that excluded zero, was 0.8% (95% CI: 0.1, 1.6), NNTH 125.

Five subjects reported hypnagogic and hypnopompic hallucinations within the first three months of treatment: 0.2% (3/1291) in the suvorexant HD group, 0.4% (2/493) in the suvorexant LD group, and none in the placebo group. The event reported for one (0.2%, 1/493) of the two subjects in the suvorexant LD group was a case of hypnagogic hallucination; the other was a hypnopompic hallucination. In contrast, all three subjects (0.2%, 3/1291) in the suvorexant HD group were cases of hypnagogic hallucinations.

Published literature estimate the lifetime prevalence of sleep paralysis at 7.6% of the general population. In the suvorexant Phase 3 trial population, the incidence of sleep paralysis was low as only five subjects reported the event within the first 3 months; all five received suvorexant treatment. Numerically more subjects reported this ECI while on suvorexant HD (0.3%, 4/1291) compared to suvorexant LD (0.2%, 1/493), and none on placebo. All cases occurred 2-3 months of starting trial treatment. Investigators deemed the sleep paralysis events in the suvorexant LD subject as not of sleep onset because the events occurred in the middle of the night. Three of the four suvorexant HD subjects had confirmed events of sleep onset paralysis on adjudication. One case resulted in treatment discontinuation.

Additional subjects on suvorexant doses of 40 mg and higher reported sleep paralysis in the Phase 2 and Phase 1 trials. In the Phase 2 trial, two subjects on suvorexant 40 mg and 80 mg reported symptoms suggestive of sleep paralysis; these events apparently occurred in the middle of night or on awakening, and not at sleep onset. In the Phase 1 trials, 2% (13/ 662) of subjects on suvorexant alone reported sleep paralysis compared to 0.3% (1/365) on placebo. All 13 subjects in the Phase 1 trial, who reported sleep paralysis on suvorexant, did so while on suvorexant doses of 40 mg to 240 mg; 6 of the 13 subjects were on suvorexant 40 mg.

The suvorexant program had no confirmed cases of narcolepsy with or without cataplexy. The external adjudication committee examined a case of muscle weakness and concluded it was not cataplexy. From the NDA safety submission, no subject among the 2,027 subjects exposed to suvorexant had confirmed cataplexy. If this is accurate, then based on "the rule of threes," one can be 95% certain that the incidence of cataplexy in suvorexant treated subjects with insomnia is less than 0.0015 (3/2027), or less than 0.0025 (3/1218) for those exposed to at least 3 months of suvorexant treatment.

The incidence of falls in the Phase 3 trials within the first 3 months of treatment was 0.8% (22/2809), and the fall risks across treatment groups were comparable. Falls occurred in less than 1% in each of the treatment groups: 0.7 % (9/1291) with suvorexant HD, 0.8% (4/493) with suvorexant LD, and 0.9 % (9/1025) with placebo. The external adjudication committee reviewed the fall events and confirmed that none of the events suggested cataplexy.

Merck assessed the effects of suvorexant treatment on driving performance using AE reports of accident-related injuries, questionnaire responses on motor vehicle accidents or traffic violations (MVAs and MVAVs), and two on-the-road driving trials (P035 and P039). In the Phase 3 trial population within 0-3 months, fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects who drove during the trial within each treatment group was: 0.3% (3/891) on suvorexant HD, 0.3% (1/342) on suvorexant LD, and 0.6% (4/692) on placebo. However with MVAVs, a numerically higher rate occurred in the suvorexant LD group (2.9%, 10/342) compared to suvorexant HD group (2.3%, 13/569) and placebo (2.3%, 12/531).

In the Phase 1 driving trials (P035 and P039), Merck observed no significant impairment of next-day driving performance based on mean standard deviation of lateral position (SDLP) after one night and eight consecutive nights of suvorexant LD or HD in both elderly and non-elderly subjects. In the driving trials some subjects who received suvorexant had increased SDLP beyond the pre-defined threshold, resulting in an imbalance in the SDLP symmetry (secondary endpoint) analyses, especially for the non-elderly subjects. Also, four non-elderly subjects felt sleepy enough to prematurely stop their driving tests. These results suggest that a potential for impairment in driving performance exists with suvorexant treatment. The sponsor provided cautionary language in the proposed label, regarding driving and suvorexant treatment, which seems appropriate.

The incidence of any ECI potentially relevant to abuse potential was comparable across treatment groups: suvorexant HD 2.0% (26/1291), suvorexant LD 3.2% (16/493), and placebo 2.2% (23/1025). One event of derealization occurred in the suvorexant HD group. Other events were of drug maladministration, with an incidence of 1.9% (25/1291) in the suvorexant HD group.

Merck evaluated, in Trial P025, abuse potential of single doses of suvorexant compared to placebo and two doses of zolpidem in healthy male and female recreational polydrug users. Based on the primary outcome, "Drug Liking visual analog score, VAS," suvorexant in all tested doses (40 mg, 80 mg, and 150 mg) showed greater abuse potential than placebo in recreational polydrug users. The mean peak effect difference from placebo for each group was 22.84 for suvorexant 40 mg, 21.99 for suvorexant 80 mg, and 20.44 for suvorexant 100 mg. The suvorexant treatment effect appeared to be similar to, or slightly better than, that of zolpidem 15 mg (24.86) or zolpidem 30 mg (28.08).

A major concern with the use of hypnotic sedatives is next-day residual effects. Merck evaluated AEs associated with residual effects and observed the highest incidence with somnolence, discussed above. Fatigue occurred less frequently, and like somnolence, it also occurred in a dose-related manner: suvorexant HD 3.8% (49/1291); suvorexant LD 2.2% (11/493); and placebo 1.8% (18/1025).

Merck evaluated another next-day residual effect, impaired psychomotor performance, using the Digit Symbol Substitution Test (DSST) values from 1,493 subjects in the Phase 3 trials, P028 and P029. They found no clinically meaningful differences between each of the suvorexant groups and placebo. Four Phase 1 trials (P002, P032, P036, and P039) evaluated next-day residual effects at 9-10 hours after suvorexant doses between 10 mg and 100 mg; these trials also failed to show significant treatment effects on DSST (number of correct responses) with suvorexant compared to placebo; a fifth Phase 1 trial P035, which assessed driving in healthy non-elderly subjects, suggested suvorexant 40 mg impairing psychomotor performance after a single dose but not after multiple doses.

Trial P035 also evaluated balance and memory, and showed a statistically significant decrease in word recall 11 hours after single dose of suvorexant 40 mg, and increase in body sway area 11 hrs after single dose of either suvorexant 20 or suvorexant 40 mg. Three other Phase 1 trials (P032, P036, and P039) evaluated balance and memory and found no significant next-day effects following suvorexant treatment.

On abrupt cessation of suvorexant treatment, no clear withdrawal effect occurred, however rebound insomnia was suggested. Merck found no obvious withdrawal effect on sudden discontinuation of suvorexant treatment; this was based on analyses of responses on Tyrer Withdrawal Symptom Questionnaire (WSQ) and reports of prespecified AEs associated with potential withdrawal. Regarding rebound effects, more subjects who switched from suvorexant HD to placebo (48.5%, 233/480) showed a decrease in total sleep time sTST on any of the three nights compared to subjects continued on placebo (37.2%, 295/793). Merck suggested that the effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, the sTST findings for both suvorexant doses, and for the elderly subgroup, support the presence of a rebound effect on abrupt cessation of suvorexant treatment.

Laboratory and vital sign data did not show evidence of suvorexant having deleterious effects. Serum cholesterol levels increased in a dose-related manner following suvorexant treatment in the Phase 2 trial. Mean serum cholesterol levels increased by 3.0 mg/dL at the suvorexant 40 mg dose level, by 2.1 mg/dL at suvorexant 20 mg dose. It is not clear that cholesterol levels were measured in the Phase 3 trials; but the sponsor suggested that the Phase 2 trial finding was not replicated in the Phase 3 population, and that the small sample size in the Phase 2 trials may have contributed to

the finding. Also, the sponsor stated that the findings are unlikely to be clinically meaningful.

#### Problem List and Recommendations for Labeling

Labeling should describe risks of ECI events that occurred with suvorexant treatment: it should include dose-related findings and a suggestion to discontinue suvorexant treatment on emergence of such events.

Avoid suvorexant use in individuals with narcolepsy-like events and suicidal ideation.

Consider periodic monitoring of serum cholesterol levels especially in individuals with cardiovascular risk factors.

Individuals taking suvorexant should be cautioned against driving or operating heavy machinery.

Consider use of lower suvorexant dose as appropriate for an individual's situation.

For Pediatric development, waiver for children under 6 years appears reasonable. Deferral until additional postmarketing data available is also reasonable given theoretical risk of narcoleptic events that are yet to be clearly defined in the adult population.

## 5.1 Methods

### 5.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for this NDA is based on the principles outlined in the Agency's GRP with a view of addressing two specific goals: First, assess the adequacy of the sponsor's safety evaluation; and second, identify and assess the significance of the adverse events observed in the safety database. The sponsor reported 35 clinical trials: two Phase 3 confirmatory efficacy trials, and one Phase 3 long-term safety trial, one Phase 2b dose-finding trial, and 31 Phase 1 clinical pharmacology trials conducted in healthy volunteers and special populations.

Suvorexant integrated safety database included 2,809 subjects with primary insomnia in the three Phase 3 trials (P028, P029, and P009), in which subjects received the proposed doses of suvorexant (15 mg to 40 mg). The sponsor also provided separate safety data from the Phase 2b and Phase 1 trials to further characterize suvorexant's safety profile. The safety data were summarized separately due to differences in trial populations, trial design, drug doses, and duration of treatment. The Phase 2 trial was analyzed separately because of its different trial design: a crossover trial that evaluated

multiple suvorexant doses (10 mg to 80 mg) over a shorter duration of four weeks compared to at least 3 months of the Phase 3 trials.

The Phase 3 and Phase 2 trials assessed safety in subjects with primary insomnia. A total of 2,027 subjects with chronic insomnia received any suvorexant dose: 1,198 non-elderly and 829 elderly subjects. The Phase 3 trials exposed 1,784 subjects to suvorexant 15 mg to 40 mg doses, of which 1,218 subjects received treatment for at least 3 months, 507 subjects for at least 6 months, and 160 subjects for at least 12 months.

**Table 65: Number of Primary Insomnia Subjects in the Phase 2 and Phase 3 Trials**

| <b>Trial</b> | <b>Trial Design</b>   | <b>Placebo</b> | <b>Suvorexant LD</b>                         | <b>Suvorexant HD</b>                         | <b>Suvorexant Total</b> |
|--------------|---|----------------|--|--|-------------------------|
| P006         | Phase 2 Dose-Finding, 2-period crossover (4-week treatment phase in each period), multicenter trial in <b>non-elderly</b> adults with primary insomnia. | 249            | Suvorexant 10 mg: 62<br>Suvorexant 20 mg: 61 | Suvorexant 40 mg: 59<br>Suvorexant 80 mg: 61 | 243                     |
| P028         | Phase 3, multicenter, RCT, DB, 3-month with 3-month DB Extension treatment in adults with primary insomnia  | 385            | 254  | 383  | 637                     |
| P029         | Phase 3, multicenter, RCT, DB, 3-month treatment  | 387            | 240  | 392  | 632                     |
| P009         | Phase 3, RCT, DB, 12-month treatment for Long-Term Safety in adults with primary insomnia   | 259            | None administered                            | 522  | 522                     |
|              |   |                |  |  | 2034                    |

(Source: Modified from Sponsor's submission ISS Page 76 Table 5.3.5.3.3:2. Except for suvorexant doses specified for P006, Suvorexant LD = 15 mg in elderly and 20 mg in the non-elderly subjects, Suvorexant HD = 30 mg in elderly and 40 mg in non-elderly subjects. RCT = randomized controlled trial; DB = double-blind)

In examining the apparent discrepancy between the total number of subjects in the suvorexant group in table 65 above for the Phase 2 and Phase 3 trials (N = 2,034) and the stated drug exposure of 2,027 subjects, I noticed that the sponsor excluded some



subjects as follow: In Trial P009, two randomized subjects did not receive treatment, one from each treatment group; therefore, the total number of subjects evaluated for safety was 779 (P009 CSR Page 112). Further, the sponsor excluded 6 cases of transient treatment errors; these were identified after database lock for P028 and P009, as cases of medication dispensing or assignment errors at the site (ISS Page 123).

The Phase 1 trials assessed healthy subjects; and subjects with renal insufficiency, hepatic impairment, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea (OSA). The trials enrolled a total of 922 subjects. Below is a summary of the initially submitted 31 Phase 1 trials.

**Table 66: Number of Subjects Enrolled in Suvorexant Clinical Pharmacology Studies in the Safety Database**

| Study Type                                  | Trial Number | Protocol Short Title  | Dosing                  | Number of Subjects               |
|---|--------------|-----------------------|-------------------------|----------------------------------|
| Comparative BA/BE                           | P007         | Biocomparison Study   | AM                      | 18                               |
|   | P041         | Biocomparison Study   | AM                      | 12                               |
| Bioavailability                             | P020         | FMI Food Effect       | AM                      | 14                               |
|   | P042         | Japanese Food Effects | AM                      | 12                               |
| Healthy Subject PK and Initial Tolerability | P001         | FIM SD Young          | AM (two panels have PM) | 40                               |
|   | P003         | MD Young              | PM                      | 40                               |
|   | P011         | SD Young Extension    | AM                      | 17                               |
|   | P012         | ADME                  | AM                      | 6                                |
|   | P018         | Dose Proportionality  | AM                      | Part 1: 32<br>Part 2: 16         |
| Intrinsic Factors                           | P004         | SD Elderly            | AM                      | 20                               |
|   | P005         | Japanese SD PK        | AM/PM                   | 32 (n = 16 in only Part II data) |
|   | P017         | Hepatic Insufficiency | AM                      | 8 moderate;<br>8 healthy         |
|   | P023         | Renal Insufficiency   | AM                      | 8 severe;<br>8 healthy           |
|   | P027         | MD Elderly            | PM                      | 75                               |
| Extrinsic Factors                           | P008         | Ketoconazole DDI      | AM                      | 10                               |
|   | P013         | OCP DDI               | PM                      | 20                               |
|   | P015         | Midazolam DDI         | AM                      | 12                               |

|  |      |  |    |                           |
|--|------|--|----|---------------------------|
|  | P016 | Digoxin DDI  | AM | 20                        |
|  | P024 | Warfarin DDI   | AM | 14                        |
|  | P026 | Paroxetine DDI   | PM | 24                        |
|  | P038 | Rifampin and Diltiazem DDI   | AM | Part I: 10<br>Part II: 20 |
| Healthy Subject PD and PK/PD                       | P002 | Healthy Subject PSG  | PM | 22                        |
|  | P010 | Alcohol Interaction  | AM | 31                        |
|  | P021 | Elderly PM Safety  | PM | 12                        |
|  | P022 | Thorough QTc   | AM | 53                        |
|  | P025 | Human Abuse Liability Part I – Qualifying Phase<br>Part II – Treatment Phase | AM | 73                        |
|  | P035 | Car Driving Study (Non-Elderly)  | PM | 28                        |
|  | P039 | Car Driving Study (Elderly)  | PM | 24                        |
|  | P040 | Healthy Subject Respiratory Safety   | PM | 12                        |
| Patient PD and PK/PD                               | P032 | Respiratory Safety Study in COPD Patients                                    | PM | 25                        |
|  | P036 | Respiratory Safety Study in OSA Patients                                     | PM | 26                        |
| <b>Total N in suvorexant safety database = 802</b> |      |  |    |                           |

(Source: Modified from Sponsor's submission ISS Page 74 Table 5.3.5.3.3:1)

The sponsor's Safety Update on 7 December 2012 provided additional suvorexant exposure data from a Phase 1 trial, the 32<sup>nd</sup> trial, which compared bioavailability of four doses of suvorexant under fasting condition in 120 subjects.

### 5.1.2 Categorization of Adverse Events

The sponsor defined an adverse experience or event (AE) as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the trial product, whether or not considered related to the use of the product. An adverse experience also included any worsening of a preexisting condition which is temporally associated with the use of the trial product. AEs reported by investigators were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The sponsor used MedDRA Version 14.1 for the pooled analyses in the ISS.

To evaluate safety concerns related to marketed sedative hypnotic medications or to suvorexant's mechanism of action, the sponsor identified specific AEs for close monitoring in the Phase 2 and Phase 3 trials. These selected AEs, termed Events of Clinical Interest (ECIs), were updated over time during the suvorexant development program. Therefore, the sponsor conducted a retrospective review of all Phase 1 trials for ECIs. Pre-specified ECIs for the Phase 3 trials included suicidal ideation or behavior,

complex sleep-related behaviors, hypnagogic and hypnopompic hallucinations, excessive daytime sleepiness, sleep paralysis, cataplexy, falls, and AEs associated with traffic or motor vehicle accidents. For the Phase 2 trial, the prespecified ECIs were narcolepsy-like events, including cataplexy-like events; suicidal thoughts or ideation; and complex sleep related behaviors.

Investigators collected AEs by open-ended questioning at each visit and recorded spontaneously reported events. At the subjects' trial visits, investigators recorded adverse events and provided additional information based on the sponsor's list of specific terms and guidance for ECIs. An independent committee of experts, blinded to treatment assignment and external to the sponsor, completed an adjudication of selected ECIs. The adjudicated ECIs were cataplexy; falls, to determine occurrence of cataplexy; and sleep onset paralysis. A summary of safety parameters that the sponsor evaluated in the Phase 3 trial is presented in the table below.

**Table 67: Safety Parameters for Phase 3 Trials in ISS**

| Safety Parameter        | Description   | Protocol             | Time Points for Data Collection  | Comment   |
|-------------------------|---|----------------------|--|---|
| AEs                     | <ul style="list-style-type: none"> <li>- Spontaneously reported by the subject</li> <li>- Based on investigator's review of physical examination and vital sign findings and lab/ECG results</li> <li>- Collected up to 14 days after the last dose of study medication according to protocols, although AEs reported after this time frame were also included</li> </ul> | P028<br>P029<br>P009 | Each visit   | <ul style="list-style-type: none"> <li>- Selected terms identified for abuse potential, residual effects, and withdrawal</li> <li>- Selected events designated as Events of Clinical Interest (ECIs)</li> </ul> |
| Laboratory safety tests | <ul style="list-style-type: none"> <li>- Hematology and blood chemistry</li> <li>- Change from baseline</li> <li>- Values exceeding predefined limits of change</li> </ul>  | P028<br>P029<br>P009 | BL, week 2, months 1, 3, and 6*<br>BL, week 2, months 1 and 3<br>BL, week 2, months 1, 3, 6, 9, and 12 |   |
| ECGs                    | <ul style="list-style-type: none"> <li>- Change from baseline</li> <li>- Values exceeding predefined limits of change</li> </ul>  | P028<br>P029<br>P009 | BL, week 2, months 1, 3, and 6*<br>BL, week 2, months 1 and 3<br>BL, week 2, months 1, 3, 6, 9, and 12 |   |

|  |  |                      |  |  |
|--|--|----------------------|--|--|
| Vital signs  | - Change from baseline<br>- Values exceeding predefined limits of change   | P028<br>P029<br>P009 | Each visit   | - PSG visits: performed in PM prior to and AM following PSG assessment<br>- Non-PSG visits: at any time during visit |
| Sleep architecture   | - Minutes and percent of time in sleep Stages 1, 2, 3 and REM  | P028<br>P029         | PSG visits   |  |
| Suicidal ideation and/or behavior                                  | - Responses provided on the Columbia Suicidality Severity Rating Scale are mapped to corresponding categories on the Columbia Classification Algorithm for Suicidality Assessment (C-CASA) | P028<br>P029<br>P009 | Each visit   |  |
| Residual effects   | - DSST: Change from baseline in number attempted, number correct   | P028<br>P029         | For Treatment Phase: BL, night 1, months 1 and 3<br>For Run-out Phase: End of Treatment Phase (BL), night 1 (of Run-out Phase)                                   | - For P028, includes subjects not continuing into the extension phase only   |
|  | - Selected AE terms<br>- Motor Vehicle Accident and Traffic Violation summary  | P028<br>P029<br>P009 | Each visit   |  |
| Withdrawal   | - Tyrer Withdrawal Symptom Questionnaire (WSQ)   | P028<br>P029<br>P009 | The first 3 days of the Run-out Phase with the last value from the double-blind treatment serving as the baseline  |  |
|  | - Selected AE terms  | P028<br>P029         | 1-week Run-out Phase   |  |
| Rebound  | - LPS, WASO  | P028<br>P029         | At the 3-month PSG visit and after the first night of the Run-out Phase with the last value from the baseline period (pre-randomization) serving as the baseline | - For P028, includes subjects not continuing into the extension phase only   |
|  | - sTSO, sTST, sWASO  | P028<br>P029<br>P009 | The first three nights of the Run-out Phase with the last value from the baseline period (pre-randomization) serving as the baseline                             |  |
| <b>BL = baseline * for Subjects completing the extension phase</b> |  |                      |  |  |

(Source: Sponsor's submission ISS Page 86 Table 5.3.5.3.3:3)

Also, the investigators reported intensity of adverse events as follows:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or do usual activity

### 5.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor provided multiple data pools to summarize the suvorexant safety experience. Although the major safety data included information from Phase 3 trials, Phase 2, and Phase 1 trials, this review depended largely on analyses of the safety population from the three Phase 3 trials (P028, P029, and P009). To gain further insight of risks associated with the trial treatment, the safety pools of the Phase 2 and Phase 1 trials were examined.

The Safety Analysis Populations included subjects in the sponsor's All Patients as Treated (APaT) population. The APaT population included all randomized subjects who received at least one dose of trial treatment. A subject's treatment group was based on actual treatment received, not randomized.

The Combined Phase 3 Population was the primary data pool for safety analyses. The Phase 3 trials had subjects treated over different intervals: Trial P028 treated subjects for up to 6 months in the treatment and extension phases, including placebo, suvorexant LD, and suvorexant HD; Trial P029 treated subjects for up to 3 months, including all three dose groups; and Trial P009 treated subjects for at least 12 months with only suvorexant HD or placebo. As a result, the sponsor created three data pools to describe the safety of suvorexant within the combined Phase 3 population as follows:

- 0-3 months: This data pool, for the Combined Phase 3 Population, provided all key safety analyses to support suvorexant LD and suvorexant HD, including subgroup analyses by age.
- 0-6 months: This data pool contained Treatment and Extension Phase data for Phase 3 trials P028 and P029. It provided safety analyses of the long-term use of suvorexant LD.
- 0-12 months: This pool, from the Combined Phase 3 Population, provided data for the safety analyses of the long-term use of suvorexant HD

The sponsor's populations for safety assessments are shown in the table below:

**Table 68: Phase 3 Trial Populations for Safety Assessment**

| Safety Populations | Placebo | Suvorexant LD | Suvorexant HD | Total | Completers |
|--------------------|---------|---------------|---------------|-------|------------|
|--------------------|---------|---------------|---------------|-------|------------|

|   |            |           |            |             |     |
|---|------------|-----------|------------|-------------|-----|
| 0-3 months<br>(Trials: P028+P029+P009)  | 1025 (36%) | 493 (18%) | 1291 (46%) | 2809 (100%) | 86% |
| 0-6 months<br>(Trials: P028+P029)       | 767 (61%)  | 493 (39%) | N/A        | 1260 (100%) | 86% |
| 0-12 months<br>(Trials: P028+P029+P009) | 1025 (44%) | N/A       | 1291 (56%) | 2316 (100%) | 78% |

Using data pooled from the 1-week Run-out Phase of Trials P028 and P029, the sponsor characterized suvorexant next-day residual effects, as well as rebound and withdrawal effects over the first 3 days of treatment cessation. Further, the sponsor summarized AEs related to suvorexant discontinuation.

## 5.2 Adequacy of Safety Assessments

### 5.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, the number of subjects exposed to suvorexant in the development program appears adequate, as it exceeds the recommended subject exposure in the ICH guidance document. The Phase 2 and Phase 3 trials exposed 2,027 subjects with primary insomnia to suvorexant as shown in the table below.

**Table 69: Chronic Insomnia Subjects Ever Exposed to Suvorexant in the Phase 2 and Phase 3 Trials**

| Cumulative Duration of Exposure | N    | %   |
|---------------------------------|------|-----|
| Ever Exposed                    | 2027 | 100 |
| 3 months or more                | 1218 | 60  |
| 6 months or more                | 507  | 25  |
| 12 months or more               | 160  | 8   |

The Phase 1 trials enrolled 802 subjects, of which 722 were exposed to suvorexant. Maximum single dose exposure was up to 240 mg.

#### Demographics

Of the 2,027 subjects with primary insomnia who were exposed to suvorexant Phase 2 and Phase 3 trials, 1,198 (59.1%) were non-elderly adults and 829 (40.9%) elderly adults 65 years or older. The mean duration of treatment for elderly subjects with any

dose of suvorexant was 177 days; most of them received treatment for between 3 and 6 months in the Phase 3 trials. In the Combined Phase 3 Population the mean age of subjects was 58 years, with a range from 18 to 90 years. The population had more females (62%) compared to males (38%). The table below summarizes the demographic characteristics of the Combined Phase 3 Population.

**Table 70: Demographic Characteristics for Subjects in Combined Phase 3 Population (P028, P029, and P009)**

| Demographic Variable                        | Placebo    | Suvorexant LD | Suvorexant HD | Total        |
|---|------------|---------------|---------------|--------------|
| Subjects with data                          | 1,025      | 493           | 1,291         | 2,809        |
| <b>Age (years)</b>                          |            |               |               |              |
| Mean  | 58         | 55            | 58            | 58           |
| SD  | 15         | 16            | 15            | 15           |
| Median                                      | 62         | 59            | 64            | 62           |
| Range                                       | 18 to 90   | 18 to 86      | 18 to 88      | 18 to 90     |
| <b>Gender N (%)</b>                         |            |               |               |              |
| Male  | 384 (37.5) | 174 (35.3)    | 507 (39.3)    | 1,065 (37.9) |
| Female                                      | 641 (62.5) | 319 (64.7)    | 784 (60.7)    | 1,744 (62.1) |
| <b>Race N (%)</b>                           |            |               |               |              |
| American Indian or Alaska Native            | 3 (0.3)    | 0 (0.0)       | 2 (0.2)       | 5 (0.2)      |
| Asian                                       | 125 (12.2) | 93 (18.9)     | 130 (10.1)    | 348 (12.4)   |
| Black                                       | 70 (6.8)   | 19 (3.9)      | 71 (5.5)      | 160 (5.7)    |
| Multiple                                    | 42 (4.1)   | 23 (4.7)      | 48 (3.7)      | 113 (4.0)    |
| Native Hawaiian or Other Pacific Islander   | 1 (0.1)    | 0 (0.0)       | 1 (0.1)       | 2 (0.1)      |
| White                                       | 784 (76.5) | 358 (72.6)    | 1,039 (80.5)  | 2,181 (77.6) |
| <b>Body Mass Index (BMI) Category N (%)</b> |            |               |               |              |
| Underweight (BMI <18.5)                     | 17 (1.7)   | 11 (2.2)      | 21 (1.6)      | 49 (1.7)     |
| Normal range (18.5 ≤ BMI <25)               | 432 (42.1) | 232 (47.1)    | 488 (37.8)    | 1,152 (41.0) |
| Overweight (25 ≤ BMI ≤30)                   | 405 (39.5) | 194 (39.4)    | 548 (42.4)    | 1,147 (40.8) |
| Obese (BMI > 30)                            | 170 (16.6) | 56 (11.4)     | 232 (18.0)    | 458 (16.3)   |
| Null  | 1 (0.1)    | 0 (0.0)       | 2 (0.2)       | 3 (0.1)      |

(Source: Sponsor's submission ISS Page 134 Table 5.3.5.3.3: 12)

## 7.2.2 Explorations for Dose Response

The Phase 2 and Phase 3 trials included 2,027 subjects with primary insomnia who were exposed to suvorexant doses of 10 mg to 80 mg. Majority of the subjects received three to six months treatment, as shown in the table below.

**Table 71: Exposure to Suvorexant by Dose and Duration in the Phase 2 and Phase 3 Trials (P006, P028, P029, and P009)**

| Suvorexant | 1 day to <1 Week | 1 Week to <1 Month | 1 to <3 Months | 3 to <6 Months | 6 to <9 Months | 9 to <12 Months | ≥12 Months | Total Subjects | Duration Range | Mean Duration |
|------------|------------------|--------------------|----------------|----------------|----------------|-----------------|------------|----------------|----------------|---------------|
| Any Dose   | 33               | 318                | 458            | 711            | 170            | 177             | 160        | 2,027          | 1 to 434 days  | 139.9 days    |
| 10 mg      | 19               | 60                 | 2              | 0              | 0              | 0               | 0          | 81             | 1 to 31 days   | 21.5 days     |
| 15 mg      | 3                | 10                 | 71             | 96             | 22             | 0               | 0          | 202            | 1 to 189 days  | 104.9 days    |
| 20 mg      | 9                | 67                 | 105            | 152            | 20             | 0               | 0          | 353            | 1 to 191 days  | 85.7 days     |
| 30 mg      | 22               | 34                 | 123            | 196            | 54             | 107             | 109        | 645            | 1 to 434 days  | 194.1 days    |
| 40 mg      | 19               | 97                 | 154            | 267            | 73             | 70              | 51         | 731            | 1 to 426 days  | 141.6 days    |
| 60 mg      | 11               | 0                  | 0              | 0              | 0              | 0               | 0          | 11             | 1 to 3 days    | 1.7 days      |
| 80 mg      | 13               | 54                 | 4              | 0              | 0              | 0               | 0          | 71             | 1 to 31 days   | 22.3 days     |

(Source: Sponsor's submission ISS Page 125 Table 5.3.5.3.3:6)

The phase 3 trials (P028, P029, and P009) exposed 1,784 subjects with primary insomnia to suvorexant. Apart from a few subjects who mistakenly took lower or higher doses, most of the subjects received suvorexant doses between 15 mg and 40 mg, as shown in the table below. The mean duration of treatment with suvorexant doses between 15 mg and 40 mg ranged from 98 to 152 days.

**Table 72: Exposure to Suvorexant by Dose in Phase 3 Trials (P028, P029, and P009)**

| Suvorexant | 1 day to <1 Week | 1 Week to <1 Month | 1 to <3 Months | 3 to <6 Months | 6 to <9 Months | 9 to <12 Months | ≥12 Months | Total Subjects | Duration Range | Mean Duration |
|------------|------------------|--------------------|----------------|----------------|----------------|-----------------|------------|----------------|----------------|---------------|
| Any Dose   | 28               | 94                 | 444            | 711            | 170            | 177             | 160        | 1,784          | 1 to 434 days  | 155.2 days    |
| 10 mg      | 18               | 1                  | 0              | 0              | 0              | 0               | 0          | 19             | 1 to 7 days    | 1.8 days      |
| 15 mg      | 3                | 10                 | 71             | 96             | 22             | 0               | 0          | 202            | 1 to 189 days  | 104.9 days    |
| 20 mg      | 7                | 12                 | 100            | 152            | 20             | 0               | 0          | 291            | 1 to 191 days  | 98.3 days     |
| 30 mg      | 21               | 34                 | 123            | 196            | 54             | 107             | 109        | 644            | 1 to 434 days  | 194.4 days    |
| 40 mg      | 17               | 41                 | 151            | 267            | 73             | 70              | 51         | 670            | 1 to 426 days  | 152.1 days    |



|       |    |   |   |   |   |   |   |    |             |          |
|-------|----|---|---|---|---|---|---|----|-------------|----------|
| 60 mg | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 11 | 1 to 3 days | 1.7 days |
| 80 mg | 9  | 0 | 0 | 0 | 0 | 0 | 0 | 9  | 1 to 5 days | 1.9 days |

(Source: Sponsor's submission ISS Page 126 Table 5.3.5.3.3:7)

### 5.2.3 Special Animal and/or In Vitro Testing

The sponsor assessed the risk of narcoleptic-like events in non-clinical studies, which appeared lacking of cataplexy-like events. FDA non-clinical reviewer, Dr. Siarey, reviewed the data and is of the opinion that narcoleptic events cannot be excluded in the dog studies.

### 5.2.4 Routine Clinical Testing

The routine clinical testing for safety appears appropriate and capable of identifying major adverse signal. The assessment for ECIs appears rigorous enough to identify and characterize a frequent occurrence of narcoleptic-like events. The Phase 3 trials evaluated subjects for safety using physical examination, body system review, electrocardiography, vital sign assessment, blood chemistry, hematology, urinalysis, concomitant medication monitoring, and adverse event reporting. Also, investigators assessed the subjects during the trials' discontinuation phase for rebound and withdrawal events, and late-occurring AEs. Further, investigators conducted routine safety assessments that appear adequate for the long-term trial P009.

### 5.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor performed specific studies examining suvorexant metabolism, clearance, and potential for interaction. The in vitro and in vivo testing appears appropriate. Please refer to Clinical Pharmacology review for details of the specific assessments.

### 5.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Suvorexant is a new molecular entity and an orexin receptor antagonist (ORA). No drug in this ORA class has previously received approval. The Phase 3 trials incorporated monitoring for toxicities associated with sedative hypnotics and narcolepsy-like events, which have been associated with brain orexin deficiency.

## 5.3 Major Safety Results

### 5.3.1 Deaths

Two deaths occurred in the suvorexant clinical development program. Both occurred in Phase 3 trials; one of the subjects received suvorexant HD, the other received placebo.

One of the subjects was a 40-year old female who was enrolled in Trial P029 at a US site in Florida. She had no known active medical history and no concomitant medications. She received suvorexant HD starting 16 June 2010 (Day 1) until Trial Day 34. The exact time of her last suvorexant dose was unknown. On Day 35, she was on a recreational ocean swim at about 08:00 h, when she was caught in a rip current and experienced a near drowning event. Following her rescue, she was admitted to an intensive care unit (ICU). Later she developed cardiac arrest, hypoxic-ischemic encephalopathy (a serious AE); and, on Trial Day 38 she was declared brain dead and removed from life support.

Another fatal case was a 58-year-old white female with a history of coronary artery disease, status post myocardial infarction and coronary stent placement, who received placebo in Trial P028. She received her last dose of trial medication on Day 70. On Trial Day 71, she experienced a stroke that was documented on computed axial tomography scan as a blood clot and swelling of her brain. She died on Trial Day 72.

Although both deaths were deemed unrelated to treatment, it remains uncertain whether a residual effect of suvorexant HD contributed to the near drowning event of the subject on active treatment. Even so, mortality between suvorexant and placebo groups was similar with one subject in each of the suvorexant HD and placebo groups. No deaths occurred in the suvorexant LD group. No deaths occurred in the Phase 1 and Phase 2 trials.

### 5.3.2 Nonfatal Serious Adverse Events

Nonfatal serious AEs (SAEs) were infrequent in the suvorexant trials. The SAEs occurred less frequently in suvorexant treated subjects than in placebo. Over 12 months, SAEs occurred in 2.8% (36/1291) of the subjects who received suvorexant HD and 3.2% (33/1025) who received placebo. Likewise, fewer subjects on suvorexant LD reported SAEs (0.6%, 3/493) compared to placebo (2.1%, 16/767) in the 0-6 months safety population. Because SAEs occurred infrequently in the Phase 3 trials, the sponsor used a 0% tables to summarize the events in the Combined Phase 3 Population over 0-6 months for suvorexant LD and over 0-12 months for suvorexant HD. The table below is a summary of the SAEs with incidence >0% in at least one treatment group in the Combined Phase 3 Population over 0-12 months.

**Table 73: SAEs in the Combined Phase 3 Population (P028, P029, and P009) over 0-12 months for Suvorexant HD**

| <b>System Organ Class (SOC)<br/>AE Preferred Term (PT)</b>  | <b>Placebo<br/>N = 1,025<br/>n (%)</b> | <b>Suvorexant HD<br/>N = 1,291<br/>n (%)</b> |
|---|--|--|
| Subjects with one or more adverse events                    | 33 (3.2)                               | 36 (2.8)                                     |
| <b>Cardiac disorders</b>                                    | <b>4 (0.4)</b>                         | <b>2 (0.2)</b>                               |
| Atrial fibrillation   | 3 (0.3)                                | 1 (0.1)                                      |
| Coronary artery disease                                     | 0 (0.0)                                | 1 (0.1)                                      |
| Myocardial infarction                                       | 1 (0.1)                                | 0 (0.0)                                      |
| <b>Ear and labyrinth disorders</b>                          | <b>0 (0.0)</b>                         | <b>2 (0.2)</b>                               |
| Meniere's disease   | 0 (0.0)                                | 1 (0.1)                                      |
| Vertigo positional  | 0 (0.0)                                | 1 (0.1)                                      |
| <b>Endocrine disorders</b>                                  | <b>0 (0.0)</b>                         | <b>1 (0.1)</b>                               |
| Autoimmune thyroiditis                                      | 0 (0.0)                                | 1 (0.1)                                      |
| <b>Gastrointestinal disorders</b>                           | <b>3 (0.3)</b>                         | <b>2 (0.2)</b>                               |
| Colitis   | 1 (0.1)                                | 0 (0.0)                                      |
| Duodenal ulcer  | 0 (0.0)                                | 1 (0.1)                                      |
| Gastroesophageal reflux disease                             | 0 (0.0)                                | 1 (0.1)                                      |
| Ileus   | 1 (0.1)                                | 0 (0.0)                                      |
| Pancreatitis  | 1 (0.1)                                | 0 (0.0)                                      |
| <b>General disorders and administration site conditions</b> | <b>0 (0.0)</b>                         | <b>1 (0.1)</b>                               |
| Non-cardiac chest pain                                      | 0 (0.0)                                | 1 (0.1)                                      |
| <b>Infections and infestations</b>                          | <b>5 (0.5)</b>                         | <b>4 (0.3)</b>                               |
| Abdominal infection   | 1 (0.1)                                | 0 (0.0)                                      |
| Diverticulitis  | 1 (0.1)                                | 2 (0.2)                                      |
| Endometritis  | 1 (0.1)                                | 0 (0.0)                                      |
| Erysipelas  | 1 (0.1)                                | 0 (0.0)                                      |
| Gastroenteritis   | 2 (0.2)                                | 0 (0.0)                                      |
| Pneumonia   | 0 (0.0)                                | 1 (0.1)                                      |
| Urinary tract infection                                     | 1 (0.1)                                | 1 (0.1)                                      |

|   |                 |                |
|---|-----------------|----------------|
| <b>Injury, poisoning and procedural complications</b>                       | <b>3 (0.3)</b>  | <b>5 (0.4)</b> |
| Clavicle fracture   | 0 (0.0)         | 1 (0.1)        |
| Compression fracture  | 0 (0.0)         | 1 (0.1)        |
| Concussion  | 0 (0.0)         | 1 (0.1)        |
| Fall  | 2 (0.2)         | 1 (0.1)        |
| Fibula fracture   | 1 (0.1)         | 0 (0.0)        |
| Joint dislocation   | 1 (0.1)         | 0 (0.0)        |
| Rib fracture  | 1 (0.1)         | 0 (0.0)        |
| Tendon rupture  | 0 (0.0)         | 1 (0.1)        |
| Tibia fracture  | 1 (0.1)         | 0 (0.0)        |
| Ulna fracture   | 0 (0.0)         | 1 (0.1)        |
| <b>Musculoskeletal and connective tissue disorders</b>                      | <b>3 (0.3)</b>  | <b>4 (0.3)</b> |
| Arthralgia  | 0 (0.0)         | 1 (0.1)        |
| Back pain   | 1 (0.1)         | 0 (0.0)        |
| Intervertebral disc protrusion  | 1 (0.1)         | 0 (0.0)        |
| Meniscal degeneration   | 1 (0.1)         | 0 (0.0)        |
| Musculoskeletal chest pain  | 0 (0.0)         | 1 (0.1)        |
| Spinal column stenosis  | 0 (0.0)         | 1 (0.1)        |
| Spondylitis   | 0 (0.0)         | 1 (0.1)        |
| <b>Neoplasms benign, malignant and unspecified (inclu cysts and polyps)</b> | <b>10 (1.0)</b> | <b>8 (0.6)</b> |
| B-cell lymphoma   | 0 (0.0)         | 1 (0.1)        |
| Basal cell carcinoma  | 3 (0.3)         | 3 (0.2)        |
| Bladder neoplasm  | 1 (0.1)         | 0 (0.0)        |
| Borderline ovarian tumor  | 1 (0.1)         | 0 (0.0)        |
| Breast cancer   | 1 (0.1)         | 0 (0.0)        |
| Hodgkin's disease   | 0 (0.0)         | 1 (0.1)        |
| Malignant melanoma  | 2 (0.2)         | 0 (0.0)        |
| Neoplasm skin   | 0 (0.0)         | 1 (0.1)        |
| Squamous cell carcinoma   | 1 (0.1)         | 1 (0.1)        |
| Uterine cancer  | 0 (0.0)         | 1 (0.1)        |

|  |                |                |
|--|----------------|----------------|
| Uterine leiomyoma                                      | 1 (0.1)        | 0 (0.0)        |
| <b>Nervous system disorders</b>                        | <b>3 (0.3)</b> | <b>6 (0.5)</b> |
| Cerebral Infarction                                    | 2 (0.2)        | 0 (0.0)        |
| Cerebrovascular accident                               | 1 (0.1)        | 0 (0.0)        |
| Cervicobrachial syndrome                               | 0 (0.0)        | 1 (0.1)        |
| Headache   | 0 (0.0)        | 1 (0.1)        |
| Hypoxic-ischemic encephalopathy                        | 0 (0.0)        | 1 (0.1)        |
| Migraine   | 0 (0.0)        | 1 (0.1)        |
| Subarachnoid hemorrhage                                | 0 (0.0)        | 1 (0.1)        |
| Transient ischemic attack                              | 0 (0.0)        | 1 (0.1)        |
| <b>Psychiatric disorders</b>                           | <b>1 (0.1)</b> | <b>1 (0.1)</b> |
| Depressed mood   | 1 (0.1)        | 0 (0.0)        |
| Suicidal ideation                                      | 1 (0.1)        | 1 (0.1)        |
| <b>Renal and urinary disorders</b>                     | <b>2 (0.2)</b> | <b>0 (0.0)</b> |
| Calculus ureteric                                      | 1 (0.1)        | 0 (0.0)        |
| Renal failure acute                                    | 1 (0.1)        | 0 (0.0)        |
| <b>Reproductive system and breast disorders</b>        | <b>1 (0.1)</b> | <b>0 (0.0)</b> |
| Vaginal prolapse                                       | 1 (0.1)        | 0 (0.0)        |
| <b>Respiratory, thoracic and mediastinal disorders</b> | <b>1 (0.1)</b> | <b>1 (0.1)</b> |
| Lung disorder  | 0 (0.0)        | 1 (0.1)        |
| Pneumothorax   | 1 (0.1)        | 0 (0.0)        |

(Source: Sponsor's submission ISS Page 167 Table 5.3.5.3.3:20)

Below is a summary of the SAEs with incidence > 0% in at least one treatment group in the Combined Phase 3 Population over 0-6 months.

**Table 74: SAEs in the Combined Phase 3 Population (P028 and P029) over 0-6 months for Suvorexant LD**

| <b>System Organ Class (SOC)<br/>AE Preferred Term (PT)</b> | <b>Placebo<br/>N=767<br/>n (%)</b> | <b>Suvorexant LD<br/>N=493<br/>n (%)</b> |
|--|------------------------------------|--|
| Subjects with one or more adverse events                   | 16 (2.1)                           | 3 (0.6)                                  |
| <b>Cardiac disorders</b>                                   | <b>1 (0.1)</b>                     | <b>1 (0.2)</b>                           |

|  |                |                |
|--|----------------|----------------|
| Atrial fibrillation  | 0 (0.0)        | 1 (0.2)        |
| Myocardial infarction  | 1 (0.1)        | 0 (0.0)        |
| <b>Gastrointestinal disorders</b>  | <b>1 (0.1)</b> | <b>0 (0.0)</b> |
| Colitis  | 1 (0.1)        | 0 (0.0)        |
| <b>Infections and infestations</b>   | <b>3 (0.4)</b> | <b>1 (0.2)</b> |
| Endometritis   | 1 (0.1)        | 0 (0.0)        |
| Gastroenteritis  | 2 (0.3)        | 0 (0.0)        |
| Pneumonia  | 0 (0.0)        | 1 (0.2)        |
| <b>Injury, poisoning and procedural complications</b>                      | <b>2 (0.3)</b> | <b>1 (0.2)</b> |
| Ankle fracture   | 0 (0.0)        | 1 (0.2)        |
| Fall   | 2 (0.3)        | 0 (0.0)        |
| Fibula fracture  | 1 (0.1)        | 0 (0.0)        |
| Rib fracture   | 1 (0.1)        | 0 (0.0)        |
| Tibia fracture   | 1 (0.1)        | 0 (0.0)        |
| <b>Musculoskeletal and connective tissue disorders</b>                     | <b>1 (0.1)</b> | <b>0 (0.0)</b> |
| Intervertebral disc protrusion   | 1 (0.1)        | 0 (0.0)        |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> | <b>6 (0.8)</b> | <b>0 (0.0)</b> |
| Basal cell carcinoma   | 1 (0.1)        | 0 (0.0)        |
| Bladder neoplasm   | 1 (0.1)        | 0 (0.0)        |
| Borderline ovarian tumor   | 1 (0.1)        | 0 (0.0)        |
| Breast cancer  | 1 (0.1)        | 0 (0.0)        |
| Malignant melanoma   | 1 (0.1)        | 0 (0.0)        |
| Uterine leiomyoma  | 1 (0.1)        | 0 (0.0)        |
| <b>Nervous system disorders</b>  | <b>2 (0.3)</b> | <b>0 (0.0)</b> |
| Cerebrovascular accident   | 2 (0.3)        | 0 (0.0)        |
| <b>Psychiatric disorders</b>   | <b>1 (0.1)</b> | <b>0 (0.0)</b> |
| Depressed mood   | 1 (0.1)        | 0 (0.0)        |
| Suicidal ideation  | 1 (0.1)        | 0 (0.0)        |
| <b>Respiratory, thoracic and mediastinal disorders</b>                     | <b>1 (0.1)</b> | <b>0 (0.0)</b> |
| Pneumothorax   | 1 (0.1)        | 0 (0.0)        |

(Source: Sponsor's submission ISS Page 170 Table 5.3.5.3.3:21)

### SAEs in the Run-out (P028 and P029) and Discontinuation (P009) Periods of the Phase 3 Trials

The Run-out (P028 and P029) and Discontinuation (P009) Phases, which followed the treatment phases in the Phase 3 trials, recorded seven SAEs. As reported by the sponsor, the SAEs included the following: meningitis in a subject on MK-LD/PBO; cellulitis, positional vertigo, and squamous cell carcinoma in subjects on MK-HD/MK-HD; breast cancer and atrial fibrillation in subjects on MK-HD/PBO; and basal cell carcinoma in one subject on PBO/PBO.

### SAEs in the Post-Treatment Follow-up and Post-Trial Period

In the Combined Phase 3 Population, ten SAEs occurred during the Post-Treatment Follow-up and Post-Study Phase. The SAEs included the following: gestational diabetes and spontaneous abortion in subjects who received suvorexant LD during the trial's treatment phase; ovarian cancer, spontaneous abortion in two subjects, and alcohol withdrawal syndrome in one subject who had received suvorexant HD; and cartilage injury, device-related infection, post-operative wound infection, and hypertension in subjects earlier treated with placebo. The sponsor stated that at the time of SAE onset, subjects had been off trial medication from 4 days to up to 4 months.

The spontaneous abortions pose some concern because all three cases occurred in subjects treated with suvorexant. The sponsor addresses the issue with the following statement: "Regarding the three events of spontaneous abortion, these AEs occurred in young adult females approximately 2 to 6 weeks after the last dose of study medication. In one instance, a subject had taken misoprostol to terminate the pregnancy. When she was found to have a blighted ovum by ultrasound and a non-viable pregnancy, the investigator determined the event as spontaneous abortion rather than therapeutic abortion. None of these three subjects had history of failed pregnancies." Below, I summarized the SAEs that occurred during the Post-Treatment Follow-Up and Post-Trial Periods of the three Phase 3 trials (P028, P029, and P009).

**Table 75: Serious Adverse Events in the Combined Phase 3 Population during Post-Treatment Follow-Up and Post-Trial Period (P028, P029, and P009)**

| <b>Trial Treatment</b> | <b>Trial</b> | <b>Trial Epoch</b> | <b>Adverse Event</b> | <b>Outcome</b> | <b>Last trial dose to onset</b> | <b>Comment</b>                              |
|------------------------|--------------|--------------------|----------------------|----------------|---------------------------------|---|
| <b>Suvorexant LD</b>   | P028         | Post Study         | Gestational diabetes | Resolved       | 3.45 Months                     | Subject AN 06111, 36 year old, Asian female |
|                        | P029         | Post Study         | Spontaneous abortion |                | 13 days                         | AN 12110, 25 year old white female          |

|                      |      |                          |                               |              |                 |   |
|----------------------|------|--------------------------|-------------------------------|--------------|-----------------|---|
| <b>Suvorexant HD</b> | P009 | Post Study               | Ovarian cancer                | Not Resolved | 2 months 4 days | AN 02629, 61 year old white female        |
|                      | P009 | Treatment Follow Up      | Spontaneous abortion          | Resolved     | 15 days         | AN 02609, 19 year old white female        |
|                      | P028 | Core Treatment Follow Up | Spontaneous abortion          | Resolved     | 14 days         | AN 07423, 30 year old, multiracial female |
|                      | P029 | Core Treatment Follow Up | Alcohol withdrawal syndrome   | Resolved     | 4 days          | AN 12115, 41 year old white male          |
| <b>Placebo</b>       | P009 | Post Study               | Cartilage injury              | Unresolved   | 22 days         | AN 03791, 51 year old white male          |
|                      | P009 | Post Study               | Device related infection      | Resolved     | 1 month 19 days | AN 04083, 70 year old white female        |
|                      | P009 | Treatment Follow Up      | Hypertension                  | Resolved     | 4 days          | AN 04650, 77 year old white male          |
|                      | P009 | Treatment Follow Up      | Postoperative wound infection | Resolved     | 11 days         | AN 04617, 66 year old white female        |

(Source: Modified from Sponsor's submission ISS Page 176 Table 5.3.5.3.3:23)

The Phase 2 trial recorded no SAEs.

#### SAEs in Phase 1 Trials

The Phase 1 trials recorded four SAEs. In one case, Subject AN 0024, a 27 year old healthy female subject in the Thorough QTc study, after a single dose of suvorexant 240 mg, reported chest pain, was hospitalized, and had an evaluation for myocardial infarction, which was negative. At the same setting, the subject had myoclonus and sleep paralysis confirmed by a neurologist.

In the second case, Subject AN 0006, a 65 year old healthy elderly male in a Multiple Dose Elderly Subjects, reported pyrexia (febrile illness) requiring hospitalization about 24 days after his last suvorexant 40 mg dose. The subject had fever, chills, nausea, vomiting, abdominal pain and confusion, elevated liver enzymes, increased lymphocytes and decreased platelet counts. He also had a slightly elevated titer for Epstein-Barr virus capsid IgG antigen. All symptoms resolved over days. While the liver function tests returned to within normal limits, the subject continued to be anemic. No final diagnosis was made.



The third case was Subject AN0016, a 34 year old black female in the Oral Contraceptive DDI study, who reported an episode of appendicitis about 9 hours after her sixth daily dose of suvorexant 40 mg. Subsequently, she was treated with a laparoscopic appendectomy without surgical complications.

The fourth case was a 32 yr old white female in the Young Driving Study. She reported an SAE of therapeutically induced abortion about 77 days after her last trial treatment of suvorexant 40 mg. In the table below, I summarize the SAEs in the Phase 1 trials.

**Table 76: SAEs in the Phase 1 Trials**

| AN                    | Gender | Race  | Age   | Suvorexant Dose   | Time Since Last Dose (d-h:m) | Onset Day Relative To Study | Onset Day Relative to Period | Adverse Experience | Duration of Adverse Experience | Action Taken             | Outcome   |
|-----------------------|--------|-------|-------|-------------------|------------------------------|-----------------------------|------------------------------|--------------------|--------------------------------|--------------------------|-----------|
| Protocol Number : 013 |        |       |       |                   |                              |                             |                              |                    |                                |                          |           |
| 16                    | F      | black | 34 yr | Suvorexant 40 mg  | 0-9:29                       | 20                          | 7                            | Appendicitis       | 11.43 hr                       | discontinued treatment   | recovered |
| Protocol Number : 022 |        |       |       |                   |                              |                             |                              |                    |                                |                          |           |
| 24                    | F      | white | 27 yr | Suvorexant 240 mg | 0-4:34                       | 12                          | 1                            | Chest pain         | 0.03 hr                        | discontinued treatment   | recovered |
| Protocol Number : 027 |        |       |       |                   |                              |                             |                              |                    |                                |                          |           |
| 6                     | M      | white | 65 yr | Post study        | 16-2:35                      | 24                          | 4                            | Pyrexia            | 1.91 mo                        | no action with test drug | recovered |
| Protocol Number : 035 |        |       |       |                   |                              |                             |                              |                    |                                |                          |           |
| 7                     | F      | white | 32 yr | Post study        | 26-15:5                      | 77                          | 14                           | Abortion induced   | 0.08 hr                        | no action with test drug | recovered |

(Source: Modified from Sponsor's submission Summary of Pooled Safety Data for Clinical Pharmacology Page 44 Table 5.3.5.3.1: 10)

### 5.3.3 Dropouts and/or Discontinuations

In Table 77 below, the sponsor summarized disposition of subjects in the Phase 3 trials, including reasons for subject discontinuations. Numerically more subjects on suvorexant HD discontinued treatment because of an adverse event compared to those on suvorexant LD or placebo. In the combined Phase 3 population (P028, P029, and P009) within 0-3 months, discontinuation of treatment because of adverse event in all subjects treated were 5.4% (70/1291) in the HD suvorexant group and 3.2% (16/493) the LD suvorexant group, compared to 4.7% (48/1025) in the placebo group. Adverse events most commonly associated with treatment discontinuation were somnolence and fatigue in the HD suvorexant group.

**Table 77: Disposition of Subjects Combined Phase 3 Population 0-3 months (P028, P029, and P009)**

|  | Protocols 028+029+009 |        |            |        |         |        |       |        |
|--|-----------------------|--------|------------|--------|---------|--------|-------|--------|
|  | MK-4305 LD            |        | MK-4305 HD |        | Placebo |        | Total |        |
|  | n                     | (%)    | n          | (%)    | n       | (%)    | n     | (%)    |
| Patients in population   | 493                   |        | 1291       |        | 1025    |        | 2809  |        |
| <b>Trial Disposition</b>   |                       |        |            |        |         |        |       |        |
| Completed  | 435                   | (88.2) | 1117       | (86.5) | 874     | (85.3) | 2426  | (86.4) |
| Discontinued   | 58                    | (11.8) | 174        | (13.5) | 151     | (14.7) | 383   | (13.6) |
| Adverse Event  | 16                    | (3.2)  | 70         | (5.4)  | 48      | (4.7)  | 134   | (4.8)  |
| Lack of Efficacy   | 8                     | (1.6)  | 33         | (2.6)  | 37      | (3.6)  | 78    | (2.8)  |
| Lost to Follow-up  | 3                     | (0.6)  | 10         | (0.8)  | 8       | (0.8)  | 21    | (0.7)  |
| Physician Decision   | 6                     | (1.2)  | 11         | (0.9)  | 3       | (0.3)  | 20    | (0.7)  |
| Pregnancy  | 1                     | (0.2)  | 2          | (0.2)  | 0       | (0.0)  | 3     | (0.1)  |
| Protocol Violation   | 10                    | (2.0)  | 7          | (0.5)  | 10      | (1.0)  | 27    | (1.0)  |
| Withdrawal by Subject  | 14                    | (2.8)  | 41         | (3.2)  | 45      | (4.4)  | 100   | (3.6)  |
| Each patient is counted once for Study Disposition based on the latest corresponding disposition record. |                       |        |            |        |         |        |       |        |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.            |                       |        |            |        |         |        |       |        |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.            |                       |        |            |        |         |        |       |        |

(Source: Sponsor's submission ISS Page 128 Table 5.3.5.3.3:8)

In the 0-6 month's period, 4.4% (56/1260) of the population discontinued because of adverse events: 3.2% (16/493) of the LD suvorexant group, and 5.2% (40/767) of the placebo group. The sponsor summarized disposition of subjects in the Phase 3 trials P028 and P029) in the table below.

**Table 78: Disposition of Subjects Combined Phase 3 Population 0-6 months (P028 and P029)**

|  | Protocols 028+029 |        |         |        |       |        |
|--|-------------------|--------|---------|--------|-------|--------|
|  | MK-4305 LD        |        | Placebo |        | Total |        |
|  | n                 | (%)    | n       | (%)    | n     | (%)    |
| Patients in population   | 493               |        | 767     |        | 1260  |        |
| <b>Trial Disposition</b>   |                   |        |         |        |       |        |
| Completed  | 420               | (85.2) | 661     | (86.2) | 1081  | (85.8) |
| Discontinued   | 73                | (14.8) | 106     | (13.8) | 179   | (14.2) |
| Adverse Event  | 16                | (3.2)  | 40      | (5.2)  | 56    | (4.4)  |
| Lack of Efficacy   | 9                 | (1.8)  | 18      | (2.3)  | 27    | (2.1)  |
| Lost to Follow-up  | 4                 | (0.8)  | 2       | (0.3)  | 6     | (0.5)  |
| Physician Decision   | 7                 | (1.4)  | 0       | (0.0)  | 7     | (0.6)  |
| Pregnancy  | 1                 | (0.2)  | 0       | (0.0)  | 1     | (0.1)  |
| Protocol Violation   | 10                | (2.0)  | 12      | (1.6)  | 22    | (1.7)  |
| Withdrawal by Subject  | 26                | (5.3)  | 34      | (4.4)  | 60    | (4.8)  |
| Each patient is counted once for Study Disposition based on the latest corresponding disposition record. |                   |        |         |        |       |        |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.            |                   |        |         |        |       |        |

(Source: Sponsor's submission ISS Page 130 Table 5.3.5.3.3:10)

Again, during 0-12 months, discontinuations from adverse events were more frequent among suvorexant-treated subjects compared to placebo as shown in the table below.

**Table 79: Disposition of Subjects Combined Phase 3 Population 0-12 months (P028, P029, and P009)**

|  | Protocols 028+029+009 |        |         |        |       |        |
|--|-----------------------|--------|---------|--------|-------|--------|
|  | MK-4305 HD            |        | Placebo |        | Total |        |
|  | n                     | (%)    | n       | (%)    | n     | (%)    |
| Patients in population   | 1291                  |        | 1025    |        | 2316  |        |
| <b>Trial Disposition</b>   |                       |        |         |        |       |        |
| Completed  | 992                   | (76.8) | 823     | (80.3) | 1815  | (78.4) |
| Discontinued   | 299                   | (23.2) | 202     | (19.7) | 501   | (21.6) |
| Adverse Event  | 101                   | (7.8)  | 62      | (6.0)  | 163   | (7.0)  |
| Lack of Efficacy   | 56                    | (4.3)  | 46      | (4.5)  | 102   | (4.4)  |
| Lost to Follow-up  | 24                    | (1.9)  | 14      | (1.4)  | 38    | (1.6)  |
| Physician Decision   | 21                    | (1.6)  | 8       | (0.8)  | 29    | (1.3)  |
| Pregnancy  | 2                     | (0.2)  | 0       | (0.0)  | 2     | (0.1)  |
| Protocol Violation   | 12                    | (0.9)  | 14      | (1.4)  | 26    | (1.1)  |
| Withdrawal by Subject  | 83                    | (6.4)  | 58      | (5.7)  | 141   | (6.1)  |
| Each patient is counted once for Study Disposition based on the latest corresponding disposition record. |                       |        |         |        |       |        |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.            |                       |        |         |        |       |        |

(Source: Sponsor's submission ISS Page 129 Table 5.3.5.3.3:9)

#### Disposition in the Run-out Period of the Combined Phase 3 Population from Trials P028 and P029

There were 1,738 subjects in the Run-out Phase of the combined P028 and P029 trials. Of these, 418 had received suvorexant LD in the Treatment Phase, including 199 subjects who continued the same suvorexant LD in the Run out Phase (MK-LD/MK-LD) and 219 subjects who switched to placebo (MK-LD/PBO). Of the 666 subjects on suvorexant HD during the treatment phase, 333 subjects continued the same suvorexant HD in the Run out Phase (MK-HD/MK-HD), while 333 switched to placebo (MK-HD/PBO). Further, 654 subjects received placebo in the treatment phase and continued the same placebo in the Run out Phase (PBO/PBO). Only 0.6% (11/1738) discontinued trial participation during the Run-out Phase. One subject discontinued because of an adverse event: Subject AN 08169, a 74-year old male, randomized to MK-HD/PBO, had received suvorexant HD in the treatment phase of P028. He experienced atrial fibrillation while on placebo after the first night of the Run-Out phase.

#### Disposition of Subjects in the Phase 2 Trial

The Phase 2 Dose Finding trial P006 randomized 254 subjects; of these, 243 subjects received at least one dose of suvorexant and 249 received at least one dose of placebo. Trial completers were 228 of 254 subjects (89.8%). Among occurred with 26 subjects (10.2%) with trial discontinuations, four subjects (1.6%) discontinued because of an

adverse event. The sponsor noted that the proportion of subjects in each group who discontinued during the treatment periods were similar between placebo (5.6%; n=14) and the suvorexant total group (4.9%; n=12). However, more subjects in the suvorexant 80 mg group discontinued compared to the other groups as shown in the table below that summarizes the disposition of subjects in the Phase 2 trial.

**Table 80: Disposition of Subjects by Treatment in the Phase 2 Dose-Finding Trial (P006)**

| Treatment Periods 1 And 2 | Placebo<br>N=249 | Suvorexant<br>10 mg<br>N=62 | Suvorexant<br>20 mg<br>N=61 | Suvorexant<br>40 mg<br>N=59 | Suvorexant<br>80 mg<br>N=61 | Suvorexant<br>Total<br>N=243 |
|---------------------------|------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------------|
| <b>Completed</b>          | 235 (94.4)       | 60 (96.8)                   | 57 (93.4)                   | 59 (100.0)                  | 55 ( 90.2)                  | 231 (95.1)                   |
| <b>Discontinued</b>       | 14 (5.6)         | 2 (3.2)                     | 4 (6.6)                     | 0 (0.0)                     | 6 (9.8)                     | 12 (4.9)                     |
| Adverse Event             | 3 (1.2)          | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 1 (1.6)                     | 1 (0.4)                      |
| Lack Of Efficacy          | 1 (0.4)          | 0 (0.0)                     | 1 (1.6)                     | 0 (0.0)                     | 0 (0.0)                     | 1 (0.4)                      |
| Lost To Follow-Up         | 0 (0.0)          | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 1 (1.6)                     | 1 (0.4)                      |
| Physician Decision        | 2 (0.8)          | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 1 (1.6)                     | 1 (0.4)                      |
| Pregnancy                 | 1 (0.4)          | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                      |
| Protocol Violation        | 1 (0.4)          | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                     | 0 (0.0)                      |
| Withdrawal By Subject     | 6 (2.4)          | 2 (3.2)                     | 3 (4.9)                     | 0 (0.0)                     | 3 (4.9)                     | 8 (3.3)                      |

(Source: Modified from Sponsor's submission ISS Page 672 Table Appendix 5.3.5.3.3:1)

#### Disposition of Subjects in the Phase 1 Trials

Of 802 subjects enrolled in the Phase 1 trials, 70 (8.7%) subjects discontinued the trials, and 15 (1.9%) of the all subjects discontinued because of adverse events.

#### Discontinuations Because of AEs

In the combined Phase 3 population 0-3 months, the rate of discontinuation because of AEs was highest with suvorexant HD. The percentages of discontinuation because of AEs in the groups are follows: 6.2% (80/1291) for suvorexant HD, 3.0% (15/493) for suvorexant LD, and 4.9% (50/1025) for placebo. The most frequent SOC category leading to discontinuation was Nervous System Disorders that occurred at the following proportions: 3.3% (42/1291) in the suvorexant HD group, 1.0% (5/493) for suvorexant LD, and 1.4% (14/1205) in placebo. The specific AE somnolence occurred most frequently with incidences of 1.7% (22/1291) in the suvorexant HD, 0.2% (1/493) for suvorexant LD, and 0.3% (3/1025) in the placebo groups.

Psychiatric disorders category, the next most frequent AE category that led to discontinuation, occurred in the treatment groups as follows: 1.0% (13/1291) suvorexant HD, 0.4% (2/493) suvorexant LD, and 0.8% (8/1025) placebo. Within this category,

insomnia was the most frequent specific AE, and it occurred most frequently in the placebo group.

AEs in the General Disorders SOC led to discontinuations in 0.8% (10/1291) suvorexant HD, 0.4% (2/493) suvorexant LD, and 0.3% (3/1025) placebo groups. In this category, fatigue most frequently led to discontinuations; it occurred in the treatment groups as follows: 0.7% (9/1291) suvorexant HD, 0.2% (1/493) suvorexant LD, and 0.0% (0/1205) placebo. The table below is a summary of AEs that led to discontinuations within 0-3 months in the combined Phase 3 population.

**Table 81: Discontinuations due to Adverse Events with Incidence >0% in any Treatment Group within 0-3 Months in Combined Phase 3 Trials (P028, P029, and P009)**

| <b>Adverse Event Category<br/>SOC</b><br>Preferred Term      | <b>Placebo<br/>N (%)</b> | <b>Suvorexant LD<br/>N (%)</b> | <b>Suvorexant HD<br/>N (%)</b> |
|--|--------------------------|--------------------------------|--------------------------------|
| Total Subjects   | 1,025 (100.0)            | 493 (100.0)                    | 1,291 (100.0)                  |
| Subjects with one or more adverse events for discontinuation | 50 (4.9)                 | 15 (3.0)                       | 80 (6.2)                       |
| <b>Cardiac disorders</b>                                     | <b>2 (0.2)</b>           | <b>1 (0.2)</b>                 | <b>3 (0.2)</b>                 |
| Atrial fibrillation  | 1 (0.1)                  | 0 (0.0)                        | 1 (0.1)                        |
| Atrial flutter   | 1 (0.1)                  | 0 (0.0)                        | 0 (0.0)                        |
| Coronary artery disease                                      | 0 (0.0)                  | 0 (0.0)                        | 1 (0.1)                        |
| Palpitations   | 0 (0.0)                  | 0 (0.0)                        | 1 (0.1)                        |
| Tachycardia  | 1 (0.1)                  | 1 (0.2)                        | 0 (0.0)                        |
| <b>Ear and labyrinth disorders</b>                           | <b>1 (0.1)</b>           | <b>0 (0.0)</b>                 | <b>1 (0.1)</b>                 |
| Vertigo  | 1 (0.1)                  | 0 (0.0)                        | 1 (0.1)                        |
| <b>Endocrine disorders</b>                                   | <b>0 (0.0)</b>           | <b>0 (0.0)</b>                 | <b>1 (0.1)</b>                 |
| Autoimmune thyroiditis                                       | 0 (0.0)                  | 0 (0.0)                        | 1 (0.1)                        |
| <b>Eye disorders</b>   | <b>0 (0.0)</b>           | <b>0 (0.0)</b>                 | <b>1 (0.1)</b>                 |
| Diplopia   | 0 (0.0)                  | 0 (0.0)                        | 1 (0.1)                        |
| Vision blurred   | 0 (0.0)                  | 0 (0.0)                        | 1 (0.1)                        |
| Visual acuity reduced  | 0 (0.0)                  | 0 (0.0)                        | 1 (0.1)                        |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| <b>Gastrointestinal disorders</b>                           | <b>4 (0.4)</b> | <b>2 (0.4)</b> | <b>3 (0.2)</b>  |
| Abdominal pain  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Aphthous stomatitis   | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Colitis   | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Constipation  | 0 (0.0)        | 2 (0.4)        | 0 (0.0)         |
| Dyspepsia   | 0 (0.0)        | 1 (0.2)        | 0 (0.0)         |
| Ileus   | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Nausea  | 1 (0.1)        | 0 (0.0)        | 1 (0.1)         |
| Paraesthesia oral   | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| <b>General disorders and administration site conditions</b> | <b>3 (0.3)</b> | <b>2 (0.4)</b> | <b>10 (0.8)</b> |
| Asthenia  | 0 (0.0)        | 1 (0.2)        | 0 (0.0)         |
| Chest pain  | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Discomfort  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Fatigue   | 0 (0.0)        | 1 (0.2)        | 9 (0.7)         |
| Feeling abnormal  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Gait disturbance  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| <b>Infections and infestations</b>                          | <b>3 (0.3)</b> | <b>0 (0.0)</b> | <b>2 (0.2)</b>  |
| Body tinea  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Bronchitis  | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Cystitis  | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Gastroenteritis   | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Nasopharyngitis   | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| <b>Injury, poisoning and procedural complications</b>       | <b>3 (0.3)</b> | <b>1 (0.2)</b> | <b>2 (0.2)</b>  |
| Ankle fracture  | 1 (0.1)        | 1 (0.2)        | 0 (0.0)         |
| Clavicle fracture   | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Fall  | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Fibula fracture   | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Rib fracture  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| Tibia fracture  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)         |
| <b>Investigations</b>                                       | <b>0 (0.0)</b> | <b>1 (0.2)</b> | <b>2 (0.2)</b>  |
| Alanine aminotransferase increased                          | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Blood calcium increased                                     | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Blood creatine phosphokinase increased                      | 0 (0.0)        | 1 (0.2)        | 0 (0.0)         |
| Blood lactate dehydrogenase decreased                       | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |
| Blood magnesium increased                                   | 0 (0.0)        | 0 (0.0)        | 1 (0.1)         |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| <b>Musculoskeletal and connective tissue disorders</b>                         | <b>4 (0.4)</b>  | <b>0 (0.0)</b> | <b>4 (0.3)</b>  |
| Back pain  | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Muscular weakness  | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Neck pain  | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Osteoarthritis   | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Pain in extremity  | 1 (0.1)         | 0 (0.0)        | 3 (0.2)         |
| <b>Neoplasms benign, malignant &amp; unspecified (incl cysts &amp; polyps)</b> | <b>4 (0.4)</b>  | <b>0 (0.0)</b> | <b>1 (0.1)</b>  |
| B-cell lymphoma  | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Bladder neoplasm   | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Borderline ovarian tumour  | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Breast cancer  | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Malignant melanoma   | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| <b>Nervous system disorders</b>  | <b>14 (1.4)</b> | <b>5 (1.0)</b> | <b>42 (3.3)</b> |
| Cerebrovascular accident   | 2 (0.2)         | 0 (0.0)        | 0 (0.0)         |
| Depressed level of consciousness   | 0 (0.0)         | 1 (0.2)        | 0 (0.0)         |
| Dizziness  | 4 (0.4)         | 1 (0.2)        | 2 (0.2)         |
| Dysaesthesia   | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Headache   | 3 (0.3)         | 2 (0.4)        | 0 (0.0)         |
| Hypoxic-ischaemic encephalopathy   | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Lethargy   | 0 (0.0)         | 0 (0.0)        | 3 (0.2)         |
| Memory impairment  | 0 (0.0)         | 0 (0.0)        | 3 (0.2)         |
| Migraine   | 0 (0.0)         | 1 (0.2)        | 1 (0.1)         |
| Paraesthesia   | 1 (0.1)         | 0 (0.0)        | 2 (0.2)         |
| Parkinson's disease  | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Poor quality sleep   | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Sedation   | 0 (0.0)         | 0 (0.0)        | 3 (0.2)         |
| Sleep paralysis  | 0 (0.0)         | 0 (0.0)        | 2 (0.2)         |
| Somnolence   | 3 (0.3)         | 1 (0.2)        | 22 (1.7)        |
| Tension headache   | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Tremor   | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| <b>Psychiatric disorders</b>   | <b>8 (0.8)</b>  | <b>2 (0.4)</b> | <b>13 (1.0)</b> |
| Abnormal dreams  | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Affective disorder   | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Alcohol abuse  | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Bradyphrenia   | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Depressed mood   | 1 (0.1)         | 0 (0.0)        | 1 (0.1)         |
| Depression   | 1 (0.1)         | 0 (0.0)        | 2 (0.2)         |
| Insomnia   | 4 (0.4)         | 0 (0.0)        | 2 (0.2)         |
| Libido decreased   | 1 (0.1)         | 0 (0.0)        | 1 (0.1)         |
| Nightmare  | 0 (0.0)         | 1 (0.2)        | 2 (0.2)         |
| Post-traumatic stress disorder   | 1 (0.1)         | 0 (0.0)        | 0 (0.0)         |
| Somnambulism   | 0 (0.0)         | 0 (0.0)        | 1 (0.1)         |
| Suicidal ideation  | 0 (0.0)         | 1 (0.2)        | 1 (0.1)         |

|   |                |                |                |
|---|----------------|----------------|----------------|
| <b>Skin and subcutaneous tissue disorders</b> | <b>2 (0.2)</b> | <b>3 (0.6)</b> | <b>0 (0.0)</b> |
| Eczema  | 1 (0.1)        | 1 (0.2)        | 0 (0.0)        |
| Rash  | 0 (0.0)        | 1 (0.2)        | 0 (0.0)        |
| Rash macular                                  | 0 (0.0)        | 1 (0.2)        | 0 (0.0)        |
| Urticaria                                     | 1 (0.1)        | 0 (0.0)        | 0 (0.0)        |
| <b>Vascular disorders</b>                     | <b>3 (0.3)</b> | <b>0 (0.0)</b> | <b>1 (0.1)</b> |
| Hypertension                                  | 1 (0.1)        | 0 (0.0)        | 0 (0.0)        |
| Hypertensive crisis                           | 1 (0.1)        | 0 (0.0)        | 0 (0.0)        |
| Ischaemia                                     | 0 (0.0)        | 0 (0.0)        | 1 (0.1)        |
| Orthostatic hypotension                       | 1 (0.1)        | 0 (0.0)        | 0 (0.0)        |

(Source: Sponsor's submission ISS Page 188 Table 5.3.5.3.3: 26)

In the age group analyses, discontinuations because of AEs during the trial's treatment phase followed the pattern of the overall population. In elderly subjects, AEs leading to discontinuations occurred in 6.4% (40/627) of suvorexant HD, 3.5% (7/202) suvorexant LD, and 5.5% (26/469) placebo groups. In the non-elderly, AEs led to discontinuations in 6.0% (40/664) of the suvorexant HD, 2.7% (8/291) of the suvorexant LD, and 4.3% (24/556) of the placebo groups. As in the overall population, the SOC categories of Nervous System Disorders, Psychiatric disorders, and General Disorders were the most frequent AEs that led to discontinuations in the age groups. Specifically, somnolence was the most frequent AE leading to discontinuation.

#### Discontinuations because of AEs in 0-6 months

In the 0-6 month population, the rates of discontinuation because of AEs were similar between suvorexant LD and placebo groups: 3.0% (15/493) in the suvorexant group and 5.2% (40/767) in the placebo group. The SOC category of Nervous System Disorders was the most frequent in leading to discontinuations: 1.0% (5/493) for suvorexant LD compared to 1.4% (11/767) for placebo. Within this SOC category, the most frequent specific AE leading to discontinuation was headache that occurred in 0.4% in each treatment group, suvorexant LD (2/493) and placebo (3/767). One case of migraine caused a discontinuation in the suvorexant LD group and a case of tension headache caused a discontinuation in the placebo group.

#### Discontinuations because of AEs in 0-12 months

Over 0-12 months, there was a small increase in the rate of discontinuation because of AEs, and it remained slightly higher with suvorexant HD treatment at 7.8% (101/1291) compared to placebo at 6.0% (62/1025). The specific AEs that led to discontinuations were similar to those in the 0-3 month population. The SOC categories of Nervous System Disorders, Psychiatric disorders, and General Disorders were the most frequent AEs that led to discontinuations. Again as in the overall population, somnolence, insomnia, and fatigue were the most frequent specific AEs that led to discontinuation. Generally, they occurred at low rates. For example, somnolence leading to



discontinuation occurred in 2.2% (28/1291) of suvorexant HD group and 0.4% (4/1025) of the placebo group.

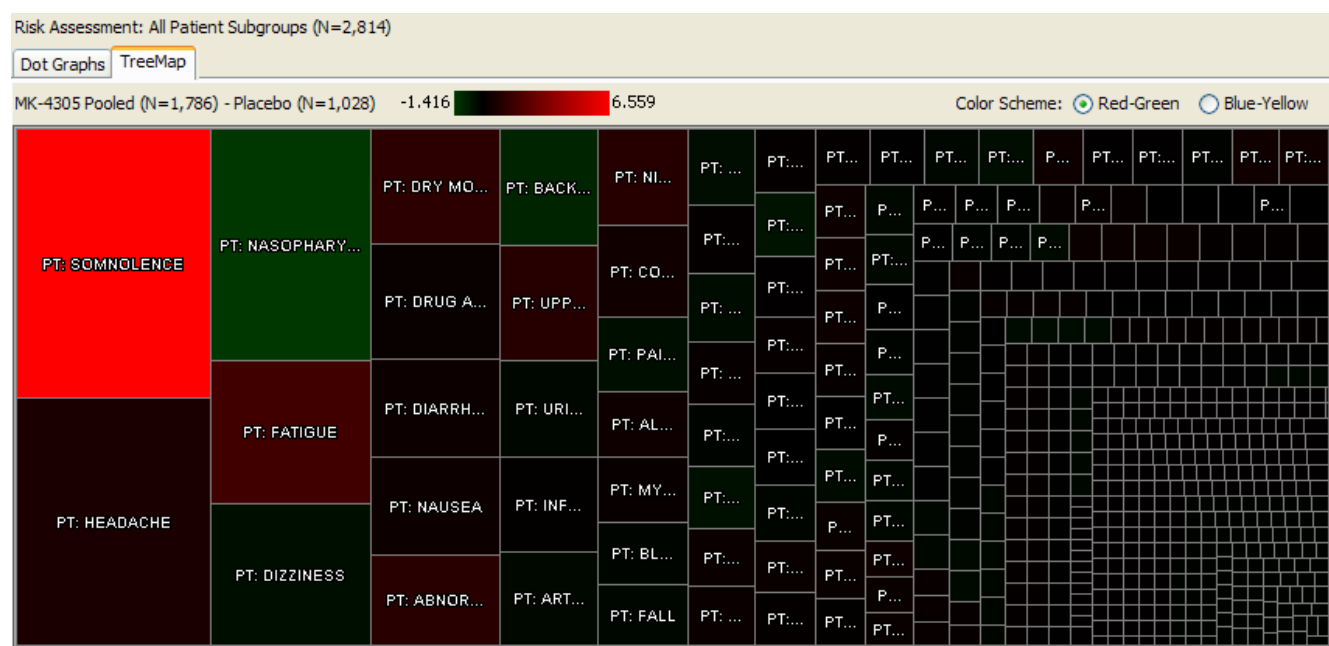
*Reviewer Comment: The incidence of discontinuation because of AEs was generally highest with suvorexant HD compared to suvorexant LD and placebo, but the differences between the treatment groups were small. Somnolence was the AE most frequently associated with discontinuations.*

### 5.3.4 Significant Adverse Events

#### Somnolence

Next day sleepiness, reported as the preferred term Somnolence and shown in the figure below, was the most frequent AE during the first three months in the suvorexant safety database. Somnolence as an AE preferred term included the following lower level terms: daytime sleepiness, drowsiness, drowsy on awakening, excessive daytime sleepiness, feeling of residual sleepiness, groggy, groggy on awakening, hard to awaken, and somnolence. This review section examines characteristics of the somnolence events and influence of treatment dose, treatment duration, and demographic factors on somnolence occurrence.

**Figure 10: Somnolence shown as the most Prominent Risk on Map based on Risk Difference Comparing Pooled Suvorexant (LD+HD) and Placebo Groups over 0-3 Months**



(Source: Clinical Reviewer Analyses; Risk Difference (RD) Heat Map in Combined P009+P028+P029, ITT population 0-3 months; Somnolence in bright red has highest RD of 6.559)

Suvorexant caused a dose-related increase in somnolence within the initial months of treatment. As shown in the table below, somnolence within 0-3 months in the combined Phase 3 population occurred in 10.7% (138/1291) of suvorexant HD, 6.7% (33/493) of suvorexant LD, and 3.0% (31/1025) of placebo groups. Regarding severity of sleepiness, the incidence of severe somnolence was higher in the suvorexant HD at 0.6% (8/1291) compared to suvorexant LD at 0.2% (1/493), and placebo at 0.1% (1/1025). A separately reported event was sedation; it included lower level terms of oversedation and sedation, and occurred in more suvorexant HD subjects, eight (0.6%), compared to none (0%) in suvorexant LD, and four (0.4%) in placebo. The incidence of somnolence including sedation events remained 11% in the suvorexant HD group and 3% in placebo. Also, discontinuation of treatment because of somnolence was highest in the HD suvorexant group as shown in the table below.

**Table 82: Somnolence Within 0-3 months in Combined Phase 3 Populations (P028, P029, and P009)**

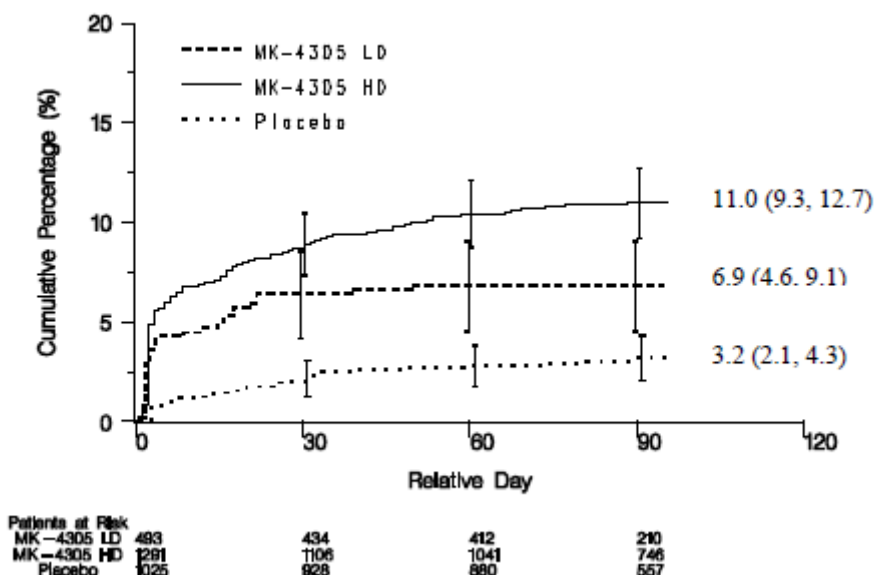
| Variable Category                            | Placebo<br>(N=1025)            | Suvorexant LD<br>(N=493)       | Suvorexant HD<br>(N=1291)        |
|--|--------------------------------|--------------------------------|----------------------------------|
| Somnolence                                   | 31 (3.0%)                      | 33 (6.7%)                      | 138 (10.7%)                      |
| Severe Somnolence                            | 1 (0.1%)                       | 1 (0.2%)                       | 8 (0.6%)                         |
| Somnolence-Trial discontinuation             | 3 (0.3%)                       | 1 (0.2%)                       | 22 (1.7%)                        |
| Somnolence by Age<br>>=65 years<br><65 years | 3.2% (15/469)<br>2.9% (16/556) | 5.4% (11/202)<br>7.6% (22/291) | 8.8% (55/627)<br>12.5% (83/664)  |
| Somnolence by sex<br>Female<br>Male          | 2.3% (15/641)<br>4.2% (16/384) | 8.5% (27/319)<br>3.4% (6/174)  | 11.1% (87/784)<br>10.1% (51/507) |

(Source: Modified from Sponsor's submission ISS Pages 427, 429, 649, 661 and 663; Tables 5.3.5.3.3: 149, 150, 257, 260, and 261)

#### Time to Onset of Somnolence

More subjects on either dose of suvorexant reported somnolence within one week of starting treatment compared to any other period in the first 3 months of treatment. Cumulative somnolence reports reached near peak within one month of treatment in the suvorexant LD group; the suvorexant HD group, which was yet to peak at one month, added another 2.5% reports beyond the first month. As shown in the figure below, the cumulative percentages of subjects who reported somnolence over the 3 months occurred in a dose-related fashion: 11.0% suvorexant HD, 6.9% suvorexant LD, and 3.2% placebo.

**Figure 11: Cumulative Percentage of Subjects Who Reported Somnolence of over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)**



(Source: Sponsor's submission ISS Page 650 Figure 5.3.5.3.3.:5)

The different somnolence **intensities** were more frequent with suvorexant HD. A dose-related increase in the different somnolence intensities – mild, moderate, and severe – occurred with treatment as shown in the table below.

**Table 83: Intensity of Somnolence by Dose Group Treated over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)**

|                        | Intensity Grading | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) |
|------------------------|-------------------|------------------|------------------------|------------------------|
| Subjects in Population |                   | 1,025            | 493                    | 1,291                  |
| Somnolence             | All               | 31 (3.0)         | 33 (6.7)               | 138 (10.7)             |
|                        | Mild              | 21 (2.0)         | 24 (4.9)               | 86 (6.7)               |
|                        | Moderate          | 9 (0.9)          | 8 (1.6)                | 44 (3.4)               |
|                        | Severe            | 1 (0.1)          | 1 (0.2)                | 8 (0.6)                |

(Source: Sponsor's submission ISS Page 649 Table 5.3.5.3.3.:257)

*Reviewer Note: The risk difference for severe somnolence reflected a dose-response relationship. The trials categorized somnolence severity as follows:*

- *Mild: Awareness of sign or symptom, but easily tolerated*
- *Moderate: Discomfort enough to cause interference with usual activity*

- *Severe: Incapacitating with inability to work or do usual activity*

*The risk difference for severe somnolence between each suvorexant dose and placebo was small, though higher in the suvorexant HD group; 0.5 with number needed to treat to cause severe somnolence or harm (NNTH) 200 for suvorexant HD, and 0.1 with NNTH 1000 for suvorexant LD. If harm is considered as moderate or severe somnolence, the risk difference is 3 (NNTH 33) for suvorexant HD, and 0.8 (NNTH 125) for suvorexant LD.*

Demographics – Somnolence by Age, by Gender, by BMI, by Age and Gender, and by Gender and BMI

Fewer elderly subjects reported somnolence while on suvorexant treatment as shown in Table 84 below and earlier in Table 82 Somnolence Within 0-3 months in Combined Phase 3 Populations. The lower somnolence reports in elderly subjects compared to non-elderly adults were consistent across dose groups and treatment periods. This may be attributed to the lower dose received by the elderly subjects at each suvorexant dose level: 15 mg and 30 mg compared to 20 and 40 mg in non-elderly subjects for suvorexant LD and HD respectively.

**Table 84: Somnolence Events by Age Groups across Treatment Periods in Phase 3 Trials**

| Variable Category  | Placebo       | Suvorexant LD  | Suvorexant HD  |
|--|---------------|----------------|----------------|
| Somnolence <b>0-3 Months</b> ,<br>Trials P028, P029, & P009  |               |                |                |
| >=65 years   | 3.2% (15/469) | 5.4% (11/202)  | 8.8% (55/627)  |
| <65 years  | 2.9% (16/556) | 7.6% (22/291)  | 12.5% (83/664) |
| Somnolence <b>0-6 Months</b> ,<br>Trials P028 & P029         |               |                |                |
| >=65 years   | 3.8% (12/318) | 5.9% (12/202)  | Not Applicable |
| <65 years  | 3.1% (14/449) | 7.6% (22/291)  | Not Applicable |
| Somnolence <b>0-12 Months</b> ,<br>Trials P028, P029, & P009 |               |                |                |
| >=65 years   | 3.4% (16/469) | Not Applicable | 10.0% (63/627) |
| <65 years  | 3.1% (17/556) | Not Applicable | 13.3% (88/664) |

(Source: Modified from Sponsor's submission ISS Pages 661, 663, 1745, 1748, 1767, 1769 Tables 5.3.5.3.3: 260, 261, Appendix 5.3.5.3.3: 200, 201, 210 and 211)

Interpreting the analyses of somnolence by Age and Gender, and by Gender and BMI may be limited by the small number of events. However, Table 85 below and earlier Table 82 suggest that females reported more somnolence events than males, particularly at the suvorexant LD level.

**Table 85: Somnolence Events in Elderly and Non-Elderly Subjects by Gender in the Combined 0-3 Months Populations (P028, P029, and P009)**

| Age Group and Gender Category | Placebo      | Suvorexant LD | Suvorexant HD  |
|-------------------------------|--------------|---------------|----------------|
| Somnolence in Age ≥65 years   |              |               |                |
| Females                       | 2.3% (7/299) | 7.5% (10/133) | 9.4% (35/372)  |
| Males                         | 4.7% (8/170) | 1.4% (1/69)   | 7.8% (20/255)  |
| Somnolence in Age <65 years   |              |               |                |
| Females                       | 2.3% (8/342) | 9.1% (17/186) | 12.6% (52/412) |
| Males                         | 3.7% (8/214) | 4.8% (5/105)  | 12.3% (31/252) |

(Source: Modified from Sponsor's submission ISS Pages 439, 441, 443, 445 Tables 5.3.5.3.3: 153 to 156)

Regarding BMI effect on incidence of somnolence, non-obese subjects showed a dose-related increase in somnolence events; this pattern was not apparent in obese subjects, as shown in the table below, probably because of small numbers of events.

**Table 86: Somnolence Events in Non-Obese, Over-Weight, and Obese Subjects in the Combined 0-3 Months Population (P028, P029, and P009)**

| Variable Category                              | Placebo       | Suvorexant LD | Suvorexant HD  |
|--|---------------|---------------|----------------|
| Somnolence in Non-Obese Subjects (BMI <25)     | 2.2% (10/449) | 7.4% (18/243) | 11.0% (56/509) |
| Somnolence in Over-weight Subjects (BMI 25-30) | 3.0% (12/405) | 7.2% (14/194) | 8.9% (49/548)  |
| Somnolence in Obese Subjects (BMI >30)         | 5.3% (9/170)  | 1.8% (1/56)   | 13.4% (31/232) |

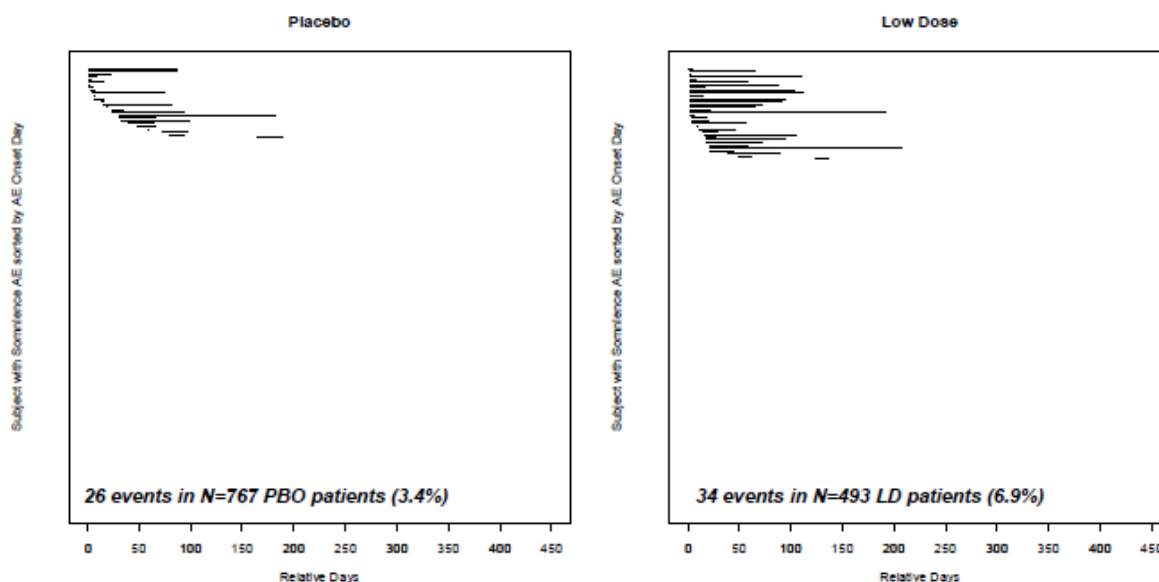
(Source: Modified from Sponsor's submission ISS Pages 511, 513, and 515 Tables 5.3.5.3.3: 187, to 189)

#### Long-Term Somnolence Events

In long-term treatment evaluations covering 0–6 months, combined P028 and P029 population, somnolence remained higher with suvorexant LD at 6.9% (34/493) compared to placebo 3.4% (26/767). The incidence of severe somnolence remained unchanged from the 0-3 month's population with suvorexant LD at 0.2% (1/493) compared to placebo at 0.1% (1/767). The cumulative percent of subjects who reported somnolence increased slightly in the treatment groups from Month 3 end to Month 6 end: 6.9% to 7.9% in the suvorexant LD group compared to 3.4% to 4.1% in the placebo group. Generally, subjects on suvorexant LD experienced longer somnolence

duration compared to those on placebo as shown in the somnolence plots for individual subjects below.

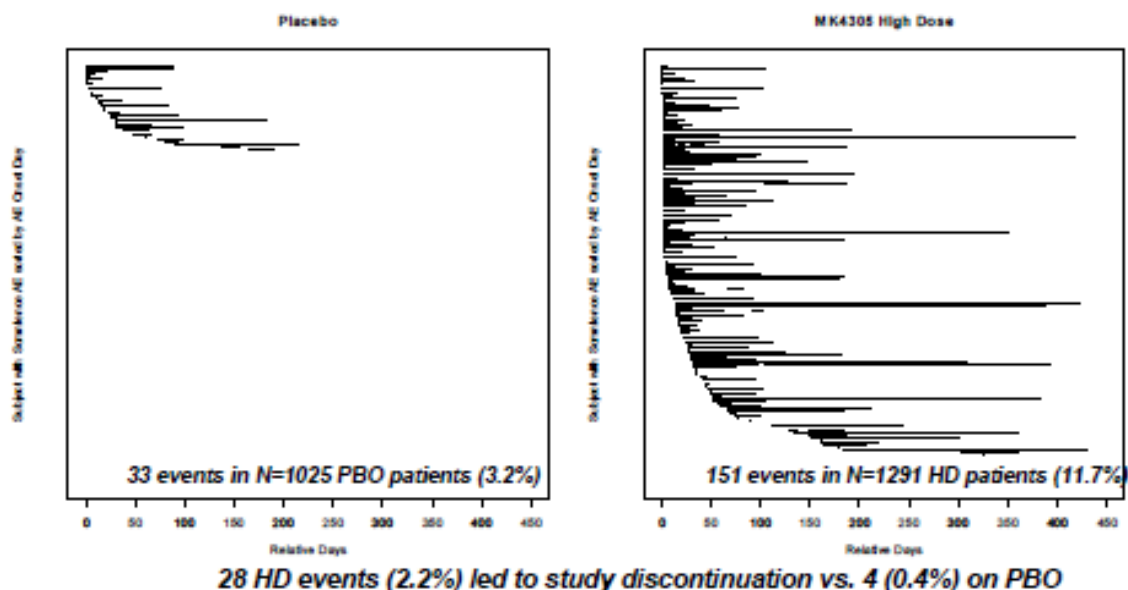
**Figure 12: Somnolence Time Course for Individual Subjects over 0–6 Months of Placebo or Suvorexant Low Dose in Combined Phase 3 Population (P028 and P029)**



(Source: Sponsor's submission ISS Page 658 Figure 5.3.5.3.3:9)

In the 12-month period evaluations of the combined Phase 3 population (P028, P029, and P009), somnolence remained higher in the suvorexant HD group at 11.7% (151/1291) compared to placebo at 3.2% (33/1025). The incidence of severe somnolence from suvorexant HD treatment was 0.6% (8/1291) compared to placebo 0.1% (1/1025); these rates were unchanged from those of the 0-3 month's evaluations. The cumulative percent of subjects who reported somnolence, based on the sponsor's Kaplan-Meier's estimates, increased in the treatment groups from Month 3 end to Month 12 end: in the suvorexant HD group 11.0% to 13.6% compared to placebo 3.2% to 3.8%. Subjects on suvorexant HD experienced longer somnolence duration compared to those on placebo as shown on the individual subject's plots below. Of note, in the 12-month assessment, 28 suvorexant HD events (2.2%) led to study discontinuation compared to 4 (0.4%) on placebo. The plots suggest that subjects who received suvorexant HD experienced somnolence events of longer duration than those treated with suvorexant LD or placebo.

**Figure 13: Subject Plots of Somnolence Events over 0-12 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)**



(Source: Sponsor's submission ISS Page 654 Figure 5.3.5.3.3:7)

#### Somnolence in Individual Phase 3 Trials

Across the individual component Phase 3 trials, as shown in the table below, the incidence of somnolence appeared consistent with those of the combined Phase 3 population of P028, P029, and P009 trials.

**Table 87: Incidence of Somnolence in Individual Phase 3 Trials**

| Trial                        | Placebo %    | Suvorexant LD % | Suvorexant HD % |
|------------------------------|--------------|-----------------|-----------------|
| <b>P028</b><br>(0-3 months)  | 3.4 (13/384) | 5.1 (13/254)    | 10.7 (41/383)   |
| <b>P029</b><br>(0-3 months)  | 3.1 (12/383) | 8.4 (20/239)    | 10.3 (40/387)   |
| <b>P009</b><br>(0-12 months) | 2.7 (7/258)  | Not applicable  | 13.2 (69/521)   |

(Source: Modified from Sponsor's submission CSR P028 Page 339 Table 12-7, CSR P029 Page 273 Table 12-6, and CSR P009 Page 198 Table 12-5)

#### Somnolence in Earlier Phase Trials

The early phase trials showed dose-related increases in somnolence with suvorexant treatment. In the Phase 2 trial P006 that included non-elderly subjects, somnolence occurred at a similar rate and in dose-related manner as observed in the Phase 3 trials:

0.4% (1/249) in Placebo, 0% (0/62) in suvorexant 10 mg, 4.9% (3/61) in suvorexant 20 mg, 11.9% (7/59) in suvorexant 40 mg, and 9.8% (6/61) in suvorexant 80 mg groups. A combination of five Phase 1 trials (P026, P032, P035, P036, and P039), in which subjects received night-time trial treatment and had next-day assessment for residual effects, somnolence occurred in 22.4% (28/125) after suvorexant treatment compared to 0.8% (5/105) after placebo. In these studies, suvorexant was administered at the clinical doses (15 or 30 mg in elderly, 20 or 40 mg in non-elderly). It remains unclear why the somnolence rate was remarkably higher in the collection of Phase 1 trials compared to the Phase 3 experience, though closer monitoring in the early phase trials may have played a role.

#### Somnolence in Marketed Drugs for the Proposed Indication

The rates of somnolence in the suvorexant Phase 3 trials appear to be comparable to those of other approved drugs for the sought indication. The table below shows the somnolence rates from a review of the prescribing information and available approval packages for some of the long-acting drugs approved for insomnia. In general, the marketed drugs were evaluated over a shorter duration of treatment thereby limiting the inter-drug comparisons of somnolence rates or other adverse events.

**Table 88: Somnolence in Some Marketed Insomnia Drugs**

| <b>Treatment</b>    | <b>N for Group</b> | <b>Percent of Subjects with Somnolence</b> | <b>Duration of studies, Other Comments</b> |
|---------------------|--------------------|--|--|
| Zolpidem CR 12.5 mg | 102                | 15%  | 3-week trial                               |
| Placebo             | 110                | 2%   | Non-elderly adults                         |
| Zolpidem CR 6.25 mg | 99                 | 6%   | 3-week trial in elderly                    |
| Placebo             | 106                | 5%   | subjects                                   |
| Eszopiclone 3 mg    | 105                | 8%   | 6-week trial in non-                       |
| Eszopiclone 2 mg    | 104                | 10%  | elderly adults.                            |
| Placebo             | 99                 | 3%   |  |
| Quazepam 7.5-15 mg  | 267                | 12%  | Short duration trials                      |
| Placebo             | 268                | 3%   | over less than a month                     |
| Temazepam 7.5-30 mg | 1076               | 9%   | Adverse event                              |
| Placebo             | 783                | 6%   | reported as                                |
|                     |                    |  | Drowsiness                                 |
| Doxepin 6 mg        | 203                | 9%   | 4 weeks,                                   |
| Doxepin 3 mg        | 157                | 6%   | Approved for                               |
| Placebo             | 278                | 4%   | maintenance only                           |

(Source: Prescribing Information for Respective Drugs)



### 5.3.5 Submission Specific Primary Safety Concerns

In this section, I address the safety concerns related to the specific adverse events termed Events of Clinical Interest (ECIs) that the sponsor identified for close evaluation: suicidal ideation, complex sleep-related behaviors, hallucinations, excessive day time sleepiness, sleep paralysis, cataplexy, falls, abuse, motor vehicle accidents and violations (MVAVs).

#### Suicidal Ideation or Behavior

The sponsor followed recommendations in an FDA draft guidance issued in 2010, "Guidance for Industry - Suicidality: Prospective Assessment of Occurrence in Clinical Trials," and prospectively assessed suicidal ideation and behavior in the Phase 2 and Phase 3 trials using the Columbia Suicidality Severity Rating Scale (C-SSRS). Each suicidal ideation or behavior event was categorized according to the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

The incidence of suicidal ideation (including "death wish") or behavior reported for the Combined Phase 3 Population over 0-3 Months was very low overall at < 0.4% (7 subjects) but **numerically higher with suvorexant HD treatment**: Suvorexant LD, 0.2% (1 subject), suvorexant HD 0.4% (5 subjects), and placebo 0.1% (1 subject). The subjects on placebo and suvorexant LD had prior history of suicidal ideation. The suvorexant LD subject, a 34-year old male, had two events, the first on Day 25 when he reported feeling depressed about his job, which he quit on Day 28. Despite starting a new job, he reported another suicidal thought Day31. This subject discontinued the trial because of the AE on Day 30.

Among the 5 subjects on suvorexant HD who reported suicidal ideation or behavior, one subject, a 61-year old male (AN 02637), had prior history of depression and suicide attempt. He reported 3 events of suicidal ideation on Days 20, 21, and 25. He discontinued trial treatment on Day 29 because of the AE. Another subject, a 70-year old male (AN 04559) reported mild suicidal ideation on Day 81 and discontinued trial treatment on Day 111 after he was diagnosed with depression. A 42-year old female (AN 11361) reported mild suicidal ideation on Day 66; she thought of taking medications as a means to end her life. However, her month-long suicidal ideation ended after she started a new social relationship; all the while she continued the trial treatment.

A 54-year old female (AN 12362) reported suicidal ideation on Day 91; she had missed Day 90 dose and had been on suvorexant HD. After an argument with her daughter, she felt like she wanted to die but had no intention of acting on the thought.

The fifth subject AN 03053 was a 38-year old male on suvorexant HD who reported suicidal ideation on Trial Day 9. He reported, "wishing to be dead", with "thoughts of not

waking up anymore felt easy, but I could control the thoughts" and subsequently discontinued from the trial because of to lack of efficacy.

Following longer treatment duration, a 21-year old male on suvorexant HD in Trial P009 reported suicidal ideation on Day 269. He was the sixth case of suicidal ideation on suvorexant HD. He had a prior history of suicidal ideation in 2004. On C-SSRS assessment at the Month 9 visit, he reported unemployment difficulties and ideation lasting 4 days. He subsequently completed the trial treatment.

**Table 89: Suicidal Ideation or Behavior with Suvorexant High Dose Compared to Placebo in Combined Phase 3 Population 0-12 Months in Trials P028, P029, and P009**

| Protocols 028+029+009   | MK-4305 HD |        | Placebo |        | Difference in % vs Placebo     |
|---|------------|--------|---------|--------|--------------------------------|
|   | n          | (%)    | n       | (%)    | Estimate (95% CI) <sup>†</sup> |
| Patients in population  | 1,291      |        | 1,025   |        |                                |
| with one or more Suicidal Ideation and/or Behaviors Adverse Events  | 6          | (0.5)  | 1       | (0.1)  | 0.3 (-0.2, 0.9)                |
| with no Suicidal Ideation and/or Behaviors Adverse Events   | 1,285      | (99.5) | 1,024   | (99.9) | -0.3 (-0.9, 0.2)               |
| <b>Psychiatric disorders</b>  |            |        |         |        |                                |
| Death wishes  | 1          | (0.1)  | 0       | (0.0)  | 0.1 (-0.3, 0.5)                |
| Suicidal ideation   | 5          | (0.4)  | 1       | (0.1)  | 0.3 (-0.2, 0.8)                |
| <sup>†</sup> Based on Miettinen & Nurminen method stratified by study (using sample size as weight); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.<br>Every patient is counted a single time for each applicable row and column.<br>A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.<br>Lower Level Term is displayed for the specific adverse events.<br>MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years. |            |        |         |        |                                |

(Source: Sponsor's submission ISS Page 210 Table 5.3.5.3.3.:31)

The C-SSRS assessment identified three additional cases of suicidal ideation as shown in Table 90 below. The investigators did not consider these as adverse events and so did not report them as ECIs. All three subjects were on suvorexant HD. One 68-year old female had a history of thyroid disease and experienced suicidal ideation from the placebo-run in period. Another, a 54-year old male had a history of depression and anxiety and reported suicidal ideation at Month 3 before withdrawing from the trial for unclear reasons. The third had no history of psychiatric illness but reported suicidal ideation at Months 1 and 3. Subsequently, he discontinued trial treatment because of lack of treatment efficacy. The sponsor added that, based on the Columbia Classification Algorithm for Suicide Assessment (C-CASA) analysis, only 3 subjects had suicidal ideation among subjects with no prior history of suicidal ideation, all three were on suvorexant HD.

**Table 90: Suicidal Events Based on Columbia Classification Algorithm for Suicide Assessment (C-CASA) with Suvorexant High Dose Compared to Placebo in Combined Phase 3 Population 0-12 Months in Trials P028, P029, and P009**

| C-CASA Category <sup>†</sup>  | Protocols 028+029+009 |                  |
|---|-----------------------|------------------|
|   | MK-4305 HD<br>n (%)   | Placebo<br>n (%) |
| Patients in population  | 1268                  | 1012             |
| with one or more events   | 8 ( 0.6)              | 0 ( 0.0)         |
| with no event   | 1260 (99.4)           | 1012 (100.0)     |
| Suicide completed   | 0 ( 0.0)              | 0 ( 0.0)         |
| Suicide attempt   | 0 ( 0.0)              | 0 ( 0.0)         |
| Preparatory acts toward imminent suicidal behavior  | 0 ( 0.0)              | 0 ( 0.0)         |
| Suicidal ideation   | 8 ( 0.6)              | 0 ( 0.0)         |
| Self-injurious behavior, no suicidal intent   | 0 ( 0.0)              | 0 ( 0.0)         |
| <sup>†</sup> C-CASA categories are derived from the Columbia Suicide Severity Rating Scale (C-SSRS).<br>Patients who were treated and had at least one post-treatment C-SSRS evaluation during the indicated phase of study period were included in the table.<br>MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years. |                       |                  |

(Source: Sponsor's submission ISS Page 214 Table 5.3.5.3.3.:33)

The sponsor reported no suicidal ideation or behavior events in the Phase 2 dose-finding trial. However, in a Phase I drug interaction trial (P026), a 21-year-old female without a prior history of suicidal ideation, reported suicidal ideation 4 days after the final dose of trial treatment, suvorexant 40 mg plus paroxetine 20 mg. The event lasted 10 days and was designated mild in intensity.

*Reviewer Comment: In all, suicidal ideation appeared more frequent in the suvorexant HD group in the phase 3 trials, though the events occurred in very low numbers. One subject in each dose group discontinued trial treatment because the suicidal ideation event. No additional subject on suvorexant LD reported suicidal ideation based on the CSSRS assessment.*

### Complex Sleep-Related Behaviors

Only 2 subjects on suvorexant HD reported complex sleep-related behaviors in the Combined Phase 3 Population over 0-3 Months.

First case, a 65-year-old male with a history of sleep talking reported an event of sleep talking on Trial Day 85 while on suvorexant HD. The event started about 2.5 hours after his last trial medication, during PSG recording. About 90 minutes after sleep talking, he lunged out of bed, and hit his head and face against a wall. A second event of complex sleep-related behavior, described as sleep walking, occurred on Day 101 after he had received no trial medication for 2 weeks (last dose given on Day 87).

The second case was a 58-year-old female who reported mild somnambulism (sleep walking) and severe sleep paralysis on Trial Day 52 while on suvorexant HD. She awoke after a dream, and during subsequent repeated arousals she felt unable to move her extremities or speak. Hours later, she was unaware when she walked to a window. No additional events occurred afterwards. She had no prior history of somnambulism. Trial medication was discontinued after the event.

No events of a complex sleep-related behavior were reported for the Combined Phase 3 Population from 0-6 months for suvorexant LD. They were not observed during the Run-out Phase in Trials P028 and P029, or in the Phase 1 and Phase 2 trials.

### **Excessive Daytime Sleepiness**

Excessive daytime sleepiness (EDS) in the suvorexant development program was defined as: uncharacteristic chronic and persistent sleepiness during the day, possibly starting as sudden involuntary sleep episodes and occurring throughout the day or over multiple consecutive days. The sleepiness was often associated with impairment in daytime function. The persistence of the sleepiness differentiated EDS from the short-lasting adverse event of somnolence. To be considered an ECI, the EDS needed to occur in a subject who had adequate sleep during the preceding night. As a result, daytime sleepiness from being awake the previous night did not qualify as an ECI of EDS.

The incidence of EDS was low in the suvorexant program. However, it occurred more frequently from suvorexant treatment in a dose-related manner in the first 3 months in the combined phase 3 population: 1.1% (14/1291) of suvorexant HD group, 0.6% (3/493) suvorexant LD, and 0.2% (2/1025) placebo. As shown in the table below, the EDS risk difference for suvorexant LD compared to placebo was 0.5% (95% CI: -0.2, 1.7); the risk difference for suvorexant HD, with a 95% confidence interval that excluded zero, was 0.8% (95% CI: 0.1, 1.6).

**Table 91: Excessive Daytime Sleepiness By Dose Group Treated over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)**

| Protocols 028+029+009   | n     | (%)    | Difference in % vs Placebo<br>Estimate (95% CI) <sup>†</sup> |
|---|-------|--------|--|
| <b>Patients in population</b>                                       |       |        |  |
| MK-4305 LD  | 493   |        |  |
| MK-4305 HD  | 1,291 |        |  |
| Placebo   | 1,025 |        |  |
| <b>with one or more Excessive Daytime Sleepiness Adverse Events</b> |       |        |  |
| MK-4305 LD  | 3     | (0.6)  | 0.5 (-0.2, 1.7)  |
| MK-4305 HD  | 14    | (1.1)  | 0.8 (0.1, 1.6)   |
| Placebo   | 2     | (0.2)  |  |
| <b>with no Excessive Daytime Sleepiness Adverse Events</b>          |       |        |  |
| MK-4305 LD  | 490   | (99.4) | -0.5 (-1.7, 0.2)   |
| MK-4305 HD  | 1,277 | (98.9) | -0.8 (-1.6, -0.1)  |
| Placebo   | 1,023 | (99.8) |  |
| <b>Nervous system disorders</b>                                     |       |        |  |
| <b>Excessive daytime sleepiness</b>                                 |       |        |  |
| MK-4305 LD  | 3     | (0.6)  | 0.5 (-0.2, 1.7)  |
| MK-4305 HD  | 14    | (1.1)  | 0.8 (0.1, 1.6)   |
| Placebo   | 2     | (0.2)  |  |

<sup>†</sup> Based on Miettinen & Nurminen method stratified by study (using sample size as weight); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison. Every patient is counted a single time for each applicable row.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the treatment groups meets the incidence criterion in the report title, after rounding.

Lower Level Term is displayed for the specific adverse events.

MK-4305 LD=MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 238 Table 5.3.5.3.3.:43)

Apart from severity of EDS, there was considerable overlap in other characteristics of the EDS among the treatment groups. Among the suvorexant HD subjects, 35.7% (5/14) reported their EDS as severe, 50.0% (7/14) as moderate, and 14.3% (2/14) as mild. The suvorexant LD reported 33.3% (1/3) as moderate EDS and 66.7% (2/3) as mild EDS. The placebo group reported one case each of mild and moderate EDS. None of the suvorexant LD and placebo cases were regarded as severe. Time to EDS onset from treatment initiation and EDS duration were not noticeably different among the treatment groups: Across the three dose groups, EDS onset after commencing treatment ranged from 7 hours to 64 days and EDS duration from 3 to 127 days (the longest duration occurred in a placebo subject). EDS resulted in treatment discontinuation in 33.3% (1/3) of the suvorexant LD group and in 71.4% (10/14) of the suvorexant HD group. Both subjects with EDS in the placebo group discontinued treatment because of the EDS event.

Over extended treatment, the suvorexant HD group recorded six additional EDS cases. In the Combined Phase 3 Population, treated over 0-12 months, EDS occurred in 1.5% (20/1291) suvorexant HD and 0.3% (3/1025) placebo. **Of the 15 subjects who reported EDS during Trial P009 treatment period, 13 subjects were on suvorexant HD and 2 subjects on placebo. In that 12-month trial, EDS led to discontinuations in 11 (5 non-elderly, 6 elderly) of the 13 subjects on suvorexant HD and both subjects on placebo.** Also, no additional EDS cases occurred in the suvorexant LD group beyond three months of treatment.

**Table 92: Excessive Daytime Sleepiness and Suvorexant High Dose over 0-12 Months among all Subjects Treated in the Combined Phase 3 Population (P028, P029, and P009)**

| Protocols 028+029+009   | MK-4305 HD |        | Placebo |        | Difference in % vs Placebo     |
|---|------------|--------|---------|--------|--------------------------------|
|   | n          | (%)    | n       | (%)    | Estimate (95% CI) <sup>†</sup> |
| Patients in population  | 1,291      |        | 1,025   |        |                                |
| with one or more Excessive Daytime Sleepiness Adverse Events  | 20         | (1.5)  | 3       | (0.3)  | 1.1 (0.3, 2.0)                 |
| with no Excessive Daytime Sleepiness Adverse Events   | 1,271      | (98.5) | 1,022   | (99.7) | -1.1 (-2.0, -0.3)              |
| <b>Nervous system disorders</b>   |            |        |         |        |                                |
| Excessive daytime sleepiness  | 20         | (1.5)  | 3       | (0.3)  | 1.1 (0.3, 2.0)                 |
| <sup>†</sup> Based on Miettinen & Nurminen method stratified by study (using sample size as weight); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.<br>Every patient is counted a single time for each applicable row and column.<br>A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.<br>Lower Level Term is displayed for the specific adverse events.<br>MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years. |            |        |         |        |                                |

(Source: Sponsor's submission ISS Page 241 Table 5.3.5.3.3.:44)

#### Other Trials

The sponsor reported two additional EDS cases in the suvorexant development program: one event occurred in a 63-year old female in the Phase 2 trial P006, who developed severe EDS of 4 hours duration after two days on suvorexant 80 mg. She completed the trial as planned. The other EDS event occurred in the Phase 1 COPD trial P032 in a 63-year old female with COPD, who developed EDS after a day of suvorexant 40mg treatment; the EDS event lasted five days.

*Reviewer note: The sponsor states, "EDS occurred more frequently with suvorexant HD. Taken together with the low overall somnolence rates reported in the program, these data indicate that for the vast majority of subjects taking suvorexant HD, clinically important next-day somnolence is not an issue." I agree that the EDS occurred more with suvorexant HD, risk difference from placebo 0.8% NNTH 125, and that the overall*

*EDS incidence in the program was low. However, its occurrence has safety implications especially when individuals taking the HD have to go about their usual duties such as driving. For such individuals, EDS will be a major issue. It is not clear that switching to a lower dose will resolve the EDS issue as the clinical trials did not explore such strategy. The EDS problem appears to be less of a problem with suvorexant LD, though the sample size did not allow for a more precise EDS estimate for the dose.*

## **Hypnagogic and Hypnopompic Hallucinations**

In the Phase 3 population, only subjects treated with suvorexant reported hypnagogic and hypnopompic hallucinations, though the incidence of this ECI in the overall suvorexant development program was low. In the suvorexant development program, hypnagogic hallucinations referred to vivid dreamlike experiences that occur during sleep onset; hypnopompic hallucinations were experiences occurring upon waking. The subjects reported what they saw, heard, felt, or smelled about things that were not actually there. The Combined Phase 3 Population had five subjects who reported hypnagogic and hypnopompic hallucinations within the first three months of treatment: 0.4% (2/493) in the suvorexant LD group and 0.2% (3/1291) in the suvorexant HD group; none of this ECI occurred in the placebo group of the population. The event reported for one (0.2%, 1/493) of the two subjects in the suvorexant LD group was a case of hypnagogic hallucination; the other was a hypnopompic hallucination. In contrast, all three subjects (0.2%, 3/1291) in the suvorexant HD group were cases of hypnagogic hallucinations.

The two subjects on suvorexant LD reported their hallucinations as mild; despite the hallucinations, the subjects completed the trial as planned. The first, Subject AN 07058, a 28-year old female in Trial P028 reported hypnagogic hallucinations on Trial Day 2 starting 1 hour after suvorexant LD. The “sensation of an inability to move and feeling the presence of an individual in bed with her” lasted 15 minutes at sleep onset. The experiences resolved by Day 15. The second subject, AN 12873, a 76-year-old male in Trial P029, reported hypnopompic hallucination starting 8.5 hours after taking suvorexant LD on Trial Day 90 and while undergoing PSG evaluation. The “out of body experience, as if subject were floating” lasted 2 minutes on awakening. He had no additional events.

The hallucinations reported by the three subjects on suvorexant HD were termed mild, moderate, and severe; one subject discontinued trial treatment because of hypnagogic hallucinations. Subject AN 12896, a 68-year old female in Trial P029, reported hypnagogic hallucinations termed severe on Trial Day 46 and mild on Day 67. The initial event, which occurred at sleep onset about the same time she received her trial treatment, was described as “a sensation in her brain of flashing lights and, as if she was being shocked in her brain by a taser. Her body became paralyzed and she began to hear vivid sounds of people coming up the stairs with a sense of violent intent on their part.” She reported having a similar event many years before the trial. Her second



hypnagogic hallucination on Day 67 was described as mild, when she heard faint murmurs of people speaking. A second subject, AN 03039, on suvorexant HD, a 58-year old male in Trial P009, had mild hypnagogic hallucination on Day 21 about 1 hour after trial treatment. This was described as “a feeling of a shadow falling over his body, being physically hunted by enemies in hospital environment, and hearing extremely loud screams.” The feelings occurred within an hour of trial treatment and lasted 39 days. The third subject, AN 04557, on suvorexant HD who experienced hypnagogic hallucination within 3 months of treatment was a 73 year-old male in Trial P009. The events, described as moderate, occurred on Days 40, 96, and 97: “A frightening feeling of being chased and reported feeling disoriented and confused. During another event, he felt like he was being dragged up the wall.” He discontinued from the trial because of the experience.

With extended treatment up to 12 months, the suvorexant HD group recorded two additional subjects who reported hallucinations. In the Combined Phase 3 Population treated over 0-12 months, as shown in the table below, a moderate event of hypnagogic hallucination associated with sleep paralysis occurred at 8 months. Another subject reported two mild episodes of hypnopompic hallucinations after 3 and 6 months of trial treatment. No cases occurred in the placebo group. No additional cases occurred in the suvorexant LD group beyond three months of treatment in the Phase 3 population.

**Table 93: Hypnagogic and Hypnopompic Hallucinations and Suvorexant High Dose over 0-12 Months among all Subjects Treated in the Combined Phase 3 Population (P028, P029, and P009)**

| Protocols 028+029+009  | MK-4305 HD |        | Placebo |         | Difference in % vs Placebo     |
|--|------------|--------|---------|---------|--------------------------------|
|  | n          | (%)    | n       | (%)     | Estimate (95% CI) <sup>†</sup> |
| Patients in population                                       | 1,291      |        | 1,025   |         |                                |
| with one or more   | 5          | (0.4)  | 0       | (0.0)   | 0.3 (-0.1, 0.8)                |
| Hypnagogic/Hypnopompic Hallucinations Adverse Events         |            |        |         |         |                                |
| with no Hypnagogic/Hypnopompic Hallucinations Adverse Events | 1,286      | (99.6) | 1,025   | (100.0) | -0.3 (-0.8, 0.1)               |
| <b>Psychiatric disorders</b>                                 |            |        |         |         |                                |
| Hypnagogic hallucination                                     | 4          | (0.3)  | 0       | (0.0)   | 0.3 (-0.1, 0.8)                |
| Hypnopompic hallucination                                    | 1          | (0.1)  | 0       | (0.0)   | 0.1 (-0.3, 0.4)                |

<sup>†</sup> Based on Miettinen & Nurminen method stratified by study (using sample size as weight); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison. Every patient is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Lower Level Term is displayed for the specific adverse events.

MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 229 Table 5.3.5.3.3.:41)



The Phase 2 trial P006 recorded no cases of hypnagogic and hypnopompic hallucinations. However, three subjects in Phase 1 trials reported the events, two hypnagogic and one hypnopompic hallucination, 60 to 75 minutes after taking suvorexant 40 mg to 60 mg doses. Also, three additional subjects in the Phase 1 population reported hypnagogic experiences, as abnormal sleep related events, while on suvorexant 40 mg. No hypnagogic and hypnopompic hallucinations or related events occurred with placebo treatment in the Phase 1 and Phase 2 trials.

*Reviewer Note: The incidence of hallucinations in this program was small. As the sponsor mentioned, referencing published literature, even though such hallucinations are frequent in narcolepsy, their prevalence can be as high as 12.5% in the general population. The small numbers of cases in this program make it difficult to determine the relationship of hallucinations and potential narcoleptic risk with suvorexant. Despite the small numbers, the following observations suggest a need for cautious evaluation of the drug's dose response: the severity of cases in the suvorexant HD group compared to suvorexant LD, a subject on suvorexant HD discontinued treatment because of the hallucinations, incidence of the events in subjects on suvorexant HD increased from 0.2% within 3 months to 0.4% within 12 months of treatment, association of the hallucinations and sleep paralysis, and the absence of events in the placebo group.*

## **Sleep paralysis**

Sleep paralysis is characterized by complete muscle atonia or weakness and has been theorized to occur from inappropriate overlap of sleep stages such as intrusion of REM activity into normal sleep transitions. The sponsor provided literature reference that estimated the lifetime prevalence of sleep paralysis at 7.6% of the general population. Higher prevalence occurs in some medical conditions such as narcolepsy, hypertension, seizure disorders, migraine, anxiety disorders, and obstructive sleep apnea; and in other situations that are associated with insomnia or other sleep disturbances such as jet lag and shift work, student status, and African descent.

Narcoleptic cataplexy closely resembles true sleep paralysis; however, narcoleptic attacks are more common at sleep onset and true sleep paralysis on awakening. In the suvorexant clinical development program, sleep paralysis referred to the temporary inability to talk or move at sleep onset, during sleep, or upon awakening. Events of sleep paralysis that occurred at sleep onset in the Phase 3 trials were adjudicated to further evaluate the timing of the events in relation to sleep onset.

Only five subjects reported sleep paralysis within the first 3 months in the Phase 3 population; all of them received suvorexant treatment. Despite the low incidence of sleep paralysis, numerically more subjects reported the ECI while on suvorexant HD compared to suvorexant LD: 0.3% (4/1291) in the suvorexant HD group and 0.2% (1/493) in the suvorexant LD group; no placebo subject reported sleep paralysis in this population. All cases occurred 2-3 months of starting trial treatment. Investigators

deemed the sleep paralysis events in the suvorexant LD subject as not of sleep onset because the events occurred in the middle of the night. The subject had three episodes of 5-minute long sleep paralysis, each starting two to four hours after trial treatment and on return from the bathroom, on Trial Days 59, 62 and 64. In the past, he had experienced similar events up until junior high school; then, the events were at sleep onset and without any medication. **Three of the four suvorexant HD subjects were confirmed events of sleep onset paralysis** on adjudication. One case resulted in treatment discontinuation.

On extended treatment for up to 12 months, the suvorexant HD group added one more subject from Trial P009 who reported sleep onset paralysis associated with hypnagogic hallucinations on Trial Day 245. This event was also confirmed by adjudication to be sleep onset paralysis. The events of sleep onset paralysis in the Combined Phase 3 Population treated over 0-12 months are shown in the table below. No cases occurred in the placebo group. Also, the suvorexant LD subjects reported no cases of sleep onset paralysis in the Phase 3 population.

**Table 94: Sleep Onset Paralysis and Suvorexant High Dose over 0-12 Months among all Subjects Treated in the Combined Phase 3 Population (P028, P029, and P009)**

| Protocols 028+029+009   | MK-4305 HD |        | Placebo |         | Difference in % vs Placebo     |
|---|------------|--------|---------|---------|--------------------------------|
|   | n          | (%)    | n       | (%)     | Estimate (95% CI) <sup>†</sup> |
| Patients in population  | 1,291      |        | 1,025   |         |                                |
| with one or more Sleep Onset Paralysis Adverse Events (confirmed by adjudication) | 4          | (0.3)  | 0       | (0.0)   | 0.3 (-0.0, 0.8)                |
| with no Sleep Onset Paralysis Adverse Events                                      | 1,287      | (99.7) | 1,025   | (100.0) | -0.3 (-0.8, 0.0)               |
| <b>Nervous system disorders</b>   |            |        |         |         |                                |
| Sleep paralysis   | 4          | (0.3)  | 0       | (0.0)   | 0.3 (-0.0, 0.8)                |

<sup>†</sup> Based on Miettinen & Nurminen method stratified by study (using sample size as weight); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison. Every patient is counted a single time for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Lower Level Term is displayed for the specific adverse events. Note: although the lower level term displays "Sleep paralysis", the verbatim term indicates occurrence during sleep onset. MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 249 Table 5.3.5.3.3.:49)

Additional subjects on suvorexant doses of 40 mg and higher reported sleep paralysis in the Phase 2 and Phase 1 studies. The sponsor's review of the Phase 2 trial data revealed two subjects on suvorexant 40 mg and 80 mg who reported symptoms suggestive of sleep paralysis; these events apparently occurred in the middle of the night or on awakening, and not at sleep onset. The first subject, a 24 year-old male, was on suvorexant 80 mg when on Day 8 he developed the symptom that lasted 2-3 minutes and occurred once a week over 16 days. The second subject, a 45-year-old male on 40

mg suvorexant, reported the symptom that lasted 10 minutes starting from Trial Day 3 and occurring once a week over 29 days.

#### Phase 1 studies

In the Phase 1 studies, 2% (13/ 662) of subjects on suvorexant alone reported sleep paralysis compared to 0.3% (1/365) on placebo. The placebo subject experienced sleep paralysis that the sponsor described in Trial P011, a dose-escalation clinical pharmacology trial, as follows: “A female subject AN 0012 experienced sleep paralysis lasting 5 minutes following placebo upon waking. The onset of sleep paralysis was 20 minutes following the placebo dose. The investigator rated this event as mild in intensity and probably related to study drug. During this time, the subject also experienced somnolence which lasted 3 hours and 15 minutes.”

All 13 subjects who reported sleep paralysis on suvorexant did so while on suvorexant doses of 40 mg to 240 mg; 6 of the 13 subjects were on suvorexant 40 mg. Below, I summarized information on sleep paralysis events that occurred in six subjects from the Phase 1 trial P025, a trial that assessed abuse potential in subjects with polydrug use.

#1: One subject, a 33-year old male, experienced an episode of sleep paralysis that lasted 6 minutes starting at 1 hour 25 minutes after he received suvorexant 150 mg. He reported “an inability to speak and was only able to move his legs slightly during the episode, which occurred as he was starting to fall asleep.”

#2: A 35 year old white female reported an episode of sleep onset paralysis 52 minutes after receiving suvorexant 150 mg dose. The event lasted about 2 minutes and was described as inability to move her extremities, open her eyes or speak.

#3: A 26 year old Asian male reported two events of sleep paralysis in Trial P025. The first event consisted of three episodes, each of which lasted 5 seconds and started 1 hour and 30 minutes, 2 hours, and 4 hours after he received suvorexant 40 mg dose. These episodes occurred when the subject, on being awoken by study staff, reported an inability or great difficulty in initiating movements. The second event occurred in another treatment period after he received suvorexant 80 mg; this was an episode of the subject being unable to speak or move, starting 39 minutes (34 minutes calculated from the CSR narrative) and lasting for 20 seconds.

#4: A 48 year old white male experienced two events of intermittent sleep paralysis. In the first treatment period, he reported intermittent episodes of sleep paralysis starting from 3 hours and 32 minutes after receiving suvorexant 150 mg dose. The episodes were described as inability to talk and initiate voluntary movements except for the eyes. The event lasted 13 minutes. The second event of sleep paralysis occurred in the fourth treatment period 1 hour and 38 minutes after receiving suvorexant 40 mg. This event included three episodes of sleep paralysis at sleep onset; each episode lasted about 10

seconds, consisted of inability to move or speak. The whole event lasted about 7 minutes, and was associated with fearful episodes of inability to take deep breaths and auditory hypnagogic hallucinations.

#5: A 29 year old female of mixed race, white and African descent, reported intermittent sleep paralysis that started 1 hour and 33 minutes after receiving suvorexant 150 mg. The event consisted of five intermittent episodes of inability to move or speak that lasted about 2 minutes; the whole event lasted 1 hour. The subject was unable to tell whether the event occurred at sleep onset but recalled having similar episodes in the past.

#6: A 47 year old white female with life-long history of sleep paralysis reported three events of sleep paralysis in study P025. The first event started 3 hours after receiving suvorexant 150 mg dose and lasted 1 hour and 20 minutes. This event consisted of intermittent episodes sleep paralysis that lasted 5-10 seconds; described as inability to move, speak, or breathe; associated with visual hallucinations; appeared to occur with sleep onset. The episodes were similar to her earlier pre-study occurrences. The second event occurred 1 hour and 10 minutes after she received suvorexant 80 mg in another treatment period; the event lasted for lasted 15 minutes. The third event of sleep paralysis occurred 1 hour and 35 minutes after she received suvorexant 40 mg and lasted 5 minutes.

Further, I summarized the narratives in the following table:

**Table 95: Sleep Paralysis in Subjects on Suvorexant in Phase 1 Trial P025**

| Study | Age, Gender            | Treatment         | Onset after Treatment  | Sleep Paralysis Experience  |
|-------|------------------------|-------------------|------------------------|---|
| P025  | 33-year old male       | Suvorexant 150 mg | 85 minutes             | <u>Sleep onset</u> , 6 minutes of inability to speak with slight mobility of legs   |
| P025  | 35-year old female     | Suvorexant 150 mg | 52 minutes             | <u>Sleep onset</u> , unable to open eyes, speak and move arms and leg   |
| P025  | 26 year old Asian male | Suvorexant 40 mg  | 90, 120, & 240 minutes | On awakening, 3 episodes, each 5 seconds  |
|       |                        | Suvorexant 80 mg  | 34 minutes             | <u>Sleep onset</u> , 20 seconds, unable to speak or move  |
| P025  | 48 year old white male | Suvorexant 150 mg | 212 minutes            | 3 episodes, each 1-2 minutes, unable to speak or initiate movements   |
|       |                        | Suvorexant 40 mg  | 98 minutes             | <u>Sleep onset</u> , 3 episodes, each lasted 10 seconds, inability to move or speak. Whole event lasted about 7 minutes Associated fearful episodes of inability to take deep breaths and auditory hypnagogic hallucinations. |

|      |                                  |                   |             |   |
|------|----------------------------------|-------------------|-------------|---|
| P025 | 29 year old female of mixed race | Suvorexant 150 mg | 93 minutes  | 5 episodes, each lasted 2 minutes, inability to move or speak.  |
| P025 | 47 year old white female         | Suvorexant 150 mg | 180 minutes | Episodes lasted 5-10 seconds; inability to move, speak, or breathe; associated with visual hallucinations |
|      |                                  | Suvorexant 80 mg  | 70 minutes  | Similar pre-study episodes may be not as frequent   |
|      |                                  | Suvorexant 40 mg  | 95 minutes  | Occurred during sleep, unclear if any are sleep onset   |

(Source: Modified from Sponsor's submission CSR P025 Pages 258 to 265 )

*Reviewer Note: The sponsor summarized the sleep paralysis experience as follows: "few self-limited AEs of sleep paralysis were reported with suvorexant. Of five events potentially associated with sleep onset, 4 were confirmed to be events of sleep onset paralysis. These AEs generally occurred within 2-3 months of treatment initiation, with no pattern of increasing incidence associated with continued treatment, and were not suggestive of any safety concern." However from my review, the sleep paralysis data from the Phase 1 trials do not appear as reassuring as the sponsor suggests, given the number of events at suvorexant doses of 40 mg and above. This may facilitate adequate dose evaluation weighing the benefits against the risks.*

## Effects on Driving and Operating Machinery

The sponsor assessed the effects of suvorexant treatment on driving performance using AE reports of accident-related injuries, questionnaire responses on motor vehicle accidents or traffic violations, and two on-the-road driving studies (P035 and P039). Please see Review Section 5.4.5 for additional review of the driving studies.

### Adverse Events Associated with Motor Vehicle Accidents

ECIs included adverse events that occurred from traffic or motor vehicle accident (MVA) in which a trial subject was a vehicle driver.

Fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects who drove during the trial was low within the treatment groups: 0.3% (1/342) on suvorexant LD, 0.3% (3/891) on suvorexant HD, and 0.6% (4/692) on placebo. None of the events was considered drug-related by the investigators. One subject a 33-year-old female, said to be upset with marital problems, had experienced concentration problem and weakness before the MVA on Trial Day 7, in which she drove into a curb and a parked car. She was on placebo treatment. The other subjects had either swerved to avoid an accident or their vehicles were hit by other drivers.

Treatment effects did not appear to be related to the MVAs in subjects on suvorexant. A 36-year-old male on suvorexant LD was driving his moped on Trial Day 49 when a car hit him and he fell on his right leg. He recovered on Trial Day 52 and subsequently completed the trial.

Among the three subjects who experienced MVAs while on suvorexant HD, a 32-year old female in Trial P009 was struck from behind by another car when she stopped at a light on Trial Day 50. She recovered from neck pain and whiplash by Trial Day 198 but subsequently withdraw from the trial. The second subject, a 46-year old male, also in Trial P009, was driving on a rainy day on Trial Day 284 when he ran into another car that was reported to have suddenly changed lanes. By Trial Day 376, he had recovered from his injuries: neck pain, external contusion, and pectoral muscle strain. He completed the trial as planned. The third subject, a 50-year old female in Trial P028 experienced an MVA, reportedly caused by another vehicle driver, at about 8.5 hours after taking trial medication on Trial Day 53. She sustained moderate cervical vertebra dislocation, pelvic contusions, and a right knee contusion. She recovered by Trial Day 78.

The Phase 1 trials reported no MVAs, but review of the Phase 2 trial P006 yielded one MVA in a subject on placebo.

#### Questionnaire-based assessment of motor vehicle accidents or traffic violations

Following an FDA recommendation at the End of Phase 2 meeting, the sponsor obtained responses to a Motor Vehicle Accidents and Violations (MVAV) Questionnaire in the Phase 3 trials. The questionnaire, in the sponsor's ISS Appendix 5.3.5.3.3: 47, collected information on subjects' driving performance preceding the trial visit. Subject involved in MVAs provided information on time and date of accident, and injuries as a result of the accident. The sponsor used the responses to assess occurrence of traffic or motor vehicle accidents and related injuries.

In the Combined Phase 3 Population, 0-3 Months, the differences in incidence of Motor Vehicle Accidents and Violations (MVAV) among the dose groups were small, although, as shown in the Table below, a numerically higher rate occurred in the suvorexant LD group (2.9%, 10/342) compared to suvorexant HD group (2.3%, 13/569) and placebo (2.3%, 12/531).

**Table 96: Motor Vehicle Accidents and Violations (MVAV) By Dose Group Treated over 0-3 Months among all Subjects Who Drove in the Combined Phase 3 Population (P028, P029, and P009)**

|   | MK-4305 LD<br>n (%) | MK-4305 HD<br>n (%) | Placebo<br>n (%) |
|---|---------------------|---------------------|------------------|
| Patients in population  | 342                 | 569                 | 531              |
| with one or more MVAV events  | 10 (2.9)            | 13 (2.3)            | 12 (2.3)         |
| with no MVAV event  | 332 (97.1)          | 556 (97.7)          | 519 (97.7)       |
| Number of MVAV events   | 11                  | 14                  | 13               |
| Number of Patients with Accidents   | 4 (1.2)             | 7 (1.2)             | 5 (0.9)          |
| Number of Accidents   | 4                   | 7                   | 5                |
| Number of Patients with citations <sup>†</sup>  | 6 (1.8)             | 7 (1.2)             | 7 (1.3)          |
| Number of citations <sup>†</sup>  | 7                   | 7                   | 8                |
| Only patients who were treated and drove during the indicated phase of the study period were included in the table. For Protocol 009, only 12 patients were included in the 0-3 month interval due to a protocol amendment that added the MVAV form; this was implemented after enrollment completed. |                     |                     |                  |
| Percents of sub-category levels calculated using the total number of patients in that sub-category as the denominator.  |                     |                     |                  |
| <sup>†</sup> Citation = violation.  |                     |                     |                  |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.   |                     |                     |                  |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.   |                     |                     |                  |

(Source: Sponsor's submission ISS Page 275 Table 5.3.5.3.3.:59)

Tables 97 and 98 below show that over extended treatment periods of 6 to 12 months with suvorexant, the incidence of MVAV was marginally increased by suvorexant LD (3.5%, 12/342) compared to placebo (2.6%, 14/532), and by suvorexant HD (4.0%, 36/891) compared to placebo (3.2%, 26/692).

**Table 97: Motor Vehicle Accidents and Violations (MVAV) and Suvorexant Low Dose over 0-6 Months among all Subjects Who Drove and Were Treated in the Combined Phase 3 Population (P028, P029, and P009)**

|  | MK-4305 LD<br>n (%) | Placebo<br>n (%) |
|--|---------------------|------------------|
| Patients in population   | 342                 | 532              |
| with one or more MVAV events   | 12 (3.5)            | 14 (2.6)         |
| with no MVAV event   | 330 (96.5)          | 518 (97.4)       |
| Number of MVAV events  | 13                  | 16               |
| Number of Patients with Accidents  | 4 (1.2)             | 7 (1.3)          |
| Number of Accidents  | 4                   | 7                |
| Number of Patients with citations <sup>†</sup>   | 8 (2.3)             | 8 (1.5)          |
| Number of citations <sup>†</sup>   | 9                   | 9                |
| Only patients who were treated and drove during the indicated phase of the study period were included in the table.    |                     |                  |
| Percents of sub-category levels calculated using the total number of patients in that sub-category as the denominator. |                     |                  |
| <sup>†</sup> Citation = violation.   |                     |                  |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.                          |                     |                  |

(Source: Sponsor's submission ISS Page 277 Table 5.3.5.3.3.:61)

**Table 98: Motor Vehicle Accidents and Violations (MVAV) and Suvorexant High Dose over 0-12 Months among all Subjects Who Drove and Were Treated in the Combined Phase 3 Population (P028, P029, and P009)**

|  | MK-4305 HD<br>n (%) | Placebo<br>n (%) |
|--|---------------------|------------------|
| Patients in population   | 891                 | 692              |
| with one or more MVAV events   | 36 (4.0)            | 22 (3.2)         |
| with no MVAV event   | 855 (96.0)          | 670 (96.8)       |
| Number of MVAV events  | 39                  | 27               |
| Number of Patients with Accidents  | 13 (1.5)            | 10 (1.4)         |
| Number of Accidents  | 13                  | 10               |
| Number of Patients with citations <sup>†</sup>   | 24 (2.7)            | 14 (2.0)         |
| Number of citations <sup>†</sup>   | 26                  | 17               |
| Only patients who were treated and drove during the indicated phase of the study period were included in the table.    |                     |                  |
| Percents of sub-category levels calculated using the total number of patients in that sub-category as the denominator. |                     |                  |
| <sup>†</sup> Citation = violation.   |                     |                  |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.                          |                     |                  |

(Source: Sponsor's submission ISS Page 276 Table 5.3.5.3.3:60)

*Reviewer note: The MVAV questionnaire was introduced after Trial P009 had commenced. Within limits of indirect comparison among treatment groups, the incidence trend over the extended treatment periods may suggest a suvorexant dose effect on the occurrence of MVAVs. This suggestion is contrary to the sponsor's position in a statement on Page 628 of the ISS (Section 5.3.5.3.3.5.8.3 Summary: Effects on Ability to Drive or Operate Machinery), "The incidence of accidents and citations were generally comparable between the treatment arms (~3%), without evidence of an increased occurrence with suvorexant, based on suvorexant dose or with continued treatment over time."*

*Despite comparable reports of accidents and traffic violations, and driving performance in the driving studies, the overall assessment suggests that suvorexant-treated individuals need to avoid driving, operating machinery, or engaging in activities that require full mental alertness until they become fully awake. In the Phase 3 trials, the incidence of motor vehicle accidents and traffic violations were comparable between suvorexant and placebo treatments. In Phase 1 driving trials, the sponsor observed no significant impairment of next-day driving performance that tested mean SDLP after one night and eight consecutive nights of suvorexant LD or HD in both elderly and non-elderly subjects. However, the trials showed that some subjects who received suvorexant had increased SDLP and four non-elderly subjects felt sleepy enough to prematurely stop their driving tests. As a result, a potential for impaired driving performance exists with suvorexant treatment. The sponsor provided cautionary language in the proposed label, which seems appropriate.*



## Cataplexy

The sponsor recorded no cases of cataplexy in the entire suvorexant development program. For the suvorexant development program, the sponsor defined cataplexy as characterized by sudden, unexpected, and fleeting muscle weakness ranging from slight weakness to complete body collapse. The cataplexy event had to be preceded by an emotional trigger or stimulus, localized to a specific muscle group or part of the body, and had to occur in a subject who was fully awake, lucid, and aware. An external adjudication committee reviewed the ECI reports and the Modified Cataplexy Questionnaire that the subject completed after the event. After reviewing 45 cases of falls and an event of muscle weakness, the committee determined none of the events in the Phase 3 trials was suggestive of cataplexy. Similarly, the Phase 2 and Phase 1 trials recorded no cataplexy events.

Cataplexy is a symptom of narcolepsy and a result of intrusion of muscle atonia, which typically occur in REM sleep, into wakefulness. Published literature suggests that narcolepsy patients with cataplexy have low cerebrospinal fluid (CSF) orexin levels, likely from progressive orexinergic neuronal death (Nishino et al, 2000; Kukkonen, 2012). The concern that orexin receptor antagonists (ORAs) including suvorexant may increase the risk of narcolepsy led the sponsor to specifically evaluate for symptoms such as cataplexy. Occurrence of cataplexy may cause falls, accidents, and injuries, and so pose a major safety concern.

An investigator in one of the Phase 3 trials referred one case of muscle weakness while on suvorexant HD treatment to the adjudication committee as an event suggestive of potential cataplexy. This case highlights two events of clinical interest (ECIs) from a subject: Excessive Daytime Sleepiness (EDS) and Muscle Weakness in Legs (Muscular Weakness). I summarize the narrative below.

### Event Suggestive of Cataplexy with EDS and Elevated Amylase Level – Summary of Narrative

Subject AN 02642, a 59 year old male, in the 12-month, double-blind, Trial P009, reported an event of muscle weakness in legs on Day 46, while on suvorexant HD. Later that day, he reported EDS that led to discontinuation from the trial. The external adjudication committee concluded upon review of the case that the Muscle Weakness event was not cataplexy.

Muscle weakness event was suggestive of potential cataplexy. The subject had a pre-trial elevation of amylase levels that apparently increased further during the first month of trial treatment. He remained asymptomatic and his amylase levels were 58 U/L at baseline, 503 U/L, and 80 U/L before trial medication was interrupted from Day 38 to Day 42. On Day 46, about 12 hours after his Day 45 treatment with suvorexant HD, he developed muscle weakness in legs that lasted 5-30 seconds. At the time of the event, he was at work, fully awake, and laughing with his co-workers when he developed

increased tiredness and, in total, three brief episodes of weakness of lower extremities. Also, he continued to feel weak for another 11 hours, and had a headache that started about 4 hours after onset of muscle weakness and lasted 2 hours.

Still on Day 46 at about 5 hours after onset of muscle weakness, the subject developed excessive daytime sleepiness that lasted up to bedtime. The daytime sleepiness episodes occurred variously at work. One episode occurred at a traffic stop; another episode of microsleep, which was witnessed by his wife, occurred while he was driving. The EDS resolved after he discontinued the trial medication. There were no reports of associated seizures, sleep paralyzes, or hallucinations.

The subject's past medical history was significant for hypertension, dyslipidemia and osteoarthritis. His concomitant medications included ezetimibe, amlodipine besylate, irbesartan, vitamin B complex, vitamins (unspecified), ubidecarenone, potassium (unspecified), glucosamine, sildenafil citrate, simvastatin. He denied use of alcohol or non-prescribed drugs within 24 hours prior to the events and denied a history of substance abuse. He drank about 2 beers a night, but not every night.

According to the sponsor's narrative concerning the muscle weakness event, the subject's responses in the Modified Cataplexy Questionnaire were positive to the following questions about situations in which the leg weakness or knee buckling occurred: when laughing, when excited, surprised, when required to make a quick verbal response in a playful or funny context, when startled, when telling or hearing a joke. The investigator was concerned the event was potentially cataplexy. Subsequently, the external adjudication committee reviewed the case and concluded that the muscle weakness event was not cataplexy.

Merck evaluated their non-clinical and clinical data, including up to 12 months suvorexant treatment, and concluded that no identified risk of cataplexy exists in the setting of clinical insomnia treatment using ORAs. Merck further supported their conclusion by noting that progressive neuronal loss led to narcolepsy, in contrast to the intermittent or transient cyclical exposure from ORAs for clinical insomnia in which the orexin receptor is exposed to a drug such as suvorexant only during the sleep period part of a day.

*Reviewer Note: So far there are no confirmed cases of narcolepsy in earlier trials of orexin antagonists. The dual orexin receptor antagonist almorexant was in an earlier development for insomnia, which was stopped for unclear reasons; the development program recorded no cases of narcolepsy or cataplexy in an early proof of concept trial. In the trial, investigators reported that almorexant treatment decreased latency to REM sleep. They added that shortened REM latency may suggest narcolepsy-like changes in sleep architecture or potential direct effects of dual orexin receptor antagonists on sleep; alternatively, it may indicate REM rebound in individuals susceptible to chronic partial REM deprivation (Hoever et al, 2012).*

*The absence of cataplexy in the development programs does not necessarily exclude the risk of drug-induced narcolepsy from exposure to ORAs. Although, the external adjudication committee concluded that the muscle weakness event summarized above was not cataplexy, features of the event present concerns for a narcoleptic process that may be associated with trial treatment. Even discounting the event, a small risk of narcoleptic events cannot be ruled out during suvorexant or other ORAs treatment, especially if the risk is so small that it will need a larger safety database to detect it. The limited experience with ORAs, especially beyond 14 months of treatment, suggests the continued need to carefully assess this drug class for the risk of cataplexy.*

*Also, the HLA status of subjects in the development program remains largely unknown. It may be that HLA interaction with ORA drug exposure is required to manifest narcoleptic symptoms such as cataplexy. The sponsor has stored blood samples from the trials that may be useful for future genomic studies. A potential evaluation is to determine the subjects HLA genotype and compare subjects with and without features of the narcolepsy components such as sleep paralysis, hypnopompic hallucinations, EDS, and muscle weakness suggestive of cataplexy.*

## Falls

The sponsor examined the Phase 3 trials for the risk of falls, which were treated as ECIs and adjudicated to determine whether the events suggested cataplexy or were associated with suvorexant treatment.

The trials defined a fall as a loss of posture or balance. An external adjudication committee reviewed the ECI report and the subject-completed Modified Cataplexy Questionnaire, and adjudicated the events to assess whether they were suggestive of cataplexy.

The incidence of falls in the Phase 3 trials within the first 3 months of treatment was low at 0.8% (22/2809), and the fall risks across treatment groups were comparable as shown in the table below. Falls occurred in less than 1% in each of the treatment groups: 0.7 % (9/1291) with suvorexant HD, 0.8% (4/493) with suvorexant LD, and 0.9 % (9/1025) with placebo. Further, each treatment group recorded at least one severe fall: 0.2 % (3/1291) with suvorexant HD, 0.2% (1/493) with suvorexant LD, and 0.1 % (1/1025) with placebo.

**Table 99: Events of Falls in the Phase 3 Trials at 0-3, 0-6, and 0-12 months**

| Variable Category   | Placebo        | Suvorexant LD | Suvorexant HD  |
|---------------------|----------------|---------------|----------------|
| Falls in 0-3 Months | 0.9 % (9/1025) | 0.8% (4/493)  | 0.7 % (9/1291) |
| Falls in 0-6 Months | 0.9% (7/767)   | 1.0% (5/493)  | Not applicable |

|                      |                |                |                |
|----------------------|----------------|----------------|----------------|
| Falls in 0-12 Months | 1.5% (15/1025) | Not applicable | 1.6% (21/1291) |
|----------------------|----------------|----------------|----------------|

(Source: Modified from Sponsor's submission ISS Pages 261, 267, and 268 Tables 5.3.5.3.3: 55, 56, and 57)

Based on the sponsor's assessment, the falls appeared not related to residual somnolence or impaired coordination, but they were associated with circumstances that led to fall such as faulty ladder or other unstable footing, icy or other slippery conditions. Brief summaries of the narratives for falls in 0-3 months are as follows:

#### Suvorexant HD

Subject AN 12253 in Trial P029, a 42-year-old female who was on suvorexant HD and reported a fall on Trial Day 40 about 22 hours after taking trial medication. She fell on an icy surface while walking to her car, sustained moderate swelling of her left knee and right foot. She recovered the same day and continued the trial treatment.

Subject AN 12288 in Trial P029, a 46-year-old male who received suvorexant HD and reported a severe fall on Trial Day 65 at about 19 hours after taking trial medication. While at work, the subject slipped on olive oil and fell down a staircase. He lost consciousness and sustained multiple non-serious musculoskeletal injuries including contusions, shoulder dislocation, and nasal fracture. He completed the trial per protocol.

Subject AN 12324 in Trial P029, a 39-year-old female was on suvorexant HD when she reported a mild fall on Trial Day 12 at about 15 hours after taking trial medication. She was hiking when she tripped and fell; afterwards she reported moderate left foot pain, from which she recovered that same day. She completed the trial per protocol.

Subject AN 07229 in Trial P028, a 61-year-old female was receiving suvorexant HD when he reported a mild fall on Trial Day 43 at about 17 hours after taking trial medication. While on a walk, she slipped on the snow and fell. She reported mild coccydynia. She completed the trial per protocol.

Subject AN 07959 in Trial P028, a 73-year-old male was on suvorexant HD treatment when he reported a mild fall on Trial Day 44 at about 11 hours after taking trial medication. He slipped on ice, fell, and sustained a mild knee contusion. He completed the trial per protocol.

Subject AN 12214 in Trial P029, a 58-year-old female assigned to suvorexant HD, reported a severe fall on Trial Day 46 at about 24 hours after taking trial medication. She slipped on the ice while walking her dog. She fell and sustained an ankle fracture but completed the trial treatment per protocol.

Subject AN 13003 in Trial P029, a 67-year-old female assigned to suvorexant HD. She had a history of multiple medical conditions including dizziness and orthostatic hypotension, and required concomitant medications. She reported two events of fall and

a vertebral (T12) compression fracture. On Trial Day 45 at about 10 hours after taking trial medication, she tripped on a comforter, had a severe fall, and sustained moderate musculoskeletal injuries including neck and lumber sprain/strain and a right foot fracture. Although the investigator considered this event to be related to study medication, she continued trial medication. On Trial Day 47 at about 9 hours after taking trial medication, she had a second fall. She awoke in the morning, felt dizzy, and fell. She was hospitalized, and diagnosed with a T12 compression fracture (serious and severe) and pneumonia. She discontinued trial medication on Trial Day 48 because of the second fall. Comorbid conditions included COPD, gastroesophageal reflux disease, hypercholesterolemia, hypothyroidism, osteoporosis, and back pain. Concomitant medications included ibandronate sodium, levothyroxine sodium, omeprazole, simvastatin, aspirin, calcium, beclomethasone dipropionate, albuterol, vitamins, acetaminophen, and dicyclomine hydrochloride.

Subject AN 04168 in Trial P009, a 75-year old female on suvorexant HD who reported a moderate fall on Trial Day 87. While taking out trash, she tripped over netting covering newly laid sod, and sustained mild knee and elbow injuries. She completed the trial per protocol.

Subject AN 07971 in Trial P028, a 68-year-old male on suvorexant HD who reported a mild fall on Trial Day 92, a day after his last trial medication. At 04:00 hours on Day 92, he awakened and fell on attempting to roll out of bed. Subsequently, he completed the trial per protocol.

#### Suvorexant LD

Subject AN 12149 in Trial P029, a 57-year-old female on suvorexant LD who reported a mild fall on Trial Day 25 at about 11 hours after taking trial medication. She was getting dressed in the morning, then felt dizzy and fell on her knee, sustaining a mild hematoma. She completed the trial per protocol.

Subject AN 07878 in Trial P028, a 75-year-old female on suvorexant LD reported a mild fall on Trial Day 32 at about 3 hours after taking trial medication. She had received laxative treatment for a colonoscopy planned for the next day and was making frequent trips to the bathroom, when she tripped over a folding door. She fell and sustained a mild skin laceration near her left eye. Subsequently, she missed two doses of trial medication on Trial Days 32 and 33. Afterwards, she completed the trial per protocol.

Subject AN 08170 in Trial P028, a 68-year-old female was receiving suvorexant LD when she reported a moderate fall on Trial Day 61 at a time unspecified relative to the earlier dose of trial medication. She fell while trying to lift a table and sustained moderate right flank bruising and pain. Subsequently, she discontinued from the trial after withdrawing consent because of family commitments.

Subject AN 12953 in Trial P029, a 73-year-old female was receiving suvorexant LD when she reported a severe fall on Trial Day 29 at about 14 hours after taking trial medication. She fell from a ladder while putting away items in the attic, fractured her right ankle, and was hospitalized. Subsequently, she discontinued from the trial on Trial Day 36.

#### Placebo

Subject AN 12814 in Trial P029, a 74-year-old female was on placebo when she reported a fall of moderate intensity on Study Day 10 at about 2 hours after taking trial medication. . She awoke to use the bathroom at 00:30, slipped on the wet kitchen floor from, a roof leak, and struck her head on the floor. She apparently lost consciousness because when she awoke on the floor the time was 02:00. She completed the trial per protocol.

Subject AN 12970 in Trial P029, a 70-year-old male was on placebo when he reported two separate events of mild falls. He reported the first fall on Trial Day 44 about 17 hours after taking trial medication when the subject fell while running with his grandson. He sustained a thigh muscle tear and a moderate rib contusion. He reported the second fall on Trial Day 78 about 12 hours after taking trial medication, when he slipped in the snow, fell, and sustained a mild right shoulder contusion. Subsequently, he completed the trial per protocol.

Subject AN 07912 in Trial P028, a 74-year-old female treated with placebo reported a mild fall on Trial Day 6 at about 19 hours after taking trial medication. She tripped on a door mat, fell, and sustained a mild hematoma on her right thigh. She completed the trial per protocol.

Subject AN 08023 in Trial P028, an 85-year-old female on placebo reported a mild fall on Trial Day 28 at about 12 hours after taking trial medication. She accidentally tripped on the edge of the rug and fell, sustaining a mild toe injury. She completed the trial per protocol.

Subject AN 08100 in Trial P028, a 66-year-old female on placebo reported a moderate fall on Trial Day 28 at about 22 hours after taking trial medication. While at work she slipped on a sanded floor, fell, and sustained a foot fracture reported to be of moderate intensity. She completed the trial per protocol.

Subject AN 07245 in Trial P028, a 51-year-old female on placebo reported a severe fall on Trial Day 49 at about 19 hours after taking trial medication. She slipped on ice while walking, and sustained severe fractures of left fibula and tibia. Later she discontinued trial medication on Day 58 because of the fractures.

Subject AN 07889 in Trial P028, a 67-year-old female on placebo reported moderate fall on Trial Day 45 (P028). She was thrown from an apparently frightened horse that she

was riding. On falling, she sustained severe rib fractures and a moderate pneumothorax. She discontinued trial medication on Trial Day 45 because of the rib fracture.

Subject AN 04294 in Trial P009, an 87-year old female on placebo reported two ECIs, **fall** and **excessive daytime sleepiness (EDS)**, in addition to the adverse events of morning dizziness and lethargy. From Day 37, she developed intermittent dizziness and lethargy that occurred in the mornings. The dizziness lasted eight days and lethargy continued to the end of the trial. On Trial Day 85, she reported a mild fall at about 19 hours after taking trial medication. She was placing two bags of groceries on a table when she lost her balance and fell. An evaluation at the Emergency Department on the same day confirmed she had chest wall contusion and upper arm strain, though the fall was reported as mild in intensity. She interrupted her trial medication for four days. About 7 weeks later, on Trial Day 136, she reported excessive daytime sleepiness of moderate intensity, which lasted 20 days. She described the events as feeling weak after lunch and sleepy for about an hour, resulting in daily naps despite having adequate night's sleep. She discontinued trial medication on Day 154 and recovered from EDS next day. Comorbid conditions included history of drug hypersensitivity, gastroesophageal reflux disease, hypothyroidism, osteoarthritis, deafness bilateral, hearing aid use and hypertension. Concomitant medications included furosemide, levothyroxine sodium, potassium (unspecified), ibandronate sodium, celecoxib, calcium (unspecified), vitamins (unspecified), omeprazole, ranibizumab, bevacizumab, nebivolol hydrochloride and hydrocodone. She denied use of alcohol within 24 hours prior to the events, or any history of substance abuse. Her discontinuation from the trial was because of EDS.

Subject AN 03061 in Trial P009, a 56-year old female on placebo reported a moderate fall on Trial Day 74 at about 12 hours after taking trial medication. She fell on being accidentally pushed by another person, lost consciousness, and sustained moderate fractures of the ulna and radius. She completed the trial per protocol.

#### Long-Term Events of Falls

At 0-6 months and at 0-12 months, the fall risks were comparable across treatment groups as shown on Table 99. In 0-12 months, increases in events of falls were noted in both suvorexant HD and placebo groups, with a risk difference of 0.1%. Also, falls reported as serious adverse events in the sponsor's CSS Table 2.7.4:7 were comparable between treatment groups: suvorexant HD group at 0.1% (1/1291) compared to placebo subjects at 0.2% (2/1025). In addition to the falls within 0-3 months, the assessments for 0-12 months recorded 11 more subjects with falls in the suvorexant HD group, including one of severe intensity and another with EDS; there were 6 more subjects for placebo, none was severe. I summarize the narratives of the severe falls and falls associated with EDS below:

Subject AN 04646 in Trial P009, a 67-year old female on suvorexant HD reported a severe fall on the morning of Trial Day 356 about 7.5 hours after taking trial medication. She awoke with nausea, went to the bathroom, and sat on the toilet. She lost consciousness and was found on floor by her husband about 30 minutes later. Also she reported associated severe malaise, which she experienced in the past after previous petit mal seizures. She recovered on the day, and subsequently completed the trial per protocol.

Subject AN 02674 in Trial P009, a 43-year old white female reported a fall and excessive daytime sleepiness. She was on suvorexant HD when she reported excessive daytime sleepiness (EDS) in the morning of Trial Day 2, at about 12 hours after taking trial drug. The EDS started while she was at work and lasted four days before it subsided. During the event she had to walk about her office to stay awake. However, the EDS was of moderate intensity and required no intervention. On Trial Day 347, the subject reported a fall that occurred at about 15 hours after she took trial drug. She was carrying gifts, not seeing where she was going, she slipped on the wet floor and fell. She reported no muscle weakness, loss of consciousness, or emotional events. She had a history of slipping and falling prior to the trial, although she had none of such falls in the preceding 6 months. During this event she sustained a 5 cm contusion of the left knee, which apparently resolved by Trial Day 358. Her comorbid conditions included a history of temporomandibular joint syndrome, hypercholesterolemia, endometriosis, and seasonal allergy. Concomitant medications included estradiol, medroxyprogesterone acetate, atorvastatin calcium, sertraline hydrochloride, calcium (unspecified), vitamin D (unspecified), vitamins (unspecified). She denied use of alcohol within 24 hours prior to the event and or a history of substance abuse. She completed the trial per protocol.

#### Falls in the Phase 1 and Phase 2 Trials

There were no reports of falls in the earlier phase trials.

*Reviewer Note: The incidence of falls in the suvorexant development program was low and the fall risks across treatment groups were comparable. An external adjudication committee of experts reviewed the fall events to assess whether they were suggestive of cataplexy. None of the cases suggested cataplexy.*

#### Next-day Residual Effects

A major concern with the use of hypnotic sedatives is residual effects the following day. These effects may influence the ability to operate heavy machinery or drive. The sponsor assessed next day residual effects in Phase 1, Phase 2, and Phase 3 trials as shown in the table below.



**Table 100: Trials with Objective Evaluations of Next Day Residual Effects Following Night Time Dosing of Suvorexant.**

| <b>Trials</b>   | <b>Doses</b>  | <b>Timepoints</b>  | <b>Measurements</b>  |
|---|---|--|--|
| <b>Phase 1 (N=125)</b>  |   |  |  |
| <b>Elderly driving (P039)</b>                                   | 15 and 30 mg, MD (N=24)   | Day 1 and 8 at 9hr post dose.  | Driving endpoints: Standard Deviation of Lane Position<br>Memory: Immediate and Delayed Word Recall (IDWR)<br>Balance: body sway (A95)<br>Psychomotor: Digit Symbol Substitution Test (DSST) |
| <b>Non-elderly driving (P035)</b>                               | 20 and 40 mg, MD (N=28)   |  |  |
| <b>COPD Study (P032)</b>  | 40mg (non-elderly) 30mg (elderly), MD, (N=25)   | Days 1 & 4 at 9hr post dose  | Memory: IDWR<br>Balance: body sway (A95)<br>Psychomotor: DSST  |
| <b>OSA study (P036)</b>   | 40mg, MD, N=26  | Days 1 & 4 at 9hr post dose  | Memory: IDWR<br>Balance: body sway (A95)<br>Psychomotor: DSST  |
| <b>Healthy PSG (P002)</b>                                       | 10, 50 and 100mg, SD (N=22)   | 10 hr post dose  | Psychomotor: Simple Reaction Time (SRT), Choice Reaction Time (CRT), DSST  |
| <b>Phase 2b</b>   |   |  |  |
| <b>Dose-Finding Trial (P006)</b>                                | MK-4305 10 mg (N=62)<br>MK-4305 20 mg (N=61)<br>MK-4305 40 mg (N=59)<br>MK-4305 80 mg (N=61)<br>nightly for 4 weeks | am portion of PSG visits (Day -14, Day -7, Day 1 and Day 28 (Period 1), Day 1 and Day 28 (Period 2)) | Psychomotor: DSST, Digit Symbol Copy Test  |
| <b>Phase 3</b>  |   |  |  |
| <b>Confirmatory Efficacy Trials (PQ cohorts, P028 and P029)</b> | High dose (30 and 40 mg), N=1291; low dose (15 and 20 mg), N=493 nightly for 3 months                               | am portion of PSG visits (Day -14, Day-7, Day 1, Day 30, Day 90, Day 91(runout))                     | Psychomotor: DSST  |

(Source: Sponsor's submission ISS Page 629 Table 5.3.5.3.3:243)

In the trials, the sponsor examined suvorexant effects on balance and memory, psychomotor performance, and AEs identified as associated with next day residual effects. I reviewed somnolence AE, a viable measure of next day residual effects, in Section 5.3.4.

#### Balance and Memory Effects

In four Phase 1 trials (P032, P036, P035, P039), the sponsor used a word learning test and body sway test (Accusway) to examine the effects of suvorexant on next-day memory and balance. The driving trial P035 with healthy non-elderly subjects showed a statistically significant decrease in word recall after the words were presented to subjects in the morning 11 hours after a single dose of suvorexant 40 mg. Also a statistically significant increase on body sway area occurred in the morning 11 hours

after a single dose of either suvorexant 20 or suvorexant 40 mg. The other three trials (P032, P036, and P039) showed no significant effects on next-day memory and balance.

#### Psychomotor Performance

The Phase 3 trials, P028 and P029, assessed residual effects of trial medication on psychomotor performance using the Digit Symbol Substitution Test (DSST). This widely used test was performed in the mornings of the PSG visits to evaluate coordination and attention processes. DSST scores, obtained from 1,493 subjects in the phase 3 trials, were based on the number of items completed correctly, incorrectly, and the number attempted.

Analysis of psychomotor performance using DSST, and assessing number of correct responses in combined Phase 3 trial population, is shown in table below. The sponsor reported no clinically meaningful differences between each of the suvorexant groups and placebo group in the baseline-adjusted number correct responses at any time point. For example, differences in LS mean at month 3 for the suvorexant doses compared to placebo were as follows: suvorexant HD -0.8 (95% CI: -1.9, 0.3), suvorexant LD -0.5 (95% CI: -1.9, 0.8). Further, the analysis of the attempted responses by time point for the Treatment Phase also yielded similar results to those for correct responses.

**Table 101: Analysis of Digit Symbol Substitution Test Number of Correct Responses by Time Point Combined Phase 3 Population: 0-3 Months**

| Treatment   | N   | Baseline<br>Mean (SD) | Time Point<br>Mean (SD)                      | Change from Baseline at Time Point |                               |
|---|-----|-----------------------|--|------------------------------------|-------------------------------|
|   |     |                       |  | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Night 1   |     |                       |  |                                    |                               |
| MK-4305 LD  | 338 | 50.8 (14.7)           | 52.7 (15.4)                                  | 1.9 ( 8.9)                         | 1.6 ( 0.8, 2.5)               |
| MK-4305 HD  | 577 | 52.8 (17.2)           | 54.1 (16.8)                                  | 1.3 ( 8.6)                         | 1.5 ( 0.8, 2.1)               |
| Placebo   | 578 | 51.7 (15.9)           | 54.1 (15.7)                                  | 2.4 ( 8.3)                         | 2.3 ( 1.7, 3.0)               |
| Month 1   |     |                       |  |                                    |                               |
| MK-4305 LD  | 321 | 51.1 (14.4)           | 53.1 (16.2)                                  | 2.0 (10.5)                         | 1.8 ( 0.8, 2.8)               |
| MK-4305 HD  | 560 | 52.7 (16.7)           | 54.4 (16.6)                                  | 1.7 (10.4)                         | 1.9 ( 1.1, 2.7)               |
| Placebo   | 551 | 51.8 (15.9)           | 54.0 (15.5)                                  | 2.2 (9.0)                          | 2.2 ( 1.4, 2.9)               |
| Month 3   |     |                       |  |                                    |                               |
| MK-4305 LD  | 307 | 50.8 (14.1)           | 53.5 (14.7)                                  | 2.7 ( 8.6)                         | 2.4 ( 1.3, 3.4)               |
| MK-4305 HD  | 526 | 53.0 (16.9)           | 54.9 (16.9)                                  | 1.9 (10.7)                         | 2.1 ( 1.3, 2.9)               |
| Placebo   | 516 | 51.7 (15.8)           | 54.7 (15.9)                                  | 3.0 (9.9)                          | 2.9 ( 2.1, 3.7)               |
| Pairwise Comparison   |     |                       | Difference in LS Means (95% CI) <sup>†</sup> |                                    |                               |
| Night 1   |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo  |     |                       | -0.9 ( -1.8, 0.1)                            |                                    |                               |
| MK-4305 LD vs. Placebo  |     |                       | -0.7 ( -1.8, 0.4)                            |                                    |                               |
| Month 1   |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo  |     |                       | -0.3 ( -1.4, 0.8)                            |                                    |                               |
| MK-4305 LD vs. Placebo  |     |                       | -0.4 ( -1.7, 0.9)                            |                                    |                               |
| Month 3   |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo  |     |                       | -0.8 ( -1.9, 0.3)                            |                                    |                               |
| MK-4305 LD vs. Placebo  |     |                       | -0.5 ( -1.9, 0.8)                            |                                    |                               |
| <sup>†</sup> Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates.<br>MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.<br>MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years. |     |                       |  |                                    |                               |

(Source: Sponsor's submission ISS Page 632 Table 5.3.5.3.3:244)

### DSST by Age

The mean DSST correct responses improved from baseline at all time points among non-elderly subjects treated with either suvorexant or placebo. No significant differences were observed among the treatment groups, as shown in the table below.

**Table 102: Digit Symbol Substitution Test Number of Correct Responses by Time Point Combined Phase 3 Population: 0-3 Months, Non-Elderly Subjects**

| Treatment   | N   | Baseline<br>Mean (SD) | Time Point<br>Mean (SD)                      | Change from Baseline at Time Point |                               |
|---|-----|-----------------------|--|------------------------------------|-------------------------------|
|   |     |                       |  | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Night 1   |     |                       |  |                                    |                               |
| MK-4305 LD  | 193 | 55.3 (13.8)           | 57.7 (14.9)                                  | 2.4 (9.9)                          | 2.1 ( 0.8, 3.3)               |
| MK-4305 HD  | 335 | 57.4 (15.8)           | 58.8 (15.6)                                  | 1.4 (9.1)                          | 1.5 ( 0.5, 2.4)               |
| Placebo   | 332 | 56.5 (16.3)           | 58.5 (16.4)                                  | 1.9 (8.9)                          | 2.0 ( 1.0, 2.9)               |
| Month 1   |     |                       |  |                                    |                               |
| MK-4305 LD  | 186 | 55.6 (13.2)           | 57.8 (15.6)                                  | 2.2 (11.1)                         | 1.9 ( 0.5, 3.3)               |
| MK-4305 HD  | 323 | 57.1 (14.8)           | 59.2 (15.1)                                  | 2.1 (10.0)                         | 2.2 ( 1.2, 3.2)               |
| Placebo   | 312 | 56.7 (16.2)           | 58.7 (15.6)                                  | 2.0 (9.5)                          | 2.0 ( 1.0, 3.1)               |
| Month 3   |     |                       |  |                                    |                               |
| MK-4305 LD  | 175 | 55.5 (12.8)           | 57.9 (14.0)                                  | 2.4 (8.9)                          | 2.2 ( 0.7, 3.6)               |
| MK-4305 HD  | 304 | 57.4 (14.9)           | 59.6 (15.4)                                  | 2.2 (11.3)                         | 2.3 ( 1.2, 3.4)               |
| Placebo   | 292 | 56.5 (16.2)           | 59.1 (15.9)                                  | 2.6 (10.6)                         | 2.6 ( 1.5, 3.8)               |
| Pairwise Comparison   |     |                       | Difference in LS Means (95% CI) <sup>†</sup> |                                    |                               |
| Night 1   |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo  |     |                       | -0.5 (-1.8, 0.8)                             |                                    |                               |
| MK-4305 LD vs. Placebo  |     |                       | 0.1 (-1.5, 1.7)                              |                                    |                               |
| Month 1   |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo  |     |                       | 0.2 (-1.3, 1.7)                              |                                    |                               |
| MK-4305 LD vs. Placebo  |     |                       | -0.1 (-1.9, 1.6)                             |                                    |                               |
| Month 3   |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo  |     |                       | -0.3 (-1.9, 1.2)                             |                                    |                               |
| MK-4305 LD vs. Placebo  |     |                       | -0.5 (-2.3, 1.4)                             |                                    |                               |
| <sup>†</sup> Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |                       |  |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.   |     |                       |  |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.   |     |                       |  |                                    |                               |

(Source: Sponsor's submission ISS Page 636 Table 5.3.5.3.3:248)

In elderly subjects, mean DSST correct responses also improved from baseline at all time points, which the sponsor attributed to the learning effect generally observed with this assessment. However, On Night 1, placebo subjects showed greater performance than suvorexant-treated subjects as shown in table below.

**Table 103: Digit Symbol Substitution Test Number of Correct Responses by Time Point Combined Phase 3 Population: 0-3 Months, Elderly Subjects**

| Treatment  | N   | Baseline<br>Mean (SD) | Time Point<br>Mean (SD)                      | Change from Baseline at Time Point |                               |
|--|-----|-----------------------|--|------------------------------------|-------------------------------|
|  |     |                       |  | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Night 1  |     |                       |  |                                    |                               |
| MK-4305 LD   | 145 | 44.7 (13.7)           | 46.0 (13.4)                                  | 1.2 (7.5)                          | 1.1 (-0.1, 2.3)               |
| MK-4305 HD   | 242 | 46.3 (17.2)           | 47.5 (16.2)                                  | 1.2 (8.0)                          | 1.4 ( 0.5, 2.3)               |
| Placebo  | 246 | 45.2 (12.7)           | 48.2 (12.4)                                  | 3.0 (7.4)                          | 2.9 ( 2.0, 3.8)               |
| Month 1  |     |                       |  |                                    |                               |
| MK-4305 LD   | 135 | 44.9 (13.7)           | 46.6 (14.6)                                  | 1.8 (9.7)                          | 1.6 ( 0.1, 3.2)               |
| MK-4305 HD   | 237 | 46.7 (17.3)           | 47.9 (16.3)                                  | 1.1 (10.9)                         | 1.4 ( 0.2, 2.5)               |
| Placebo  | 239 | 45.4 (13.1)           | 47.9 (13.1)                                  | 2.5 (8.4)                          | 2.4 ( 1.3, 3.5)               |
| Month 3  |     |                       |  |                                    |                               |
| MK-4305 LD   | 132 | 44.6 (13.3)           | 47.7 (13.7)                                  | 3.1 (8.2)                          | 2.7 ( 1.2, 4.1)               |
| MK-4305 HD   | 222 | 47.0 (17.5)           | 48.5 (16.8)                                  | 1.4 (9.7)                          | 1.9 ( 0.8, 3.0)               |
| Placebo  | 224 | 45.4 (12.8)           | 48.9 (13.9)                                  | 3.5 (9.0)                          | 3.3 ( 2.2, 4.5)               |
| Pairwise Comparison  |     |                       | Difference in LS Means (95% CI) <sup>†</sup> |                                    |                               |
| Night 1  |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo   |     |                       | -1.5 (-2.8, -0.2)                            |                                    |                               |
| MK-4305 LD vs. Placebo   |     |                       | -1.8 (-3.3, -0.3)                            |                                    |                               |
| Month 1  |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo   |     |                       | -1.0 (-2.6, 0.6)                             |                                    |                               |
| MK-4305 LD vs. Placebo   |     |                       | -0.8 (-2.7, 1.2)                             |                                    |                               |
| Month 3  |     |                       |  |                                    |                               |
| MK-4305 HD vs. Placebo   |     |                       | -1.5 (-3.1, 0.1)                             |                                    |                               |
| MK-4305 LD vs. Placebo   |     |                       | -0.7 (-2.5, 1.2)                             |                                    |                               |
| † Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |                       |  |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.  |     |                       |  |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.  |     |                       |  |                                    |                               |

(Source: Sponsor's submission ISS Page 637 Table 5.3.5.3.3:249)

In the Phase 2 trial P006, the sponsor reported that the baseline-adjusted number correct on DSST assessment was generally not different between suvorexant doses and placebo, and that the confidence intervals for comparisons between suvorexant and placebo all included 0, except for an isolated case on Day 1 for suvorexant 20 mg. The results for DSST attempted responses by time point were similar to those of the correct responses.

In five Phase 1 trials (P002, P035, P039, P032, P036), the sponsor used DSST, simple reaction time (SRT), and choice reaction time (CRT) to evaluate psychomotor performance 9 to 11 hours post nighttime dose of suvorexant in 125 subjects. Trial P002 tested single doses of suvorexant 10 mg to 100 mg in 22 males aged 18 to 44 years. P035 and P039 were driving trials in non-elderly and elderly subjects, respectively; each trials tested suvorexant LD (15 mg or 20 mg) and suvorexant HD (30

mg or 40 mg). Trials P032 and P036 assessed respiratory safety in subjects with COPD and OSA, respectively; both trials evaluated the suvorexant HD dose. Only the driving trial (PN035) in healthy non-elderly subjects showed a statistically significant decrease in number of correct for DSST (3 item decrease) at 11 hr after a single dose of suvorexant 40 mg compared to placebo. However, the same study failed to show such significant effects on DSST following 8-day consecutive doses of suvorexant.

*Reviewer Note: Although four of five trials failed to show significant treatment effects on DSST (# of correct) with suvorexant compared to placebo, the results of the driving trial PN035 in healthy non-elderly subjects suggests suvorexant 40 mg can impair psychomotor performance after a single dose. Also in the Phase 3 trials, the point estimates of the DSST correct responses suggest that subjects on suvorexant LD or HD have reduced number of correct responses, though not statistically significant, compared to placebo. Despite, the clinical significance of the differences observed is unclear.*

#### Specific AEs Associated with Residual Effects

The sponsor's ISS Table 5.3.5.3.3:256 showed the AEs associated with residual effects. Somnolence had the highest incidence: suvorexant HD 10.7% (138/1291); suvorexant LD 6.7% (33/493); and placebo 3.0% (31/1025). Fatigue occurred less frequently: suvorexant HD 3.8% (49/1291); suvorexant LD 2.2% (11/493); and placebo 1.8% (18/1025).

## 5.4 Supportive Safety Results

### 5.4.1 Common Adverse Events

The sponsor reported a higher incidence of any AEs in suvorexant HD subjects with 51.0% (658/1291) compared to suvorexant LD with 46.5% (229/493) or placebo with 46.6% (478/1025). Similarly, in subjects treated for up to 12 months in the combined phase 3 population, more AEs occurred in the suvorexant HD group (59.9%) than in placebo (52.7%). As shown in the table below, suvorexant HD also had more subjects who discontinued the trial because of AEs within 0-3 months.

**Table 104: Adverse Event Categories in Combined Phase 3 Trial Populations**

| Category                   | Placebo<br>(N=1025) | Suvorexant LD<br>(N=493) | Suvorexant HD<br>(N=1291) |
|----------------------------|---------------------|--------------------------|---------------------------|
| Any Adverse Event<br>(AEs) | 478 (46.6%)         | 229 (46.5%)              | 658 (51.0%)               |

|                                |           |           |           |
|--------------------------------|-----------|-----------|-----------|
| AEs with trial discontinuation | 50 (4.9%) | 15 (3.0%) | 80 (6.2%) |
| Deaths                         | 1 (0.0%)  | 0 (0.0%)  | 1 (0.0%)  |
| Serious AEs                    | 23 (2.2%) | 3 (0.6%)  | 18 (1.4%) |

(Source: Modified from Sponsor's submission ISS Page 138 Table 5.3.5.3.3:13)

The table below summarizes the common AEs, which occurred at an incidence of at least 2% in one or more treatment groups, by system organ class (SOC) and treatment group in the Combined Phase 3 Population within 0-3 Months. In that first 3 months of treatment, subjects on suvorexant HD reported more adverse events in the Nervous system disorders SOC with 21.4% (276/1291) compared to suvorexant LD 16.8% (83/493) or placebo 13.2% (135/1025). Infections and infestations SOC had similar incidences among the treatment groups.

The most common AEs, having incidence 2% or more that occurred more frequently in the suvorexant group than placebo were somnolence and fatigue. Other AEs were slightly more frequent in the suvorexant group: headache, abnormal dreams, dry mouth, and upper respiratory tract infection. Headache events in the first 3 months in the combined Phase 3 population was more frequent from suvorexant treatment, but without a dose-response relationship: 6.6% (85/1291) of suvorexant HD group, 7.3% (36/493) suvorexant LD, and 6.0% (61/1025) placebo. Falls and AEs related to motor vehicle accidents were infrequent and appeared not related to treatment.

**Table 105: Adverse Events (AEs) by System Organ Class (SOC) and AE Preferred Term (PT) ≥ 2% in One or More Treatment Groups in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)**

| <b>System Organ Class (SOC)<br/>AE Preferred Term (PT)</b>  | <b>Placebo<br/>(N=1025)<br/>n (%)</b> | <b>Suvorexant<br/>LD (N=493)<br/>n (%)</b> | <b>Suvorexant<br/>HD (N=1291)<br/>n (%)</b> |
|---|---------------------------------------|--|---|
| <b>Eye disorders</b>  | <b>18 (1.8)</b>                       | <b>11 (2.2)</b>                            | <b>23 (1.8)</b>                             |
| <b>Gastrointestinal disorders</b>                           | <b>82 (8.0)</b>                       | <b>39 (7.9)</b>                            | <b>121 (9.4)</b>                            |
| Diarrhea  | 15 (1.5)                              | 12 (2.4)                                   | 21 (1.6)                                    |
| Dry mouth   | 14 (1.4)                              | 9 (1.8)                                    | 36 (2.8)                                    |
| Nausea  | 16 (1.6)                              | 7 (1.4)                                    | 27 (2.1)                                    |
| <b>General disorders and administration site conditions</b> | <b>46 (4.5)</b>                       | <b>31 (6.3)</b>                            | <b>92 (7.1)</b>                             |
| Fatigue   | 18 (1.8)                              | 11 (2.2)                                   | 49 (3.8)                                    |
| <b>Infections and infestations</b>                          | <b>147 (14.3)</b>                     | <b>70 (14.2)</b>                           | <b>161 (12.5)</b>                           |
| Nasopharyngitis   | 56 (5.5)                              | 26 (5.3)                                   | 49 (3.8)                                    |
| Upper respiratory tract infection                           | 12 (1.2)                              | 8 (1.6)                                    | 28 (2.2)                                    |
| Urinary tract infection                                     | 20 (2.0)                              | 8 (1.6)                                    | 15 (1.2)                                    |

|  |                   |                  |                   |
|--|-------------------|------------------|-------------------|
| <b>Injury, poisoning and procedural complications</b>  | <b>57 (5.6)</b>   | <b>31 (6.3)</b>  | <b>62 (4.8)</b>   |
| Drug administration error                              | 23 (2.2)          | 16 (3.2)         | 25 (1.9)          |
| <b>Investigations</b>                                  | <b>39 (3.8)</b>   | <b>22 (4.5)</b>  | <b>57 (4.4)</b>   |
| <b>Metabolism and nutrition disorders</b>              | <b>9 (0.9)</b>    | <b>4 (0.8)</b>   | <b>31 (2.4)</b>   |
| <b>Musculoskeletal and connective tissue disorders</b> | <b>80 (7.8)</b>   | <b>25 (5.1)</b>  | <b>107 (8.3)</b>  |
| Back pain  | 23 (2.2)          | 7 (1.4)          | 16 (1.2)          |
| <b>Nervous system disorders</b>                        | <b>135 (13.2)</b> | <b>83 (16.8)</b> | <b>276 (21.4)</b> |
| Dizziness  | 29 (2.8)          | 15 (3.0)         | 32 (2.5)          |
| Headache   | 61 (6.0)          | 36 (7.3)         | 85 (6.6)          |
| Somnolence   | 31 (3.0)          | 33 (6.7)         | 138 (10.7)        |
| <b>Psychiatric disorders</b>                           | <b>32 (3.1)</b>   | <b>28 (5.7)</b>  | <b>85 (6.6)</b>   |
| Abnormal dreams  | 10 (1.0)          | 9 (1.8)          | 27 (2.1)          |
| <b>Respiratory, thoracic and mediastinal disorders</b> | <b>28 (2.7)</b>   | <b>18 (3.7)</b>  | <b>48 (3.7)</b>   |
| <b>Skin and subcutaneous tissue disorders</b>          | <b>29 (2.8)</b>   | <b>18 (3.7)</b>  | <b>34 (2.6)</b>   |

(Source: Sponsor's submission ISS Page 146 Table 5.3.5.3.3.:15)

#### Common AEs in 0-6 months

In the 0-6 months Phase 3 trial population (P028 and P029), 49.3% (243/493) of the subjects who received suvorexant LD reported one or more AE; this incidence was comparable to 49.0% (376/767) in the placebo group. Below I summarize the common AEs that occurred with an incidence  $\geq 2\%$  in a treatment group in the 6 months treatment period.

**Table 106: Adverse Events  $\geq 2\%$  of Subjects in Suvorexant Low Dose or Placebo Group in the Combined Phase 3 Population 0-6 Months (P028 and P029)**

| <b>System Organ Class (SOC)</b><br>AE Preferred Term (PT)   | <b>Placebo</b><br>(N = 767)<br>n (%) | <b>Suvorexant LD</b><br>(N = 493)<br>n (%) |
|---|--------------------------------------|--|
| <b>Cardiac disorders</b>                                    | <b>16 (2.1)</b>                      | <b>9 (1.8)</b>                             |
| <b>Eye disorders</b>  | <b>14 (1.8)</b>                      | <b>11 (2.2)</b>                            |
| <b>Gastrointestinal disorders</b>                           | <b>63 (8.2)</b>                      | <b>40 (8.1)</b>                            |
| Diarrhea  | 11 (1.4)                             | 12 (2.4)                                   |
| <b>General disorders and administration site conditions</b> | <b>37 (4.8)</b>                      | <b>32 (6.5)</b>                            |
| Fatigue   | 14 (1.8)                             | 11 (2.2)                                   |
| <b>Infections and infestations</b>                          | <b>128 (16.7)</b>                    | <b>77 (15.6)</b>                           |
| Nasopharyngitis   | 47 (6.1)                             | 29 (5.9)                                   |
| Urinary tract infection                                     | 20 (2.6)                             | 8 (1.6)                                    |



|  |                   |                  |
|--|-------------------|------------------|
| <b>Injury, poisoning and procedural complications</b>  | <b>47 (6.1)</b>   | <b>38 (7.7)</b>  |
| Drug administration error                              | 19 (2.5)          | 20 (4.1)         |
| <b>Investigations</b>                                  | <b>30 (3.9)</b>   | <b>23 (4.7)</b>  |
| <b>Musculoskeletal and connective tissue disorders</b> | <b>62 (8.1)</b>   | <b>30 (6.1)</b>  |
| Back pain  | 22 (2.9)          | 8 (1.6)          |
| <b>Nervous system disorders</b>                        | <b>102 (13.3)</b> | <b>85 (17.2)</b> |
| Dizziness  | 19 (2.5)          | 15 (3.0)         |
| Headache   | 46 (6.0)          | 37 (7.5)         |
| Somnolence   | 26 (3.4)          | 34 (6.9)         |
| <b>Psychiatric disorders</b>                           | <b>21 (2.7)</b>   | <b>30 (6.1)</b>  |
| Abnormal dreams  | 5 (0.7)           | 10 (2.0)         |
| <b>Respiratory, thoracic and mediastinal disorders</b> | <b>21 (2.7)</b>   | <b>19 (3.9)</b>  |
| Cough  | 8 (1.0)           | 10 (2.0)         |
| <b>Skin and subcutaneous tissue disorders</b>          | <b>28 (3.7)</b>   | <b>21 (4.3)</b>  |

(Source: Sponsor's submission ISS Page 740 Table Appendix 5.3.5.3.3:16)

#### Common Adverse Events 0-12months

In the period of 0-12 months, subjects in the suvorexant HD group had a higher incidence of AEs (59.9%, 773/1291) compared to placebo (52.7%, 540/1025). AEs in the Nervous system disorders SOC occurred most frequently and at a higher rate in the suvorexant HD group (24.9%, 322/1291) compared to placebo (15.3%, 157/1025). Somnolence was more frequently reported in subjects treated with suvorexant HD (11.7%, 151/1291) than placebo (3.2%, 33/1025). Fatigue occurred in 4.7% (61/1291) in the suvorexant group compared to 1.9% (19/1025) in placebo. Abnormal dreams in subjects treated for over 3 months occurred in 2.6% (34/1291) of the suvorexant group compared to 1.1% (11/1025) of placebo.

Below I summarize the common AEs that occurred with an incidence  $\geq 2\%$  in a treatment group in the 6 months treatment period.

**Table 107: Adverse Events  $\geq 2\%$  of Subjects in Suvorexant High Dose or Placebo Group in the Combined Phase 3 Population 0-12 Months (P028, P029 and P009)**

| <b>System Organ Class (SOC)</b><br>AE Preferred Term (PT) | <b>Placebo</b><br>(N = 1025)<br>n (%) | <b>Suvorexant HD</b><br>(N = 1291)<br>n (%) |
|---|---------------------------------------|---|
| <b>Cardiac disorders</b>                                  | <b>24 (2.3)</b>                       | <b>26 (2.0)</b>                             |
| <b>Eye disorders</b>                                      | <b>25 (2.4)</b>                       | <b>35 (2.7)</b>                             |
| <b>Gastrointestinal disorders</b>                         | <b>98 (9.6)</b>                       | <b>160 (12.4)</b>                           |
| Diarrhea  | 20 (2.0)                              | 26 (2.0)                                    |
| Dry mouth   | 15 (1.5)                              | 43 (3.3)                                    |
| Nausea  | 20 (2.0)                              | 33 (2.6)                                    |

|   |                   |                   |
|---|-------------------|-------------------|
| <b>General disorders and administration site conditions</b> | <b>53 (5.2)</b>   | <b>120 (9.3)</b>  |
| Fatigue   | 19 (1.9)          | 61 (4.7)          |
| <b>Infections and infestations</b>                          | <b>194 (18.9)</b> | <b>257 (19.9)</b> |
| Influenza   | 16 (1.6)          | 30 (2.3)          |
| Nasopharyngitis   | 67 (6.5)          | 95 (7.4)          |
| Upper respiratory tract infection                           | 19 (1.9)          | 37 (2.9)          |
| Urinary tract infection                                     | 26 (2.5)          | 21 (1.6)          |
| <b>Injury, poisoning and procedural complications</b>       | <b>78 (7.6)</b>   | <b>99 (7.7)</b>   |
| Drug administration error                                   | 31 (3.0)          | 32 (2.5)          |
| <b>Investigations</b>                                       | <b>57 (5.6)</b>   | <b>85 (6.6)</b>   |
| <b>Metabolism and nutrition disorders</b>                   | <b>15 (1.5)</b>   | <b>38 (2.9)</b>   |
| <b>Musculoskeletal and connective tissue disorders</b>      | <b>104 (10.1)</b> | <b>163 (12.6)</b> |
| Arthralgia  | 18 (1.8)          | 29 (2.2)          |
| <b>Musculoskeletal and connective tissue disorders</b>      | <b>104 (10.1)</b> | <b>163 (12.6)</b> |
| Back pain   | 29 (2.8)          | 25 (1.9)          |
| <b>Nervous system disorders</b>                             | <b>157 (15.3)</b> | <b>322 (24.9)</b> |
| Dizziness   | 35 (3.4)          | 41 (3.2)          |
| Headache  | 68 (6.6)          | 101 (7.8)         |
| Somnolence  | 33 (3.2)          | 151 (11.7)        |
| <b>Psychiatric disorders</b>                                | <b>36 (3.5)</b>   | <b>107 (8.3)</b>  |
| Abnormal dreams   | 11 (1.1)          | 34 (2.6)          |
| Nightmare   | 7 (0.7)           | 27 (2.1)          |
| <b>Respiratory, thoracic and mediastinal disorders</b>      | <b>39 (3.8)</b>   | <b>72 (5.6)</b>   |
| <b>Skin and subcutaneous tissue disorders</b>               | <b>37 (3.6)</b>   | <b>42 (3.3)</b>   |
| <b>Vascular disorders</b>                                   | <b>17 (1.7)</b>   | <b>29 (2.2)</b>   |

(Source: Sponsor's submission ISS Page 714 Table Appendix 5.3.5.3.3:13)

#### Common AEs in Phase 2 Dose-Finding Trial

In the Phase 2 trial, more subjects who received suvorexant reported AEs (25.9%, 63/243) compared to placebo (20.1%, 50/249). The increase in the frequency of AEs was particularly evident at suvorexant doses of 40 mg and 80 mg as shown in the table below. Consistent with the Phase 3 trial experience, AEs in the Nervous system disorders SOC occurred most frequently than other categories and were more frequent at higher suvorexant doses. Somnolence was more frequently reported in subjects treated with suvorexant in a dose-related manner. Below I summarize the common AEs that occurred with an incidence  $\geq 2\%$  in one or more treatments group in the Phase 2 trial P006.

**Table 108: Adverse Events ≥ 2% of Subjects by Treatment Group in Phase 2 Population (P006)**

| <b>System Organ Class (SOC)</b><br>AE Preferred Term        | <b>Placebo</b><br>n (%) | <b>Suvorexant</b><br><b>10 mg</b><br>n (%) | <b>Suvorexant</b><br><b>20 mg</b><br>n (%) | <b>Suvorexant</b><br><b>40 mg</b><br>n (%) | <b>Suvorexant</b><br><b>80 mg</b><br>n (%) | <b>Total</b><br><b>Suvorexant</b><br>n (%) |
|---|-------------------------|--|--|--|--|--|
| Subjects in population                                      | 249                     | 62   | 61   | 59   | 61   | 243  |
| Subjects with one or more adverse events                    | 50 (20.1)               | 11 (17.7)                                  | 12 (19.7)                                  | 18 (30.5)                                  | 22 (36.1)                                  | 63 (25.9)                                  |
| <b>Gastrointestinal disorders</b>                           | <b>8 (3.2)</b>          | <b>1 (1.6)</b>                             | <b>1 (1.6)</b>                             | <b>1 (1.7)</b>                             | <b>3 (4.9)</b>                             | <b>6 (2.5)</b>                             |
| <b>General disorders and administration site conditions</b> | <b>4 (1.6)</b>          | <b>0 (0.0)</b>                             | <b>1 (1.6)</b>                             | <b>3 (5.1)</b>                             | <b>2 (3.3)</b>                             | <b>6 (2.5)</b>                             |
| <b>Infections and infestations</b>                          | <b>7 (2.8)</b>          | <b>2 (3.2)</b>                             | <b>3 (4.9)</b>                             | <b>3 (5.1)</b>                             | <b>4 (6.6)</b>                             | <b>12 (4.9)</b>                            |
| Upper respiratory tract infection                           | 1 (0.4)                 | 1 (1.6)                                    | 2 (3.3)                                    | 0 (0.0)                                    | 2 (3.3)                                    | 5 (2.1)                                    |
| Urinary tract infection                                     | 2 (0.8)                 | 0 (0.0)                                    | 0 (0.0)                                    | 3 (5.1)                                    | 2 (3.3)                                    | 5 (2.1)                                    |
| <b>Investigations</b>                                       | <b>6 (2.4)</b>          | <b>5 (8.1)</b>                             | <b>1 (1.6)</b>                             | <b>3 (5.1)</b>                             | <b>2 (3.3)</b>                             | <b>11 (4.5)</b>                            |
| Alanine aminotransferase increased                          | 1 (0.4)                 | 1 (1.6)                                    | 0 (0.0)                                    | 2 (3.4)                                    | 1 (1.6)                                    | 4 (1.6)                                    |
| Blood creatine phosphokinase increased                      | 2 (0.8)                 | 0 (0.0)                                    | 0 (0.0)                                    | 2 (3.4)                                    | 0 (0.0)                                    | 2 (0.8)                                    |
| <b>Musculoskeletal and connective tissue disorders</b>      | <b>5 (2.0)</b>          | <b>1 (1.6)</b>                             | <b>0 (0.0)</b>                             | <b>4 (6.8)</b>                             | <b>1 (1.6)</b>                             | <b>6 (2.5)</b>                             |
| Muscular weakness   | 0 (0.0)                 | 0 (0.0)                                    | 0 (0.0)                                    | 2 (3.4)                                    | 1 (1.6)                                    | 3 (1.2)                                    |
| <b>Nervous system disorders</b>                             | <b>9 (3.6)</b>          | <b>2 (3.2)</b>                             | <b>5 (8.2)</b>                             | <b>9 (15.3)</b>                            | <b>12 (19.7)</b>                           | <b>28 (11.5)</b>                           |
| Dizziness   | 0 (0.0)                 | 0 (0.0)                                    | 1 (1.6)                                    | 0 (0.0)                                    | 3 (4.9)                                    | 4 (1.6)                                    |
| Headache  | 6 (2.4)                 | 0 (0.0)                                    | 1 (1.6)                                    | 3 (5.1)                                    | 3 (4.9)                                    | 7 (2.9)                                    |
| Sedation  | 1 (0.4)                 | 0 (0.0)                                    | 0 (0.0)                                    | 0 (0.0)                                    | 2 (3.3)                                    | 2 (0.8)                                    |
| Somnolence  | 1 (0.4)                 | 1 (1.6)                                    | 3 (4.9)                                    | 6 (10.2)                                   | 7 (11.5)                                   | 17 (7.0)                                   |
| <b>Psychiatric disorders</b>                                | <b>3 (1.2)</b>          | <b>1 (1.6)</b>                             | <b>0 (0.0)</b>                             | <b>2 (3.4)</b>                             | <b>5 (8.2)</b>                             | <b>8 (3.3)</b>                             |
| Abnormal dreams   | 2 (0.8)                 | 1 (1.6)                                    | 0 (0.0)                                    | 0 (0.0)                                    | 3 (4.9)                                    | 4 (1.6)                                    |
| <b>Respiratory, thoracic and mediastinal disorders</b>      | <b>5 (2.0)</b>          | <b>0 (0.0)</b>                             | <b>0 (0.0)</b>                             | <b>2 (3.4)</b>                             | <b>2 (3.3)</b>                             | <b>4 (1.6)</b>                             |
| Oropharyngeal pain  | 2 (0.8)                 | 0 (0.0)                                    | 0 (0.0)                                    | 0 (0.0)                                    | 2 (3.3)                                    | 2 (0.8)                                    |

(Source: Sponsor's submission ISS Page 787 Table Appendix 5.3.5.3.3:24)

## Drug-Related Adverse Events

In the Phase 3 trials 0-3 months, a higher incidence of drug-related AEs occurred in subjects who received suvorexant HD (25.5%, 329/1291) compared to those who received suvorexant LD (22.1%, 109/493) or placebo (15.0%, 154/1025). Below I summarize occurrence of the dose-related AEs.

**Table 109: Drug-related AEs  $\geq$  2% in One or More Treatment Groups in the Combined Phase 3 Population 0-3 Months (P028, P029, and P009)**

| <b>System Organ Class (SOC)</b><br>AE Preferred Term (PT)   | <b>Placebo</b><br>(N = 1,025)<br>n (%) | <b>Suvorexant LD</b><br>(N = 493)<br>n (%) | <b>Suvorexant HD</b><br>(N = 1,291)<br>n (%) |
|---|--|--|--|
| <b>Gastrointestinal disorders</b>                           | <b>31 (3.0)</b>                        | <b>17 (3.4)</b>                            | <b>65 (5.0)</b>                              |
| Dry mouth   | 11 (1.1)                               | 8 (1.6)                                    | 32 (2.5)                                     |
| <b>General disorders and administration site conditions</b> | <b>24 (2.3)</b>                        | <b>20 (4.1)</b>                            | <b>64 (5.0)</b>                              |
| Fatigue   | 13 (1.3)                               | 11 (2.2)                                   | 40 (3.1)                                     |
| <b>Investigations</b>                                       | <b>14 (1.4)</b>                        | <b>12 (2.4)</b>                            | <b>22 (1.7)</b>                              |
| <b>Nervous system disorders</b>                             | <b>82 (8.0)</b>                        | <b>58 (11.8)</b>                           | <b>200 (15.5)</b>                            |
| Headache  | 31 (3.0)                               | 21 (4.3)                                   | 36 (2.8)                                     |
| Somnolence  | 26 (2.5)                               | 30 (6.1)                                   | 126 (9.8)                                    |
| <b>Psychiatric disorders</b>                                | <b>25 (2.4)</b>                        | <b>19 (3.9)</b>                            | <b>60 (4.6)</b>                              |

(Source: Sponsor's submission ISS Page 156 Table 5.3.5.3.3.:17)

## Drug-related AEs during Long-term Treatment

In the 0-6 months Phase 3 trial population (P028 and P029), AEs with incidence  $\geq$ 1% in a treatment group occurred more frequently in subjects who received suvorexant LD (22.5%, 111/493) compared to those who received placebo (15.6%, 120/767). Below I summarize the analyses of drug-related AEs covering 6 months treatment.

**Table 110: Drug-related AEs  $\geq$  1% in One or More Treatment Groups in the Combined Phase 3 Population 0-6 Months (P028 and P029)**

| <b>System Organ Class (SOC)</b><br>AE Preferred Term (PT) | <b>Placebo</b><br>(N = 767)<br>n (%) | <b>Suvorexant LD</b><br>(N = 493)<br>n (%) | <b>Suvorexant-Placebo</b><br><b>Difference in %</b> |
|---|--------------------------------------|--|---|
|   |                                      |  | <b>Estimate (95% CI)</b>                            |
| <b>Gastrointestinal disorders</b>                         | <b>19 (2.5)</b>                      | <b>17 (3.4)</b>                            | <b>1.0 (-0.9, 3.2)</b>                              |
| Dry mouth   | 8 (1.0)                              | 8 (1.6)                                    | 0.6 (-0.7, 2.2)                                     |
| Nausea  | 8 (1.0)                              | 6 (1.2)                                    | 0.2 (-1.0, 1.7)                                     |

|   |                 |                  |                         |
|---|-----------------|------------------|-------------------------|
| <b>General disorders and administration site conditions</b> | <b>19 (2.5)</b> | <b>20 (4.1)</b>  | <b>1.6 (-0.4, 3.9)</b>  |
| Fatigue   | 11 (1.4)        | 11 (2.2)         | 0.8 (-0.7, 2.6)         |
| <b>Investigations</b>                                       | <b>11 (1.4)</b> | <b>12 (2.4)</b>  | <b>1.0 (-0.5, 2.9)</b>  |
| <b>Musculoskeletal and connective tissue disorders</b>      | <b>8 (1.0)</b>  | <b>5 (1.0)</b>   | <b>-0.0 (-1.2, 1.4)</b> |
| <b>Nervous system disorders</b>                             | <b>65 (8.5)</b> | <b>59 (12.0)</b> | <b>3.5 (0.1, 7.1)</b>   |
| Dizziness   | 10 (1.3)        | 8 (1.6)          | 0.3 (-1.0, 2.0)         |
| Headache  | 24 (3.1)        | 21 (4.3)         | 1.1 (-0.9, 3.5)         |
| Somnolence  | 24 (3.1)        | 31 (6.3)         | 3.2 (0.8, 5.9)          |
| <b>Psychiatric disorders</b>                                | <b>19 (2.5)</b> | <b>20 (4.1)</b>  | <b>1.6 (-0.4, 3.9)</b>  |
| Abnormal dreams   | 5 (0.7)         | 8 (1.6)          | 1.0 (-0.2, 2.6)         |
| Nightmare   | 4 (0.5)         | 6 (1.2)          | 0.7 (-0.3, 2.2)         |
| <b>Skin and subcutaneous tissue disorders</b>               | <b>6 (0.8)</b>  | <b>8 (1.6)</b>   | <b>0.8 (-0.3, 2.5)</b>  |

(Source: Sponsor's submission ISS Page 822 Table 5.3.5.3.3.:33)

In the 12 months Combined Phase 3 Trial Population (P028, P029 and P009), subjects who received suvorexant HD reported more drug-related AEs with an incidence  $\geq 1\%$  in at least one of the treatment groups compared to subjects who received placebo: 28.5% (368/1291) in suvorexant HD compared to 16.9% (173/1025) in placebo. Again, nervous system disorders accounted for the most frequent drug-related AEs, as shown in the table below. Dizziness, headache, and somnolence occurred at incidences of over 2%; and, somnolence occurred more frequently in the suvorexant HD group (10.5%, 136/1291) than in the placebo group (2.7%, 28/1025).

**Table 111: Drug-related AEs  $\geq 1\%$  in One or More Treatment Groups in the Combined Phase 3 Population 0-12 Months (P028, P029 and P009)**

| <b>System Organ Class (SOC)<br/>AE Preferred Term (PT)</b>  | <b>Placebo<br/>(N = 1025)<br/>n (%)</b> | <b>Suvorexant HD<br/>(N = 1291)<br/>n (%)</b> | <b>Suvorexant-Placebo<br/>Difference in %</b> |
|---|---|---|---|
|   |   |   | <b>Estimate (95% CI)</b>                      |
| <b>Gastrointestinal disorders</b>                           | <b>33 (3.2)</b>                         | <b>73 (5.7)</b>                               | <b>1.9 (0.1, 3.6)</b>                         |
| Dry mouth   | 12 (1.2)                                | 37 (2.9)                                      | 1.5 (0.3, 2.7)                                |
| Nausea  | 11 (1.1)                                | 18 (1.4)                                      | 0.3 (-0.7, 1.2)                               |
| <b>General disorders and administration site conditions</b> | <b>26 (2.5)</b>                         | <b>72 (5.6)</b>                               | <b>3.0 (1.4, 4.6)</b>                         |
| Fatigue   | 14 (1.4)                                | 45 (3.5)                                      | 2.1 (0.8, 3.4)                                |
| <b>Investigations</b>                                       | <b>19 (1.9)</b>                         | <b>30 (2.3)</b>                               | <b>0.3 (-1.0, 1.5)</b>                        |
| <b>Metabolism and nutrition disorders</b>                   | <b>5 (0.5)</b>                          | <b>16 (1.2)</b>                               | <b>0.8 (-0.0, 1.6)</b>                        |

|  |                 |                   |                        |
|--|-----------------|-------------------|------------------------|
| <b>Musculoskeletal and connective tissue disorders</b> | <b>10 (1.0)</b> | <b>22 (1.7)</b>   | <b>0.7 (-0.3, 1.7)</b> |
| <b>Nervous system disorders</b>                        | <b>90 (8.8)</b> | <b>222 (17.2)</b> | <b>8.0 (5.2, 10.7)</b> |
| Dizziness  | 20 (2.0)        | 24 (1.9)          | -0.4 (-1.7, 0.7)       |
| Headache   | 32 (3.1)        | 42 (3.3)          | 0.1 (-1.4, 1.6)        |
| Somnolence   | 28 (2.7)        | 136 (10.5)        | 7.8 (5.9, 9.8)         |
| <b>Psychiatric disorders</b>                           | <b>27 (2.6)</b> | <b>71 (5.5)</b>   | <b>2.6 (0.9, 4.2)</b>  |
| Abnormal dreams  | 10 (1.0)        | 28 (2.2)          | 1.0 (-0.1, 2.1)        |
| Nightmare  | 6 (0.6)         | 21 (1.6)          | 1.0 (0.1, 1.9)         |
| <b>Skin and subcutaneous tissue disorders</b>          | <b>8 (0.8)</b>  | <b>13 (1.0)</b>   | <b>0.2 (-0.7, 1.0)</b> |

(Source: Sponsor's submission ISS Page 811 Table 5.3.5.3.3.:30)

#### Drug-Related Adverse Events in Phase 2 Dose-Finding Trial P006

The Phase 2 trial reported drug-related AEs in the Nervous system disorders SOC more frequently than other systems. Below I summarize dose-related occurrence of the AEs from the Phase 2 trial P006.

**Table 112: Suvorexant-Related Adverse Events with Incidence > 2% for One or More Treatments among All Treated Subjects in Treatment Periods 1 and 2 of Trial P006**

| <b>Category</b>   | <b>Placebo<br/>N (%)</b> | <b>Suvorexant<br/>10 mg<br/>N (%)</b> | <b>Suvorexant<br/>20 mg<br/>N (%)</b> | <b>Suvorexant<br/>40 mg<br/>N (%)</b> | <b>Suvorexant<br/>80 mg<br/>N (%)</b> | <b>Total<br/>Suvorexant<br/>N (%)</b> |
|---|--------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Subjects  | 249                      | 62                                    | 61                                    | 59                                    | 61                                    | 243                                   |
| Subjects with one or more adverse events                    | 17 (6.8)                 | 3 (4.8)                               | 4 (6.6)                               | 13 (22.0)                             | 14 (23.0)                             | 34 (14.0)                             |
| <b>General disorders and administration site conditions</b> | <b>1 (0.4)</b>           | <b>0 (0.0)</b>                        | <b>0 (0.0)</b>                        | <b>2 (3.4)</b>                        | <b>2 (3.3)</b>                        | <b>4 (1.6)</b>                        |
| <b>Musculoskeletal and connective tissue disorders</b>      | <b>3 (1.2)</b>           | <b>0 (0.0)</b>                        | <b>0 (0.0)</b>                        | <b>3 (5.1)</b>                        | <b>1 (1.6)</b>                        | <b>4 (1.6)</b>                        |
| Muscular weakness   | 0 (0.0)                  | 0 (0.0)                               | 0 (0.0)                               | 2 (3.4)                               | 1 (1.6)                               | 3 (1.2)                               |
| <b>Nervous system disorders</b>                             | <b>5 (2.0)</b>           | <b>1 (1.6)</b>                        | <b>3 (4.9)</b>                        | <b>10 (16.9)</b>                      | <b>10 (16.4)</b>                      | <b>24 (9.9)</b>                       |
| Headache  | 3 (1.2)                  | 0 (0.0)                               | 0 (0.0)                               | 3 (5.1)                               | 1 (1.6)                               | 4 (1.6)                               |
| Sedation  | 0 (0.0)                  | 0 (0.0)                               | 0 (0.0)                               | 0 (0.0)                               | 2 (3.3)                               | 2 (0.8)                               |
| Somnolence  | 1 (0.4)                  | 0 (0.0)                               | 3 (4.9)                               | 7 (11.9)                              | 6 (9.8)                               | 16 (6.6)                              |
| <b>Psychiatric disorders</b>                                | <b>3 (1.2)</b>           | <b>1 (1.6)</b>                        | <b>0 (0.0)</b>                        | <b>2 (3.4)</b>                        | <b>5 (8.2)</b>                        | <b>8 (3.3)</b>                        |
| Abnormal dreams   | 2 (0.8)                  | 1 (1.6)                               | 0 (0.0)                               | 0 (0.0)                               | 3 (4.9)                               | 4 (1.6)                               |

(Source: Modified from Sponsor's submission CSR P006 Page 158 Table 12-8)

## 5.4.2 Laboratory Findings

The sponsor evaluated laboratory results using mean changes from baseline over time and values that met predetermined criteria for change relative to normal range. The laboratory results in hematology and chemistry categories are summarized as follows:

### Hematology

The mean changes in hematological parameters from baseline to Month 3 were generally comparable among the treatment groups. The table below shows a summary of the results.

**Table 113: Hematology Mean Changes from Baseline to Month 3 in Combined Phase 3 Population 0-3 months (P028, P029, and P009)**

|                                       |               | n    | Baseline     |              | Value        |               | Change from Baseline |               |
|---------------------------------------|---------------|------|--------------|--------------|--------------|---------------|----------------------|---------------|
| Visit                                 | Treatment     |      | Mean (SD)    | [ Min, Max ] | Mean (SD)    | [ Min, Max ]  | Mean (SD)            | [Min, Max]    |
| Basophils (10 <sup>3</sup> /microL)   |               |      |              |              |              |               |                      |               |
| Month 3                               | Suvorexant LD | 424  | 0.00 (0.02)  | [0.0, 0.2]   | 0.00 (0.02)  | [0.0, 0.1]    | -0.00 (0.03)         | [-0.2, 0.1]   |
|                                       | Suvorexant HD | 1118 | 0.01 (0.02)  | [0.0, 0.2]   | 0.01 (0.03)  | [0.0, 0.2]    | 0.00 (0.03)          | [-0.2, 0.1]   |
|                                       | Placebo       | 875  | 0.01 (0.02)  | [0.0, 0.1]   | 0.01 (0.02)  | [0.0, 0.2]    | -0.00 (0.03)         | [-0.1, 0.2]   |
| Eosinophils (10 <sup>3</sup> /microL) |               |      |              |              |              |               |                      |               |
| Month 3                               | Suvorexant LD | 424  | 0.17 (0.14)  | [0.0, 1.4]   | 0.18 (0.14)  | [0.0, 1.3]    | 0.01 (0.12)          | [-1.2, 0.5]   |
|                                       | Suvorexant HD | 1118 | 0.17 (0.14)  | [0.0, 1.2]   | 0.18 (0.17)  | [0.0, 2.5]    | 0.01 (0.13)          | [-0.5, 2.4]   |
|                                       | Placebo       | 875  | 0.19 (0.18)  | [0.0, 2.9]   | 0.19 (0.17)  | [0.0, 1.8]    | 0.00 (0.13)          | [-1.1, 1.1]   |
| Hematocrit (%)                        |               |      |              |              |              |               |                      |               |
| Month 3                               | Suvorexant LD | 424  | 41.73 (4.33) | [27.3, 80.3] | 41.31 (4.01) | [25.6, 54.7]  | -0.42 (3.06)         | [-43.7, 6.1]  |
|                                       | Suvorexant HD | 1119 | 41.61 (3.88) | [29.3, 60.9] | 41.45 (3.92) | [27.5, 55.5]  | -0.16 (2.25)         | [-15.8, 13.6] |
|                                       | Placebo       | 878  | 41.64 (3.80) | [31.1, 56.5] | 41.57 (3.98) | [ 23.4, 57.5] | -0.07 (2.50)         | [-13.2, 20.3] |
| Hemoglobin (g/L)                      |               |      |              |              |              |               |                      |               |
| Month 3                               | Suvorexant LD | 424  | 13.96 (1.52) | [7.7, 26.4]  | 13.78 (1.42) | [7.1, 18.1]   | -0.18 (0.96)         | [-13.7, 2.1]  |
|                                       | Suvorexant HD | 1119 | 13.98 (1.33) | [9.0, 20.1]  | 13.86 (1.33) | [8.4, 18.0]   | -0.12 (0.70)         | [-5.1, 4.8]   |
|                                       | Placebo       | 878  | 13.95 (1.30) | [10.1, 18.0] | 13.88 (1.36) | [8.0, 19.3]   | -0.07 (0.77)         | [-3.4, 6.5]   |
| Lymphocytes (10 <sup>3</sup> /microL) |               |      |              |              |              |               |                      |               |
| Month 3                               | Suvorexant LD | 424  | 2.11 (0.67)  | [0.7, 4.5]   | 2.09 (0.67)  | [0.5, 4.2]    | -0.02 (0.46)         | [-2.2, 1.9]   |
|                                       | Suvorexant HD | 1118 | 1.99 (0.65)  | [0.7, 6.3]   | 1.98 (0.65)  | [0.6, 6.9]    | -0.02 (0.48)         | [-2.4, 3.0]   |
|                                       | Placebo       | 875  | 2.09 (0.70)  | [0.7, 5.5]   | 2.08 (0.70)  | [0.5, 6.3]    | -0.02 (0.54)         | [-2.9, 4.4]   |
| Monocytes (10 <sup>3</sup> /microL)   |               |      |              |              |              |               |                      |               |
| Month 3                               | Suvorexant LD | 424  | 0.40 (0.24)  | [0.0, 3.2]   | 0.40 (0.21)  | [0.0, 3.1]    | 0.01 (0.24)          | [-2.6, 2.5]   |
|                                       | Suvorexant HD | 1118 | 0.41 (0.18)  | [0.0, 1.5]   | 0.39 (0.16)  | [0.0, 1.2]    | -0.02 (0.16)         | [-0.8, 0.9]   |
|                                       | Placebo       | 875  | 0.40 (0.17)  | [0.0, 1.5]   | 0.40 (0.17)  | [0.0, 1.3]    | 0.00 (0.16)          | [-0.6, 0.8]   |

| Neutrophils (10 <sup>3</sup> /microL) |               |      |               |             |              |             |              |             |
|---------------------------------------|---------------|------|---------------|-------------|--------------|-------------|--------------|-------------|
| Month 3                               | Suvorexant LD | 424  | 3.50 (1.27)   | [0.2, 8.1]  | 3.47 (1.39)  | [0.4, 10.8] | -0.04 (1.23) | [-6.2, 6.8] |
|                                       | Suvorexant HD | 1118 | 3.66 (1.34)   | [0.4, 11.6] | 3.54 (1.31)  | [0.4, 12.4] | -0.12 (1.20) | [-7.0, 6.2] |
|                                       | Placebo       | 875  | 3.58 (1.37)   | [0.4, 9.3]  | 3.58 (1.39)  | [0.1, 11.1] | -0.00 (1.18) | [-6.5, 7.6] |
| Platelets (10 <sup>3</sup> /microL)   |               |      |               |             |              |             |              |             |
| Month 3                               | Suvorexant LD | 419  | 232.2 (58.1)  | [67, 551]   | 230.9 (59.5) | [41, 571]   | -1.2 (33.6)  | [-224, 222] |
|                                       | Suvorexant HD | 1085 | 228.8 (54.4)  | [111, 621]  | 226.3 (54.6) | [98, 795]   | -2.5 (27.9)  | [-128, 174] |
|                                       | Placebo       | 850  | 233.9 ( 54.0) | [101, 586]  | 233.5 (55.0) | [101, 571]  | -0.4 (31.3)  | [-204, 162] |
| Leukocytes (10 <sup>3</sup> /microL)  |               |      |               |             |              |             |              |             |
| Month 3                               | Suvorexant LD | 424  | 6.21 (1.63)   | [2.3, 11.5] | 6.17 (1.72)  | [2.4, 13.3] | -0.04 (1.33) | [-5.6, 6.3] |
|                                       | Suvorexant HD | 1119 | 6.26 (1.62)   | [2.8, 15.7] | 6.12 (1.62)  | [2.5, 17.0] | -0.14 (1.28) | [-6.3, 5.6] |
|                                       | Placebo       | 878  | 6.30 (1.75)   | [2.2, 14.4] | 6.28 (1.78)  | [2.3, 16.1] | -0.02 (1.27) | [-6.3, 7.4] |

(Source: Sponsor's submission ISS Page 942 Table Appendix 5.3.5.3.3:48)

## Chemistry

The sponsor observed no clinically significant mean changes for the chemistry parameters in the different treatment groups from baseline to Month 3. The table below shows a summary of the results.

**Table 114: Chemistry Mean Changes from Baseline to Month 3 in Combined Phase 3 Population 0-3 months (P028, P029, and P009)**

|                            |               | n    | Baseline    |              | Value       |              | Change from Baseline |              |
|----------------------------|---------------|------|-------------|--------------|-------------|--------------|----------------------|--------------|
| Visit                      | Treatment     |      | Mean (SD)   | [ Min, Max ] | Mean (SD)   | [ Min, Max ] | Mean (SD)            | [ Min, Max ] |
| Albumin (g/dL)             |               |      |             |              |             |              |                      |              |
| Month 3                    | Suvorexant LD | 437  | 4.40 (0.28) | [ 3.5, 5.3]  | 4.36 (0.30) | [3.3, 5.2]   | -0.04 (0.28)         | [-0.8, 0.8]  |
|                            | Suvorexant HD | 1140 | 4.42 (0.27) | [ 3.3, 5.6]  | 4.36 (0.27) | [3.4, 5.3]   | -0.06 (0.26)         | [-1.1, 0.9]  |
|                            | Placebo       | 900  | 4.41 (0.27) | [ 3.4, 5.4]  | 4.37 (0.28) | [3.2, 5.6]   | -0.04 (0.26)         | [-1.2, 1.2]  |
| Alkaline Phosphatase (U/L) |               |      |             |              |             |              |                      |              |
| Month 3                    | Suvorexant LD | 436  | 69.4 (21.9) | [15, 239]    | 70.4 (23.2) | [25, 282]    | 1.0 (11.5)           | [-47, 108]   |
|                            | Suvorexant HD | 1134 | 70.7 (21.7) | [11, 309]    | 69.6 (20.1) | [12, 190]    | -1.2 (11.9)          | [-248, 73]   |
|                            | Placebo       | 899  | 71.0 (21.0) | [26, 166]    | 71.2 (22.0) | [25, 238]    | 0.1 (10.8)           | [-64, 90]    |
| ALT (U/L)                  |               |      |             |              |             |              |                      |              |
| Month 3                    | Suvorexant LD | 436  | 19.6 (9.7)  | [6, 66]      | 19.1 (10.5) | [4, 88]      | -0.5 ( 8.7)          | [-38, 62]    |
|                            | Suvorexant HD | 1139 | 20.6 (10.3) | [4, 95]      | 20.0 (13.5) | [4, 246]     | -0.6 (11.9)          | [-78, 216]   |
|                            | Placebo       | 900  | 20.3 (10.1) | [4, 88]      | 20.8 (11.5) | [4, 100]     | 0.5 ( 8.7)           | [-51, 65]    |
| Amylase (U/L)              |               |      |             |              |             |              |                      |              |
| Month 1                    | Suvorexant HD | 421  | 73.4 (30.4) | [25, 243]    | 72.5 (36.5) | [14, 503]    | -0.9 (26.0)          | [-67, 445]   |
|                            | Placebo       | 207  | 71.4 (34.0) | [21, 349]    | 68.1 (37.4) | [7, 416]     | -3.3 (16.3)          | [-73, 67]    |
| AST (U/L)                  |               |      |             |              |             |              |                      |              |



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NDA #204569  
Suvorexant, MK-4305

|   |               |      |               |              |               |              |                |               |
|---|---------------|------|---------------|--------------|---------------|--------------|----------------|---------------|
| Month 3   | Suvorexant LD | 437  | 21.5 (6.9)    | [9, 64]      | 21.3 (7.5)    | [10, 63]     | -0.3 (6.4)     | [-23, 38]     |
|   | Suvorexant HD | 1140 | 21.7 (6.6)    | [8, 78]      | 21.6 (8.8)    | [9, 191]     | -0.1 (8.4)     | [-54, 167]    |
|   | Placebo       | 900  | 21.7 (6.4)    | [7, 55]      | 22.1 (7.5)    | [7, 74]      | 0.3 (6.3)      | [-30, 53]     |
| <b>Bilirubin (mg/dL)</b>                        |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 0.536 (0.263) | [0.16, 2.53] | 0.513 (0.254) | [0.14, 2.03] | -0.022 (0.193) | [-1.09, 1.10] |
|   | Suvorexant HD | 1140 | 0.518 (0.253) | [0.11, 1.99] | 0.506 (0.247) | [0.12, 2.35] | -0.012 (0.197) | [-1.21, 1.57] |
|   | Placebo       | 900  | 0.519 (0.251) | [0.12, 1.92] | 0.507 (0.251) | [0.14, 1.94] | -0.012 (0.185) | [-0.94, 0.80] |
| <b>Blood Urea Nitrogen (mg/dL)</b>              |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 14.8 (4.3)    | [6, 32]      | 15.1 (4.6)    | [6, 42]      | 0.3 (3.7)      | [-14, 20]     |
|   | Suvorexant HD | 1140 | 15.8 (4.6)    | [4, 35]      | 16.0 (4.7)    | [4, 48]      | 0.2 (3.6)      | [-14, 21]     |
|   | Placebo       | 900  | 15.3 (4.7)    | [3, 40]      | 15.7 (5.2)    | [4, 59]      | 0.4 (3.9)      | [-14, 39]     |
| <b>Calcium (mg/dL)</b>                          |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 436  | 9.47 (0.41)   | [8.1, 11.2]  | 9.38 (0.41)   | [8.4, 11.8]  | -0.08 (0.41)   | [-1.4, 2.4]   |
|   | Suvorexant HD | 1133 | 9.56 (0.45)   | [5.4, 11.7]  | 9.44 (0.45)   | [6.2, 12.6]  | -0.12 (0.40)   | [-2.1, 2.4]   |
|   | Placebo       | 899  | 9.53 (0.42)   | [7.4, 11.3]  | 9.47 (0.44)   | [6.8, 12.1]  | -0.06 (0.41)   | [-3.1, 1.8]   |
| <b>Creatine Kinase (U/L)</b>                    |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 109.8 (83.7)  | [6, 672]     | 107.4 (109.6) | [19, 1921]   | -2.4 (105.7)   | [-510, 1673]  |
|   | Suvorexant HD | 1140 | 115.8 (128.2) | [20, 3395]   | 112.8 (88.8)  | [13, 1383]   | -3.0 (95.9)    | [-2012, 753]  |
|   | Placebo       | 900  | 114.0 (111.7) | [19, 1576]   | 113.5 (86.4)  | [18, 863]    | -0.5 (85.1)    | [-1184, 772]  |
| <b>Chloride (mmol/L)</b>                        |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 436  | 103.6 (2.4)   | [95, 112]    | 103.7 (2.5)   | [95, 111]    | 0.1 (2.4)      | [-6, 7]       |
|   | Suvorexant HD | 1136 | 103.4 (2.5)   | [90, 111]    | 103.6 (2.4)   | [88, 111]    | 0.2 (2.3)      | [-9, 9]       |
|   | Placebo       | 899  | 103.2 (2.5)   | [92, 110]    | 103.5 (2.4)   | [94, 112]    | 0.3 (2.4)      | [-8, 12]      |
| <b>Creatinine Clearance Estimation (mL/min)</b> |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 82.3 (25.0)   | [27, 201]    | 82.9 (25.9)   | [23, 201]    | 0.6 (9.6)      | [-40, 44]     |
|   | Suvorexant HD | 1140 | 82.8 (26.5)   | [33, 242]    | 82.4 (26.9)   | [31, 218]    | -0.4 (10.3)    | [-46, 56]     |
|   | Placebo       | 899  | 82.2 (25.8)   | [31, 214]    | 81.9 (26.3)   | 20, 224]     | -0.4 (10.4)    | [-79, 100]    |
| <b>Creatinine (mg/dL)</b>                       |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 0.92 (0.18)   | [0.6, 1.7]   | 0.92 (0.19)   | [0.6, 1.7]   | 0.00 (0.10)    | [-0.3, 0.6]   |
|   | Suvorexant HD | 1140 | 0.94 (0.19)   | [0.5, 1.9]   | 0.95 (0.19)   | [0.5, 1.8]   | 0.01 (0.10)    | [-0.4, 0.6]   |
|   | Placebo       | 899  | 0.93 (0.18)   | [0.5, 2.0]   | 0.94 (0.21)   | [0.4, 3.0]   | 0.01 (0.13)    | [-0.4, 2.0]   |
| <b>Glucose (mg/dL)</b>                          |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 98.2 (19.3)   | [45, 199]    | 97.9 (21.1)   | [46, 225]    | -0.3 (17.8)    | [-79, 80]     |
|   | Suvorexant HD | 1140 | 98.6 (24.0)   | [47, 374]    | 99.6 (26.7)   | [43, 402]    | 1.0 (21.3)     | [-189, 170]   |
|   | Placebo       | 897  | 97.5 (19.4)   | [50, 293]    | 99.6 (24.4)   | [20, 355]    | 2.1 (22.3)     | [-119, 275]   |
| <b>Bicarbonate (mEq/L)</b>                      |               |      |               |              |               |              |                |               |
| Month 3   | Suvorexant LD | 437  | 26.2 (2.5)    | [16, 33]     | 26.6 (2.7)    | [15, 34]     | 0.5 (2.7)      | [-16, 8]      |
|   | Suvorexant HD | 1138 | 26.2 (2.4)    | [16, 34]     | 26.4 (2.4)    | [17, 37]     | 0.2 (2.6)      | [-10, 18]     |
|   | Placebo       | 899  | 26.3 (2.4)    | [17, 35]     | 26.5 (2.5)    | [18, 33]     | 0.2 (2.5)      | [-11, 9]      |
| <b>Potassium (mEq/L)</b>                        |               |      |               |              |               |              |                |               |

|                                     |               |      |              |             |              |             |              |             |
|-------------------------------------|---------------|------|--------------|-------------|--------------|-------------|--------------|-------------|
| Month 3                             | Suvorexant LD | 436  | 4.22 (0.42)  | [ 2.9, 5.9] | 4.24 (0.40)  | [2.5, 5.5]  | 0.02 (0.42)  | [-1.5, 1.8] |
|                                     | Suvorexant HD | 1132 | 4.26 (0.41)  | [ 2.7, 5.9] | 4.27 (0.40)  | [3.1, 6.1]  | 0.00 (0.40)  | [-1.5, 1.4] |
|                                     | Placebo       | 899  | 4.23 (0.41)  | [ 2.6, 6.1] | 4.26 (0.40)  | [3.0, 6.0]  | 0.02 (0.43)  | [-2.2, 1.6] |
| <b>Lactose Dehydrogenase (U/L)</b>  |               |      |              |             |              |             |              |             |
| Month 3                             | Suvorexant LD | 436  | 165.1 (34.9) | [65, 357]   | 162.2 (41.4) | [62, 563]   | -2.9 (33.2)  | [-165, 300] |
|                                     | Suvorexant HD | 1139 | 167.0 (34.3) | [72, 447]   | 165.2 (34.5) | [62, 423]   | -1.8 (25.3)  | [-136, 166] |
|                                     | Placebo       | 898  | 165.5 (34.3) | [64, 382]   | 165.0 (33.9) | [68, 400]   | -0.5 (28.7)  | [-264, 251] |
| <b>Triacylglycerol Lipase (U/L)</b> |               |      |              |             |              |             |              |             |
| Month 1                             | Suvorexant HD | 421  | 41.8 (18.2)  | [15, 160]   | 40.6 (21.6)  | [13, 223]   | -1.1 (19.1)  | [-122, 137] |
|                                     | Placebo       | 207  | 41.9 (21.5)  | [14, 211]   | 39.8 (18.9)  | [8, 142]    | -2.1 (18.2)  | [-152, 97]  |
| <b>Magnesium (mEq/L)</b>            |               |      |              |             |              |             |              |             |
| Month 3                             | Suvorexant LD | 436  | 1.74 (0.13)  | [1.2, 2.3]  | 1.73 (0.13)  | [1.4, 2.1]  | -0.01 (0.12) | [-0.5, 0.4] |
|                                     | Suvorexant HD | 1133 | 1.78 (0.15)  | [1.1, 2.3]  | 1.73 (0.15)  | [1.1, 2.2]  | -0.05 (0.13) | [-0.6, 0.6] |
|                                     | Placebo       | 899  | 1.76 (0.15)  | [1.1, 2.3]  | 1.73 (0.14)  | [1.1, 2.2]  | -0.03 (0.13) | [-0.9, 0.6] |
| <b>Phosphate (mg/dL)</b>            |               |      |              |             |              |             |              |             |
| Month 3                             | Suvorexant LD | 437  | 3.73 (0.58)  | [2.2, 7.4]  | 3.74 (0.52)  | [2.0, 6.7]  | 0.01 (0.51)  | [-3.1, 2.6] |
|                                     | Suvorexant HD | 1140 | 3.70 (0.54)  | [1.4, 6.9]  | 3.71 (0.55)  | [ 2.1, 7.3] | 0.01 (0.52)  | [-2.6, 3.8] |
|                                     | Placebo       | 898  | 3.70 (0.52)  | [1.8, 5.5]  | 3.71 (0.54)  | [1.2, 7.0]  | 0.01 (0.51)  | [-2.6, 3.7] |
| <b>Sodium (mEq/L)</b>               |               |      |              |             |              |             |              |             |
| Month 3                             | Suvorexant LD | 436  | 140.6 (2.2)  | [32, 147]   | 140.8 (2.6)  | [132, 169]  | 0.2 (2.6)    | [-10, 27]   |
|                                     | Suvorexant HD | 1136 | 140.6 (2.3)  | [130, 149]  | 140.5 (2.2)  | [125, 147]  | -0.1 (2.3)   | [-10, 7]    |
|                                     | Placebo       | 898  | 140.5 (2.3)  | [128, 149]  | 140.6 (2.2)  | [130, 147]  | 0.1 (2.2)    | [-9, 7]     |
| <b>Urate (mg/dL)</b>                |               |      |              |             |              |             |              |             |
| Month 3                             | Suvorexant LD | 437  | 5.18 (1.36)  | [1.9, 10.4] | 5.22 (1.39)  | [1.9, 10.7] | 0.04 (0.75)  | [-2.9, 2.1] |
|                                     | Suvorexant HD | 1140 | 5.30 (1.38)  | [0.8, 10.0] | 5.40 (1.41)  | [0.8, 12.6] | 0.10 (0.71)  | [-3.7, 3.5] |
|                                     | Placebo       | 900  | 5.23 (1.34)  | [1.6, 10.3] | 5.29 (1.36)  | [1.8, 11.6] | 0.06 (0.71)  | [-3.2, 3.4] |

(Source: Sponsor's submission ISS Page 942 Table Appendix 5.3.5.3.3:48. Note: Sampling for amylase and lipase levels was interrupted during development program, so table includes values for only suvorexant HD and placebo groups at Month 1, which had the largest sample size.)

## Urinalysis

The sponsor's analyses showed no meaningful differences in the mean changes from baseline of the urinalysis measurements among the treatment groups.

## Phase 2 Dose-Finding Trial Laboratory Experience - Mean Change from Baseline to Week 4 in Phase 2 Trial (P006)

Suvorexant increased serum cholesterol levels in a dose-related manner with the maximum mean increase of 6.0 mg/dL at suvorexant 80 mg dose, as shown in the table below. The sponsor suggested that this finding was not replicated in the Phase 3 population, and that the small sample size in the Phase 2 trials may have contributed to

the finding. Also, the sponsor stated that the findings are unlikely to be clinically meaningful.

**Table 115: Serum Cholesterol Levels Mean Change from Baseline to Week 4 in Phase 2 Trial (P006)**

| Treatment        | N   | Baseline Mean (mg/dL) | Treatment Mean (g/dL) | Change from Baseline (g/dL) |
|------------------|-----|-----------------------|-----------------------|-----------------------------|
| Placebo          | 228 | 202.3 (40.37)         | 198.6 (38.99)         | -3.7 (25.59)                |
| Suvorexant 10 mg | 56  | 204.8 (40.58)         | 206.0 (47.30)         | 1.2 (27.67)                 |
| Suvorexant 20 mg | 58  | 199.9 (42.69)         | 202.2 (40.65)         | 2.3 (25.94)                 |
| Suvorexant 40 mg | 59  | 201.9 (43.88)         | 205.0 (48.50)         | 3.1 (22.60)                 |
| Suvorexant 80 mg | 55  | 199.3 (32.52)         | 205.3 (32.30)         | 6.0 (19.65)                 |
| Total Suvorexant | 228 | 201.5 (40.06)         | 204.6 (42.53)         | 3.1 (24.08)                 |

(Source: Modified from Sponsor's submission ISS Page 974 Table Appendix 5.3.5.3.3:49).

*Reviewer Note: The sponsor stated that these observations on cholesterol levels are not likely to be clinically meaningful given the small sample size within each treatment group in the trial, about 60 in each dose arm, and the absence of changes in the combined Phase 3 population. I was unable to locate the sponsor's analyses on serum cholesterol levels from the Phase 3 trials in either the ISS or laboratory result dataset. From the lists of laboratory tests in the Phase 3 trial protocols, I did not find lipid panel or cholesterol tests. For potential long-term users of suvorexant, knowledge of the effect on cholesterol levels will be important. A rise in serum cholesterol levels to the extent found in the Phase 2 trial, up to 6 g/dL difference from placebo, may not be trivial especially if maintained over a longer period.*

#### Subjects Who Met Predefined Criteria for Change Relative to Normal Range in Laboratory Measurements

The sponsor summarized the count of subjects who met predefined criteria for change relative to normal range of laboratory measurements. As shown in the table below, more subjects met the criterion for raised levels of potassium in the suvorexant HD group (2.4%, 31/1284) compared to suvorexant LD group (1.0%, 5/ 485) or placebo (1.0%, 10/1011). One subject's value increased to a maximum of 6.8 mEq/L and was reported as an AE, though not considered related to suvorexant. The subject completed the trial with a potassium level of 4.1 mEq/L. In the 0-12 month's assessments, suvorexant HD continued to maintain higher frequency of subjects who met the criterion for raised potassium levels.

**Table 116: Laboratory Measurements by Count of Subjects Who Met Predefined Criteria for Change Relative to Normal Range in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)**

| Protocols 028+029+009                 |                           | Suvorexant LD<br>(N=493)<br>n/m (%) | Suvorexant HD<br>(N=1291)<br>n/m (%) | Placebo<br>(N=1025)<br>n/m (%) |
|---------------------------------------|---------------------------|-------------------------------------|--------------------------------------|--------------------------------|
| Laboratory Parameter                  | Predefined Limit          |                                     |                                      |                                |
| <b>Hematology</b>                     |                           |                                     |                                      |                                |
| Hematocrit (%) (Male)                 | ≤94.9% LLN                | 1/169 (0.6)                         | 16/505 (3.2)                         | 7/375 (1.9)                    |
| Hematocrit (%) (Female)               | ≤94.1% LLN                | 6/315 (1.9)                         | 13/777 (1.7)                         | 10/635 (1.6)                   |
| Hemoglobin (gm/dL) (Male)             | ≤90.5% LLN                | 1/169 (0.6)                         | 9/505 (1.8)                          | 5/375 (1.3)                    |
| Hemoglobin (gm/dL) (Female)           | ≤81.9% LLN                | 4/315 (1.3)                         | 2/777 (0.3)                          | 2/635 (0.3)                    |
| Leukocytes (10 <sup>3</sup> /microL)  | ≤64.2% LLN<br>≥149.0% ULN | 2/484 (0.4)<br>2/484 (0.4)          | 3/1282 (0.2)<br>3/1282 (0.2)         | 1/1010 (0.1)<br>0/1010 (0.0)   |
| Neutrophils (10 <sup>3</sup> /microL) | ≤37.0% LLN                | 5/484 (1.0)                         | 6/1282 (0.5)                         | 1/1009 (0.1)                   |
| Eosinophils (10 <sup>3</sup> /microL) | ≥147.0% ULN               | 3/484 (0.6)                         | 4/1282 (0.3)                         | 8/1009 (0.8)                   |
| Platelet (10 <sup>3</sup> /microL)    | ≤57.7% LLN<br>≥177.7% ULN | 1/484 (0.2)<br>0/484 (0.0)          | 0/1277 (0.0)<br>1/1277 (0.1)         | 0/1006 (0.0)<br>0/1006 (0.0)   |
| <b>Hepatic Function</b>               |                           |                                     |                                      |                                |
| Bilirubin (mg/dL)                     | ≥166.7% ULN               | 2/485 (0.4)                         | 7/1285 (0.5)                         | 7/1011 (0.7)                   |
| Alkaline Phosphatase (IU/L)           | ≥300.0% ULN               | 0/485 (0.0)                         | 0/1284 (0.0)                         | 0/1011 (0.0)                   |
| Aspartate Aminotransferase (IU/L)     | ≥300.0% ULN               | 1/485 (0.2)                         | 3/1285 (0.2)                         | 1/1011 (0.1)                   |
| Alanine Aminotransferase (IU/L)       | ≥300.0% ULN               | 2/485 (0.4)                         | 7/1284 (0.5)                         | 3/1011 (0.3)                   |
| <b>Renal Function</b>                 |                           |                                     |                                      |                                |
| Creatinine (mg/dL)                    | ≥142.9% ULN               | 1/485 (0.2)                         | 1/1285 (0.1)                         | 5/1011 (0.5)                   |
| <b>Clinical Chemistry</b>             |                           |                                     |                                      |                                |
| Sodium (mEq/L)                        | ≤94.7% LLN<br>≥105.4% ULN | 0/485 (0.0)<br>1/485 (0.2)          | 2/1285 (0.2)<br>1/1285 (0.1)         | 0/1011 (0.0)<br>0/1011 (0.0)   |
| Potassium (mEq/L)                     | ≤88.2% LLN<br>≥111.1% ULN | 1/485 (0.2)<br>5/485 (1.0)          | 2/1284 (0.2)<br>31/1284 (2.4)        | 4/1011 (0.4)<br>10/1011 (1.0)  |

N = Number of subjects treated by trial medication (took at least one tablet of study drug) during the indicated phase.

m = Number of treated subjects with valid post-treatment value of the parameter.

n = Number of subjects meeting the predefined limit criteria.

ULN = Upper limit of normal range; LLN = Lower limit of normal range.

Suvorexant LD= Suvorexant 20 mg for subjects <65 years and Suvorexant 15 mg for subjects ≥65 years.

Suvorexant HD= Suvorexant 40 mg for patients <65 years and Suvorexant 30 mg for patients ≥65 years.

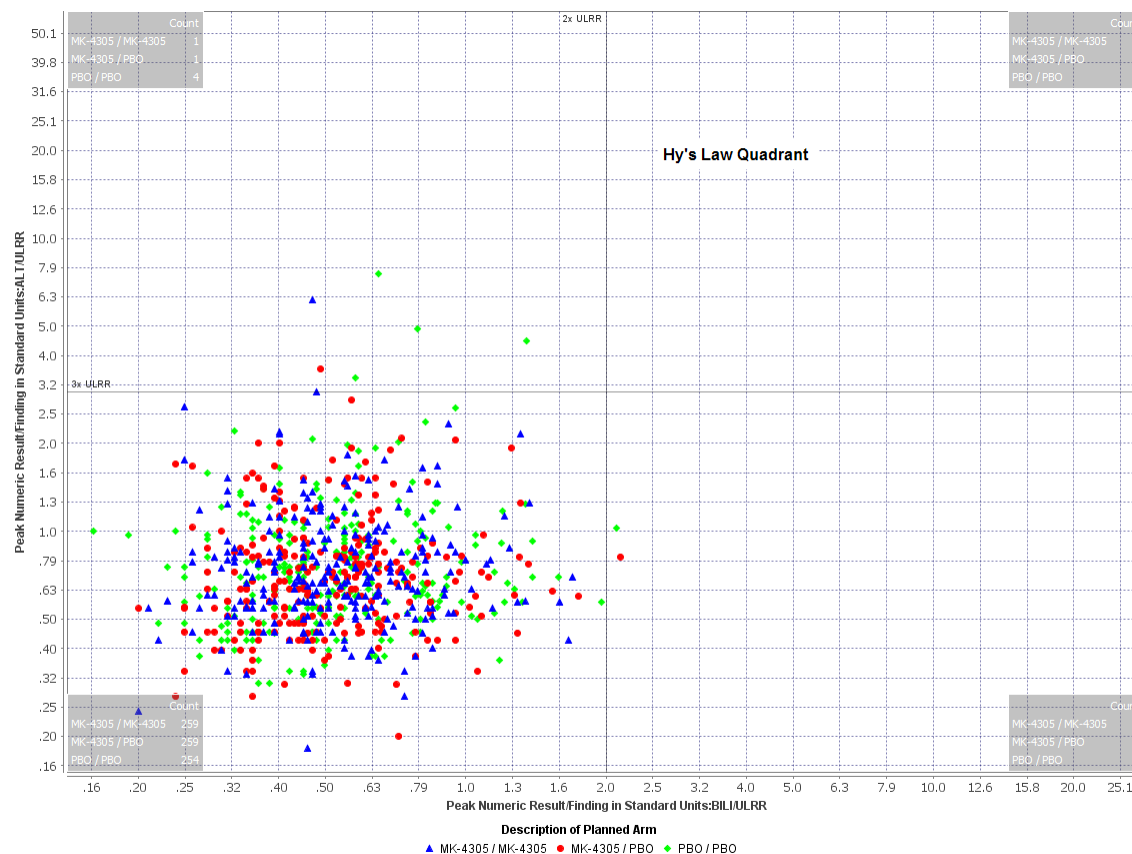
(Source: Sponsor's submission ISS Page 286 Table 5.3.5.3.3:62)

### Hepatic Enzymes

The frequency of subjects identified with increased ALT or AST in the suvorexant development program was similar across dose groups. Subjects who achieved >3 times upper limit of normal range (ULN) for ALT within 0-3 months were as follows: suvorexant HD 0.5% (7/1284), suvorexant LD 0.4% (2/485), and placebo 0.3%

(3/1011). AST findings were similarly comparable. The sponsor found no cases of Hy's Law in the development program. CDER analyzed the long-term Phase trial (P009) for cases of Hy's Law and found none as shown in the figure below.

**Figure 14: Analysis Showing Absence of Hy's Law Cases in the Long-term Phase 3 Trial P009**



Hy's Law in P009 showing no cases in Hy's Law Quadrant (RUQ)

(Source: CDER Review Team and Clinical Reviewer Analyses)

### 5.4.3 Vital Signs

Merck summarized the vital sign measurements in terms of mean change from baseline; they noted no clinically meaningful changes or trends in the vital sign parameters with suvorexant treatment. The table below summarizes the mean change in vital signs from baseline at Week 2 and Month 3 for the different treatment groups in the combined phase 3 population.

**Table 117: Vital Sign Change from Baseline at Week 2 and Month 3 in Combined Phase 3 Population (P028, P029, and P009)**

| Vital Sign Parameter           | Placebo       | Suvorexant LD | Suvorexant HD  |
|--------------------------------|---------------|---------------|----------------|
| Diastolic BP (mmHg)            |               |               |                |
| Week 2                         | -1.4 (n=1001) | -1.1 (n=479)  | -1.5 (n=1272)  |
| Month 3                        | -0.5 (n=375)  | -0.1 (n=129)  | -0.9 (n=623)   |
| Systolic Blood Pressure (mmHg) |               |               |                |
| Week 2                         | -2.4 (n=1001) | -2.2 (n=479)  | -2.2 (n=1272)  |
| Month 3                        | -1.3 (n=375)  | 0.2 (n=129)   | -1.3 (n=623)   |
| Pulse Rate (beats/min)         |               |               |                |
| Week 2                         | 1.7 (n=1001)  | 1.6 (n=479)   | 0.2 (n=1273)   |
| Month 3                        | -0.5 (n=375)  | -0.2 (n=129)  | -1.2 (n=623)   |
| Respiratory Rate (breaths/min) |               |               |                |
| Week 2                         | 0.0 (n=995)   | 0.1 (n=477)   | -0.1 (n=1263)  |
| Month 3                        | 0.0 (n=372)   | -0.4 (n=129)  | -0.3 (n=616)   |
| Temperature (°C)               |               |               |                |
| Week 2                         | -0.01 (n=996) | 0.00 (n=478)  | -0.05 (n=1263) |
| Month 3                        | 0.01 (n=370)  | -0.04 (n=129) | -0.02 (n=615)  |
| Weight (kg)                    |               |               |                |
| Week 2                         | 0.2 (n=998)   | 0.1 (n=476)   | 0.1 (n=1267)   |
| Month 3                        | 0.0 (n=373)   | 0.1 (n=129)   | 0.2 (n=623)    |

(Source: Modified from Sponsor's submission ISS Page 984 Table Appendix 5.3.5.3.3:51).

In the assessments by percentage of subjects who met predefined criteria for change from baseline, no meaningful differences occurred among the treatment groups for blood pressure, pulse rate, respiratory rate, or temperature. However, weight reductions and increases of 7% or more from baseline occurred more in the suvorexant LD group compared to suvorexant HD, or placebo.

#### 5.4.4 Electrocardiograms (ECGs)

The sponsor observed no clinically meaningful mean changes or trends in changes in ECG parameters. In the Phase 3 trials, P028 and P029, ECG measurements occurred at baseline, ends of Week 2, Months 1 and 3, and on trial discontinuation. Suvorexant did not appear to have remarkable effects on the ECG measurements in terms of mean changes in intervals from baseline over time and QTc values that met predetermined criteria for change from baseline. The table below is a summary of the mean change from baseline in ECG parameters at 3 months.

**Table 118: ECG Mean Change from Baseline at 3 Months in Combined Phase 3 Population (P028, P029, and P009)**

| ECG Parameter                     | Placebo  |              | Suvorexant LD |              | Suvorexant HD |               |
|-----------------------------------|----------|--------------|---------------|--------------|---------------|---------------|
|                                   | Baseline | MCB          | Baseline      | MCB          | Baseline      | MCB           |
| Ventricular Heart Rate (mean BPM) | 64.7     | 0.1 (n=898)  | 64.7          | -0.5 (n=437) | 65.1          | -1.1 (n=1152) |
| PR Interval (msec)                | 166.0    | -0.1 (n=882) | 164.8         | 0.2 (n=432)  | 166.8         | 1.0 (n=1132)  |
| QRS Interval (msec)               | 90.9     | 0.2 (n=895)  | 90.7          | 0.2 (n=436)  | 92.3          | 0.1 (n=1146)  |
| QT interval (msec)                | 404.6    | 0.4 (n=877)  | 406.3         | 3.1 (n=432)  | 404.1         | 2.7 (n=1125)  |
| QTcB (msec)                       | 416.9    | 0.4 (n=877)  | 418.9         | 1.2 (n=432)  | 417.7         | -0.5 (n=1125) |
| RR Interval (msec)                | 950.4    | 0.3 (n=898)  | 948.9         | 7.4 (n=437)  | 942.9         | 17.0 (n=1152) |

(Source: Modified from Sponsor's submission ISS Page 1003 Table Appendix 5.3.5.3.3:56. MCB = Mean Change from Baseline; BPM = Beats per minute; n = No of subjects evaluated)

Also, evaluation of the age subgroups for ECG changes from baseline showed no remarkable changes with suvorexant treatment. For example, the sponsor's ISS Appendix 5.3.5.3.3: 132 and Appendix 5.3.5.3.3: 133 tables show the mean changes in QTc (Bazett's) from baseline to 3 months in elderly subjects were -0.8 for suvorexant HD, 0.4 for suvorexant LD, and -1.9 for Placebo. For non-elderly subjects, the QTc changes were -0.2 for suvorexant HD, 1.7 for suvorexant LD, and 2.3 for placebo.

#### ECG Findings, Subjects that Met Predefined Criteria for Change from Baseline

The incidence of subjects who met predefined criteria for QTc Interval change from baseline was comparable across the treatment groups in the 0-3 Months period. For QTc Interval change from baseline between 30 and 60 msec the incidence for each treatment group was: suvorexant HD, 10.2% (130/1276); suvorexant LD, 10.0% (48/482); and placebo, 10.6% (107/1005). For QTc Interval change from baseline more than 60 msec, incidence for each group was: suvorexant HD, 0.2% (2/1276); suvorexant LD, 0.2% (2/482); and placebo, 0.7% (7/1005). The table below summarizes the proportion of subjects who met the QTc Interval change from baseline of more than 500 msec at different periods: 0-3, 0-6, and 0-12 Months.

**Table 119: Subjects with QTc Interval >500 msec as ECG Measurements that Met Predefined Criterion for Change from Baseline in the Phase 3 Trials over Time**

| Treatment Period  | Placebo<br>(N=1025) | Suvorexant LD<br>(N=493) | Suvorexant HD<br>(N=1291) |
|---|---------------------|--------------------------|---------------------------|
| 0-3 Months<br>QTc interval Bazett >500 msec<br>(Trials P028, P029, P009)  | 0.1 % (1/1008)      | 0.0 % (0/483)            | 0.2 % (2/1280)            |
| 0-6 Months<br>QTc interval Bazett >500 msec<br>(Trials P028, P029)        | 0.0% (0/755)        | 0.0% (0/483)             | Not applicable            |
| 0-12 Months<br>QTc interval Bazett >500 msec<br>(Trials P028, P029, P009) | 0.1% (1/1010)       | Not applicable           | 0.2% (2/1281)             |

(Source: Modified from Sponsor's ISS Pages 307-312 Tables 5.3.5.3.3:76- 80)

In the Phase 2 trial, no subject achieved a treatment-emergent QTc value of 500 msec or more.

#### Sleep Architecture on Polysomnography

Merck provided a summary of time to REM sleep onset that I reproduce in the table below. From Night 1 through Month 3, subjects on suvorexant entered REM sleep about 20 to 35 minutes faster than those on placebo. The percentage of subjects on suvorexant who enter REM sleep within 15 minutes does not increase from Night 1 to Month 3, as shown in the table below. On page 314 of the sponsor's ISS, Merck states that based on the data there was no evidence to suggest that subjects treated with suvorexant who experienced shorter REM onset (<15 minutes), increased REM duration, or REM percent, were more likely to experience adverse events of clinical concern, including EDS.

**Table 120: Time to REM from Sleep Onset and Subjects with REM Onset Less Than 15 Minutes by Treatment Group and Time Point in Combined Phase 3 Population 0-3 Months (P028 and P029, PQ Cohort)**

| Summary REM Onset Measure                          | Suvorexant LD  | Suvorexant HD  | Placebo        |
|--|----------------|----------------|----------------|
| <b>Night 1</b>                                     | <b>N = 339</b> | <b>N = 580</b> | <b>N = 576</b> |
| Mean time to onset of first epoch of REM (minutes) | 69.2           | 63.7           | 101            |
| Number (%) of subjects with REM onset <15 minutes  | 14 (4.1%)      | 38 (6.6%)      | 6 (1.0%)       |
| <b>Month 1</b>                                     | <b>N = 321</b> | <b>N = 554</b> | <b>N = 550</b> |



|  |                |                |                |
|--|----------------|----------------|----------------|
| Mean time to onset of first epoch of REM (minutes) | 80.1           | 80.2           | 100.9          |
| Number (%) of subjects with REM onset <15 minutes  | 9 (2.8%)       | 21 (3.8%)      | 5 (0.9%)       |
| <b>Month 3</b>                                     | <b>N = 304</b> | <b>N = 517</b> | <b>N = 518</b> |
| Mean time to onset of first epoch of REM (minutes) | 81.5           | 76.9           | 96             |
| Number (%) of subjects with REM onset <15 minutes  | 8 (2.6%)       | 27 (5.2%)      | 12 (2.3%)      |

(Source: Modified from Sponsor's ISS Page 315 Table 5.3.5.3.3:82)

*Reviewer Comment: There are subjects with missing values after Night 1, thereby limiting comparisons between time points. If it is verifiable that subjects with missing values were unlikely to have shortened their REM sleep latency at a rate lower than the subjects with values at 3 months, then it is reasonable to suggest that suvorexant treatment over 3 months does not appear to be associated with narcoleptic changes in these Phase 3 trial population.*

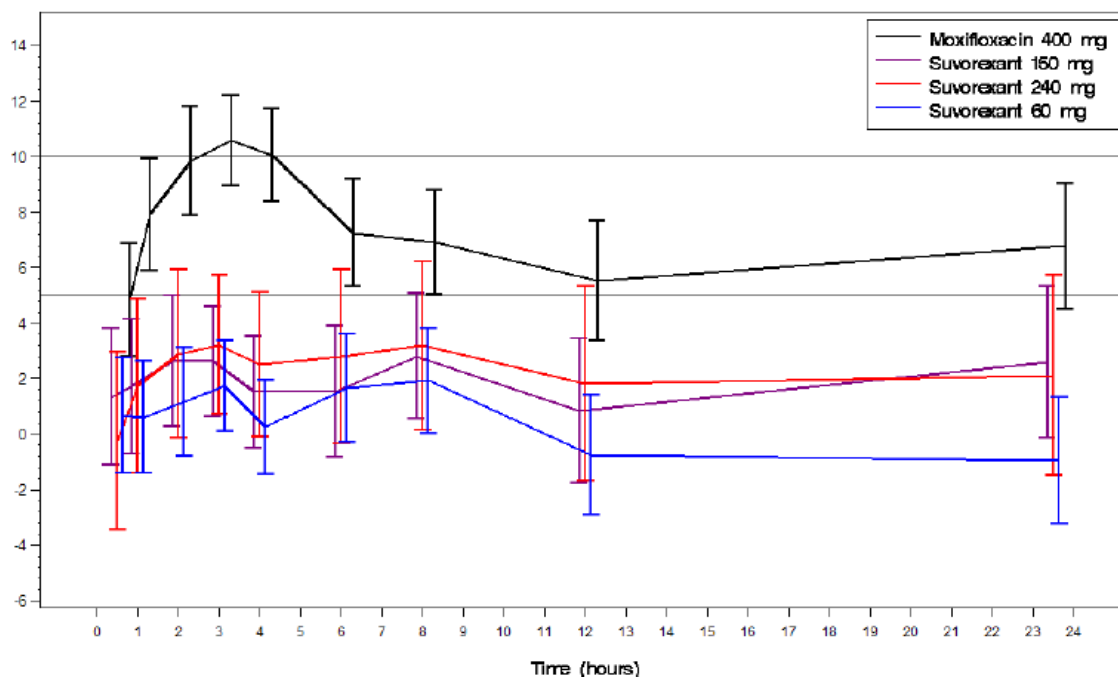
#### 5.4.5 Special Safety Studies/Clinical Trials

The studies reviewed in this section are mainly Phase 1 trials. Please refer to Clinical Pharmacology review for additional details of the trials.

#### Thorough QT Trial (P022)

Merck conducted a Thorough QTc Trial (P022) in Healthy Subjects to examine the effect of suvorexant on the QTc interval. CDER's interdisciplinary review (IR) team for QT Studies evaluated the sponsor's Thorough QT Study and detected no significant QTc prolongation effect of suvorexant. Further, the IR team remarked that the largest upper bounds of the 2-sided 90% CI for the mean difference between suvorexant and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. Assay sensitivity was established, as the largest lower bound of the two-sided 90% CI (unadjusted) for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms, as shown in the figure below.

**Figure 15: Mean and 90% CI  $\Delta\Delta$ QTcF Time Course for Suvorexant and Moxifloxacin**



*All CIs are unadjusted, including moxifloxacin.*

(Source: CDER Interdisciplinary Review Team for TQT studies Consult Report Page 13 Figure 5)

Below is a summary of my safety review of the thorough QT trial P022.

The randomized, placebo-controlled, double-blind, 4-period, crossover Thorough QTc (TQT) trial enrolled 53 healthy male (n=28) and female (n=25) volunteers, aged 20 to 45 years. The subjects received single doses of suvorexant 240 mg, 150 mg or 60 mg, matching placebo, and moxifloxacin 400 mg as the positive control. The 240 mg and 150 mg dose data were pooled for analysis. The sponsor reported that the maximum mean difference between suvorexant up to supratherapeutic doses had 90% confidence interval below 10 ms, the threshold for regulatory concern as recommended in the ICH E14 guidance. As stated by the sponsor, “The maximum mean difference in the QT interval prolongation was 4.13 msec with a 90% CI of 2.03 and 6.23 msec and was recorded at 8 hours in the 240/150 mg Suvorexant treatment. For both the therapeutic and supratherapeutic doses, all confidence intervals lay completely below 10 msec.” The positive result from moxifloxacin group showed assay sensitivity with a maximum mean QTcF change from baseline difference from placebo of 11.06 msec with a 90% CI of 8.99 and 13.16, recorded at 3 hours postdose.

Two subjects on suvorexant 240 mg developed SAEs, prompting the sponsor to decrease the maximum trial dose from 240 mg to 150 mg during the trial. One subject,

AN 0024, a 27-year old female reported a serious adverse experience of chest pain, requiring hospitalization. She had a negative work-up for myocardial infarction. She also had myoclonus and sleep paralysis during the evaluation. The second subject, AN 0014, developed a non-serious adverse experience of respiratory depression, described as shallow respiration and transiently decreased O<sub>2</sub> saturation (from between 96% and 98% to 90%), about 1 hour 19 minutes after receiving suvorexant 240 mg. She discontinued from the trial.

In the trial, the most frequent AEs (>10%) overall were somnolence (18 subjects, 34%), dizziness (9 subjects, 17%), headache (9 subjects, 17%), fatigue (9 subjects, 17%), application site pruritus at electrode sites (6 subjects, 11.3%), and abnormal dreams (6 subjects, 11.3%).

### **Renal Insufficiency (Trial P023)**

In a Phase 1 PK trial (P023), Merck evaluated safety of suvorexant in subjects aged 18 to 70 years with renal impairment, as part of the clinical development program. The aim of the trial was to determine whether suvorexant exposures were similar in subjects with renal impairment and healthy subjects. In the open-label PK trial, eight subjects with severe renal impairment, with 24-hour urinary creatinine clearance of 30 ml/min or less, and eight healthy controls received a single dose suvorexant 20 mg. The controls were matched by age, gender, race, and BMI to the renal impairment subjects. All subjects completed the trial.

The sponsor reported that total and unbound suvorexant plasma level was similar between subjects with severe renal impairment and healthy matched control subjects. Suvorexant had a median T<sub>max</sub> of 2 hours in severe renal impairment subjects and 1 hour in the matched control subjects. The mean apparent terminal half life was 13.5 hours for both populations. The trial recorded no SAEs, deaths, or subject discontinuations because of an adverse experience. Four healthy subjects reported 5 adverse experiences: three headache and two dry mouth events. Further, two subjects with severe renal impairment reported a total of 2 adverse events, somnolence and oligomenorrhoea. As result, Merck recommended no dose adjustment with renal impairment. Of note, this trial did not evaluate the suvorexant 40 mg dose.

### **Hepatic impairment (Trial P017)**

In a Phase 1 PK trial (P017), the sponsor evaluated safety and PK characteristics of suvorexant in male and female subjects aged 18 to 65 years with hepatic impairment. In the open-label PK trial, eight subjects with moderate hepatic impairment, defined by Child-Pugh scale score of 7 to 9, and eight healthy controls received a single dose suvorexant 20 mg. The controls were matched to hepatic impairment subjects by age, gender, race, and BMI. All subjects completed the trial.

On completion, the result showed similar suvorexant exposure in the controls and hepatic impairment subjects. Apparent half life was longer in the hepatic impairment subjects at 19.1 hours compared to the healthy subjects at 14.7 hours. With regards to safety, the trial reported no deaths, no SAEs, and no discontinuations resulting from AEs. Somnolence occurred in 75% (6/8) of the hepatic impairment subjects and 63% (5/8) of the control healthy subjects.

## **Respiratory Safety**

Merck conducted three studies to assess respiratory safety – P032 in COPD subjects, P036 in OSA subjects, and P040 in healthy adults. CDER's pulmonary review team is reviewing the results of the trials. Below is a brief overview of the trial reports.

### **Respiratory Safety – Healthy Subjects (Trial P040)**

In a Phase 1, placebo-controlled, double-blind, 3-period crossover trial design, the sponsor evaluated the effect of a single dose of suvorexant on mean oxygen saturation (SaO<sub>2</sub>), using pulse oximetry, during total sleep time (TST) in healthy subjects. The trial also assessed safety, apnea-hypopnea index (AHI), and PK characteristics of suvorexant in the 12 male (n=8) and female (n=4) subjects, aged 18 to 55 years, and with body mass index (BMI) 30 kg/m<sup>2</sup> or less. There was a 5-day washout between the trial treatment periods. After a 4-hour fast, subjects received, in each treatment period, a single evening dose of suvorexant 150 mg, suvorexant 40 mg, or matching placebo. Then the subjects were evaluated overnight in the sleep laboratory using 8-hour PSG recording and SaO<sub>2</sub> monitoring. PSG sleep was scored based on the American Academy of Sleep Medicine (AASM) Manual for Scoring of Sleep and Associated Events criteria into the 4 stages of sleep. The sponsor obtained PSG scoring, SaO<sub>2</sub>, and AHI parameter derivation at a central PSG laboratory that was blinded to treatment, period, and time postdose.

The results as summarized by the sponsor in the table below showed no statistically significant difference in mean SaO<sub>2</sub> during TST between each suvorexant dose and placebo. Also, the mean SaO<sub>2</sub> during wake, NREM, and REM sleep stages and AHI did not appear to be statistically significantly different.

**Table 121: Suvorexant Effects on Pharmacodynamic (PD) Endpoints of Respiratory Function in Trial P040**

| Endpoint   | Suvorexant<br>150 mg    | Suvorexant<br>40 mg     | Placebo                 | Difference<br>(150 mg<br>Suvorexant -<br>Placebo) of<br>LSmean<br>(90% CI) | Difference<br>(40 mg<br>Suvorexant -<br>Placebo) of<br>LSmean<br>(90% CI) | MSE <sup>‡</sup> |
|--|-------------------------|-------------------------|-------------------------|--|---|------------------|
|  | LSmean<br>(95% CI)      | LSmean<br>(95% CI)      | LSmean<br>(95% CI)      |  |   |                  |
| Mean SaO <sub>2</sub> during<br>TST (%)  | 96.67<br>(95.79, 97.55) | 96.33<br>(95.45, 97.21) | 96.67<br>(95.79, 97.55) | -0.00<br>(-0.90, 0.90)   | -0.33<br>(-1.23, 0.57)  | 1.64             |
| Mean SaO <sub>2</sub> during<br>Wake (%)   | 96.83<br>(96.09, 97.58) | 96.75<br>(96.00, 97.50) | 97.25<br>(96.50, 98.00) | -0.42<br>(-1.22, 0.38)   | -0.50<br>(-1.30, 0.30)  | 1.29             |
| Mean SaO <sub>2</sub> during<br>NREM (%)   | 96.75<br>(95.89, 97.61) | 96.17<br>(95.31, 97.02) | 96.75<br>(95.89, 97.61) | -0.00<br>(-0.87, 0.87)   | -0.58<br>(-1.45, 0.29)  | 1.53             |
| Mean SaO <sub>2</sub> during<br>REM (%)  | 96.67<br>(95.79, 97.55) | 96.33<br>(95.45, 97.21) | 96.83<br>(95.95, 97.71) | -0.17<br>(-1.07, 0.73)   | -0.50<br>(-1.40, 0.40)  | 1.64             |
| Apnea-hypopnea<br>index <sup>§</sup>   | -0.82<br>(-2.62, 0.99)  | 0.15<br>(-1.65, 1.95)   | -0.63<br>(-2.44, 1.17)  | -0.18<br>(-1.68, 1.31)   | 0.78<br>(-0.71, 2.28)   | 4.49             |
| <sup>‡</sup> Estimate of within subject variance.<br><sup>§</sup> For AHI test, change from baseline is analyzed where screening PSG visit serves as baseline, mean =3.62, SD=3.26, (N=12).<br>SaO <sub>2</sub> = Oxygen Saturation, TST = Total Sleep Time. |                         |                         |                         |  |   |                  |

(Source: Sponsor's submission Clinical Study Report Trial P040 Page 51 Table 11-1)

With regards to safety, the trial reported no deaths, no SAEs, and no discontinuations resulting from AEs. More AEs occurred with suvorexant 150 mg compared to other treatments. Five of the 12 subjects in the 150 mg suvorexant treatment reported 1 or more adverse experiences. With the suvorexant 150 mg dose treatment, the most frequently reported adverse experiences were dizziness in 3 subjects (25%), headache in 2 subjects (17%), and somnolence in 2 subjects (17%). The suvorexant 40 mg and placebo groups recorded no incidence of somnolence. No suicidal ideation or suicidal behavior was recorded based on the Columbia-Classification Algorithm for Suicide Assessment (C-CASA).

### Respiratory Safety – COPD (Trial P032)

In trial P032, Merck used a randomized, placebo-controlled, double-blind, 2-period crossover trial design to evaluate subjects with COPD for safety and oxygen saturation (SaO<sub>2</sub>) during multiple doses of suvorexant treatment.

The trial enrolled 25 male and female subjects, aged 18 to 85 years, with mild or moderate COPD according to the modified GOLD criteria, and with a BMI 40 kg/m<sup>2</sup> or less. Subjects received a suvorexant 40 mg (non-elderly) or 30 mg (elderly) or matching placebo once daily, about 30 minutes before nighttime PSG recording time, for 4 consecutive days, with a 7-day washout between each treatment period. Overnight PSG recording occurred on Days 1 and 4. One subject discontinued the trial, though not because of an adverse event.

Although single and multiple doses of suvorexant did not appear to reduce mean SaO<sub>2</sub> during total sleep time compared to placebo, slight increases occurred in Percentage of Total Sleep Time that SaO<sub>2</sub> was less than 85% with multiple dose suvorexant treatment – treatment difference of 0.32% (90% CI; 0.00, 0.63) compared to placebo. Likewise, Apnea-hypopnea index (AHI) increased by with multiple dose suvorexant treatment 2.05 (90% CI; 0.33, 3.77) compared to placebo.

With regards to safety, overall, somnolence and headache occurred most frequently each in 12% (3/25) of the subjects. The trial reported no deaths, no SAEs, and no discontinuations resulting from AEs. However, an ECI of sleep paralysis occurred in Subject AN0046, reported event at about 8.5 hours after suvorexant 40 mg treatment on Trial Day 1.

### **Respiratory Safety – OSA (Trial P036)**

The sponsor conducted Trial P036 in subjects with mild to moderate obstructive sleep apnea (OSA); this trial was similar to Trial P032 that I described above. Trial P036 enrolled 26 subjects, 19 males and 7 females, aged 18 to 65 years. The subjects received a suvorexant 40 mg or matching placebo once every evening for 4 consecutive days, with a 5-day washout between each treatment period. One subject discontinued from the trial, not from an AE. On completion, multiple doses of suvorexant 40 mg produced a small increase in mean AHI; the observed mean AHI treatment difference, suvorexant minus placebo, on Day 4 was 2.66 (90% CI; 0.22, 5.09). Overall, somnolence occurred in 19.2% (5/26) of the subjects and nausea in 8% of the subjects; these were the most frequently reported AEs. No somnolence event occurred with placebo. There were no deaths, no SAEs, and no discontinuations resulting from AEs.

### **Middle of the Night Safety in Elderly Subjects (Trial P021)**

Merck conducted a randomized, double-blind, placebo-controlled 3-period crossover trial (P021) to evaluate middle of the night safety after suvorexant treatment in elderly subjects. The trial evaluated effects of single nighttime doses of suvorexant 30 mg, zolpidem 5 mg, and placebo on safety, PK, and nighttime psychomotor performance in 12 healthy elderly male (n=7) and female (n=5) subjects, aged 65 to 80 years. The investigators awakened the subjects at 1.5 hours, 4 hours, and 8 hours post-dose. At each time-point, the investigators assessed the subjects on postural stability (equilibrium and ataxia) using Accusway stabilometric platform, cognitive performance (attention and concentration) using Choice Reaction Time (CRT) and Immediate and Delayed Word Recall (IDWR). Accusway platform analyzed stability as a 95% confidence interval area of ellipse around center of positional trajectory (A95), as a measure of body sway or equilibrium and ataxia. On trial completion, **Suvorexant 30 mg at 1.5 hours post-dose, increased A95 by 49% at eyes-open condition.** No statistically significant difference from placebo in A95 occurred at eyes-closed condition. In contrast, zolpidem 5mg, at 1.5 hour post-dose, increased A95 body sway by 97% at eyes-open and 113% at eyes-closed conditions. These increases in body sway

indicated some impaired balance at 1.5 hour post-dose for both drugs, worse on zolpidem. For both drugs, there were no statistically significant differences from placebo in body sway at 4 or 8 hours postdose, and no impaired episodic memory at 4 hour post dose. The trial report further showed that **suvorexant 30 mg significantly prolonged reaction time indicating slowed information processing and impaired attention at 1.5 hour**, but not at 4 and 8 hour post dose.

Eight subjects reported 14 clinical adverse events while on suvorexant 30 mg; fatigue and somnolence were the most frequent of these events. Six subjects on zolpidem 5 mg reported nine clinical adverse events, dizziness was the most frequent. On placebo, one subject reported severe eye pain two days after the placebo treatment. Also, one subject on placebo in period 1 discontinued after developing an erythematous rash 1.5 hours after treatment. The trial recorded no SAEs and no deaths.

### **Driving Trial in Non-elderly Subjects (Trial P035)**

Highway Car Driving Assessment of Next-day Residual Effects of Suvorexant  
Trial Title: A Multiple Dose Study to Evaluate Next Day Effects of MK-4305 (Suvorexant) on Driving Performance in Healthy Non-Elderly Subjects

The trial's primary objective was to evaluate the next day residual effects of suvorexant as assessed by highway driving performance after single dose administration in healthy non-elderly male and female subjects.

To achieve trial objectives, the sponsor stated the following hypotheses:

Primary: At least 1 dose of suvorexant (20 or 40 mg) does not produce next-day residual effects as compared to placebo as assessed by mean SDLP (standard deviation of lateral position) on highway driving after single dose administration in healthy non-elderly subjects. Specifically, the true mean treatment difference between suvorexant and placebo (suvorexant minus placebo) on SDLP (on Day 2) is less than 2.4 cm.

Secondary:

1. Single doses of zopiclone produce next-day residual effects as compared to placebo as assessed by SDLP on highway driving in healthy non-elderly subjects. Specifically, a true mean treatment difference between zopiclone and placebo (zopiclone – PBO) on SDLP of 2.5 cm is expected.
2. At least 1 dose of suvorexant (20 or 40 mg) does not produce next-day residual effects as compared to placebo as assessed by SDLP on highway driving after repeated dose administration (8 days) in healthy non-elderly subjects. Specifically, the true mean treatment difference between suvorexant and placebo (suvorexant – PBO) on SDLP is less than 2.4 cm.

3. At least 1 dose of suvorexant (20 or 40 mg) does not result in next day driving impairment as measured by SDLP after single-dose and repeated-dose administration. Specifically, the distribution of changes in SDLP (suvorexant – PBO) above +2.4 cm and below -2.4 cm is symmetric around zero.
4. Single doses of 7.5 mg zopiclone result in next day driving impairment as measured by SDLP. Specifically, the distribution of changes in SDLP (zopiclone – PBO) above +2.4 cm and below -2.4 cm is not symmetric around zero. There are more subjects with increases in SDLP than those with decreases in SDLP.
5. Estimation: The effects of suvorexant (20 and 40 mg) on mean standard deviation of speed (SDS) of highway driving as compared to placebo after single and repeated dose (8 days) administration will be estimated.
6. Estimation: The effects of suvorexant (20 and 40 mg) on word learning tests and Body Sway as compared to placebo after single and repeated dose (8 days) administration will be estimated.
7. Suvorexant is safe and well tolerated after single and repeated dose administration of 20 and 40 mg in healthy non-elderly subjects.

Trial P035 was a randomized, double-blind, placebo and active controlled, multiple oral dose, 4-period crossover trial to evaluate highway car driving performance the day after bedtime treatment with suvorexant 20 mg, suvorexant 40 mg, zopiclone (active control), or placebo. The PD, PK, and safety trial enrolled 28 non-elderly male and female subjects, aged 21 to 64 years to receive each treatment for 8 days per period with a 7-day washout between periods. Following overnight stays on Days 1 and 8, the subjects underwent an hour long driving test on the highway on Days 2 and 9 at about 9 hours from trial treatment. They were evaluated on the following tests at about 11 hours from trial treatment: Body Sway Test, Bond-Lader VAS, Word Learning Test, and DSST. Investigators also collected PK samples during the trial.

#### Key Trial Assessments

Pharmacodynamics: the primary PD variable was SDLP for car driving performance, with emphasis on both the mean between-treatment differences and the percentage of subjects whose individual difference from placebo were beyond specific cut points of positive and negative 1.5, 2, 2.4, 3, 3.5, and 4. The secondary endpoints were: standard deviation of speed (SDS) of highway driving, Word Learning Tests, DSST, Bond-Lader VAS, Driving Instructor VAS, and A95 in the eyes closed position for Body Sway assessment.

The sponsor analyzed mean SDLP using a linear mixed model that was applied to individual values of SDLP, with fixed factors for treatment, day (2 and 9), period, treatment by day interaction, and random factor for subject. Multiple hypotheses for treatment effect were tested in a step-wise manner. The suvorexant 20 mg dose on Day 2 was tested first. The mean treatment difference (suvorexant minus placebo) of SDLP on Day 2 based on the model results was calculated. If the 90% confidence interval of the treatment difference was below 2.4 cm, then the hypothesis was supported for 20



mg suvorexant, allowing the hypothesis for the higher dose suvorexant 40 mg to be tested. If one of the two doses was supported, the hypothesis was supported for suvorexant. The sponsor performed a similar hypothesis testing for Day 9 as a secondary hypothesis.

In the other key PD assessment, Symmetry Analyses for SDLP, the sponsor used a generalized sign test to determine whether the distribution of differences (suvorexant minus placebo) above 2.4 and below -2.4 was symmetric about zero. The percentage of subjects lying above 2.4 was compared to 50% using the binomial distribution. A non-significant result (one-sided,  $\alpha=0.05$ ) supported the hypothesis for a particular day and dose. The active control zopiclone was similarly evaluated.

The results showed that the 90% confidence intervals for suvorexant 20 mg and 40 mg were below the pre-specified clinical bound of 2.4 cm on both Days 2 and 9, suggesting a lack of next-day residual effects by either of the tested suvorexant doses. In contrast, the 90% confidence intervals around the SDLP treatment difference for zopiclone on Days 2 and 9 both lay above 0 cm, suggesting next-day residual effects and demonstrating assay sensitivity. The sponsor summarized the results in the following table:

**Table 122: Standard Deviation of Lateral Position (SDLP) on Driving Assessment after Treatment with Suvorexant 20 mg, Suvorexant 40 mg and Zopiclone 7.5 mg in Non-elderly Subjects from Trial P035**

| Day | Treatment        | N  | LS Mean SDLP (cm) |               | Difference From Placebo (cm) |              |
|-----|------------------|----|-------------------|---------------|------------------------------|--------------|
|     |                  |    | Mean              | 95% CI        | Mean                         | 90% CI       |
| 2   | Placebo          | 28 | 15.53             | (14.53,16.53) |                              |              |
|     | Zopiclone 7.5 mg | 28 | 17.66             | (16.66,18.66) | 2.14                         | (1.49,2.79)  |
|     | Suvorexant 20 mg | 28 | 16.54             | (15.54,17.54) | 1.01                         | (0.36,1.66)  |
|     | Suvorexant 40 mg | 28 | 17.19             | (16.19,18.19) | 1.66                         | (1.01,2.31)  |
| 9   | Placebo          | 27 | 15.47             | (14.46,16.47) |                              |              |
|     | Zopiclone 7.5 mg | 28 | 16.91             | (15.91,17.91) | 1.45                         | (0.79,2.10)  |
|     | Suvorexant 20 mg | 28 | 15.94             | (14.94,16.94) | 0.48                         | (-0.18,1.13) |
|     | Suvorexant 40 mg | 28 | 16.77             | (15.77,17.77) | 1.31                         | (0.65,1.96)  |

(Source: Sponsor's submission Clinical Study Report P035 Page 60 Table 11-1)

On symmetry analysis of SDLP, the percentage of subjects with SDLP treatment difference (suvorexant minus placebo) above 2.4 cm was significantly greater than that

below -2.4 cm on both Day 2 and Day 9 for suvorexant 40 mg, and on Day 2 only for suvorexant 20 mg. The sponsor summarized the symmetry analysis in the table below.

**Table 123: Symmetry Analysis for Individual Differences in Standard Deviation of Lateral Position (SDLP) on Driving Assessment after Treatment with Suvorexant 20 mg, Suvorexant 40 mg and Zopiclone 7.5 mg in Non-elderly Subjects from Trial P025**

| Treatment                             | Day=2               |                     |                     | Day=9               |                     |                     |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                                       | Suvorexant<br>20 mg | Suvorexant<br>40 mg | Zopiclone<br>7.5 mg | Suvorexant<br>20 mg | Suvorexant<br>40 mg | Zopiclone<br>7.5 mg |
| n+1 <sup>†</sup>                      | 6                   | 10                  | 14                  | 2                   | 6                   | 8                   |
| n-1 <sup>‡</sup>                      | 0                   | 2                   | 1                   | 1                   | 0                   | 0                   |
| m = n+1 + n-1                         | 6                   | 12                  | 15                  | 3                   | 6                   | 8                   |
| Test Statistic <sup>§</sup>           | 2.45                | 2.31                | 3.36                | 0.58                | 2.45                | 2.83                |
| Reject Null Hypothesis? <sup>  </sup> | Yes                 | Yes                 | Yes                 | No                  | Yes                 | Yes                 |

<sup>†</sup> n+1 = number of subjects with treatment difference (from placebo)  $\geq 2.4$  cm.  
<sup>‡</sup> n-1 = number of subjects with treatment difference (from placebo)  $\leq -2.4$  cm.  
<sup>§</sup> Test Statistic =  $(n+1 - n-1)/\sqrt{m}$ .  
<sup>||</sup> Reject Null hypothesis if test statistic  $> 1.74$ , which is the critical value for general sign test with exact unconditional approach for sample size N=28 and N=27.  
 Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.

(Source: Sponsor's submission Clinical Study Report P035 Page 61 Table 11-2)

Other trial results as summarized by the sponsor include:

- There was a statistically significant increase in SDS following single and multiple doses of suvorexant 40 mg, and following a single dose of suvorexant 20 mg (at 9 hours postdose).
- There was no statistically significant effect on memory following single and multiple doses of suvorexant 20 mg (at 11 hours postdose). But a statistically significant decrease in delayed word recall was found following a single dose of suvorexant 40 mg.
- There was no statistically significant effect on balance as assessed by Body Sway Test following multiple doses of suvorexant 20 mg or suvorexant 40 mg (at 11 hours postdose). But a statistically significant increase on Body Sway Area (A95) was observed following a single dose of suvorexant 20 mg or suvorexant 40 mg.

#### Safety Assessment in Driving Trial P035

Regarding safety, the trial reported one serious clinical adverse experience of induced abortion in Subject AN 0007 who became pregnant during the trial and subsequently had an elective abortion after the trial. The trial recorded no deaths. Twenty-five (25) subjects reported a total of 132 clinical adverse experiences.

#### Safety Assessment for Suvorexant 40 mg in Driving Trial P035

While on suvorexant 40 mg, 17 (60.7%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 40 mg were somnolence (25.0%,

7/28) headache (17.9%, 5/28), and fatigue (14.3%, 4/28). Three subjects (AN 0006, AN 0007, and AN 0016) stopped driving test early on Day 2.

#### Safety Assessment for Suvorexant 20 mg in Driving Trial P035

While on suvorexant 20 mg, 10 (35.7%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 20 mg were headache (25.0%, 7/28) and somnolence (14.3%, 4/28). Two subjects (AN 0007, and AN 0021) stopped driving test early, one subject on Day 2 and the other on Day 9 (AN 0007).

#### Safety Assessment for Zopiclone 7.5 mg in Driving Trial P035

While on Zopiclone 7.5 mg, 10 (35.7%) subjects reported at least one AE. The most frequently reported AE was dysgeusia (25%, 7/28). No subject stopped driving test early.

#### Placebo

The adverse events reported for placebo treatment included experience from the zopiclone treatment period between Days 2 to 7 when the subjects received placebo between Day 1 and Day 8 zopiclone treatment. While on placebo, 21 (75.0%) subjects reported at least one AE. The most frequently reported AEs were headache (39.3%, 11/28), fatigue (17.9%, 5/28), and dyssomnia (10.7%, 3/28). No subject stopped driving test early.

*Reviewer Note: Assessing the trial results beyond the primary hypothesis is problematic because of the sheer number of comparisons. Regulatory decisions based on results of secondary hypotheses can be difficult, especially with the background of multiple hypotheses tested in a small sized trial. Based on the primary hypothesis, suvorexant showed no significant impairment in driving. But there are other issues. Premature stopping of driving, seen with suvorexant 40 mg and 20 mg treatment, suggests impairment in driving that may not be captured on SDLP analysis. Symmetry of SDLP analysis is another suggestion of driving impairment with suvorexant 40 mg and 20 mg treatment. Interpretation of all these analyses is limited by the fact that this trial's sample size was small. However, the gravity of the consequences of impaired driving, such as in accidents, demand that cautionary language be in place in the label for individuals taking suvorexant to avoid driving or operating heavy machinery.*

#### **Driving Trial in Elderly Subjects (P039)**

Trial P039 was similarly designed as Trial P035. However, Trial P039 enrolled 24 elderly male and female subjects, aged 65 to 80 years. The key findings as summarized by the sponsor are as follows:

Suvorexant at 15 mg and 30 mg did not produce next-day residual effects (RE) on highway driving assessed at 9-hr postdose by SDLP (mean and symmetry analysis),

following single dose and multiple doses (8 consecutive days) administration. The table below shows the mean SDLP analyses.

**Table 124: SDLP on Driving Assessment after Treatment with Suvorexant 15 mg, Suvorexant 30 mg and Zopiclone 7.5 mg in Elderly Subjects from Trial P039**

| Day | Treatment        | N  | LS Mean |               | Difference from PBO |              |
|-----|------------------|----|---------|---------------|---------------------|--------------|
|     |                  |    | Mean    | 95% CI        | Mean                | 90% CI       |
| 2   | Placebo          | 24 | 16.67   | (15.48,17.86) |                     |              |
|     | Zopiclone 7.5 mg | 24 | 18.56   | (17.37,19.75) | 1.89                | (1.22,2.55)  |
|     | MK-4305 15 mg    | 24 | 16.24   | (15.05,17.43) | -0.43               | (-1.10,0.23) |
|     | MK-4305 30 mg    | 24 | 17.04   | (15.85,18.23) | 0.37                | (-0.30,1.03) |
| 9   | Placebo          | 24 | 15.41   | (14.22,16.60) |                     |              |
|     | Zopiclone 7.5 mg | 24 | 16.58   | (15.39,17.78) | 1.17                | (0.51,1.84)  |
|     | MK-4305 15 mg    | 24 | 15.50   | (14.31,16.69) | 0.09                | (-0.58,0.76) |
|     | MK-4305 30 mg    | 24 | 16.01   | (14.82,17.20) | 0.60                | (-0.06,1.27) |

(Source: Sponsor's submission Clinical Study Report P039 Page 59 Table 11-1)

Further SDLP symmetry analysis is shown in the table below. Note that more subjects treated with suvorexant 30 mg had treatment difference from placebo above 2.4 cm compared to below -2.4 cm at Days 2 and 9; however, the apparent asymmetry was not statistically significant.

**Table 125: SDLP Symmetry Analysis on Driving Assessment after Treatment with Suvorexant 15 mg, Suvorexant 30 mg and Zopiclone 7.5 mg in Elderly Subjects from Trial P039**

| Treatment                             | Day=2            |                  |                     | Day=9            |                  |                     |
|---------------------------------------|------------------|------------------|---------------------|------------------|------------------|---------------------|
|                                       | MK-4305<br>15 mg | MK-4305<br>30 mg | Zopiclone<br>7.5 mg | MK-4305<br>15 mg | MK-4305<br>30 mg | Zopiclone<br>7.5 mg |
| n+1 <sup>†</sup>                      | 0                | 3                | 8                   | 0                | 5                | 6                   |
| n-1 <sup>‡</sup>                      | 3                | 1                | 0                   | 0                | 1                | 1                   |
| m = n+1 + n-1                         | 3                | 4                | 8                   | 0                | 6                | 7                   |
| Test Statistic <sup>§</sup>           | -1.73            | 1                | 2.83                | N.D.             | 1.63             | 1.89                |
| Reject Null Hypothesis? <sup>  </sup> | No               | No               | Yes                 | No               | No               | Yes                 |

<sup>†</sup>n+1 = number of subjects with treatment difference from placebo  $\geq 2.4$  cm.  
<sup>‡</sup>n-1 = number of subjects with treatment difference from placebo  $\leq -2.4$  cm.  
<sup>§</sup>Test Statistic =  $(n+1 - n-1)/\sqrt{m}$ .  
<sup>||</sup> Reject Null hypothesis if test statistic > 1.74, which is the critical value for general sign test with exact unconditional approach for sample size N=24.  
 Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.

(Source: Sponsor's submission Clinical Study Report P039 Page 60 Table 11-2)

Other trial findings as summarized by the sponsor include the following:

- Single doses of zopiclone (7.5 mg) demonstrated assay sensitivity on highway driving as assessed by SDLP (mean and symmetry analysis) at 9-hr postdose.
- Based on the standard deviation of speed of highway driving test, suvorexant (15 mg and 30 mg) did not show any statistically significant next-day residual effect following single and multiple dose administration.
- Based on the word learning and body sway tests, suvorexant (15 mg and 30 mg) did not show any statistically significant next-day effect on memory and balance assessed at 11-hr postdose following single and multiple doses administration.
- Based on digital symbol substitution test, Bond and Lader VAS and Driving Instructor VAS, suvorexant (15 mg and 30 mg) did not show any statistically significant next-day effects assessed at 11-hr postdose following single and multiple dose administration.

#### Safety Assessment in Driving Trial P039

Regarding safety, no SAEs, deaths, or trial discontinuations because of AEs occurred in the trial. The most frequently reported AEs were somnolence, poor sleep quality, headache, nightmare and dysgeusia. Twenty-four subjects reported a total of 102 clinical AEs.

#### Safety Assessment for Suvorexant 30 mg in Driving Trial P039

While on suvorexant 30 mg, 13 (54.2%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 30 mg were headache (20.8%, 5/24) and somnolence (29.2%, 7/24). No subject stopped driving test early.

#### Safety Assessment for Suvorexant 15 mg in Driving Trial P039

While on suvorexant 15 mg, 14 (58.3%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 15 mg was poor quality sleep (25.0%, 6/24).

#### Safety Assessment for Zopiclone 7.5 mg in Driving Trial P039

While on Zopiclone 7.5 mg, 11 (45.8%) subjects reported at least one AE. The most frequently reported AEs were dysgeusia (12.5%, 3/24), headache (12.5%, 3/24) and somnolence (12.5%, 3/24).

#### Placebo in Driving Trial P039

The adverse events reported for placebo treatment included experience from the zopiclone treatment period between Days 2 to 7 when the subjects received placebo between Day 1 and Day 8 zopiclone treatment. While on placebo, 13 (54.2%) subjects reported at least one AE. The most frequently reported AEs were headache (29.2%, 7/24), somnolence (16.7%, 4/24), poor quality sleep (12.5%, 3/24), and (12.5%, 3/24).

*Reviewer Note: Based on the primary hypothesis of Trial P039, suvorexant shows no significant impairment in driving by elderly subjects at both suvorexant 15 mg and*

*suvorexant 30 mg doses. No premature stopping of driving occurred with either dose. However, the SDLP symmetry analysis, though without statistical significance, hints at possible driving impairment with suvorexant 30 mg on Days 2 and 9. Again, interpretation of these analyses is limited by the trial's small sample size.*

#### 5.4.6 Immunogenicity

No immunogenicity studies were required.

### 5.5 Other Safety Explorations

#### 5.5.1 Dose Dependency for Adverse Events

The sponsor recommends suvorexant 40 mg for non-elderly adults and 30 mg for the elderly for insomnia treatment in its proposed label. Also, the sponsor leaves room for use of lower doses depending on a subject's dose tolerance. The information presented on dose dependency for AEs may serve as a useful guide for physicians in making the dose changes. Somnolence, as reviewed in section 5.3.4., appears to be the most appropriate AE for assessment of suvorexant dose response. Below I summarize other AEs that occurred in a dose-related manner in the Phase 3 trials.

Fatigue in the first 3 months in the combined phase 3 population was observed more frequently from suvorexant treatment in a dose-related manner: 3.8% (49/1291) of suvorexant HD group, 2.2% (11/493) suvorexant LD, and 1.8% (18/1025) placebo.

Abnormal dreams (nightmares) in the first 3 months in the combined phase 3 population were more frequent from suvorexant treatment (2%, 36/1784), in an apparent a dose-response relationship: 2.1% (27/1291) of suvorexant HD group, 1.8% (9/493) suvorexant LD, and 1.0% (10/1025) placebo.

In the combined phase 3 population 0-3 months, dry mouth was more frequent from suvorexant treatment (2.5%, 45/1784), in an apparent a dose-related manner: 2.8% (36/1291) of suvorexant HD group, 1.8% (9/493) of suvorexant LD, and 1.4% (14/1025) of placebo.

Infections and Infestations, as an AE group (in the first 3 months in the combined phase 3 population), were comparable among treatment groups: 12.5% (161/1291) of suvorexant HD group, 14.2% (70/493) of suvorexant LD, and 14.3% (147/1025) of placebo. Similarly, nasopharyngitis rates were comparable between suvorexant treatment and placebo. In contrast, AEs specifically termed "Upper respiratory tract infection (URI)" appeared slightly higher with suvorexant treatment, in a dose-response relationship: 2.2% (28/1291) of suvorexant HD group, 1.6% (8/493) of suvorexant LD, and 1.2% (12/1025) of placebo.

#### Dose Dependency for AEs in the Phase 2 Trial P006

The Phase 2 trial experience concerning suvorexant-related AEs that show dose response, in which suvorexant HD showed higher risk than suvorexant LD, were summarized in review section 5.4.1 under Drug-Related Adverse Events in Phase 2 Dose-Finding Trial P006. Briefly, the most frequent dose-related AE in the Phase 2 trial was somnolence with incidence: 0.4% (1/249) from placebo, 4.9% (3/62) suvorexant 20 mg, 11.9% (7/59) suvorexant 40 mg, and 9.8% (6/61) suvorexant 80 mg. No somnolence event occurred while 62 subjects received suvorexant 10 mg. Muscular weakness, under musculoskeletal and connective tissue disorders SOC, occurred in suvorexant 40 mg (3.4%, 2/59), and suvorexant 80 mg (1/61) treatment periods. The incidence of abnormal dreams, under psychiatric disorders SOC, was highest at the maximum suvorexant dose: placebo (0.8%, 2/249), suvorexant 10 mg (1.6%, 1/62), and suvorexant 80 mg (4.9%, 3/61).

#### 5.5.2 Time Dependency for Adverse Events

I reviewed the time dependency for select AEs above in section 5.3.4, section 5.3.5, and section 5.4.1.

#### 5.5.3 Drug-Demographic Interactions

##### Age

The sponsor analyzed AEs by age group in the Combined Phase 3 Population 0-3 Months (Trials P028, P029, and P009). The incidence of any AE in non-elderly subjects was increased on suvorexant HD treatment (51.5%, 342/664) compared to suvorexant LD (44.7%, 130/291) or placebo (44.2%, 246/556). However, the incidence of any AE in elderly subjects was similar among the treatment groups: suvorexant HD (50.4%, 316/627), suvorexant LD (49.0%, 99/202) or placebo (49.5%, 232/469). Two deaths occurred among the non-elderly subjects, one on placebo and the other on suvorexant 40 mg. Below, I summarize AE categories by the demographic factor Age. In review section 5.3.4, I summarized the AE somnolence by demographic factors, including age.

**Table 126: Summary of Adverse Events by Demographic Factor Age in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)**

| Demographic Variable                    | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total |
|---|------------------|------------------------|------------------------|-------|
| Subjects in Overall Population          | 1025             | 493                    | 1291                   | 2809  |
| <b>Age – Non-elderly (&lt;65years )</b> |                  |                        |                        |       |
| Subjects with data                      | 556              | 291                    | 664                    | 1511  |
| At least one AE                         | 246 (44.2)       | 130 (44.7)             | 342 (51.5)             | 718   |

|  |            |           |            |      |
|--|------------|-----------|------------|------|
| Drug-related AE, investigator determined | 85 (15.3)  | 67 (23.0) | 180 (27.1) | 332  |
| SAE                                      | 12 (2.2)   | 0 (0.0)   | 6 (0.9)    | 18   |
| Discontinued because of AE               | 24 (4.3)   | 8 (2.7)   | 40 (6.0)   | 72   |
| Discontinued because of SAE              | 8 (1.4)    | 0 (0.0)   | 4 (0.6)    | 12   |
| Deaths                                   | 1 (0.2)    | 0 (0.0)   | 1 (0.2)    | 2    |
| <b>Age – Elderly (&gt;=65years )</b>     |            |           |            |      |
| Subjects with data                       | 469        | 202       | 627        | 1298 |
| At least one AE                          | 232 (49.5) | 99 (49.0) | 316 (50.4) | 647  |
| Drug-related AE, investigator determined | 69 (14.7)  | 42 (20.8) | 149 (23.8) | 260  |
| SAE                                      | 11 (2.3)   | 3 (1.5)   | 12 (1.9)   | 26   |
| Discontinued because of AE               | 26 (5.5)   | 7 (3.5)   | 40 (6.4)   | 73   |
| Discontinued because of SAE              | 4 (0.9)    | 5 (0.8)   | 1 (0.5)    | 10   |
| Deaths                                   | 0 (0.0)    | 0 (0.0)   | 0 (0.0)    | 0    |

(Source: Modified from Sponsor's ISS Pages 331-334 Tables 5.3.5.3.3:90-91)

#### Gender

The incidence of any AE in males was higher on suvorexant HD treatment (48.7%, 2472/507) compared to suvorexant LD (40.8%, 71/174) or placebo (43.0%, 165/384). In females, the incidence of any AE was mildly increased on suvorexant HD (52.4%, 411/784), compared to suvorexant LD (49.5%, 158/319) or placebo (48.8%, 313/641). Among females, the placebo and suvorexant 40 mg groups each recorded one death. Below, I summarize AE categories by gender. In review section 5.3.4, I summarized the AE somnolence by demographic factors, including gender.

**Table 127: Summary of Adverse Events by Demographic Factor Gender in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)**

| Demographic Variable                     | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total |
|--|------------------|------------------------|------------------------|-------|
| Subjects in Overall Population           | 1025             | 493                    | 1291                   | 2809  |
| <b>Male</b>                              |                  |                        |                        |       |
| Subjects with data                       | 384              | 174                    | 507                    | 1065  |
| At least one AE                          | 165 (43.0)       | 71 (40.8)              | 247 (48.7)             | 483   |
| Drug-related AE, investigator determined | 52 (13.5)        | 36 (20.7)              | 125 (24.7)             | 213   |
| SAE                                      | 8 (2.1)          | 0 (0.0)                | 7 (1.4)                | 15    |
| Discontinued because of AE               | 16 (4.2)         | 7 (4.0)                | 35 (6.9)               | 58    |



|  |            |            |            |      |
|--|------------|------------|------------|------|
| Discontinued because of SAE              | 2 (0.5)    | 0 (0.0)    | 5 (1.0)    | 7    |
| Deaths                                   | 0 (0.0)    | 0 (0.0)    | 0 (0.0)    | 0    |
| <b>Female</b>                            |            |            |            |      |
| Subjects with data                       | 641        | 319        | 784        | 1744 |
| At least one AE                          | 313 (48.8) | 158 (49.5) | 411 (52.4) | 882  |
| Drug-related AE, investigator determined | 102 (15.9) | 73 (22.9)  | 204 (26.0) | 379  |
| SAE                                      | 15 (2.3)   | 3 (0.9)    | 11 (1.4)   | 29   |
| Discontinued because of AE               | 34 (5.3)   | 8 (2.5)    | 45 (5.7)   | 87   |
| Discontinued because of SAE              | 10 (1.6)   | 1 (0.3)    | 4 (0.5)    | 15   |
| Deaths                                   | 1 (0.1)    | 0 (0.0)    | 1 (0.1)    | 2    |

(Source: Modified from Sponsor's ISS Page 425 Tables 5.3.5.3.3:148)

In ISS Tables 5.3.5.3.3:149-150, the sponsor showed that the incidence of somnolence was higher with suvorexant LD in females (8.5%, 27/319) than in males (3.4%, 6/174), but it was similar with suvorexant HD between males (10.1%, 51/507) and females (11.1% (87/784). For placebo, the incidence of somnolence was 4.2% (16/384) for males and 2.3% (15/641) for females. Some other AEs such as headache, abnormal dreams, nightmares, and dry mouth were more frequent in females.

#### Race

The Combined Phase 3 Population 0-3 Months consisted mainly of Caucasian subjects. The population was 77.6% (2181/2809) White race and 12.4% (348/2809) Asian. The small number of subjects in other race subgroups limits the ability to detect risk differences by race.

#### BMI

Obese subjects showed a dose-related increase in frequency of any AEs: 48.2% (82/170) with placebo, 53.6% (30/56) with suvorexant LD, and 56.9% (132/232) with suvorexant HD. In other weight categories, the frequency of AEs was similar and lower than in obese subjects. The rates of the AE somnolence by BMI category was summarized in review section 5.3.4. Below, I summarize the AE categories by BMI subgroups.

**Table 128: Summary of Adverse Events by Demographic Factor BMI in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)**

| Demographic Variable           | Placebo<br>N (%) | Suvorexant LD<br>N (%) | Suvorexant HD<br>N (%) | Total |
|--------------------------------|------------------|------------------------|------------------------|-------|
| Subjects in Overall Population | 1025             | 493                    | 1291                   | 2809  |

|  |            |            |            |      |
|--|------------|------------|------------|------|
| <b>Underweight (BMI &lt;18.5) and Normal range (18.5 ≤ BMI &lt;25)</b> |            |            |            |      |
| Subjects with data   | 449        | 243        | 509        | 1201 |
| At least one AE  | 198 (44.1) | 107 (44.0) | 251 (49.3) | 556  |
| Drug-related AE, investigator determined                               | 65 (14.5)  | 55 (22.6)  | 134 (26.3) | 254  |
| SAE  | 9 (2.0)    | 1 (0.4)    | 6 (1.2)    | 16   |
| Discontinued because of AE   | 25 (5.6)   | 9 (3.7)    | 32 (6.3)   | 66   |
| Discontinued because of SAE  | 8 (1.8)    | 1 (0.4)    | 4 (0.8)    | 13   |
| Deaths   | 1 (0.2)    | 0 (0.0)    | 1 (0.2)    | 2    |
| <b>Overweight (25 ≤ BMI ≤30)</b>                                       |            |            |            |      |
| Subjects with data   | 405        | 194        | 548        | 1147 |
| At least one AE  | 197 (48.6) | 92 (47.4)  | 273 (49.8) | 562  |
| Drug-related AE, investigator determined                               | 61 (15.1)  | 44 (22.7)  | 131 (23.9) | 236  |
| SAE  | 8 (2.0)    | 0 (0.0)    | 8 (1.5)    | 16   |
| Discontinued because of AE   | 15 (3.7)   | 6 (3.1)    | 29 (5.3)   | 50   |
| Discontinued because of SAE  | 2 (0.5)    | 0 (0.0)    | 3 (0.5)    | 5    |
| Deaths   | 0 (0.0)    | 0 (0.0)    | 0 (0.0)    | 0    |
| <b>Obese (BMI &gt; 30)</b>   |            |            |            |      |
| Subjects with data   | 170        | 56         | 232        | 458  |
| At least one AE  | 82 (48.2)  | 30 (53.6)  | 132 (56.9) | 244  |
| Drug-related AE, investigator determined                               | 28 (16.5)  | 10 (17.9)  | 64 (27.6)  | 102  |
| SAE  | 6 (3.5)    | 2 (3.6)    | 4 (1.7)    | 12   |
| Discontinued because of AE   | 10 (5.9 )  | 0 (0.0)    | 18 (7.8)   | 28   |
| Discontinued because of SAE  | 2 (1.2)    | 0 (0.0)    | 2 (0.9)    | 4    |
| Deaths   | 0 (0.0)    | 0 (0.0)    | 0 (0.0)    | 0    |

(Source: Modified from Sponsor's ISS Pages 508-510 Tables 5.3.5.3.3:184-186)

#### 5.5.4 Drug-Disease Interactions

Diseases associated with respiratory compromise – COPD, and OSA are discussed in review section 5.4.5 Special Studies. Also discussed in section 5.4.5 are the safety of suvorexant in subjects with hepatic impairment and renal impairment.

#### Suvorexant-Depression Interaction

Among the three Phase 3 trials, only the long-term safety Trial P009 included subjects with major depression. P009 assessed subjects for depressive features based on the 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16). At baseline, most subjects had no depression, QIDS mean total score for suvorexant HD was 4.5 and placebo 4.3. The sponsor reported in the P009 CSR that there were no significant differences between suvorexant HD and placebo for the change from baseline in QIDS-SR16 total score during the 12-month treatment, but improvements appeared to occur on individual QIDS items related to sleep in favor of suvorexant HD: Item 1, Falling Asleep; and Item 2, Sleep During Night. Other items showed no consistent differences between treatment groups. Further, the sponsor conducted subgroup analyses by QIDS severity at baseline ( $<10$  and  $\geq 10$ ) to determine whether baseline depressive symptoms posed any safety risk. These analyses yielded no evidence of an interaction between baseline depression severity and treatment, suggesting no worsening depression features.

#### 5.5.5 Drug-Drug Interactions

The Phase 2 (P006) and Phase 3 trials (P028 and P029) excluded concomitant use of psychotropic and other CNS active drugs, except as needed brief use of centrally-acting analgesics and muscle relaxants, pseudoephedrine, and sedating antihistamines. The long-term Phase 3 trial P009 allowed use of sedating antihistamines, concomitant use of antidepressant medications, except monoamine oxidase inhibitors and tricyclic antidepressants. Despite the measures, concomitant use of the drugs was uncommon; this limits the ability to draw useful conclusion on drug interactions from the Phase 3 trials. The sponsor conducted Phase 1 drug interaction trials that were reviewed under Clinical Pharmacology.

### 5.6 Additional Safety Evaluations

#### 5.6.1 Human Carcinogenicity

The sponsor's ISS contained no formal assessment of any association of suvorexant with neoplastic disease in the clinical development program. In the combined Phase 3 population, 14 cases of the SOC category of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" occurred within 0-3 months. More subjects who received placebo treatment reported neoplastic disease in the combined Phase 3 population 0-3 months. The incidence of SOC category was 0.5% (6/1291) in the suvorexant HD group and 0.8% (8/1025) in the placebo group. Suvorexant LD recorded no case. Neoplasms found in subjects on suvorexant HD but not in the placebo group include B-cell lymphoma (0.1%, 1/1291), Bowen's disease (0.1%, 1/1291), Haemangioma of liver (0.1%, 1/1291), Morton's neuroma (0.1%, 1/1291), and skin neoplasm (0.1%, 1/1291). Likewise, in the 0-12 months assessments, the incidence of

neoplastic disease was higher in the placebo group (1.1% (11/1291) compared to suvorexant HD (0.9%, 12/1025). These results, added to the relatively short exposure period to suvorexant, prevent a reasonable assessment of any relationship between suvorexant and neoplastic disease.

### 5.6.2 Human Reproduction and Pregnancy Data

The sponsor identified five pregnancies during the suvorexant development program. One case resulted in the birth of a healthy baby. Another had elective abortion. One of the three cases of spontaneous abortion was not confounded by concomitant medications. Although the incidence of spontaneous abortion may be low in the clinical development program, this may be an issue for surveillance. Below, I summarize the pregnancy cases in the suvorexant development program.

Subject AN 02609 in Trial P009, a 19-year-old female on suvorexant HD for 18 days and on Day 19 she had a positive urine pregnancy test. She stopped trial medications, but on Day 32 she had a spontaneous abortion. The estimated gestation of the pregnancy was 32 days at the time of the miscarriage, as she had a negative pregnancy at trial randomization.

Subject AN 02609 in Trial P028, a 36-year-old female on suvorexant LD had a positive pregnancy test on Trial Day 49, about 27 days after her last menstrual period. Her last trial medication was on Day 48. She discontinued from the trial on Day 53; 124 days later she reported gestational diabetes. The subject delivered a healthy female baby by caesarean section 220 days after she discontinued the trial. Afterwards, her gestational diabetes was reported as resolved.

Subject AN 07423 in Trial P028, a 30-year-old female on suvorexant HD reported being pregnant on Trial Day 61. Her last trial medication was on Day 60. She discontinued from the trial on Day 61. She had a spontaneous abortion on Day 72, but she had taken 4 tablets of misoprostol on Days 59 and 60. Ultrasound examination on Day 61 revealed gestational sac without a heartbeat. A second ultrasound 11 days later confirmed an anembryonic gestation and a non-serious AE of blighted ovum. The subject discontinued the trial because of the pregnancy. Concomitant medications include medroxyprogesterone acetate.

Subject AN 12110 in Trial P029, a 25-year-old female on suvorexant LD reported a positive pregnancy test on Trial Day 56 (October 7). Her last menstrual period was on August 30. Her last trial medication was reported as Day 54 and she discontinued from the trial because of allergic dermatitis. On Day 97, she had a spontaneous abortion. At the time of the miscarriage, her estimated gestation of the pregnancy was about 10 weeks. Concomitant medications included desogestrel and almotriptan malate.

Subject AN 0007 in a Phase 1 car driving trial P035, a 32-year-old female had a positive pregnancy test during a post trial evaluation 12 days after her last dose of eight consecutive days of suvorexant 40 mg. She had elective abortion afterwards.

There were no reports of lactation in any of the clinical trials.

### 5.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor has not tested suvorexant in the pediatric population.

Under the Pediatric Research Equity Act (PREA), Merck was required to provide in the NDA an assessment of the safety and effectiveness of suvorexant for the claimed indication insomnia in pediatric subjects unless this requirement was waived, deferred, or inapplicable.

For this NDA, Merck proposes pediatric clinical trials that were previously submitted to the Agency under a Proposed Pediatric Study Request (PPSR) to the suvorexant IND. Merck maintains that the PPSR reflects its general proposal for pediatric development. Further, Merck plans to revise or update the pediatric development plans, as well as the PPSR, based on feedback from the entire NDA review.

The sponsor's pediatric plan includes a request for deferral, a proposal for a full waiver for pediatric subjects under the age of 6 years, and a request for issuance of a Written Request that was included as part of the PPSR submission.

The proposed plan will support the use of suvorexant for the treatment of insomnia in pediatric subjects with comorbid ADHD, ages 6 to less than 18 years.

Under the pediatric plan, Merck has proposed four clinical studies as follows:

- Phase I single dose, study to evaluate the safety, tolerability, and pharmacokinetic, properties of suvorexant in pediatric insomnia subjects with co-morbid ADHD, ages 6 to less than 17 years
- Phase I dose escalation study to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic properties of suvorexant in pediatric insomnia subjects with comorbid ADHD and/or ASD (specifically, high functioning autism (HFA) and/or Asperger's Syndrome (AS)) ages 6 to less than 17.
- Phase III multicenter, 8-week, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of suvorexant in children, 6 to less than 18 years of age, who have insomnia with co-morbid ADHD.
- A long term (up to 12 months) safety extension study for subjects who had participated in the 8-week efficacy trial in order to evaluate the safety of chronic treatment with suvorexant in this population.

Waiver Request

The Sponsor requests waivers for the following indications:

- All age groups of pediatric subjects for the indication of treatment of primary insomnia,
- Pediatric subjects below the age of 6 for the indication of treatment of insomnia in pediatric subjects with co-morbid ADHD.

Merck justified the requests based on the difficulty with identifying and diagnosing insomnia in pediatric subjects below the age of 6 and the understanding that primary insomnia is poorly described in pediatrics, particularly under the age of 12. Also, identification and selection of adolescent subjects with pure insomnia will be difficult because of common overlap of less specific sleep disturbances.

#### Deferral Request

The Sponsor requests a deferral for initiation of the pediatric studies. Merck proposes to initiate the studies after data from a rat oral juvenile toxicity study are available and after sufficient postmarketing data are collected and analyzed (approximately late 2016). Based on projections, Merck suggests that data from the pediatric program would be available for submission to FDA approximately late 2023.

#### 5.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

##### Overdose

None of the subjects who reported overdose in the Phase 3 and Phase 2 trials had other AEs associated with the overdose event.

The sponsor reported that during the Phase 3 trials (P028, P029, P009), 9 (0.7%) on suvorexant HD, 2 (0.4%) on suvorexant LD (total of 11 subjects on suvorexant), and 10 on placebo reported overdose. Yet no other concurrent AEs were observed.

The Thorough QT trial (P022) had two subjects who developed AEs on receiving suvorexant 240 mg. As described above, one subject developed chest pain, myoclonus, and sleep paralysis, with a negative work up for myocardial infarction. The other subject had excessive somnolence and respiratory depression. A third subject AN0024 in the COPD trial P024, a 59-year-old male with moderate COPD was accidentally overdosed at the trial site with suvorexant 280 mg in a day. He reported no AEs.

##### Drug Abuse Potential

FDA's Controlled Substance Staff (CSS) review team is at present reviewing Merck's assessment of suvorexant's abuse potential. The sponsor suggests that the potential for abuse of suvorexant appears to be low, considering the lack of nonclinical evidence of abuse potential and the overall clinical data, which showed no consistent patterns of intentional suvorexant misuse and no obvious withdrawal syndrome.

To examine the abuse potential for suvorexant, the sponsor conducted a Human Abuse Liability trial in recreational polydrug users, Trial P025, and analyzed ECIs potentially relevant to abuse potential in the Phase 1 and Phase 3 trials. The ECIs of interest include: depersonalization, derealization, dissociation, euphoric mood, hallucination, mania, and potential trial medication misuse.

In the Combined Phase 3 Population 0-3 months, the incidence of any ECI potentially relevant to abuse potential was comparable across treatment groups: suvorexant HD 2.0% (26/1291), suvorexant LD 3.2% (16/493), and placebo 2.2% (23/1025). One event of derealization occurred in the suvorexant HD group. Other events were of drug maladministration, yielding an incidence of 1.9% (25/1291) in the suvorexant HD group.

In the 0-6 months' evaluation, the incidence of abuse potential events was higher in the suvorexant group compared to placebo: suvorexant LD 4.1% (20/493) and placebo 2.5% (19/767). All events were cases of drug maladministration.

In 0-12 months' evaluation, the events were similar between treatment groups: suvorexant HD 2.6% (34/1291), and placebo 3.0% (31/1025). Among the eight additional events in the suvorexant HD group, one event of auditory hallucination and one of visual hallucination were observed in the 0-12 months. Other events were drug maladministration. The sponsor explained that the majority of drug maladministration events (96.8%) were accidental where subjects lost trial medication (pills or bottles) or denied taking additional trial medication.

For the Phase 2 trial, ECIs of abuse potential were not prespecified, but a retrospective data review yielded two cases of hallucinations: One visual hallucination occurred in a 62 year-old female on suvorexant 80 mg (Day 14 of treatment); the other occurred in a 45 year-old male on Day 1 of the placebo washout following suvorexant 40 mg treatment.

#### Trial in Recreational Polydrug Users to Evaluate Abuse Potential of Suvorexant (Trial P025)

P0025 was a randomized, double-blind, balanced, placebo- and active comparator-controlled, 6-way crossover study to evaluate the abuse potential of single doses of suvorexant compared to placebo and two doses of zolpidem in healthy male and female recreational polydrug users, aged 20 to 53 years. The subjects received one of the following six treatments per treatment period in a randomized, double-blinded, and balanced fashion: Placebo, Zolpidem 15 mg, Zolpidem 30 mg, Suvorexant 40 mg, Suvorexant 80 mg, and Suvorexant 150 mg. The treatment periods were separated by washout periods of at least 10 days to avoid carry-over effects. The subjects needed to have a negative urine drug screen to enter a dosing period. The primary endpoint was "Drug Liking" visual analog scale (VAS), based on a scores ranging from 0 for "Strong

Disliking” to 100 for “Strong Liking” in response to a question: “At this moment, my liking for this drug is ... “

#### Trial P025 Results Summary

Based on the primary outcome, “Drug Liking VAS,” suvorexant in all tested doses (40 mg, 80 mg, and 150 mg) showed greater abuse potential than placebo in recreational polydrug users. The mean peak effect difference from placebo for each group was 22.84 for suvorexant 40 mg, 21.99 for suvorexant 80 mg, and 20.44 for suvorexant 100 mg. The treatment effect appeared to be similar to that of zolpidem. Below is the sponsor’s summary of the primary endpoint analyses.

**Table 129: Peak Effect for Drug Liking Visual Analog Scale (VAS), Following Single-Dose Treatment with Suvorexant, Zolpidem, or Placebo in Healthy Recreational Polydrug Users (Trial P025)**

|  | Suvorexant<br>40 mg              | Suvorexant<br>80 mg              | Suvorexant<br>150 mg              | Zolpidem<br>15 mg                | Zolpidem<br>30 mg                | Placebo                |
|--|----------------------------------|----------------------------------|-----------------------------------|----------------------------------|----------------------------------|------------------------|
| N  | 34                               | 35                               | 34                                | 33                               | 33                               | 34                     |
| <b>Time (hr) to Peak Effect-max</b>  |                                  |                                  |                                   |                                  |                                  |                        |
| Mean<br>(SD)   | 2.13<br>( 2.24)                  | 3.03<br>( 2.93)                  | 2.94<br>( 3.11)                   | 2.15<br>( 1.67)                  | 3.09<br>( 2.74)                  | 1.85<br>( 2.48)        |
| <b>Peak Effect-max</b>   |                                  |                                  |                                   |                                  |                                  |                        |
| Mean<br>95% CI   | 76.38<br>( 70.3, 82.5)           | 75.53<br>( 69.5, 81.5)           | 73.98<br>( 67.9, 80.1)            | 78.40<br>( 72.3, 84.5)           | 81.62<br>( 75.5, 87.8)           | 53.54<br>( 47.5, 59.6) |
| <b>Difference vs Placebo</b>   |                                  |                                  |                                   |                                  |                                  |                        |
| Mean<br>95% CI <sup>†</sup><br>P-value   | 22.84<br>( 15.9, 29.7)<br><.0001 | 21.99<br>( 15.1, 28.9)<br><.0001 | 20.44<br>( 13.5, 27.3)<br><.0001  | 24.86<br>( 17.9, 31.9)<br><.0001 | 28.08<br>( 21.1, 35.1)<br><.0001 |                        |
| <b>Difference vs Zolpidem 15 mg</b>  |                                  |                                  |                                   |                                  |                                  |                        |
| Mean<br>95% CI <sup>‡</sup><br>P-value   | -2.02<br>( -9.0, 5.0)<br>0.5691  | -2.87<br>( -9.8, 4.1)<br>0.4176  | -4.43<br>( -11.4, 2.6)<br>0.2137  |                                  |                                  |                        |
| <b>Difference vs Zolpidem 30 mg</b>  |                                  |                                  |                                   |                                  |                                  |                        |
| Mean<br>95% CI <sup>‡</sup><br>P-value   | -5.24<br>( -12.2, 1.7)<br>0.1395 | -6.09<br>( -13.0, 0.9)<br>0.0853 | -7.64<br>( -14.6, -0.7)<br>0.0318 |                                  |                                  |                        |
| <sup>†</sup> For suvorexant vs placebo, CI below 15 supports the first primary hypothesis. For zolpidem vs. placebo, CI above zero supports the second primary hypothesis.<br><sup>‡</sup> For suvorexant vs. zolpidem, CI below zero supports the secondary hypothesis. |                                  |                                  |                                   |                                  |                                  |                        |

(Source: Sponsor’s submission P025 Clinical Study Report Page 83 Table 11-1)

The incidence of abuse potential AEs was lower in suvorexant dose groups compared to zolpidem: 17.6% (6/34) for suvorexant 150mg, 20.0% (7/35) suvorexant 80mg, 17.1% (6/35) suvorexant 40mg, 54.3% (19/35) zolpidem 30mg, 38.2% (13/34) zolpidem 15mg, 0.0% (0/36) placebo. When the dose groups were combined for each drug, the



incidences of abuse potential AEs were 30.6% for suvorexant and 58.3% for zolpidem. The incidence of euphoric mood was lower in suvorexant dose groups compared to zolpidem: 5.9% (2/34) for suvorexant 150mg, 2.9% (1/35) suvorexant 80mg, 5.7% (2/35) suvorexant 40mg, 8.6% (3/35) zolpidem 30mg, 11.8% (4/34) zolpidem 15mg, 0.0% (0/36) placebo. Hallucination occurred in 0.0% of the suvorexant, zolpidem 15 mg, and placebo groups, but occurred in 8.6% (3/35) of zolpidem 30 mg group.

#### Tolerance

Merck stated that, with the efficacy results of the Phase 3 trials, there was no evidence to suggest tolerance to drug effect during treatment duration ranging from 3 months to 1 year.

#### Withdrawal

In the Phase 3 trials, Merck defined withdrawal as emergence or worsening on three or more items on the Tyrer Withdrawal Symptom Questionnaire (WSQ) on a night of the first three nights of the Run-out Phase. The proportion of subjects with the positive WSQ responses after switching from suvorexant to placebo was compared to those who continued on suvorexant. Merck noted no significant differences at any timepoint or by suvorexant dose between subjects switched from suvorexant to placebo compared to those who continued suvorexant. The results summarized below, from the sponsor's ISS table, provide information on withdrawal effects based on "Yes" responses on 3 or more emergent or worsening withdrawal symptom out of 20 WSQ Items, and obtained in the Combined Phase 3 Population Run-out Phase following trial treatment.

**Table 130: Analysis of Withdrawal Based on Response to Withdrawal Symptom Questionnaire Items in the Combined Phase 3 Population Run-out Phase Following Treatment Phase (P028, P029, and P009)**

| Protocols<br>028+029+009  | Night of Run-out |          |         |                                    |         |                     |                           |          |
|---|------------------|----------|---------|------------------------------------|---------|---------------------|---------------------------|----------|
|   | Night 1          |          | Night 2 |                                    | Night 3 |                     | Across Nights 1, 2, and 3 |          |
|   | N                | n (%)    | N       | n (%)                              | N       | n (%)               | N                         | n (%)    |
| MK LD / MK LD   | 157              | 6 (3.8)  | 160     | 5 (3.1)                            | 151     | 7 (4.6)             | 172                       | 11 (6.4) |
| MK LD / PBO   | 184              | 7 (3.8)  | 186     | 13 (7.0)                           | 182     | 9 (4.9)             | 197                       | 17 (8.6) |
| MK HD / MK HD   | 398              | 6 (1.5)  | 396     | 16 (4.0)                           | 387     | 9 (2.3)             | 424                       | 23 (5.4) |
| MK HD / PBO   | 393              | 12 (3.1) | 383     | 13 (3.4)                           | 381     | 8 (2.1)             | 414                       | 22 (5.3) |
| PBO / PBO   | 677              | 17 (2.5) | 681     | 19 (2.8)                           | 664     | 18 (2.7)            | 726                       | 36 (5.0) |
| Pairwise Comparison   |                  |          |         | Point Differences (%) <sup>†</sup> |         | 95% CI <sup>‡</sup> |                           |          |
| Night 1   |                  |          |         |                                    |         |                     |                           |          |
| MK HD / MK HD versus MK HD / PBO  |                  |          |         | -1.6                               |         | (-4.0, 0.5)         |                           |          |
| MK LD / MK LD versus MK LD / PBO  |                  |          |         | 0.1                                |         | (-4.3, 4.8)         |                           |          |
| Night 2   |                  |          |         |                                    |         |                     |                           |          |
| MK HD / MK HD versus MK HD / PBO  |                  |          |         | 0.6                                |         | (-2.2, 3.4)         |                           |          |
| MK LD / MK LD versus MK LD / PBO  |                  |          |         | -3.9                               |         | (-8.9, 0.9)         |                           |          |
| Night 3   |                  |          |         |                                    |         |                     |                           |          |
| MK HD / MK HD versus MK HD / PBO  |                  |          |         | -0.7                               |         | (-4.0, 2.4)         |                           |          |
| MK LD / MK LD versus MK LD / PBO  |                  |          |         | -0.2                               |         | (-5.0, 5.1)         |                           |          |
| Night 1, 2, or 3  |                  |          |         |                                    |         |                     |                           |          |
| MK HD / MK HD versus MK HD / PBO  |                  |          |         | 0.2                                |         | (-3.0, 3.3)         |                           |          |
| MK LD / MK LD versus MK LD / PBO  |                  |          |         | -2.1                               |         | (-7.7, 3.5)         |                           |          |
| Worsening or emerging were compared to end of treatment.  |                  |          |         |                                    |         |                     |                           |          |
| <sup>†</sup> Total of three or more symptoms across the three nights (e.g., one withdrawal symptom on Night 1 and 2 other withdrawal symptoms on Night 3). Worsening or emerging when compared to end of treatment. |                  |          |         |                                    |         |                     |                           |          |
| <sup>‡</sup> 95% Confidence Interval computed using a method by Miettinen and Nurminen stratified for study (using sample size as weight).  |                  |          |         |                                    |         |                     |                           |          |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.   |                  |          |         |                                    |         |                     |                           |          |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.   |                  |          |         |                                    |         |                     |                           |          |
| PBO = Placebo.  |                  |          |         |                                    |         |                     |                           |          |
| MK LD / MK LD, MK LD / PBO, MK HD / MK HD, MK HD / PBO, PBO / PBO = therapy received during Treatment phase / therapy received during Run-out phase.  |                  |          |         |                                    |         |                     |                           |          |
| n = Number of patients with withdrawal.   |                  |          |         |                                    |         |                     |                           |          |

(Source: Sponsor's submission ISS Page 582 Table 5.3.5.3.3:208)

Subgroup analyses were limited by the small number of events. On Night 1, elderly subjects switched from suvorexant HD to placebo reported significantly more responses to the WSQ (4.4% [n=9]) compared to subjects continuing on suvorexant HD (0.9% [n=2]). The intergroup difference in WSQ responses for "suvorexant HD continued on suvorexant HD" versus "suvorexant HD switched to placebo" was -5.3 (95% CI, -11.0, -1.0). Merck suggests that this difference does not appear to be clinically important because of the low incidence of withdrawal symptoms overall, the absence of patterns observed in individual WSQ item responses, and lack of subjective report of AEs associated with potential withdrawal.

Also, Merck found no reports of AEs associated with potential withdrawal, based on predefined terms, during the Run-out Phase of Trials P028 and P029, Randomized

Discontinuation Phase of Trial P009, and placebo-washout period of the Phase 2 trial P006. The sponsor summarized the overall withdrawal assessment as suggesting the absence of withdrawal phenomenon associated with abrupt discontinuation of suvorexant.

### Rebound Effects

The sponsor evaluated rebound insomnia objectively with PSG measurements of WASO and LPS, and subjectively with sTST, sTSO, and sWASO values. Both types of parameters had their values at each time point on any of the three days after treatment discontinuation, the Run-out Phase after core trial treatment, compared to pretreatment baseline values. Then the sponsor analyzed percentage of subjects who developed worsening of each parameter and the mean change from baseline in the parameter values. Specific analysis of interest was to compare each suvorexant dose group switched to placebo and group of placebo subjects continued on placebo in the Run-out Phase of the trials.

### Subjective Parameters

#### Rebound Effects by sTST

In the combined Phase 3 population (Trials P028, P029, and P009), more subjects who switched from suvorexant HD to placebo (48.5%, 233/480) showed a decrease in total sleep time sTST on any of the three nights compared to subjects continued on placebo (37.2%, 295/793). The treatment difference between the groups was 10.8% (95% CI; 5.2, 16.5); note that the confidence interval excludes 1. For subjects switching from suvorexant LD to placebo, the treatment difference from the continued placebo group was a smaller 4.8% (95% CI; -2.7, 12.4). The sponsor's table below shows the sTST values on the different nights. In other analyses, the mean sTST did not decrease from baseline in any treatment group at any time point.

**Table 131: sTST Rebound Effects in Combined Phase 3 Population Run-out Phase Following Treatment Phase (P028, P029, and P009)**

| Protocols<br>028+029+009   | Night of Run-out |            |         |                                    |         |                     |                  |            |
|--|------------------|------------|---------|------------------------------------|---------|---------------------|------------------|------------|
| Treatment  | Night 1          |            | Night 2 |                                    | Night 3 |                     | Night 1, 2, or 3 |            |
|  | N                | n (%)      | N       | n (%)                              | N       | n (%)               | N                | n (%)      |
| MK LD / MK LD  | 184              | 44 (23.9)  | 181     | 38 (21.0)                          | 184     | 39 (21.2)           | 194              | 76 (39.2)  |
| MK LD / PBO  | 206              | 55 (26.7)  | 195     | 39 (20.0)                          | 201     | 53 (26.4)           | 213              | 88 (41.3)  |
| MK HD / MK HD  | 451              | 90 (20.0)  | 441     | 78 (17.7)                          | 431     | 71 (16.5)           | 477              | 148 (31.0) |
| MK HD / PBO  | 448              | 157 (35.0) | 449     | 132 (29.4)                         | 453     | 136 (30.0)          | 480              | 233 (48.5) |
| PBO / PBO  | 744              | 201 (27.0) | 755     | 164 (21.7)                         | 733     | 165 (22.5)          | 793              | 295 (37.2) |
| Pairwise Comparison  |                  |            |         | Point Differences (%) <sup>†</sup> |         | 95% CI <sup>‡</sup> |                  |            |
| Night 1  |                  |            |         |                                    |         |                     |                  |            |
| MK HD / PBO versus PBO / PBO   |                  |            |         | 8.1                                |         | ( 2.6, 13.6)        |                  |            |
| MK LD / PBO versus PBO / PBO   |                  |            |         | -0.1                               |         | (-6.8, 7.2)         |                  |            |
| Night 2  |                  |            |         |                                    |         |                     |                  |            |
| MK HD / PBO versus PBO / PBO   |                  |            |         | 6.6                                |         | ( 1.5, 11.9)        |                  |            |
| MK LD / PBO versus PBO / PBO   |                  |            |         | -0.4                               |         | (-6.5, 6.4)         |                  |            |
| Night 3  |                  |            |         |                                    |         |                     |                  |            |
| MK HD / PBO versus PBO / PBO   |                  |            |         | 6.0                                |         | ( 0.9, 11.3)        |                  |            |
| MK LD / PBO versus PBO / PBO   |                  |            |         | 6.0                                |         | (-0.6, 13.2)        |                  |            |
| Night 1, 2, or 3   |                  |            |         |                                    |         |                     |                  |            |
| MK HD / PBO versus PBO / PBO   |                  |            |         | 10.8                               |         | ( 5.2, 16.5)        |                  |            |
| MK LD / PBO versus PBO / PBO   |                  |            |         | 4.8                                |         | (-2.7, 12.4)        |                  |            |
| <sup>†</sup> Percentage Point Difference.  |                  |            |         |                                    |         |                     |                  |            |
| <sup>‡</sup> 95% Confidence Interval computed using a method by Miettinen and Nurminen stratified for study (using sample size as weight).           |                  |            |         |                                    |         |                     |                  |            |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.  |                  |            |         |                                    |         |                     |                  |            |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.  |                  |            |         |                                    |         |                     |                  |            |
| PBO = Placebo.   |                  |            |         |                                    |         |                     |                  |            |
| MK LD / MK LD, MK LD / PBO, MK HD / MK HD, MK HD / PBO, PBO / PBO = therapy received during Treatment phase / therapy received during Run-out phase. |                  |            |         |                                    |         |                     |                  |            |
| N = Number of randomized patients who took at least one dose of Run-out phase study medication and has a value at baseline and during Run-out phase. |                  |            |         |                                    |         |                     |                  |            |
| n = Number of patients with rebound.   |                  |            |         |                                    |         |                     |                  |            |

(Source: Sponsor's submission ISS Page 594 Table 5.3.5.3.3.:216)

Because the sTST pattern was suggestive of rebound effect, I examined the sTST results in the Age subgroups. In ISS Table 5.3.5.3.3.:231, the sponsor showed that more elderly subjects who switched from suvorexant HD to placebo (59.2%, 138/233) registered a decrease in sTST on any of the three nights compared to subjects continued on placebo (38.4%, 138/359). The treatment difference between the groups was 21.1% (95% CI; 12.7, 29.1). Similar treatment differences occurred on each of the individual three nights of the Run-out Phase. Likewise, more elderly subjects who switched from suvorexant LD to placebo (51.1%, 45/88) recorded an sTST decrease on any of the three nights compared to subjects continued on placebo (38.4%, 138/359), with a treatment difference of 14.4% (95% CI; 2.5, 26.1). In the elderly subjects on Night

1, sTST increased in the continued placebo group with the mean change in sTST from baseline of 39.3 minutes. In contrast, the mean change was 4.3 minutes for suvorexant HD to placebo and 12.1 minutes for suvorexant LD to placebo transitions. In non-elderly subjects, the percentage of subjects with a decrease in sTST on any night from baseline was comparable across all treatment groups: suvorexant HD to placebo 38.5%, suvorexant LD to placebo 34.4%, and continued placebo 36.2%,

#### Rebound Effects by sTSO

Neither the percentage of subjects showing an increase in time to sleep onset sTSO nor the mean change from baseline analyses suggested suvorexant rebound effects. Percentage of subjects who reported an increase in sTSO on any of the three nights was similar across treatment groups: suvorexant HD/placebo, 37.7% (181/480); suvorexant LD/placebo, 36.2% (77/213); and placebo/placebo, 34.0% (270/793).

#### Rebound Effects by sWASO

Again, neither the percentage of subjects showing an increase in awakenings after sleep onset sWASO nor the mean change from baseline analyses suggested suvorexant rebound effects. Percentage of subjects who reported an increase in sWASO on any of the three nights was similar across treatment groups: suvorexant HD/placebo, 42.1% (201/478); suvorexant LD/placebo, 40.8% (87/213); and placebo/placebo, 37.1% (293/790). The mean change in sWASO did not increase in any of the treatment groups.

#### Objective Parameters

##### Rebound Effects by WASO

More subjects who switched from suvorexant HD to placebo (33.6%, 71/211) showed an increase in PSG-measured WASO on any of the three nights compared to subjects continued on placebo (24.1%, 105/436). The sponsor's table below shows the difference in percentage of subjects with WASO increases between suvorexant HD to placebo and placebo continued treatment transitions, a treatment difference of 9.6% (95% CI, 2.2, 17.2). However, no mean increases in WASO relative to baseline were observed in any treatment group.

**Table 132: Rebound Effects Assessment by Proportion of Subjects with WASO Increases after Suvorexant Discontinuation in Trials P028 and P029**

| Protocols 028+029<br>Treatment | First Night of Run-out             |                     |
|--------------------------------|------------------------------------|---------------------|
|                                | N                                  | n (%)               |
| MK LD / MK LD                  | 121                                | 11 (9.1)            |
| MK LD / PBO                    | 129                                | 43 (33.3)           |
| MK HD / MK HD                  | 210                                | 18 (8.6)            |
| MK HD / PBO                    | 211                                | 71 (33.6)           |
| PBO / PBO                      | 436                                | 105 (24.1)          |
| Pairwise Comparison            | Point Differences (%) <sup>†</sup> | 95% CI <sup>‡</sup> |
| MK HD / PBO versus PBO / PBO   | 9.6                                | ( 2.2, 17.2)        |
| MK LD / PBO versus PBO / PBO   | 8.6                                | ( -0.0, 18.0)       |

<sup>†</sup> Percentage Point Difference.  
<sup>‡</sup> 95% Confidence Interval computed using a method by Miettinen and Nurminen stratified for study (using sample size as weight).  
MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.  
MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.  
PBO = Placebo.  
MK LD / MK LD, MK LD / PBO, MK HD / MK HD, MK HD / PBO, PBO / PBO = therapy received during Treatment phase / therapy received during Run-out phase.  
N = Number of randomized patients who took at least one dose of Run-out phase study medication and has a value at baseline and during Run-out phase.  
n = Number of patients with rebound.

(Source: Sponsor's submission ISS Page 590 Table 5.3.5.3.3.:212)

#### Rebound Effects by LPS

Neither the percentage of subjects showing an increase LPS nor the mean change from baseline analyses suggested suvorexant rebound effects. Percentage of subjects who reported an increase in LPS on any of the three nights was similar across treatment groups: suvorexant HD/placebo, 16.8% (36/214); suvorexant LD/placebo, 18.3% (24/131); and placebo/placebo, 16.4.0% (72/439). No group recorded worsening of mean LPS change from baseline. All treatment groups showed similar mean LPS decreases from baseline: suvorexant HD/placebo, -33.6 minutes; suvorexant LD/placebo, -34.5 minutes; and placebo/placebo, -32.7 minutes.

#### Rebound Effects in the Phase 2 Trial P006

The sponsor summarized the Phase 2 trial experience on suvorexant by stating that the results from the Phase 2 trial did not show evidence of clinically meaningful return of insomnia symptoms based on assessment of sleep onset and maintenance. Below, I present some of the findings of the Phase 2 trial from the sponsor's ISS regarding rebound effects.

#### Rebound Effects by sTST

- The percentage of subjects with an sTST decrease from baseline was higher with suvorexant 40 mg on Night 2 and with suvorexant 20 mg on any night compared to placebo.

- The mean change in sTST from baseline in minutes significantly decreased on Night 2 with suvorexant 40 mg only.

#### Rebound Effects by sWASO

- The percentage of subjects with a significant increase in sWASO from baseline was seen with suvorexant 10 mg on Night 1, suvorexant 80 mg on Nights 1 and 3, and suvorexant 40 mg on any night.
- The mean change in sWASO from baseline in minutes significantly increased with suvorexant 10 mg on Night 1 only.

#### Rebound Effects by sTSO

- The percentage of subjects with a significant increase in sTSO from baseline was seen with suvorexant 10 mg on any night.

*Reviewer Note: The sponsor summarized the rebound effects as showing no clinically meaningful differences between suvorexant and placebo, based on mean change from baseline on either sleep onset or maintenance measures. Further, no rebound effects were observed on measures of sleep onset based on the percentage of subjects with any worsening compared to baseline. Interestingly, the sponsor suggests that rebound effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, I believe that sTST findings for suvorexant, in both doses and in the elderly subgroup, are suggestive of a rebound effect.*

## 5.7 Additional Submissions / Safety Issues

### 4-Month Safety Update Report

On 7 December 2012 the sponsor submitted a 4-month safety update report (SUR) that included the clinical study report for a Phase 1 trial: Protocol 051: A Two-Part, Single-Dose, Comparative Bioavailability Study of Four Dose Strengths of MK-4305 Tablets under Fasting Conditions.

This non-IND trial was conducted between 29 April 2012 and 11 May 2012 in Canada to meet Japanese requirements. All other suvorexant studies were submitted to the NDA and there are no ongoing trials.

This trial was a Phase 1, randomized, open-label, 2-part, 2-period, single dose, 2-treatment, 2-sequence, crossover trial conducted in a single center. The trial compared bioavailability of different drug strengths that achieved the same dose: two 15 mg tablets compared to one 30 mg tablet, and two 20 mg tablets compared to one 40 mg tablet. Healthy young adults (N=120), aged 20-55 years, and including 63 males and 57 females were enrolled.

In Part 1, subjects (N=60) were randomized to dosing sequence AB or BA, where A = 2 x 15 mg dose and B = 1 x 30 mg dose. Each treatment was a total single dose of 30 mg. Part 2 subjects (N=60) were randomized to dosing sequence CD or DC, where C = 2 x 20 mg dose and B = 1 x 40 mg dose. Each Part 2 treatment was a total single dose of 40 mg.

Over a 2-week period, each subject under fasting conditions received a single dose of the trial treatment in each period. The two single-dose treatments of a sequence were separated by a 7-day interval. The outcomes were PK and safety assessments.

On completion of the trial, two 15 mg tablets were found bioequivalent to one 30 mg tablet. Also, two 20 mg tablets and one 40 mg tablet were bioequivalent. With regards to safety, the trial reported no deaths, no SAEs, no ECIs, and no discontinuations resulting from AEs.

*Reviewer Note: I agree with the sponsor's opinion that this 4-month SUR data do not impact the sections 4-6 of the proposed draft labeling. Also, the data from the 32 Clinical Pharmacology studies revealed no reports of cataplexy, motor vehicle accidents, falls or complex sleep related behaviors..*

## **6 Postmarket Experience**

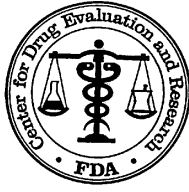
Suvorexant is not approved in any country. As a result, there is no postmarketing experience with the drug.



## 7 Appendices

### 7.1 Literature Review/References

1. Hoeber P, Dorffner G, Beneš H, Penzel T, Danker-Hopfe H, Barbanoj MJ, Pillar G, Saletu B, Polo O, Kunz D, Zeitlhofer J, Berg S, Partinen M, Bassetti CL, Högl B, Ebrahim IO, Holsboer-Trachsler E, Bengtsson H, Peker Y, Hemminger UM, Chiossi E, Hajak G, Dingemans J. Orexin receptor antagonism, a new sleep-enabling paradigm: a proof-of-concept clinical trial. *Clin Pharmacol Ther.* 2012 Jun;91(6):975-85. doi: 10.1038/clpt.2011.370.
2. Kukkonen JP. Physiology of the orexinergic/hypocretinergic system: a revisit in 2012. *Am J Physiol Cell Physiol.* 2013 Jan 1;304(1):C2-32. doi: 10.1152/ajpcell.00227.2012. Epub 2012 Oct 3.
3. Morin CM, Benca R. Chronic insomnia. *Lancet.* 2012 Mar 24;379:1129-41
4. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet.* 2000 Jan 1;355(9197):39-40.
5. The Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report February 27, 2013. Drowsy Driving-19 States and the District of Columbia, 2009-2010. *JAMA.* 2013;309(8):760-762.
6. Mignot E. Physiology: The perfect hypnotic? *Science.* 2013 Apr 5;340(6128):36-8.
7. Morin CM, Bélanger L, LeBlanc M, Ivers H, Savard J, Espie CA, Mérette C, Baillargeon L, Grégoire JP. The natural history of insomnia: a population-based 3-year longitudinal study. *Arch Intern Med.* 2009 Mar 9;169(5):447-53.
8. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med.* 2007 Aug 15;3(5 Suppl):S7-10.
9. Rosenberg RP. Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. *Ann Clin Psychiatry.* 2006 Jan-Mar;18(1):49-56.
10. Vermeeren A. Residual effects of hypnotics: epidemiology and clinical implications. *CNS Drugs.* 2004;18(5):297-328.



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA Serial**

**Number:** 204569 (0000)

**Drug Name:** Suvorexant

**Indication(s):** Insomnia

**Applicant:** Merck

**Date(s):**



**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics I

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**Keyword(s):** Multiplicity; Dose-Response; Randomization Ratio; Dosing by Age Group

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## 1 EXECUTIVE SUMMARY

The clinical trial efficacy data provided in this application seems to clearly support the efficacy of Suvorexant for Sleep Maintenance. In the application there are two similarly designed 3 month placebo controlled phase 3 studies (study 28 and study 29) and one early phase 2B dose finding crossover study. The evidence for an effect on Sleep Onset was weaker than that for maintenance. In one study at the 3 month visit night the effect on latency as measured objectively by Polysomnography did not achieve statistical significance, thus failing to replicate the statistically significant effect demonstrated in the other study. However, the high dose effect at Month 1 was significant in both studies and there was replication of the effect on the corresponding subjective assessment, the patient reported weekly average of the Time to Sleep Onset, at Month 3 (as well as Month 1).

The Suvorexant phase 3 studies were ambitious in that they aimed to demonstrate effects for both elderly and non-elderly patients on both Sleep Maintenance and Onset, in terms of both an objective and a subjective assessment for each, in the same study. They also put more weight on the high dose (the low dose had 30 to 40% less patients by design) and the multiplicity adjustment method tested the high dose first, such that the low dose could only be tested if the high dose was first significant at multiple timepoints on both subjective and objective assessments. After taking into account the prespecified adjustments for multiple testing the low dose was only statistically significant for objective latency to persistent sleep in study 28 (not significant for objective latency in study 29 or for subjective time to sleep onset in study 28 or study 29). However, the low dose was statistically significant for objective and subjective primary endpoints for maintenance in both of these studies.

In the non-elderly next day driving study the 40 mg dose had significant asymmetry of differences from placebo with significantly more being positive and higher than the impairment threshold of interest (2.40) on both days 2 and 9. The low dose also was significant on day 2 but not on day 9. There was also some other evidence that the driving effect might be dose related which would suggest considering a lower dose if it was still efficacious.

In a prior phase 2B crossover study in non-elderly adults a lower dose, 10 mg, as well as a higher dose, 80 mg, were studied in addition to the adult doses used later in Phase 3. There was a suggestion of efficacy of 10 mg, particularly for wake time after sleep onset, based on this study data but there is no existing means of replication for the 10 mg dose and no 10 mg data for the elderly.

## 2 INTRODUCTION

### 2.1 Overview

The IND number associated with the development of this drug for this indication is IND 101,847. Suvorexant is a selective antagonist for orexin receptors OX<sub>1</sub>R and OX<sub>2</sub>R. In the two confirmatory efficacy trials of suvorexant (P028 and P029), efficacy and safety of suvorexant were evaluated in replicate core 3-month Treatment Phases. These trials were similarly designed as combined-age (with enrollment of both non-elderly and elderly adults) and combined-measure studies (with data collected for both objective and subjective efficacy measures). Based on the results of the Phase 2b 2 period crossover trial (P006) comparing each of 10 mg, 20 mg, 40 mg, and 80 mg separately with placebo, the Phase 3 dose of primary focus, to be confirmed in non-elderly patients (< 65 years), was 40 mg (referred to as "suvorexant high dose [HD]"). Based on evidence for slightly higher exposures in elderly patients in Phase 1 studies, suvorexant HD in elderly patients was 30 mg. Thus exposure levels for suvorexant HD were anticipated to be similar for non-elderly and elderly patients enabling the pooling of efficacy and safety data across age groups. A lower dose (LD) of 20 mg in non-elderly and 15 mg in elderly was also evaluated in these two trials, but with a smaller sample size than HD (the sponsor's intention was to pool the samples across the two studies for more precise estimation of LD effects). Selection of patients with insomnia in the confirmatory trials (P028 and P029) relied on objective polysomnograph (PSG) criteria for the PQ-Cohort (patients with both PSG and e-diary data) and subjective questionnaire (e-diary) criteria for the Q-Cohort (patients with e-diary data only). Table 1 summarizes the features of the key efficacy studies.

**Table 1 Key Suvorexant Efficacy Studies**

| Study             | # of Subjects per Arm  | Follow-up Period                            | Completer N (%)  | Primary Efficacy   | Study Population                                     |
|-------------------|--|---|--|--|--|
| P28:<br>Phase 3   | <u>N</u><br>Placebo: 385<br>LD 255<br>HD 383   | 3 months                                    | 341 (88.6)<br>230 (90.6)<br>345 (90.1)   | <b><u>Latency</u>    <u>Maintenance</u></b><br><b>LPS        WASO</b><br><b>sTSO       sTST</b><br><b>at months 1 and 3</b><br><b>PSG and diary based measures</b> | 42%<br>Elderly<br>34%<br>North America<br>62%Female  |
| P29<br>Phase 3    | <u>N</u><br>Placebo: 389<br>LD 240<br>HD 392   | 3 months                                    | 330 (85.3%)<br>205 (85.4%)<br>346 (88.3%)  | <b><u>Latency</u>    <u>Maintenance</u></b><br><b>LPS        WASO</b><br><b>sTSO       sTST</b><br><b>at months 1 and 3</b><br><b>PSG and diary based measures</b> | 41%<br>Elderly<br>48%<br>North America<br>67%Female  |
| P006:<br>Phase 2b | 2 Period Crossover<br>Placebo: 10 mg<br>10 mg: Placebo<br>Placebo: 20 mg<br>20 mg: Placebo<br>Placebo: 40 mg<br>40 mg: Placebo<br>Placebo: 80 mg<br>80 mg: Placebo | 1 month for each Period plus 1 week washout | 31(94%)<br>32(94%)<br>33(91%)<br>32(81%)<br>32(94%)<br>32(84%)<br>31(90%)<br>31(90%) | <b>Sleep Efficiency at Night 1 and 28</b><br><b>Secondary Endpoints WASO and LPS</b>   | Non-Elderly<br>87%<br>North America<br>58%<br>Female |

## 2.2 Data Sources

At the time of review the locations of the primary endpoint data for the two key studies were as follows. The polysomnographic endpoint data are in the files ADPSG and the subjective endpoint weekly average data are in the files ADMDD.

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[\\Cdsub1\evsprod\NDA204569\0000\m5\datasets\p029\analysis\datasets\](\\Cdsub1\evsprod\NDA204569\0000\m5\datasets\p029\analysis\datasets)

Analysis datasets for the phase 2b crossover study, P006, were not provided in the original submission but were provided later during the review following an FDA request for them.

[\\Cdsub1\evsprod\NDA204569\0014\m5\datasets\p006\analysis\datasets\](\\Cdsub1\evsprod\NDA204569\0014\m5\datasets\p006\analysis\datasets)

### 3 STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study P028

The primary therapy period of this study was from 25-May-2010 to 22-Nov-2011.

The original protocol (amendment 2) was dated 18 February 2010 and there were protocol clarification letters dated 05 May 2010, 31 March 2010 and 01 Aug 2011. Changes to the statistical analysis plans as detailed in the protocol were made in memos dated 31 August 2011 and 8 December 2011 .

##### 3.1.1.1 Study Design and Statistical Methods

###### **Objectives:**

###### Maintenance

1. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by change from baseline in mean subjective total sleep time (sTSTm) on the daily sleep e-diary at Month 1.
2. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by the change from baseline in wakefulness after persistent sleep onset (WASO) at Month 1.
3. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by change from baseline in mean subjective total sleep time (sTSTm) on the daily sleep e-diary at Month 3.
4. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by the change from baseline in wakefulness after persistent sleep onset (WASO) at Month 3.

###### Onset

5. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by change from baseline in mean subjective time to sleep onset (sTSOm) on the daily sleep e-diary at Month 1.
6. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by the change from baseline in latency to onset of persistent sleep (LPS) at Month 1.

7. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by change from baseline in mean subjective time to sleep onset (sTSOm) on the daily sleep e-diary at Month 3.
8. To evaluate the efficacy of MK-4305 high dose compared with placebo in improving insomnia, as measured by the change from baseline in latency to onset of persistent sleep (LPS) at Month 3.

This was a randomized, double-blind (with in-house blinding), placebo-controlled, parallel group, multicenter questionnaire and PSG study to assess the safety, tolerability and efficacy of MK-4305 in the treatment of patients with Primary Insomnia.

The overall study was comprised of a screening period (including a 2-week single-blind placebo run-in), a 3-month double-blind core treatment period, an optional 3-month double-blind extension, and a 1-week double-blind run-out period at the conclusion of a patient's treatment (occurring either after the core treatment period or after completion of the extension period for participating patients). Patients were recruited to either the Questionnaire-only cohort (Q-cohort) or the PSG-plus-Questionnaire cohort (PQ-cohort). The SPONSOR was to identify which sites were to be enrolling patients into the individual cohorts. Patients in both cohorts were to complete a daily sleep questionnaire via an electronic diary (e-diary). Patients in the PQ-cohort were to additionally undergo PSG assessments.

The run-in period was to commence at Visit 2 and continue until the patient returned at Visit 3. Patients who continued to meet the overall and cohort-specific inclusion/exclusion criteria at Visit 3 were to be randomized in a 3:2:3 ratio to receive either MK-4305 [high dose], MK-4305 [low dose], or placebo. The dose of MK-4305 received was to be determined by age group as follows:

Non-elderly (18 to < 65 years): MK-4305 high and low doses were to be 40 and 20 mg, respectively.

Elderly (≥ 65 years): MK-4305 high and low doses were to be 30 and 15 mg, respectively.

During the core treatment period, all patients were to return to the clinic after randomization, for visits at the end of Week 2, and the end of Months 1, 2, and 3. For patients in the PQ cohort, the visits at Night 1 and end of Months 1 and 3 were to be overnight PSG visits. Q-cohort was to advance to Visit 2 and Visit 3 to assess for continued patient eligibility prior to randomization.

PQ-cohort was to advance to Visit 2-PSG: Screening PSG and Visit 2a-PSG: Baseline PSG, during which specific PSG criteria must be met and exclusionary sleep disorders ruled out at each respective overnight visit.

## **Efficacy Analyses**

The primary hypotheses were to be evaluated by comparing the MK-4305 high dose to placebo for maintenance endpoints: change from baseline in mean subjective total sleep time (sTSTm) and change from baseline in wakefulness after persistent sleep onset (WASO) at Months 1 and 3; and for onset endpoints: change from baseline in mean subjective time to sleep onset (sTSOm) and change from baseline in latency to onset of persistent sleep (LPS) at Months 1 and 3, while the high dose secondary hypotheses were to be evaluated for the same endpoints at Week 1 (sTSTm and sTSOm) or Night 1 (WASO and LPS). Statistical significance for the primary hypotheses was to be based on the following multiplicity strategy to control the overall Type I error at the two-sided 5%

significance level: to account for the evaluation of two distinct indications a Bonferroni approach was to be used; within each indication, a fixed sequential testing procedure was to be used to move from the first set of primary hypotheses (Month 1) to the next set of primary hypotheses (Month 3). Within each time point, a Hochberg approach was to be used to evaluate the objective and subjective endpoints.

### **Power and Sample Size**

This study was to randomize 360 patients into the MK-4305 high dose and placebo groups, and 240 patients into the MK-4305 low dose group (total N of 960); these are the sample sizes that were to be used to evaluate the questionnaire endpoints. This includes patients in the PQ-cohort (75% of sample size) as well as the Q-cohort (25% of sample size). For the PSG endpoints (i.e., collected in the PQ-cohort), a total of 270 patients were to be randomized to the MK-4305 high dose and placebo groups, and 180 patients were to be randomized to the MK-4305 low dose.

Based upon the sample sizes noted above and assuming that the overall dropout rate is approximately 1% at Night 1 (for PSG endpoints), 5% at Week 1 (for questionnaire endpoints), 10% at Month 1, and 20% at Month 3 (and similar among the treatment groups), the study would have 91% power to declare all primary maintenance endpoints significant (i.e., for MK-4305 high dose vs. placebo) in accordance with the multiplicity strategy noted above. The study also would have 62% power to declare all primary onset endpoints significant (i.e., for MK-4305 high dose vs. placebo); the probability of declaring both Month 1 onset endpoints significant and at least one Month 3 onset endpoint significant is 81%. These probabilities are based upon estimates of standardized effect sizes (reduced by 10% to account for study variability) from Period 1 of the MK-4305 Phase IIb study (Protocol 006).

### **Changes in Planned Analyses**

Changes to the analysis were prespecified in two protocol clarification letters (dated 8/31/2011 and 12/8/2011).

Based upon the sponsor's blinded data review there were some questionable e-diary daily patient data where sTSO+sTST+sWASO was more than 24 hours which the sponsor thought may lack reliability. These records were therefore to be removed prior to deriving the weekly means for each variable in the e-diary. The number of such occurrences was to be summarized separately.

Handling of patients enrolling multiple times (within, or between P028 and P029) was to be as follows.

Sequential Enrollments for Same Subject: The first subject ID was to be included in any summaries or analyses of data involving the following analysis datasets: APR, FAS, APT or APaT. Subsequent subject IDs (for this same patient) were to be excluded from all of the analysis datasets since these data do not represent an independent assessment of efficacy or safety.

Overlapping Enrollments for Same Subject Within Same Study or In Different Studies: All subject IDs from this patient were to be excluded from all of the analysis datasets since there are potential questions regarding the validity (e.g., patient fraud) of data from such a patient.

Definition of Sleep Onset Latency (SOL) in the protocol was changed to: 'the duration of time measured from lights off to the first epoch of 3 consecutive stage S1 or any epoch of stage S2, S3, or stage R,' to be in accordance with current practice of the central scorer.

For the primary efficacy analysis model, region is five levels for subjective endpoints and 4 levels for objective endpoints. Prior to unblinding, it was decided to define region according to the protocol rather than the follow-up Protocol Clarification Letter.

The day ranges for PSG analysis endpoints are defined as follows: Night 1 (Day 1), Month 1 (+/-10 days from the target Day 30), and Month 3 (+/-14 days from the target Day 89). The protocol had specified +/-7 days from the target dates at Months 1 and 3; however, during blinded data review it was noted that multiple observations would have been excluded if these tighter day ranges were used, so a decision was made prior to unblinding to use the wider ranges noted. Primary and secondary hypotheses related to PSG endpoints were also conducted using the protocol-specified day ranges to evaluate robustness of results.

## **Derivations of Efficacy Endpoints**

### **PSG Data**

Sleep stage scoring of the PSG recordings will be performed according to R&K criteria for each 30-second epoch by a central sleep scoring laboratory. Each 30-second epoch will be scored as wake, Stage 1, 2, 3, 4 or REM. The primary, secondary and exploratory PSG endpoints for analysis will be derived from this information. The day ranges for PSG analysis endpoints are defined as follows: Night 1 (Day 1), Month 1 (+/-7 days from the target Day 30), and Month 3 (+/-7 days from the target Day 89).

### **Questionnaire Data**

For the morning and evening questionnaire data, "weekly" averages will be calculated. Questionnaire data provided on the nights in the sleep lab will be excluded from the derivation of these weekly averages since: a) the subjective endpoints may be influenced by being at the sleep lab versus in the outpatient environment; b) the time in bed is limited to 8 hours in the sleep lab. Specifically, weekly averages will be derived by taking the mean of all available daily measurements (excluding the mornings following any PSG nights) falling within the corresponding day range noted below. Note that patients must have at least 3 days of data during each week to calculate a weekly average; otherwise, the mean value will be considered missing for that week/month. Also Note that if a patient ends the extension period earlier than the target day (180), then up to last 14 days (after day 155) leading to the end of the extension period will be the day range for Month 6. The baseline value will be the mean of the last 7 (non-missing) measurements obtained during the placebo run-in period.

### **Patients Who Do Not Fall Asleep and Other Conventions**

For the PSG, total sleep time (TST) may be recorded as 0; the frequency of such cases will be summarized in the report. In this case, the patient likely did not fall asleep for a whole night. Since the at-risk time for WASO and NAW is 0, WASO and NAW are undefined and will be set as missing. The best result for LPS is 0 minutes.

When a patient does not fall asleep, it is the worst outcome. Since the at-risk time for LPS is the duration of time in bed (TIB), which is 8 hours for PSG nights, the LPS will be set as 8 hours if TST=0.

For the e-diary, if the answer to the question "Did you fall asleep at all last night?" is "no" (i.e., sTST=0) and is confirmed by a follow-up question, then imputations for morning edairy endpoints were to be employed as noted below for the same reasons described above.

Additionally, a "worst value" of 1 is imputed for sQUAL when sTST=0.

sTSO = 480 minutes

sNAW = missing

sWASO = missing

sQUAL = 1 (i.e., "Poor")

sNAW may be recorded as 0. When sTST>0, sNAW=0, and sWASO is missing, sWASO was to be imputed as 0.

### **Efficacy Analysis Populations**

The PSG Full Analysis Set (FAS-PSG) population was to serve as the primary population for the analysis of PSG efficacy data. The FAS-PSG population consists of all randomized patients who have: at least one post-randomization PSG observation subsequent to administration of at least one dose of study treatment; baseline data for those analyses that require baseline data.

The e-diary Full Analysis Set (FAS–e-diary) population was to serve as the primary population for the analysis of e-diary efficacy data. The FAS–e-diary population consists of all randomized patients who have: at least one post-randomization e-diary observation (i.e., weekly mean) subsequent to administration of at least one dose of study treatment; baseline data for those analyses that require baseline data. Note that the number of patients included in the FAS populations may vary across endpoints due to the degree of missing data for each endpoint.

### **Statistical Methods for Efficacy Analyses**

For the analysis of change from baseline in sTSTm, WASO, sTSOm, and LPS, a longitudinal data analysis(LDA) method was to be used. This model assumes a different mean for each treatment at each of the repeated time points in the analysis. In this model, time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model was to adjust for baseline value of the response variable (if applicable), age group (non-elderly vs. elderly), region, gender, treatment, time, and the interaction of treatment by time.

To evaluate efficacy hypotheses (e.g., LPS at Month 1), efficacy data were to be included in the model for all time points assessed during the 3-month treatment period; however, appropriate contrasts were to be used to test the treatment difference of interest (e.g., at Month 1). An unstructured covariance matrix was to be used to model the correlation among repeated measurements.

To evaluate the robustness of the efficacy findings based on LDA, a nonparametric approach using Multiple Imputation followed by an aligned rank analysis (Hodges and Lehmann and Mogg and Mehrotra ) was to be performed as a sensitivity analysis

for the primary and secondary endpoints.

If inconsistent results were observed between the primary analysis (LDA) and the sensitivity analysis (the nonparametric approach mentioned above) for a particular primary or secondary endpoint, an additional nonparametric approach, the ETRANK procedure, was to be used as a sensitivity analysis to analyze the incomplete repeated measures data for that endpoint to evaluate the effect of drop-outs on the treatment difference.

For the analysis of responders (e.g., based on change from baseline in ISI total score 6 points), a generalized linear mixed model was to be used. This model assumes a binary distribution for the response and uses a logit link. The treatment difference in terms of log odds ratio was to be estimated and tested from this model using the SAS PROC GLIMMIX procedure. All other aspects of the responder analysis are analogous to the primary analysis for ISI total score.

### **DETAILS OF NON-PARAMETRIC SENSITIVITY ANALYSIS**

Step 1 (handling missing data): Ten multiple imputed complete data sets were to be constructed using regression where a regression model is fitted to each variable with missing values with previous variables as covariates. In other words, imputation was to be carried out sequentially over time (e.g., Night 1, Month 1, then Month 3 for PSG endpoints) for the time points at which imputation is required separately for each treatment group. SAS PROC MI was to be used to implement the imputation procedure which assumes the missing data are missing at random (MAR) and limits imputation to monotone missing patterns. Intermittent missing data (expected to be a relatively small percentage of the missing data) was to be imputed by carrying the last observed data forward.

For each multiple imputed aligned data set, Step 2 through Step 4 were to then be performed.

Step 2 (alignment to adjust for covariates): Patients were to be grouped according to the following covariates: baseline (dichotomous at the median), age (non-elderly, elderly), region, and gender (and Q-cohort/PQ-cohort for diary endpoints). Each intersection of these covariates was to be considered as a block. At each particular time point, the data was to be centered by subtracting the block median from each observation within each block.

The centered data are now "aligned" or adjusted for all covariates (Hodges and Lehmann).

Step 3 (assigning ranks): at each time point ranks were to be assigned to the aligned data.

Step 4 (rank analysis): Wilcoxon sum rank test was to be performed on the ranks.

Step 5 (combine results): The 10 Wilcoxon sum rank tests from the 10 multiple imputed aligned data sets were to be combined using SAS PROC MIANALYZE.

### **Multiplicity**

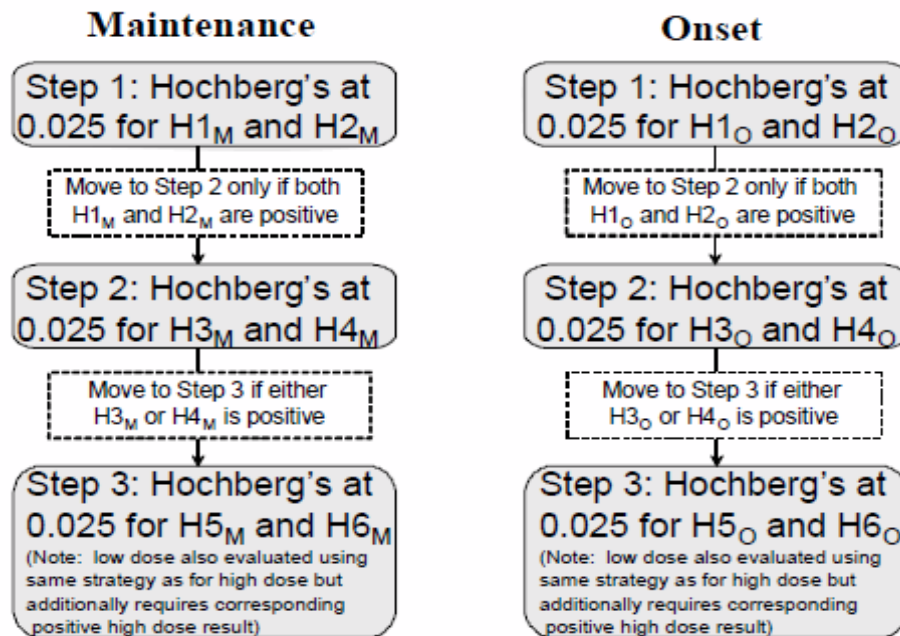
While nominal p-values were to be computed for all comparisons of MK-4305 high dose with placebo, statistical significance for the primary and secondary hypotheses was to be based on the following multiplicity strategy. To account for the evaluation of two distinct indications a Bonferroni approach was to be used; that is, endpoints evaluated to assess the sleep maintenance effect (sTSTm and WASO) were to be tested at the two-sided 2.5% level and endpoints evaluated to assess the sleep onset effect (sTSOm and LPS) were to be tested at the two-sided 2.5% level. Within each indication, a fixed sequential testing procedure was to be used to move from the first set of primary hypotheses (Month 1)

to the next set of primary hypotheses (Month 3) Within each time point, a Hochberg approach was to be used to evaluate the subjective (e.g., sTSTm) and objective (e.g., WASO) endpoints; however, to move sequentially from Month 1 to Month 3 (as noted above), both the subjective and objective endpoints needed to be significant according to this procedure. If only one of the endpoints at Month 1 was significant, then that endpoint was declared positive, but the testing procedure for the indication stopped and no further conclusions could be made regarding the effect of MK-4305 high dose at Month 3. Hence the overall Type I error among all primary hypotheses was to be controlled at the two-sided 5% significance level.

In addition, statistical significance for the high dose secondary hypotheses within each indication was to be based on the following: if either Month 3 hypothesis was positive (sTSTm or WASO for maintenance indication and sTSOm or LPS for onset indication) according to the multiplicity strategy described above, then the set of secondary hypotheses (Week 1/Night 1) was to be tested using a Hochberg approach at the two-sided 2.5% level. This strategy is further illustrated in Figure 1 below.

Low dose comparisons to placebo within each indication for the primary and secondary endpoints were to be evaluated if at least one of the Month 3 endpoints is positive for the high dose (according to the multiplicity strategy noted above). Evaluation of these low dose hypotheses was to follow the same multiplicity strategy as noted for the high dose with one additional requirement: for a particular endpoint, the high dose must be positive in order to declare the low dose positive.

**Figure 1 Multiplicity Adjustment Method used in Phase 3 Studies**



Note: This figure was copied from page 113 of the protocol

H1<sub>M</sub>: High Dose – Placebo=0 for sTST at Month 1 ; H2<sub>M</sub>: High Dose – Placebo=0 for WASO at Month 1

H3<sub>M</sub>: High Dose – Placebo=0 for sTST at Month 3 ; H4<sub>M</sub>: High Dose – Placebo=0 for WASO at Month 3

H5<sub>M</sub>: High Dose – Placebo=0 for sTST at Night 1 ; H6<sub>M</sub>: High Dose – Placebo=0 for WASO at Night 1

To get the corresponding Onset hypotheses replace sTST with sTSO and WASO with LPS in the Maintenance ones.

### 3.1.1.2 Patient Disposition

Of the 1022 patients randomized into the study, 254 and 383 patients were randomized to suvorexant LD and suvorexant HD, respectively, and 385 were randomized to placebo. Of these, one patient (AN 07264) was randomized and did not take any assigned study therapy (placebo group); therefore, 1021 patients received at least one dose of study drug and were evaluated for safety. This patient discontinued due to physician decision. A total of 916 (89.6%) patients completed the Treatment Phase and 105 (10.3%) discontinued the study. Note that three patients attended the End of Month 3 visit but did not complete all assessments.

The proportion of patients who discontinued during the Treatment Phase was similar between placebo and the suvorexant treatment groups and ranged from 9.4% to 11.2%. The most common reason for discontinuation in the Treatment Phase (as well as in both age groups) was due to an AE, with incidences ranging from 2.4% to 3.9% for suvorexant and 5.5% for placebo. The discontinuation rate among treatment groups was similar for non-elderly and elderly patients.

**Table 2 Study 28: Patient Disposition**

|   | MK-4305 LD<br>n (%) | MK-4305 HD<br>n (%) | Placebo<br>n (%) | Total<br>n (%) |
|---|---------------------|---------------------|------------------|----------------|
| <b>Not Randomized</b>   |                     |                     |                  | 1856           |
| <b>Patients in population</b>   | 254                 | 383                 | 385              | 1022           |
| <b>Study Disposition</b>  |                     |                     |                  |                |
| Not Treated   | 0 (0.0)             | 0 (0.0)             | 1 (0.3)          | 1 (0.1)        |
| Completed Treatment <sup>†</sup>  | 230 (90.6)          | 345 (90.1)          | 341 (88.6)       | 916 (89.6)     |
| Discontinued during Treatment   | 24 (9.4)            | 38 (9.9)            | 43 (11.2)        | 105 (10.3)     |
| Adverse Event   | 6 (2.4)             | 15 (3.9)            | 21 (5.5)         | 42 (4.1)       |
| Withdrawal by Subject   | 6 (2.4)             | 8 (2.1)             | 12 (3.1)         | 26 (2.5)       |
| Protocol Violation  | 5 (2.0)             | 3 (0.8)             | 1 (0.3)          | 9 (0.9)        |
| Lost to Follow-up   | 1 (0.4)             | 1 (0.3)             | 0 (0.0)          | 2 (0.2)        |
| Lack of Efficacy  | 1 (0.4)             | 7 (1.8)             | 9 (2.3)          | 17 (1.7)       |
| Pregnancy   | 1 (0.4)             | 1 (0.3)             | 0 (0.0)          | 2 (0.2)        |
| Physician Decision  | 4 (1.6)             | 3 (0.8)             | 0 (0.0)          | 7 (0.7)        |
| <b>Protocol Milestone</b>   |                     |                     |                  |                |
| Completed Treatment   | 230 (90.6)          | 345 (90.1)          | 341 (88.6)       | 916 (89.6)     |
| Continuing Into Extension   | 100 (39.4)          | 172 (44.9)          | 151 (39.2)       | 423 (41.4)     |
| Continuing Into Run-Out   | 128 (50.4)          | 172 (44.9)          | 186 (48.3)       | 486 (47.6)     |
| Not Treated in Run-Out  | 0 (0.0)             | 1 (0.3)             | 0 (0.0)          | 1 (0.1)        |
| Not Continuing Into Extension Or Run-Out <sup>†</sup>   | 2 (0.8)             | 1 (0.3)             | 4 (1.0)          | 7 (0.7)        |
| Discontinued during Treatment (not cont into Ext or RO)   | 24 (9.4)            | 38 (9.9)            | 43 (11.2)        | 105 (10.3)     |
| Each patient is counted once for Study Disposition and Protocol Milestone based on the latest corresponding disposition record. |                     |                     |                  |                |
| <sup>†</sup> AN 7156, 7073, and 8052 attended V7 but did not complete all assessments.  |                     |                     |                  |                |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.                                   |                     |                     |                  |                |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.                                   |                     |                     |                  |                |

Note: This table was copied from the sponsor's study report, page 201



### **3.1.1.3 Baseline Demographics and Disease Characteristics**

Approximately two-thirds of patients were female; further, the gender distribution across treatment groups was generally similar. The ages ranged from 18 to 87 years, with a mean age of 56 years. Of the treated patients, 429 (42.0%) were elderly. The distribution of age was similar among the treatments groups. Patients were predominantly White, non-Hispanic or Latino and enrolled from sites in North America or Europe. By design more patients were enrolled into the PQ-cohort (76.0%); the proportion of patients in each treatment group was similar within each cohort. Baseline characteristics for the non-elderly and elderly patients were generally similar. Baseline characteristics were generally comparable across the cohorts with the exception of race (as the Q cohort was enrolled exclusively by sites in Japan) and body mass index (BMI). The distribution of BMI for the Q-cohort was skewed toward normal and underweight (BMI < 25: 78.9%) as compared to the PQ-cohort (BMI < 25: 42.4%); this observation is likely due to the fact that the Q-cohort was comprised exclusively of patients from Japan. The treatment groups were generally comparable with regard to baseline values of efficacy measures.

Table 3 summarizes baseline demographics of randomized patients and Table 4 summarizes efficacy measures at baseline.

**Table 3 Study 28: Baseline Demographics**

| Variable  | Levels                                  | Placebo        | LD             | HD             | All            |
|-----------|---|----------------|----------------|----------------|----------------|
| age       | Mean (SD)                               | 56.1<br>(15.0) | 55.2<br>(15.7) | 55.7<br>(15.3) | 55.7<br>(15.3) |
| agegrp    |   | .              | .              | .              | . (.)          |
| agegrp    | <65                                     | 224<br>(58.2)  | 148<br>(58.0)  | 222<br>(58.0)  | 594.<br>(58.1) |
| agegrp    | ≥65                                     | 161<br>(41.8)  | 107<br>(42.0)  | 161<br>(42.0)  | 429<br>(41.9). |
| bmi       | Mean (SD)                               | 25.2<br>(4.2)  | 25.2<br>(4.2)  | 25.1<br>(4.1)  | 25.1<br>(4.1)  |
| cohort    | Q                                       | 94 (24.4)      | 61 (23.9)      | 92 (24.0)      | 247<br>(24.1)  |
| cohort    | PQ                                      | 291<br>(75.6)  | 194<br>(76.1)  | 291<br>(76.0)  | 776<br>(75.9)  |
| ethnicity | Hispanic<br>or Latino                   | 37 (9.6)       | 36 (14.1)      | 42 (11.0)      | 115<br>(11.2)  |
| ethnicity | Not<br>Hispanic<br>or Latino            | 348<br>(90.4)  | 219<br>(85.9)  | 341<br>(89.0)  | 908<br>(88.8)  |
| sex       | F                                       | 246<br>(63.9)  | 163<br>(63.9)  | 230<br>(60.1)  | 639<br>(62.5)  |
| sex       | M                                       | 139<br>(36.1)  | 92 (36.1)      | 153<br>(39.9)  | 384<br>(37.5)  |
| race      | ASIAN                                   | 99 (25.7)      | 66 (25.9)      | 98 (25.6)      | 263<br>(25.7)  |
| race      | BLACK OR<br>AFRICAN<br>AMERICAN         | 25 (6.5)       | 15 (5.9)       | 18 (4.7)       | 58 (5.7)       |
| race      | MULTI-<br>RACIAL                        | 15 (3.9)       | 5 (2.0)        | 14 (3.7)       | 34 (3.3)       |
| race      | NATIVE<br>HAWAIIAN<br>OR OTHER<br>PACIF | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 1 (0.1)        |
| race      | WHITE                                   | 245<br>(63.6)  | 169<br>(66.3)  | 253<br>(66.1)  | 667<br>(65.2)  |
| Region    | Asia/<br>Eastern<br>Europe/<br>Africa   | 18 (4.7)       | 9 (3.5)        | 12 (3.1)       | 39 (3.8)       |
| region    | Europe                                  | 134<br>(34.8)  | 89 (34.9)      | 135<br>(35.2)  | 358<br>(35.0)  |
| region    | Japan                                   | 94 (24.4)      | 61 (23.9)      | 92 (24.0)      | 247<br>(24.1)  |
| region    | North<br>America                        | 125<br>(32.5)  | 92 (36.1)      | 129<br>(33.7)  | 346<br>(33.8)  |
| region    | Other<br>Cent<br>South<br>America       | 14 (3.6)       | 4 (1.6)        | 15 (3.9)       | 33 (3.2)       |

**Table 4 Study 28: Baseline Efficacy Measures**

| Variable | Levels    | Placebo         | LD              | HD              | All             |
|----------|-----------|-----------------|-----------------|-----------------|-----------------|
| LPS      | Mean (SD) | 66.2<br>(44.1)  | 68.9<br>(49.7)  | 61.8<br>(39.1)  | 65.2<br>(43.8)  |
| TST      | Mean (SD) | 307.5<br>(63.5) | 299.8<br>(62.8) | 308.3<br>(65.5) | 305.9<br>(64.1) |
| WASO     | Mean (SD) | 114.9<br>(45.7) | 119.2<br>(46.5) | 117.7<br>(49.6) | 117.0<br>(47.4) |
| sTSTom   | Mean (SD) | 66.9<br>(40.5)  | 63.3<br>(37.1)  | 68.0<br>(50.1)  | 66.4<br>(43.6)  |
| sTSTm    | Mean (SD) | 315.7<br>(65.1) | 322.6<br>(57.3) | 316.1<br>(67.2) | 317.6<br>(64.1) |
| sWASOPm  | Mean (SD) | 119.5<br>(77.0) | 117.6<br>(68.6) | 118.7<br>(68.5) | 118.7<br>(71.8) |
| sWASOm   | Mean (SD) | 78.2<br>(52.5)  | 73.8<br>(45.0)  | 78.4<br>(50.7)  | 77.2<br>(50.1)  |

### 3.1.1.4 Sponsor's Results

Of 1023 patients randomized to the three treatment groups, one patient (AN 07126 noted below) enrolled in more than one suvorexant study in an overlapping fashion and these data were subsequently excluded from all summaries and analyses according to rules documented prior to unblinding. Excluding this one patient, 1022 patients were randomized in this study; this population constitutes the All Patients Randomized (APR) set.

#### Subjective Sleep Maintenance –sTSTm

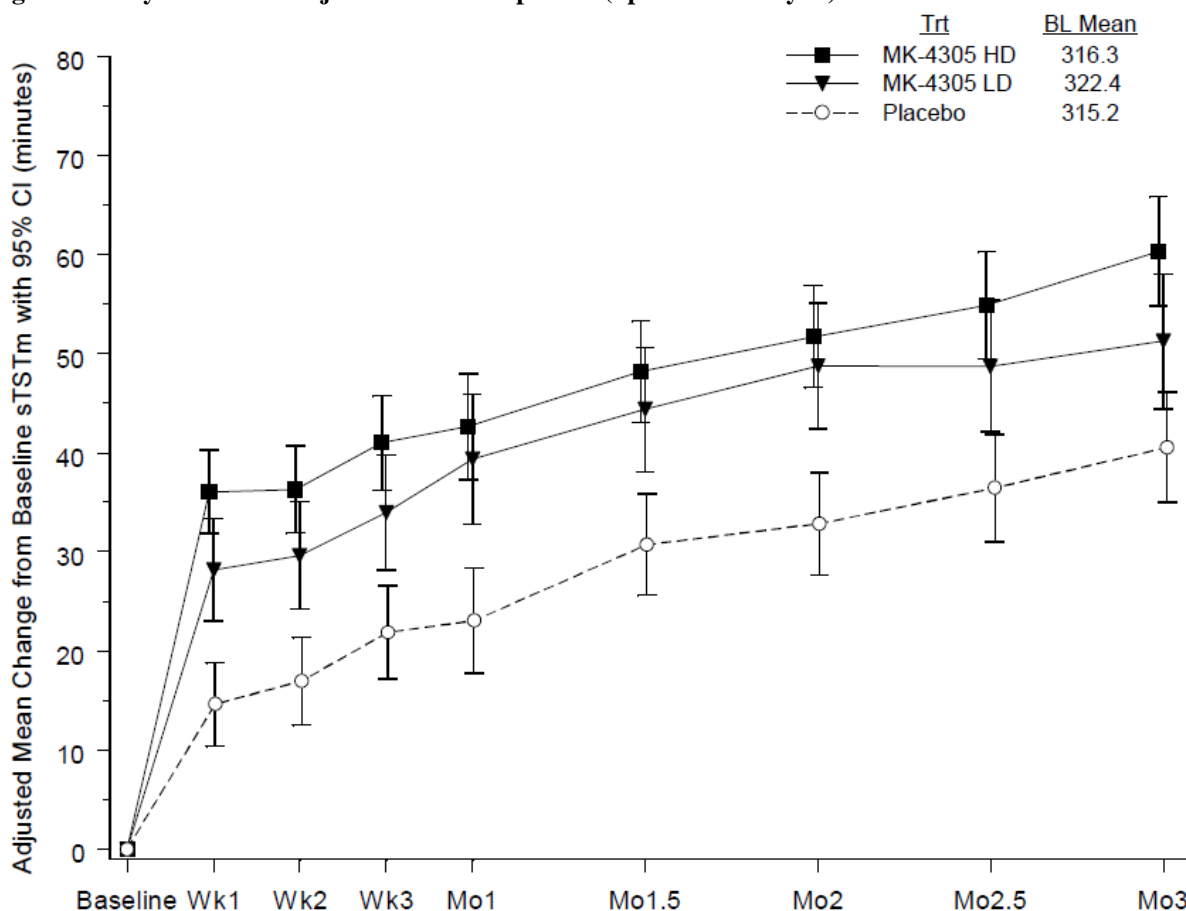
The analyses shown in Table 5 and Figure 2 suggest that suvorexant HD was superior to placebo in increasing subjective total sleep time at the primary (Month 1 and Month 3) timepoints and also at the secondary (Week 1) timepoint (all p-values < 0.00001). The improvements in sTSTm from baseline for suvorexant HD ranged from 36.0 to 60.3 minutes on average. Patients on suvorexant HD improved on average 19.6 to 21.4 minutes more than placebo patients. Nominal (and multiplicity-adjusted) p-values suggest that suvorexant LD was more efficacious than placebo in increasing sTSTm at the primary and secondary timepoints (all p-values < 0.025). The improvements in sTSTm from baseline for suvorexant LD ranged from 28.2 to 51.2 minutes on average. Patients on suvorexant LD improved 10.7 to 16.3 minutes more than placebo.

**Table 5 Study 28: Mean Subjective Total Sleep Time (Sponsor's Analysis)**

| Treatment  | N   | Baseline<br>Mean (SD)            | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                               |
|--|-----|----------------------------------|-------------------------|------------------------------------|-------------------------------|
|  |     |                                  |                         | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Week 1   |     |                                  |                         |                                    |                               |
| MK-4305 LD   | 248 | 322.4 ( 57.3)                    | 349.6 ( 59.0)           | 27.2 ( 40.8)                       | 28.2 ( 23.0, 33.4)            |
| MK-4305 HD   | 379 | 316.3 ( 67.4)                    | 352.6 ( 72.0)           | 36.3 ( 46.0)                       | 36.0 ( 31.8, 40.2)            |
| Placebo  | 376 | 315.2 ( 65.2)                    | 330.4 ( 67.5)           | 15.3 ( 42.9)                       | 14.6 ( 10.4, 18.8)            |
| Month 1  |     |                                  |                         |                                    |                               |
| MK-4305 LD   | 244 | 322.7 ( 57.7)                    | 361.5 ( 66.3)           | 38.7 ( 50.5)                       | 39.4 ( 32.8, 45.9)            |
| MK-4305 HD   | 363 | 317.6 ( 64.0)                    | 361.9 ( 72.3)           | 44.2 ( 57.8)                       | 42.6 ( 37.3, 48.0)            |
| Placebo  | 365 | 317.7 ( 65.3)                    | 341.0 ( 69.6)           | 23.4 ( 52.0)                       | 23.1 ( 17.7, 28.4)            |
| Month 3  |     |                                  |                         |                                    |                               |
| MK-4305 LD   | 228 | 325.4 ( 56.7)                    | 375.7 ( 61.3)           | 50.3 ( 55.2)                       | 51.2 ( 44.4, 58.1)            |
| MK-4305 HD   | 348 | 316.6 ( 65.8)                    | 378.9 ( 72.4)           | 62.2 ( 58.0)                       | 60.3 ( 54.8, 65.8)            |
| Placebo  | 339 | 316.7 ( 64.5)                    | 358.8 ( 64.8)           | 42.1 ( 56.4)                       | 40.6 ( 35.0, 46.1)            |
| Pairwise Comparison  |     | Difference in LS Means (95% CI)† |                         |                                    | p-Value†                      |
| Week 1   |     |                                  |                         |                                    |                               |
| MK-4305 HD vs. Placebo   |     | 21.4 ( 15.5, 27.4)               |                         |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo   |     | 13.6 ( 6.9, 20.3)                |                         |                                    | 0.00007                       |
| Month 1  |     |                                  |                         |                                    |                               |
| MK-4305 HD vs. Placebo   |     | 19.6 ( 12.0, 27.1)               |                         |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo   |     | 16.3 ( 7.9, 24.8)                |                         |                                    | 0.00016                       |
| Month 3  |     |                                  |                         |                                    |                               |
| MK-4305 HD vs. Placebo   |     | 19.7 ( 11.9, 27.6)               |                         |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo   |     | 10.7 ( 1.9, 19.5)                |                         |                                    | 0.01711                       |
| † Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |                                  |                         |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.  |     |                                  |                         |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.  |     |                                  |                         |                                    |                               |

Note: This table was copied from page 259 of the sponsor's study report

**Figure 2 Study 28: Mean Subjective Total Sleep Time (Sponsor's Analysis)**



Note: This figure was copied from page 260 of the sponsor's study report

### Subjective Sleep Onset – sTSOm

Table 6 presents summary statistics and analysis results for sTSOm at the key timepoints during the Treatment Phase for both the HD and LD suvorexant. The analyses show that suvorexant HD was superior to placebo in decreasing sTSOm at the primary (Month 1 and Month 3) timepoints and also at the secondary (Week 1) timepoint (all p-values < 0.01). The improvements in sTSOm from baseline for suvorexant HD ranged from 15.3 to 25.7 minutes on average. Patients on suvorexant HD improved 5.7 to 8.4 minutes more than those on placebo.

Nominal (but not multiplicity-adjusted) p-values provide evidence to suggest that suvorexant LD was more efficacious than placebo in decreasing sTSOm at Month 3 and Week 1. The improvements from baseline in sTSOm for suvorexant LD ranged from 15.2 to 22.5 minutes on average. Patients on suvorexant LD improved 5.2 to 5.6 minutes more than placebo.

**Table 6 Study 28: Mean subjective Time to Sleep Onset (Sponsor's Analysis)**

| Treatment  | N   | Baseline<br>Mean (SD)            | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                               |
|--|-----|----------------------------------|-------------------------|------------------------------------|-------------------------------|
|  |     |                                  |                         | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Week 1   |     |                                  |                         |                                    |                               |
| MK-4305 LD   | 248 | 63.6 ( 37.3)                     | 49.1 ( 33.1)            | -14.5 ( 28.4)                      | -15.2 (-18.7, -11.7)          |
| MK-4305 HD   | 379 | 67.9 ( 50.2)                     | 51.7 ( 44.7)            | -16.2 ( 32.7)                      | -15.3 (-18.1, -12.4)          |
| Placebo  | 376 | 67.2 ( 40.7)                     | 57.1 ( 40.1)            | -10.1 ( 33.9)                      | -9.6 (-12.5, -6.7)            |
| Month 1  |     |                                  |                         |                                    |                               |
| MK-4305 LD   | 244 | 62.7 ( 36.7)                     | 46.3 ( 32.0)            | -16.4 ( 31.5)                      | -17.1 (-21.4, -12.9)          |
| MK-4305 HD   | 363 | 65.3 ( 41.2)                     | 44.6 ( 32.1)            | -20.7 ( 36.9)                      | -19.1 (-22.6, -15.7)          |
| Placebo  | 365 | 65.7 ( 39.4)                     | 52.9 ( 40.7)            | -12.8 ( 41.2)                      | -11.7 (-15.2, -8.2)           |
| Month 3  |     |                                  |                         |                                    |                               |
| MK-4305 LD   | 228 | 60.5 ( 34.7)                     | 40.1 ( 28.8)            | -20.4 ( 27.5)                      | -22.5 (-26.3, -18.7)          |
| MK-4305 HD   | 348 | 66.4 ( 45.5)                     | 38.9 ( 33.0)            | -27.4 ( 36.6)                      | -25.7 (-28.8, -22.6)          |
| Placebo  | 339 | 66.6 ( 39.9)                     | 47.7 ( 35.8)            | -18.9 ( 39.3)                      | -17.3 (-20.4, -14.2)          |
| Pairwise Comparison  |     | Difference in LS Means (95% CI)† |                         |                                    | p-Value†                      |
| Week 1   |     |                                  |                         |                                    |                               |
| MK-4305 HD vs. Placebo   |     | -5.7 ( -9.7, -1.6)               |                         |                                    | 0.00609                       |
| MK-4305 LD vs. Placebo   |     | -5.6 (-10.2, -1.1)               |                         |                                    | 0.01564                       |
| Month 1  |     |                                  |                         |                                    |                               |
| MK-4305 HD vs. Placebo   |     | -7.4 (-12.3, -2.5)               |                         |                                    | 0.00298                       |
| MK-4305 LD vs. Placebo   |     | -5.4 (-10.9, 0.0)                |                         |                                    | 0.05191                       |
| Month 3  |     |                                  |                         |                                    |                               |
| MK-4305 HD vs. Placebo   |     | -8.4 (-12.8, -4.0)               |                         |                                    | 0.00019                       |
| MK-4305 LD vs. Placebo   |     | -5.2 (-10.2, -0.3)               |                         |                                    | 0.03771                       |
| † Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |                                  |                         |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.  |     |                                  |                         |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.  |     |                                  |                         |                                    |                               |

Note: This table was copied from page 268 of the sponsor's study report

### Objective Sleep Maintenance –WASO

Table 7 presents summary statistics and analysis results for WASO at the key timepoints during the Treatment Phase for both the HD and LD of suvorexant. The analyses show that suvorexant HD was superior to placebo in decreasing WASO at the primary (Month 1 and Month 3) timepoints and also at the secondary (Night 1) timepoint (all p-values < 0.00001). The improvements in WASO from baseline for suvorexant HD ranged from 45.0 to 58.0 minutes on average. Patients on suvorexant HD improved 22.9 to 38.4 minutes more than placebo. Nominal (and multiplicity-adjusted with sTSTm) p-values also suggest that suvorexant LD was more efficacious than placebo in decreasing WASO at the primary and secondary timepoints (all p-values < 0.0001). The improvements in WASO from

baseline for suvorexant LD ranged from 41.6 to 52.1 minutes on average. Patients on suvorexant LD improved 16.6 to 32.5 minutes more than those on placebo.

**Table 7 Study 28: Mean Objective WASO (Sponsor's Analysis)**

| Treatment   | N   | Baseline<br>Mean (SD)            | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                      |
|---|-----|----------------------------------|-------------------------|------------------------------------|----------------------|
|   |     |                                  |                         | Mean (SD)                          | LS Mean (95% CI)†    |
| Night 1   |     |                                  |                         |                                    |                      |
| MK-4305 LD  | 192 | 119.5 (46.4)                     | 65.3 (42.3)             | -54.3 (44.7)                       | -52.1 (-57.4, -46.8) |
| MK-4305 HD  | 291 | 117.7 (49.6)                     | 59.2 (37.3)             | -58.5 (48.5)                       | -58.0 (-62.3, -53.7) |
| Placebo   | 287 | 115.1 (45.9)                     | 96.0 (50.5)             | -19.1 (47.5)                       | -19.6 (-23.9, -15.3) |
| Month 1   |     |                                  |                         |                                    |                      |
| MK-4305 LD  | 185 | 119.1 (46.0)                     | 72.1 (45.2)             | -47.0 (45.4)                       | -45.0 (-51.2, -38.9) |
| MK-4305 HD  | 272 | 116.1 (47.9)                     | 72.0 (46.4)             | -44.1 (50.1)                       | -45.0 (-50.1, -39.9) |
| Placebo   | 272 | 113.6 (45.0)                     | 95.7 (54.5)             | -17.9 (55.3)                       | -18.7 (-23.7, -13.6) |
| Month 3   |     |                                  |                         |                                    |                      |
| MK-4305 LD  | 172 | 118.2 (46.7)                     | 75.5 (54.5)             | -42.7 (50.5)                       | -41.6 (-48.0, -35.2) |
| MK-4305 HD  | 251 | 113.9 (45.3)                     | 67.8 (42.6)             | -46.1 (48.2)                       | -47.9 (-53.2, -42.6) |
| Placebo   | 251 | 115.3 (46.0)                     | 90.0 (53.2)             | -25.3 (50.7)                       | -25.0 (-30.3, -19.8) |
| Pairwise Comparison   |     | Difference in LS Means (95% CI)† |                         | p-Value†                           |                      |
| Night 1   |     |                                  |                         |                                    |                      |
| MK-4305 HD vs. Placebo  |     | -38.4 (-44.5, -32.3)             |                         | <.00001                            |                      |
| MK-4305 LD vs. Placebo  |     | -32.5 (-39.3, -25.7)             |                         | <.00001                            |                      |
| Month 1   |     |                                  |                         |                                    |                      |
| MK-4305 HD vs. Placebo  |     | -26.3 (-33.5, -19.2)             |                         | <.00001                            |                      |
| MK-4305 LD vs. Placebo  |     | -26.4 (-34.3, -18.4)             |                         | <.00001                            |                      |
| Month 3   |     |                                  |                         |                                    |                      |
| MK-4305 HD vs. Placebo  |     | -22.9 (-30.3, -15.4)             |                         | <.00001                            |                      |
| MK-4305 LD vs. Placebo  |     | -16.6 (-24.8, -8.3)              |                         | 0.00009                            |                      |
| †Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |                                  |                         |                                    |                      |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.   |     |                                  |                         |                                    |                      |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.   |     |                                  |                         |                                    |                      |

Note: This table was copied from the sponsor's study report, page 265

## Objective Sleep Onset – LPS

Table 8 presents summary statistics and analysis results for LPS at the key timepoints during the Treatment Phase for both the HD and LD of suvorexant (see Figure 11 also). The analyses show that suvorexant HD was superior to placebo in decreasing LPS at the primary (Month 1 and Month 3) timepoints and also at the secondary (Night 1) timepoint (p-values < 0.001). The improvements in LPS from baseline for suvorexant HD ranged from 30.6 to 36.0 minutes on average. Patients on suvorexant HD improved 9.4 to 11.2 minutes more than those on placebo.

Nominal (but not multiplicity-adjusted, except Month 1) p-values suggest that suvorexant LD was more efficacious than placebo in decreasing LPS at the primary and secondary timepoints. The improvements in LPS from baseline for suvorexant LD ranged from 29.9 to 34.7 minutes on average. Patients on suvorexant LD improved 8.1 to

10.3 minutes more than placebo.

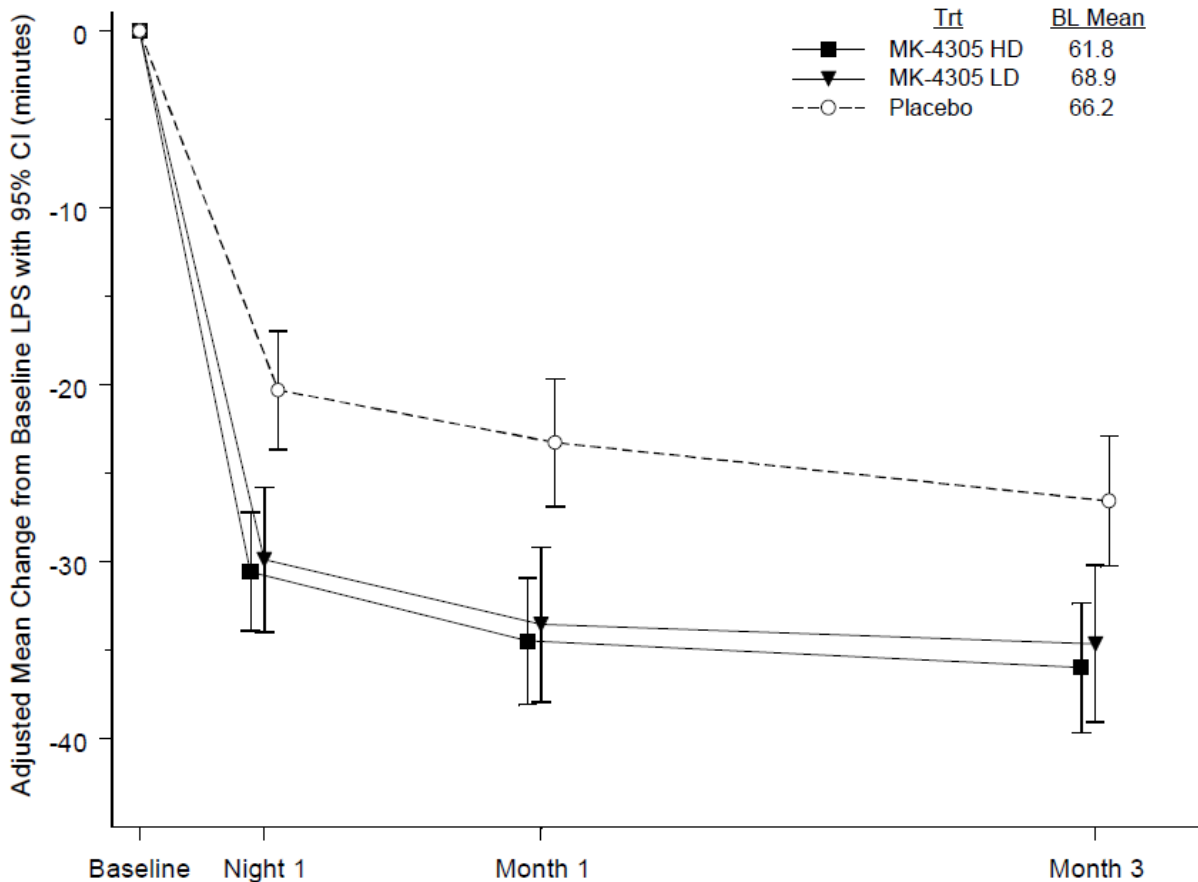
Table 8 Study 28 Mean Change from Baseline in Objective LPS (Sponsor's Analysis)

| Treatment   | N   | Baseline<br>Mean (SD)            | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                      |
|---|-----|----------------------------------|-------------------------|------------------------------------|----------------------|
|   |     |                                  |                         | Mean (SD)                          | LS Mean (95% CI)†    |
| Night 1   |     |                                  |                         |                                    |                      |
| MK-4305 LD  | 193 | 68.9 (49.7)                      | 35.5 (27.8)             | -33.4 (48.0)                       | -29.9 (-34.0, -25.8) |
| MK-4305 HD  | 291 | 61.8 (39.1)                      | 33.8 (25.6)             | -28.0 (41.3)                       | -30.6 (-33.9, -27.2) |
| Placebo   | 290 | 66.2 (44.1)                      | 44.6 (37.3)             | -21.6 (45.2)                       | -20.3 (-23.6, -17.0) |
| Month 1   |     |                                  |                         |                                    |                      |
| MK-4305 LD  | 185 | 67.7 (46.7)                      | 31.7 (27.9)             | -36.0 (45.5)                       | -33.6 (-37.9, -29.2) |
| MK-4305 HD  | 275 | 61.7 (39.8)                      | 29.9 (23.7)             | -31.8 (41.9)                       | -34.5 (-38.1, -30.9) |
| Placebo   | 272 | 66.2 (44.0)                      | 41.8 (39.6)             | -24.4 (51.4)                       | -23.3 (-26.9, -19.7) |
| Month 3   |     |                                  |                         |                                    |                      |
| MK-4305 LD  | 172 | 65.5 (43.7)                      | 30.2 (24.1)             | -35.2 (42.4)                       | -34.7 (-39.1, -30.2) |
| MK-4305 HD  | 254 | 61.4 (40.0)                      | 28.0 (24.9)             | -33.5 (42.7)                       | -36.0 (-39.7, -32.4) |
| Placebo   | 251 | 65.7 (43.9)                      | 38.6 (38.5)             | -27.1 (52.0)                       | -26.6 (-30.2, -22.9) |
| Pairwise Comparison   |     | Difference in LS Means (95% CI)† |                         | p-Value†                           |                      |
| Night 1   |     |                                  |                         |                                    |                      |
| MK-4305 HD vs. Placebo  |     | -10.3 (-15.0, -5.5)              |                         | 0.00002                            |                      |
| MK-4305 LD vs. Placebo  |     | -9.6 (-14.9, -4.3)               |                         | 0.00041                            |                      |
| Month 1   |     |                                  |                         |                                    |                      |
| MK-4305 HD vs. Placebo  |     | -11.2 (-16.3, -6.1)              |                         | 0.00002                            |                      |
| MK-4305 LD vs. Placebo  |     | -10.3 (-16.0, -4.6)              |                         | 0.00040                            |                      |
| Month 3   |     |                                  |                         |                                    |                      |
| MK-4305 HD vs. Placebo  |     | -9.4 (-14.6, -4.3)               |                         | 0.00037                            |                      |
| MK-4305 LD vs. Placebo  |     | -8.1 (-13.8, -2.3)               |                         | 0.00606                            |                      |
| †Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |                                  |                         |                                    |                      |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.   |     |                                  |                         |                                    |                      |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.   |     |                                  |                         |                                    |                      |

Note: This table was copied from page 271 of sponsor's study report



**Figure 3 Study 28 Mean Change from Baseline in Objective LPS (Sponsor's Analysis)**



Note: This figure was copied from page 272 of sponsor's study report

### Additional Analyses

The results of the aligned rank sensitivity analyses were consistent with the primary analysis for suvorexant HD at Month 1 and Week 1. However, the results of the aligned rank analyses were not statistically significant for suvorexant HD at Month 3 ( $p=0.07450$ ). As specified in the protocol, in the event that the primary and sensitivity analyses provided different conclusions, an alternative rank analysis, ETRANK, would be conducted. The ETRANK analysis is consistent with the primary analysis for suvorexant HD at Month 3. One reason the two rank analyses yield different results is that ETRANK uses an analysis that penalizes the ranks of patients who drop out due to lack of efficacy or an AE (i.e., drop-outs potentially related to treatment), and Entsuah scores that make the ranks symmetric around the median.

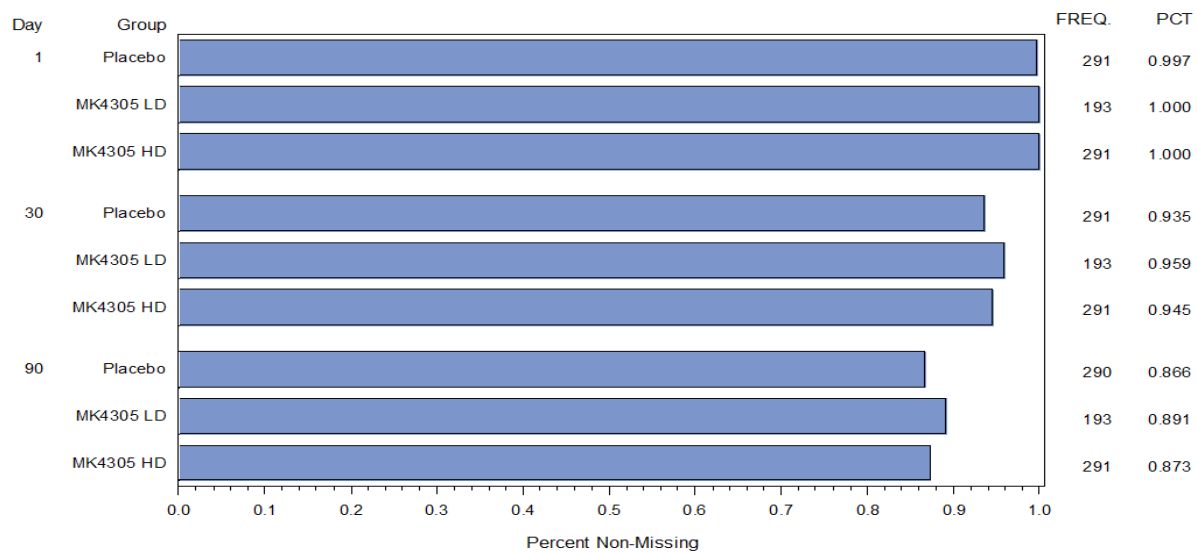
To further explore the comparison of suvorexant and placebo with respect to LPS, a post-hoc analysis was also performed on changes from baseline in log-transformed LPS,  $\log(\text{LPS})$ . The log-transformation reduces the influence of potential outliers and departures from normality. The results of the analysis on log-transformed LPS agree with the results from the primary analysis for suvorexant HD and LD for each of the key timepoints, except suvorexant LD at Month 3.

### 3.1.1.5 Reviewer's Results

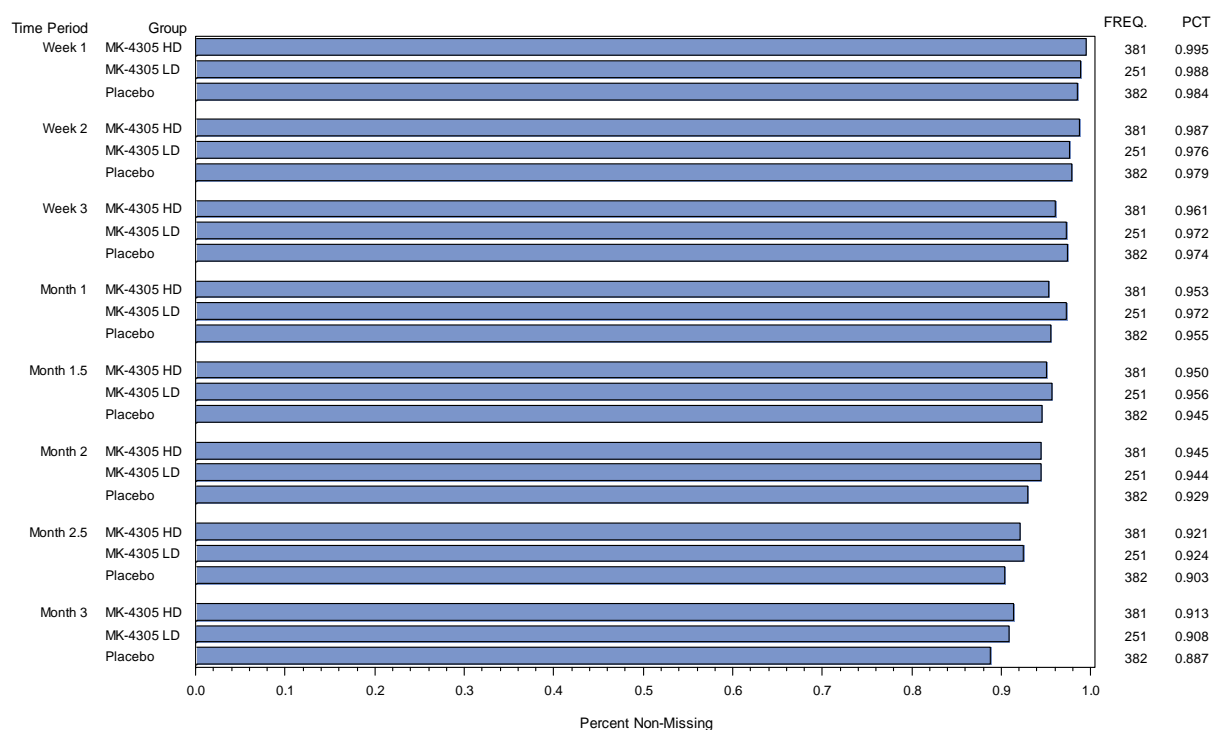
This reviewer verified the sponsor's primary analyses. The change from baseline in LPS exhibited potentially significant non-normality. Therefore, a log transformed sensitivity analysis was undertaken. A log transformed sensitivity analysis of LPS confirmed the significance of the high dose at each timepoint (e.g., at month 1:  $p=0.0102$ ).

Figure 4 shows the extent of missing data for LPS, which was limited to about 13% at Month 3

**Figure 4 Study 28: Percentages of Randomized Patients with non-Missing LPS data over Time**



**Figure 5 Study 28: Percentages of Randomized Patients with non-Missing sTST data over Time**



Missing data percentages were similar for the other two endpoints WASO and subjective Time to sleep onset.

Analyses of completers only were consistent with the primary analysis. For sTSO weekly averages at month 1 estimated differences from placebo for completers (N=862) were -12.9 (p<0.0001) for the high dose and -9.7 (p=0.0019) for the low dose.

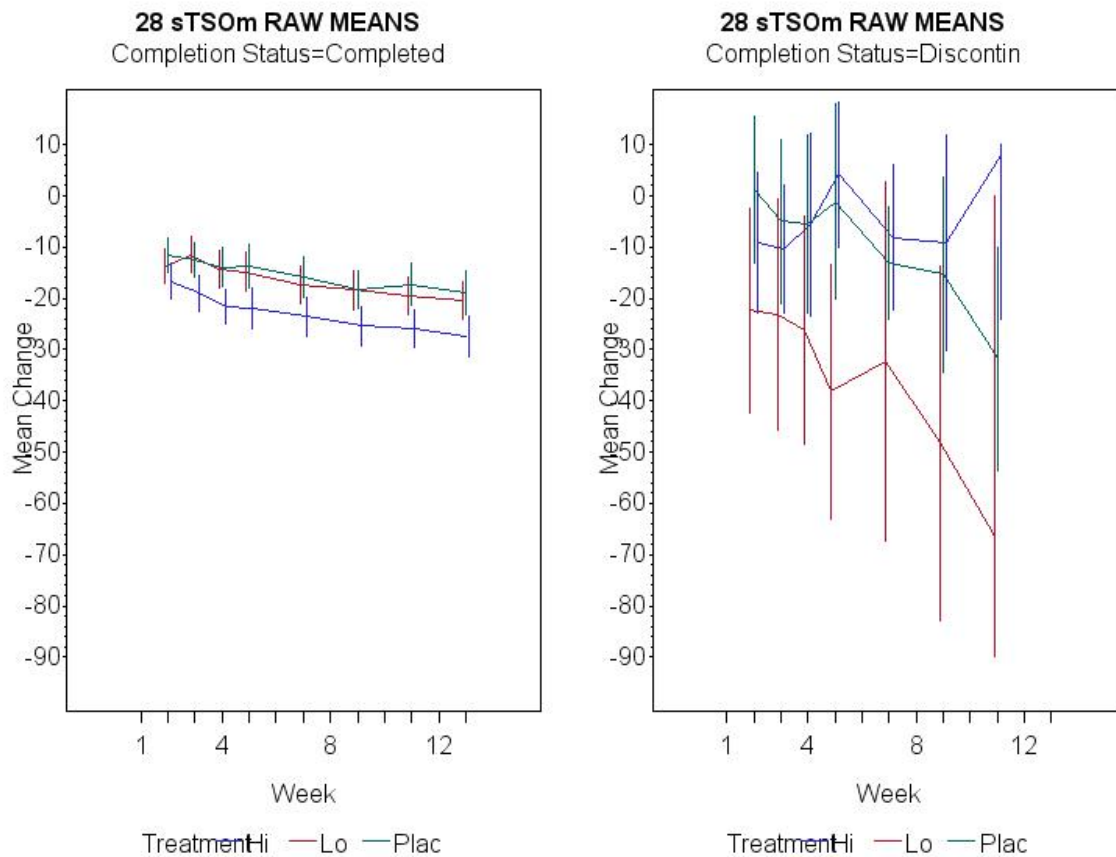
For sTSO weekly averages the low dose vs. placebo comparison (-3.46, p=0.146) was not nominally significant at month 3 based on a baseline carried forward in the event of missing data (BOCF) sensitivity analysis. Such an analysis might be a reasonable, conservative analysis for insomnia since for typical insomnia medications effects are apparent on the first night but might not be sustained later so that an LOCF analysis would be contraindicated. Analysis of completers (N=915) was not nominally significant for the low dose at month 1 (-4.2833, p=0.0729) or month 3 (-3.5084, p=0.1763). This reviewer also performed a multiple imputation sensitivity analysis for missing data. Twenty imputations were made by the Monte Carlo Markov chain method within each treatment group to get a monotone missing data pattern (no intermittent missingness). Next, for each imputation the remaining monotone missing data was imputed using a regression model developed from the placebo group data, which may be conservative when applied to the other groups. The regression model used the same covariates as the primary

analysis model as well as including any previous timepoints of the variable of interest as covariates (e.g., night 1 LPS was a covariate in the regression model for the night 30 LPS). This multiple(20) imputation analysis using an imputation model based on the placebo group was not nominally significant for the low dose vs. placebo comparison at month 1 or 3 compared to the multiplicity adjusted level of 0.025 (Month 1: -5.9,  $p=0.035$ , Month 3: -4.8  $p=0.061$ ). Figure 6 illustrates why this may be, i.e., there is a somewhat surprising phenomenon for sTSOm whereby the mean change for the low dose was very good compared to placebo (and also compared to completers) in the discontinued randomized patients subgroup. Unlike the low dose comparisons those for the high dose were still nominally significant in these sensitivity analyses. It may be worth noting that the low dose had only half the sample size of the high dose by design and all of the alpha for type I error spending was allocated to the high dose vs. placebo comparisons. At night 1 in the discontinued subgroup the low group mean LPS as measured by PSG was also markedly better than placebo but it was more comparable at the last data point available for the discontinued patient subgroup, which was month 1, thus reducing concerns about missing data bias for the analysis of LPS. An analysis of LPS for completers only ( $N=652$  for PSG) supported the results of the primary analysis (Month 1 differences: low -10.8,  $p=0.0006$ , hi: -13.0,  $p<0.0001$ ).

For sTST a completers analysis ( $N=915$ , low diff. 14.3,  $p=0.001$ ; hi diff. 20.7  $p<0.0001$ ) supported the primary analysis as did baseline carried forward for missing data or multiple imputation based on a placebo based imputation mode for all group's missing data. The sTST pattern for discontinued subjects was similar to that for sTSO except to a lesser degree and the low group mean was not numerically better than placebo at Month 2.5 the last visit for which this subgroup had data. Therefore, there is less obvious concern for bias due to missing data for sTST.

For completeness a sensitivity analysis with patients ( $n=4$ ) reporting more than 24 hours in a day's diary data unmodified (rather than the data being excluded as prespecified) was done. The prespecified exclusion of this questionable data did not seem to influence the results.

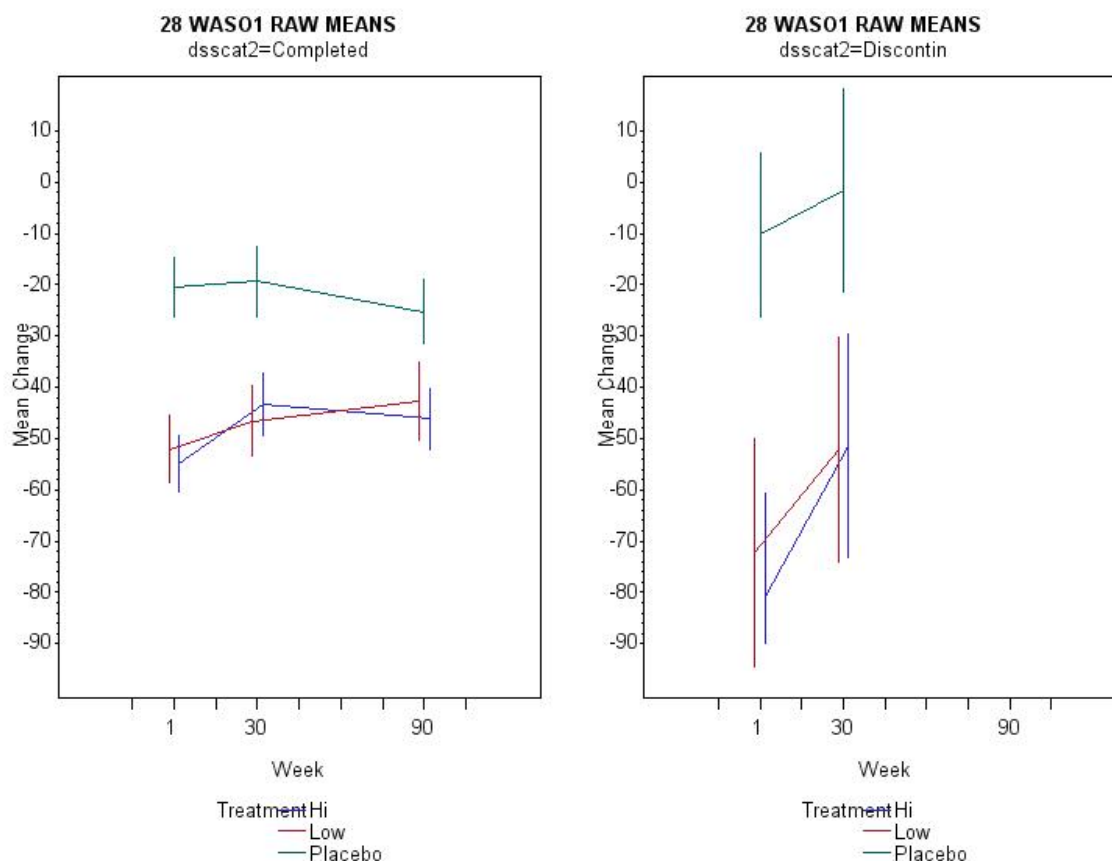
**Figure 6 Study 28 Mean Change from Baseline in sTSO over Time by Completion Status**



Note: N=42 placebo, 23 low dose, and 32 high dose discontinued

For objective WASO as for sTSO earlier effects were bigger for both MK4305 groups in the discontinued subgroup as seen in Figure 7. However, additional sensitivity analyses based on BOCF as well as a multiple imputation analysis using a placebo based model for all group's missing data supported the primary analysis. An analysis of completers (N=652) found an estimated mean difference from placebo of -25.7 for the high dose and -25.5 for the low dose at 1 month (both  $p < 0.0001$ ).

**Figure 7 Study 28 Mean Change from Baseline in WASO over Time by Completion Status**



Note: 39 placebo, 21 low dose, and 40 high dose discontinued

### 3.1.2 Study P029

The primary therapy period for the study was 28 July 2010 to 26 Oct 2011. The original protocol was dated February 8, 2010; there was a protocol clarification letter dated May 5, 2010.

#### 3.2.1.1 Study Design and Statistical Methods

This study design was nearly identical to that for study 28 (so please refer to section 3.1.1.1 for details).

#### 3.2.1.2 Patient Disposition

Of the 1019 patients randomized into the study, 240 and 392 patients were randomized to suvorexant LD and HD, respectively and 387 were randomized to placebo. Of these, 10 patients were randomized but did not take any assigned study therapy (1, 5, and 4 patients in suvorexant LD, suvorexant HD, and placebo treatment groups respectively). Nine of these patients did not

meet entry criteria and were discontinued due to protocol violation prior to receiving study medication; one patient was accidentally randomized after the primary investigator withdrew from the study. Therefore, a total of 1009 patients received at least one dose of study drug and were evaluated for safety.

Of the treated subjects, a total of 881 (86.5%) patients completed the Treatment Phase, and 128 (12.6%) patients discontinued at some point during the study(see Table 9). The most common reason for discontinuing the study was due to an AE.

The proportion of patients who discontinued during the Treatment Phase was similar between placebo (13.7%) and the suvorexant LD (14.2%) treatment groups. Fewer patients assigned to suvorexant HD group discontinued during treatment than placebo (10.5% vs 13.7%, respectively). The rate of discontinuation due to an AE was similar among treatment groups. The discontinuation rate among treatment groups was similar for non-elderly and elderly patients. The most common reason for discontinuing the study in both age cohorts was due to an AE.

**Table 9 Study 29: Disposition of Patients**

|   | MK-4305 LD<br>n (%) | MK-4305 HD<br>n (%) | Placebo<br>n (%) | Total<br>n (%) |
|---|---------------------|---------------------|------------------|----------------|
| <b>Not Randomized</b>   |                     |                     |                  | 1856           |
| <b>Patients in population</b>   | 240                 | 392                 | 387              | 1019           |
| <b>Study Disposition</b>  |                     |                     |                  |                |
| Not Treated   | 1 (0.4)             | 5 (1.3)             | 4 (1.0)          | 10 (1.0)       |
| Completed Treatment†  | 205 (85.4)          | 346 (88.3)          | 330 (85.3)       | 881 (86.5)     |
| Discontinued during Treatment   | 34 (14.2)           | 41 (10.5)           | 53 (13.7)        | 128 (12.6)     |
| Adverse Event   | 10 (4.2)            | 19 (4.8)            | 17 (4.4)         | 46 (4.5)       |
| Withdrawal by Subject   | 8 (3.3)             | 9 (2.3)             | 19 (4.9)         | 36 (3.5)       |
| Protocol Violation  | 5 (2.1)             | 4 (1.0)             | 8 (2.1)          | 17 (1.7)       |
| Lost to Follow-up   | 2 (0.8)             | 4 (1.0)             | 1 (0.3)          | 7 (0.7)        |
| Lack of Efficacy  | 7 (2.9)             | 4 (1.0)             | 8 (2.1)          | 19 (1.9)       |
| Physician Decision  | 2 (0.8)             | 1 (0.3)             | 0 (0.0)          | 3 (0.3)        |
| <b>Protocol Milestone</b>   |                     |                     |                  |                |
| Completed Treatment   | 205 (85.4)          | 346 (88.3)          | 330 (85.3)       | 881 (86.5)     |
| Continuing Into Run-Out   | 205 (85.4)          | 344 (87.8)          | 327 (84.5)       | 876 (86.0)     |
| Not Continuing Into Run-Out†  | 0 (0.0)             | 2 (0.5)             | 3 (0.8)          | 5 (0.5)        |
| Discontinued during Treatment (not continuing into RO)  | 34 (14.2)           | 41 (10.5)           | 53 (13.7)        | 128 (12.6)     |
| Each patient is counted once for Study Disposition and Protocol Milestone based on the latest corresponding disposition record. |                     |                     |                  |                |
| † AN 12041 attended V7 but did not complete all assessments.  |                     |                     |                  |                |
| MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.                                   |                     |                     |                  |                |
| MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.                                   |                     |                     |                  |                |

Note: This table was copied from page 159 of the sponsor's study report

### 3.2.1.1 Patient Demographics and Baseline Disease Characteristics

The ages ranged from 18 to 86 years with the mean age of 56 years. Of the treated patients, 410 (40.6%) were elderly. The distribution of age was similar among the treatment groups.

Approximately two-thirds of patients enrolled in this study were female; further, the gender distribution across treatment groups was also generally similar. Patient characteristics show that patient characteristics for the non-elderly and elderly were generally similar.

Some differences between the two cohorts were observed in terms of region, race and ethnicity. In contrast to the PQ-Cohort, where most patients were recruited either in NA or Europe, in the Q-Cohort, most patients were from regions characterized as Other (which included Latin America, Korea, and India). The majority of the patients in the PQ-Cohort were White (91.3%) and Non Hispanic or Latino (81.2%). On the other hand, only 48.7% of the patients in the Q-Cohort were White, 23.6% were Asian, 27% were Other, and approximately two third of the patients were Non Hispanic or Latino. Other baseline characteristics (age, gender, BMI) were generally similar in the two cohorts.

**Table 10 Study 29: Baseline Demographics and Disease Characteristics (Randomized Patients)**

| Variable | Statistic or Subgroup [N(%)]     | Placebo      | LD           | HD           | All          |
|----------|----------------------------------|--------------|--------------|--------------|--------------|
| age      | Mean (SD)                        | 56.5 (15.4)  | 55.6 (16.1)  | 56.6 (15.0)  | 56.3 (15.4)  |
| agegrp   | < 65                             | 231 (59.4)   | 144 (60.0)   | 233 (59.4)   | 608 (59.6)   |
| agegrp   | ≥ 65                             | 158 (40.6)   | 96 (40.0)    | 159 (40.6)   | 413 (40.4)   |
| bmi      | Mean (SD)                        | 26.1 (4.1)   | 25.6 (3.9)   | 26.4 (4.3)   | 26.1 (4.2)   |
| ethgrp   | Hispanic                         | 87 (22.4)    | 55 (22.9)    | 91 (23.2)    | 233 (22.8)   |
| ethgrp   | NonHispanic                      | 302 (77.6)   | 185 (77.1)   | 301 (76.8)   | 788 (77.2)   |
| race     | AMERICAN INDIAN OR ALASKA NATI   | 2 (0.5)      | .            | 1 (0.3)      | 3 (0.3)      |
| race     | ASIAN                            | 27 (6.9)     | 27 (11.3)    | 28 (7.1)     | 82 (8.0)     |
| race     | BLACK                            | 22 (5.7)     | 4 (1.7)      | 20 (5.1)     | 46 (4.5)     |
| race     | MULTIRACIAL                      | 28 (7.2)     | 19 (7.9)     | 30 (7.7)     | 77 (7.5)     |
| race     | WHITE                            | 310 (79.7)   | 190 (79.2)   | 313 (79.8)   | 813 (79.6)   |
| sex      | Female                           | 250 (64.3)   | 158 (65.8)   | 271 (69.1)   | 679 (66.5)   |
| sex      | Male                             | 139 (35.7)   | 82 (34.2)    | 121 (30.9)   | 342 (33.5)   |
| cohort   | Q                                | 88 (22.6)    | 90 (37.5)    | 90 (23.0)    | 268 (26.2)   |
| cohort   | PQ                               | 301 (77.4)   | 150 (62.5)   | 302 (77.0)   | 753 (73.8)   |
| reggrp2  | Asia/ Central and Eastern Europe | 56 (14.4)    | 41 (17.1)    | 43 (11.0)    | 140 (13.7)   |
| reggrp2  | Central and South America        | 29 (7.5)     | 24 (10.0)    | 32 (8.2)     | 85 (8.3)     |
| reggrp2  | Europe                           | 114 (29.3)   | 77 (32.1)    | 115 (29.3)   | 306 (30.0)   |
| reggrp2  | North America                    | 190 (48.8)   | 98 (40.8)    | 202 (51.5)   | 490 (48.0)   |
| LPS      | Mean (SD)                        | 68.0 (42.8)  | 65.3 (47.8)  | 67.3 (48.8)  | 67.2 (46.2)  |
| TST      | Mean (SD)                        | 302.6 (64.0) | 301.8 (68.2) | 302.3 (67.5) | 302.3 (66.2) |
| WASO     | Mean (SD)                        | 118.4 (49.1) | 119.6 (50.8) | 119.4 (51.3) | 119.0 (50.3) |
| sTSTm    | Mean (SD)                        | 310.2 (77.1) | 298.3 (81.9) | 315.3 (77.0) | 309.3 (78.5) |

### 3.1.2.1 Sponsor's Results

Based upon findings from a monitoring visit, an audit was performed on Site 120 from Russia which suggested that data from this site may lack reliability and integrity. Therefore, in a protocol clarification letter the sponsor stipulated that this site was not to be included in the primary efficacy analysis.



Based on the multiplicity testing strategy:

Suvorexant HD (40 mg for patients <65 years and 30 mg for patients ≥65 years) was superior to placebo in improving sleep maintenance as measured by the change from baseline in sTSTm and change from baseline in WASO, at Month 1, Month 3, and Week 1/Night 1, respectively.

Suvorexant HD (40 mg for patients <65 years and 30 mg for patients ≥65 years) was superior to placebo in improving sleep onset as measured by the change from baseline in sTSOm, at Month 1, Month 3, and Week 1/Night 1, respectively. It was also superior to placebo in improving sleep onset as measured by the change from baseline in LPS, at Month 1 and Night 1, respectively, but not at Month 3.

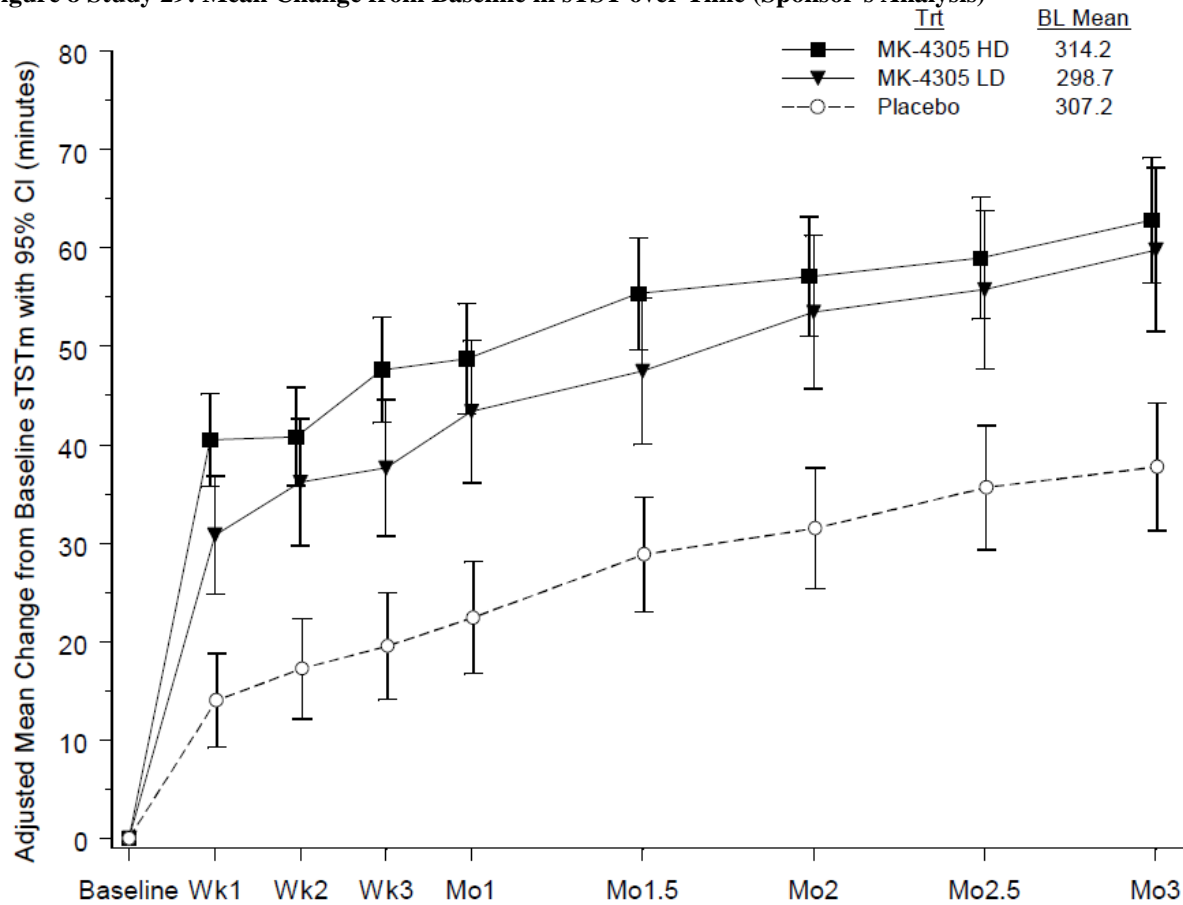
### **Subjective Sleep Maintenance –sTSTm**

Figure 8 and Table 11 present summary statistics and analysis results for sTSTm at the key timepoints during the Treatment Phase for both the HD and LD of suvorexant.

The analyses suggest that suvorexant HD was superior to placebo in increasing subjective total sleep time at the primary (Month 1 and Month 3) timepoints and also at the secondary (Week 1) timepoint (all p-values < 0.00001). The increases from baseline in sTSTm for suvorexant HD ranged from 40.4 to 62.8 minutes on average and were 25.1 to 26.4 minutes greater than those for placebo.

The increases in sTSTm from baseline for suvorexant LD ranged from 30.8 to 59.8 minutes on average and were 16.8 to 22.1 minutes greater than those for placebo.

**Figure 8 Study 29: Mean Change from Baseline in sTST over Time (Sponsor's Analysis)**



Note: This figure was copied from page 205 of the sponsor's study report

**Table 11 Study 29: Change from Baseline in Mean Subjective Total Sleep Time (Sponsor's Analysis)**

| Treatment              | N   | Baseline                                     | Time Point    | Change from Baseline at Time Point |                               |
|------------------------|-----|--|---------------|------------------------------------|-------------------------------|
|                        |     | Mean (SD)                                    | Mean (SD)     | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Week 1                 |     |  |               |                                    |                               |
| MK-4305 LD             | 231 | 298.7 ( 82.2)                                | 331.0 ( 86.9) | 32.3 ( 50.8)                       | 30.8 ( 24.8, 36.8)            |
| MK-4305 HD             | 373 | 314.2 ( 77.4)                                | 354.2 ( 83.1) | 39.9 ( 51.1)                       | 40.4 ( 35.7, 45.1)            |
| Placebo                | 364 | 307.2 ( 77.2)                                | 322.1 ( 81.0) | 14.9 ( 39.6)                       | 14.0 ( 9.2, 18.7)             |
| Month 1                |     |  |               |                                    |                               |
| MK-4305 LD             | 219 | 300.8 ( 78.8)                                | 346.1 ( 90.0) | 45.3 ( 60.5)                       | 43.4 ( 36.1, 50.6)            |
| MK-4305 HD             | 365 | 314.0 ( 77.4)                                | 362.2 ( 81.5) | 48.2 ( 60.6)                       | 48.7 ( 43.1, 54.3)            |
| Placebo                | 350 | 308.2 ( 77.6)                                | 332.3 ( 80.8) | 24.1 ( 51.0)                       | 22.4 ( 16.7, 28.1)            |
| Month 3                |     |  |               |                                    |                               |
| MK-4305 LD             | 197 | 306.7 ( 69.5)                                | 371.6 ( 72.3) | 64.8 ( 62.7)                       | 59.8 ( 51.5, 68.1)            |
| MK-4305 HD             | 340 | 314.8 ( 75.9)                                | 378.3 ( 79.3) | 63.5 ( 67.3)                       | 62.8 ( 56.4, 69.2)            |
| Placebo                | 325 | 311.8 ( 71.8)                                | 352.7 ( 78.4) | 40.9 ( 60.7)                       | 37.7 ( 31.2, 44.2)            |
| Pairwise Comparison    |     | Difference in LS Means (95% CI) <sup>‡</sup> |               |                                    | p-Value <sup>‡</sup>          |
| Week 1                 |     |  |               |                                    |                               |
| MK-4305 HD vs. Placebo |     | 26.4 ( 19.8, 33.1)                           |               |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo |     | 16.8 ( 9.1, 24.5)                            |               |                                    | 0.00002                       |
| Month 1                |     |  |               |                                    |                               |
| MK-4305 HD vs. Placebo |     | 26.3 ( 18.3, 34.3)                           |               |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo |     | 20.9 ( 11.7, 30.2)                           |               |                                    | <0.00001                      |
| Month 3                |     |  |               |                                    |                               |
| MK-4305 HD vs. Placebo |     | 25.1 ( 16.0, 34.2)                           |               |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo |     | 22.1 ( 11.5, 32.6)                           |               |                                    | 0.00004                       |

<sup>†</sup> Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, cohort, gender, treatment, time point, and treatment-by-time point interaction as covariates.

MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.

MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

Note: This table was copied from page 204 of the sponsor's study report

## Objective Sleep Maintenance – WASO

Table 12 presents summary statistics and analysis results for WASO at the key timepoints during the Treatment Phase for both suvorexant HD and LD. The analyses show that suvorexant HD was superior to placebo in decreasing WASO at the primary (Month 1 and Month 3) timepoints and also at the secondary (Night 1) timepoint (all p-values <0.0001). The decreases from baseline in WASO for suvorexant HD ranged from 51.9 to 63.3 minutes on average and were 29.4 to 42.0 minutes greater than those for placebo.

Nominal p-values also suggest that suvorexant LD was more efficacious than placebo in decreasing WASO at the primary and secondary timepoints (all nominal p-values <0.0001). The decreases from baseline in WASO for suvorexant LD ranged from 46.6 to 58.3 minutes on average and were 24.1 to 37.0 minutes greater than those for placebo.

**Table 12 Study 29: Change from Baseline in Mean Objective WASO (Sponsor's Analysis)**

| Treatment               | N   | Baseline<br>Mean (SD)                        | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                               |
|-------------------------|-----|--|-------------------------|------------------------------------|-------------------------------|
|                         |     |  |                         | Mean (SD)                          | LS Mean (95% CI) <sup>1</sup> |
| Night 1                 |     |  |                         |                                    |                               |
| MKC-4305 LD             | 144 | 119.3 (50.8)                                 | 61.3 (41.5)             | -58.0 (49.9)                       | -58.3 (-65.0, -51.6)          |
| MKC-4305 HD             | 285 | 119.5 (51.5)                                 | 55.9 (37.5)             | -63.5 (51.6)                       | -63.3 (-68.0, -58.6)          |
| Placebo                 | 283 | 118.3 (49.4)                                 | 97.9 (54.5)             | -20.4 (57.5)                       | -21.3 (-26.1, -16.6)          |
| Month 1                 |     |  |                         |                                    |                               |
| MKC-4305 LD             | 132 | 118.0 (51.7)                                 | 72.5 (48.9)             | -45.4 (56.5)                       | -46.6 (-53.8, -39.3)          |
| MKC-4305 HD             | 278 | 120.9 (51.2)                                 | 67.3 (40.8)             | -53.5 (53.5)                       | -51.9 (-56.9, -46.9)          |
| Placebo                 | 270 | 118.0 (49.3)                                 | 96.2 (56.4)             | -21.8 (56.7)                       | -22.5 (-27.5, -17.4)          |
| Month 3                 |     |  |                         |                                    |                               |
| MKC-4305 LD             | 127 | 120.1 (52.5)                                 | 64.7 (43.4)             | -55.5 (53.8)                       | -56.0 (-63.3, -48.6)          |
| MKC-4305 HD             | 260 | 121.6 (51.1)                                 | 65.5 (40.2)             | -56.1 (51.4)                       | -54.2 (-59.3, -49.1)          |
| Placebo                 | 252 | 118.3 (49.6)                                 | 94.1 (55.1)             | -24.1 (59.7)                       | -24.8 (-30.0, -19.6)          |
| Pairwise Comparison     |     | Difference in LS Means (95% CI) <sup>2</sup> |                         | p-Value <sup>3</sup>               |                               |
| Night 1                 |     |  |                         |                                    |                               |
| MKC-4305 HD vs. Placebo |     | -42.0 (-48.6, -35.3)                         |                         | <.00001                            |                               |
| MKC-4305 LD vs. Placebo |     | -37.0 (-45.1, -28.8)                         |                         | <.00001                            |                               |
| Month 1                 |     |  |                         |                                    |                               |
| MKC-4305 HD vs. Placebo |     | -29.4 (-36.6, -22.3)                         |                         | <.00001                            |                               |
| MKC-4305 LD vs. Placebo |     | -24.1 (-33.0, -15.3)                         |                         | <.00001                            |                               |
| Month 3                 |     |  |                         |                                    |                               |
| MKC-4305 HD vs. Placebo |     | -29.4 (-36.7, -22.1)                         |                         | <.00001                            |                               |
| MKC-4305 LD vs. Placebo |     | -31.1 (-40.1, -22.2)                         |                         | <.00001                            |                               |

<sup>1</sup>Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates.

MKC-4305 LD = MKC-4305 20 mg for patients <65 years and MKC-4305 15 mg for patients ≥65 years.

MKC-4305 HD = MKC-4305 40 mg for patients <65 years and MKC-4305 30 mg for patients ≥65 years.

Note: this table was copied from page 210 of the sponsor's study report

### Subjective Sleep Onset – sTSOm

Table 13 presents summary statistics and analysis results for sTSOm at the key timepoints during the Treatment Phase for both suvorexant HD and LD. The analyses show that suvorexant HD was superior to placebo in decreasing sTSOm at the primary (Month 1 and Month 3) timepoints and also at the secondary (Week 1) timepoint (all p-values <0.00005). The decreases from baseline in sTSOm for suvorexant HD ranged from 19.7 to 33.7 minutes on average and were 12.8 to 13.2 minutes greater than those for placebo.

Nominal p-values also suggest that suvorexant LD was more efficacious than placebo in decreasing sTSOm at the primary and secondary timepoints (all nominal p-values <0.05000). The decreases from baseline in sTSOm for suvorexant LD ranged from 14.2 to 28.1 minutes on average and were 6.9 to 7.6 minutes greater than those for placebo.

**Table 13 Study 29 Mean Change from Baseline in sTSO (Sponsor's Analysis)**

| Treatment   | N   | Baseline<br>Mean (SD)                        | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                               |
|---|-----|--|-------------------------|------------------------------------|-------------------------------|
|   |     |  |                         | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Week 1  |     |  |                         |                                    |                               |
| MK-4305 LD  | 231 | 86.1 ( 78.3)                                 | 70.6 ( 75.9)            | -15.5 ( 35.3)                      | -14.2 (-18.4, -10.0)          |
| MK-4305 HD  | 373 | 75.2 ( 62.5)                                 | 56.1 ( 59.0)            | -19.1 ( 33.2)                      | -19.7 (-23.0, -16.4)          |
| Placebo   | 364 | 82.6 ( 77.5)                                 | 74.7 ( 76.0)            | -7.9 ( 32.9)                       | -6.7 (-10.0, -3.3)            |
| Month 1   |     |  |                         |                                    |                               |
| MK-4305 LD  | 219 | 83.1 ( 74.5)                                 | 60.4 ( 74.6)            | -22.7 ( 47.9)                      | -21.0 (-26.4, -15.6)          |
| MK-4305 HD  | 365 | 75.1 ( 62.8)                                 | 48.7 ( 54.2)            | -26.5 ( 46.2)                      | -26.9 (-31.1, -22.8)          |
| Placebo   | 350 | 82.0 ( 77.8)                                 | 66.5 ( 66.8)            | -15.5 ( 43.6)                      | -14.1 (-18.4, -9.9)           |
| Month 3   |     |  |                         |                                    |                               |
| MK-4305 LD  | 197 | 75.5 ( 54.8)                                 | 43.7 ( 36.8)            | -31.7 ( 44.7)                      | -28.1 (-33.7, -22.4)          |
| MK-4305 HD  | 340 | 74.1 ( 62.4)                                 | 40.3 ( 38.6)            | -33.8 ( 50.7)                      | -33.7 (-38.0, -29.3)          |
| Placebo   | 325 | 77.2 ( 66.1)                                 | 55.4 ( 56.0)            | -21.8 ( 47.5)                      | -20.5 (-24.9, -16.1)          |
| Pairwise Comparison   |     | Difference in LS Means (95% CI) <sup>†</sup> |                         |                                    | p-Value <sup>†</sup>          |
| Week 1  |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -13.1 (-17.7, -8.4)                          |                         |                                    | <0.00001                      |
| MK-4305 LD vs. Placebo  |     | -7.5 (-12.9, -2.2)                           |                         |                                    | 0.00593                       |
| Month 1   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -12.8 (-18.8, -6.9)                          |                         |                                    | 0.00003                       |
| MK-4305 LD vs. Placebo  |     | -6.9 (-13.7, -0.0)                           |                         |                                    | 0.04975                       |
| Month 3   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -13.2 (-19.4, -7.0)                          |                         |                                    | 0.00003                       |
| MK-4305 LD vs. Placebo  |     | -7.6 (-14.7, -0.4)                           |                         |                                    | 0.03894                       |
| <sup>†</sup> Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, cohort, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |  |                         |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.   |     |  |                         |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.   |     |  |                         |                                    |                               |

Note: This table was copied from page 213 of the sponsor's study report

### Objective Sleep Onset – LPS

Table 14 and Figure 9 present summary statistics and analysis results for LPS at the key timepoints during the Treatment Phase for both suvorexant HD and LD. The analyses show that suvorexant HD was superior to placebo in decreasing LPS at the primary Month 1 timepoint and the secondary Night 1 timepoint (p-values <0.00005), but not at the primary Month 3 timepoint (p-value = 0.26510). The decreases from baseline in LPS for suvorexant HD ranged from 34.7 to 36.7 minutes on average and were 12.7 to 12.1 minutes greater than those for placebo at Night 1 and Month 1, respectively. While the decrease in LPS from baseline at Month 3 of 32.2 minutes for suvorexant HD was nearly as large as the differences observed at Night 1 and Month 1, indicative of a sustained response to suvorexant, the increasing placebo response between Night 1 and Month 3 may have contributed to a non-significant difference from placebo of only 3.6 minutes (p-value = 0.26510).

Nominal p-values also suggest that suvorexant LD was more efficacious than placebo in decreasing LPS at the primary Month 1 and secondary Night 1 timepoints (nominal p-values

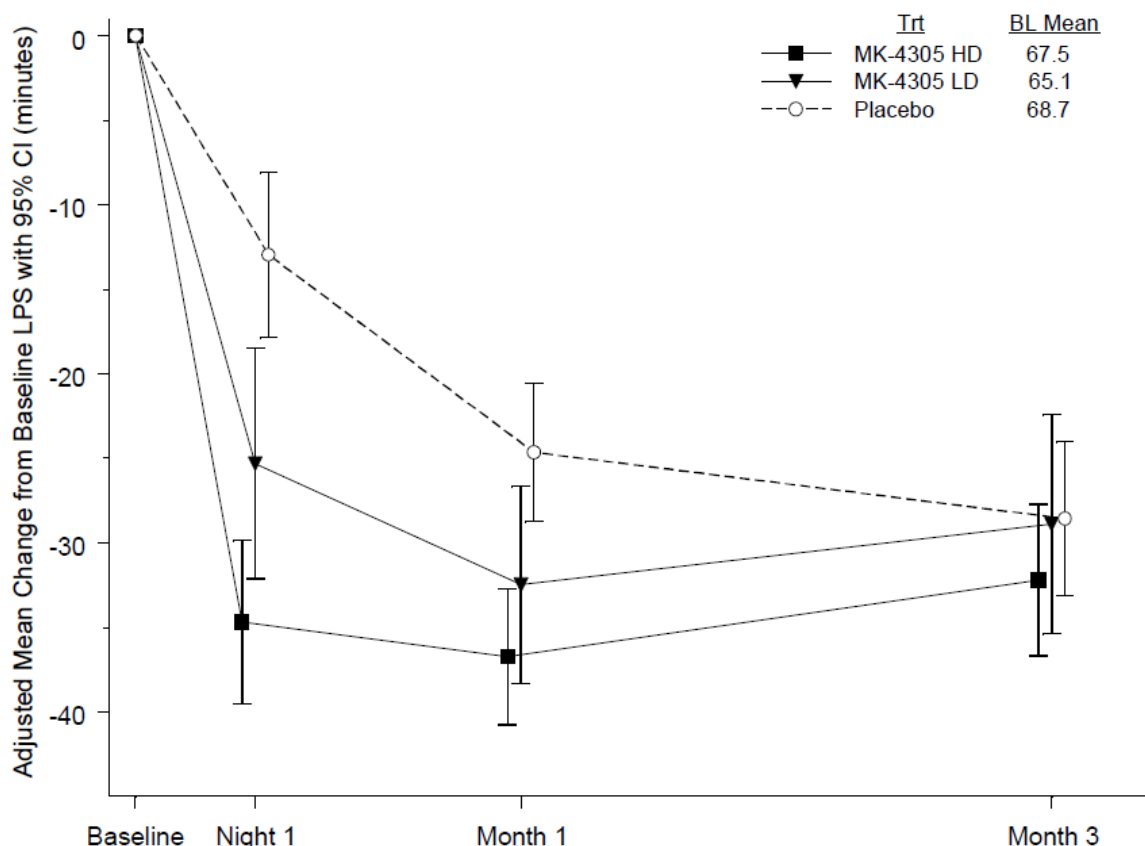
<0.05000). The decreases from baseline in LPS for suvorexant LD ranged from 25.3 to 32.5 minutes on average and were 12.4 and 7.8 minutes greater than those for placebo at Night 1 and Month 1, respectively. The decrease from baseline in LPS at Month 3 of 28.9 minutes for suvorexant LD was in fact greater than the change from baseline of 25.3 observed at Night 1, but the increasing placebo response between Night 1 and Month 3 resulted in a difference from placebo of only 0.3 minutes which had a nominal p-value = 0.93219.

**Table 14 Study 29: Mean Change from Baseline in LPS (Sponsor's Analysis)**

| Treatment   | N   | Baseline<br>Mean (SD)                        | Time Point<br>Mean (SD) | Change from Baseline at Time Point |                               |
|---|-----|--|-------------------------|------------------------------------|-------------------------------|
|   |     |  |                         | Mean (SD)                          | LS Mean (95% CI) <sup>†</sup> |
| Night 1   |     |  |                         |                                    |                               |
| MK-4305 LD  | 144 | 65.1 (47.0)                                  | 41.9 (32.7)             | -23.1 (40.3)                       | -25.3 (-32.2, -18.5)          |
| MK-4305 HD  | 289 | 67.5 (49.4)                                  | 33.0 (24.2)             | -34.5 (48.0)                       | -34.7 (-39.5, -29.9)          |
| Placebo   | 284 | 68.7 (43.3)                                  | 54.9 (60.8)             | -13.8 (62.3)                       | -13.0 (-17.8, -8.1)           |
| Month 1   |     |  |                         |                                    |                               |
| MK-4305 LD  | 133 | 66.2 (47.4)                                  | 34.6 (26.6)             | -31.6 (47.5)                       | -32.5 (-38.3, -26.7)          |
| MK-4305 HD  | 280 | 66.7 (46.5)                                  | 30.8 (28.2)             | -35.9 (48.3)                       | -36.7 (-40.8, -32.7)          |
| Placebo   | 271 | 68.9 (43.3)                                  | 43.2 (44.4)             | -25.7 (53.9)                       | -24.6 (-28.7, -20.6)          |
| Month 3   |     |  |                         |                                    |                               |
| MK-4305 LD  | 127 | 66.1 (48.3)                                  | 38.0 (34.9)             | -28.1 (47.8)                       | -28.9 (-35.4, -22.4)          |
| MK-4305 HD  | 262 | 67.3 (47.6)                                  | 35.6 (42.6)             | -31.8 (55.3)                       | -32.2 (-36.7, -27.7)          |
| Placebo   | 255 | 70.2 (44.0)                                  | 39.6 (36.1)             | -30.6 (49.5)                       | -28.6 (-33.1, -24.0)          |
| Pairwise Comparison   |     | Difference in LS Means (95% CI) <sup>†</sup> |                         | p-Value <sup>†</sup>               |                               |
| Night 1   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -21.7 (-28.6, -14.9)                         |                         | <.00001                            |                               |
| MK-4305 LD vs. Placebo  |     | -12.4 (-20.7, -4.0)                          |                         | 0.00392                            |                               |
| Month 1   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -12.1 (-17.8, -6.4)                          |                         | 0.00004                            |                               |
| MK-4305 LD vs. Placebo  |     | -7.8 (-15.0, -0.7)                           |                         | 0.03063                            |                               |
| Month 3   |     |  |                         |                                    |                               |
| MK-4305 HD vs. Placebo  |     | -3.6 (-10.1, 2.8)                            |                         | 0.26510                            |                               |
| MK-4305 LD vs. Placebo  |     | -0.3 (-8.3, 7.6)                             |                         | 0.93219                            |                               |
| <sup>†</sup> Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates. |     |  |                         |                                    |                               |
| MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.   |     |  |                         |                                    |                               |
| MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.   |     |  |                         |                                    |                               |

Note: This table was copied from page 216 of the sponsor's study report

**Figure 9 Study 29: Adjusted Means for Change from Baseline in Latency to Persistent Sleep**



Note: This figure was copied from page 217 of the sponsor's study report

### Additional Sponsor Sensitivity Analyses

To evaluate the robustness of these objective sleep onset results, a nonparametric procedure using aligned ranks on change from baseline in LPS was performed.

This procedure confirmed statistical significance of the reduction in LPS for suvorexant HD at Night 1, but missed statistical significance at Month 1 (the p-value of 0.03874 was not  $\leq 0.02500$ ). The aligned rank procedure performed at Month 3 confirmed the non-significant result of the primary analysis approach for Month 3 (p-value = 0.14313). The nominal p-values for the comparison of suvorexant LD versus placebo using the aligned rank procedure were  $> 0.05000$  for each of the 3 key timepoints.

Since the results of the analysis at Month 1 using the aligned rank procedure provided a different conclusion than the primary mixed model analysis approach for Month 1, another robust rank procedure (ETRANK) was performed on LPS at Month 1 as specified by the data analysis plan in the protocol. The results using the ETRANK procedure show that LPS was significantly reduced for suvorexant HD as compared with placebo at Month 1. ETRANK penalizes the ranks of patients who dropped out due to lack of efficacy or AE (i.e., drop-outs potentially related to treatment), and it also uses

Entsuaah scores that are symmetric, which may contribute to the difference in results given by these two rank procedures. The ETRANK procedure performed on LPS at Month 3 also showed a significant reduction in LPS for suvorexant HD as compared with placebo at Month 3.

To further explore the comparison of suvorexant and placebo with respect to LPS, a post-hoc analysis was also performed on changes from baseline in log-transformed LPS,  $\log(\text{LPS})$ . The log-transformation reduces the influence of potential outliers and departures from normality. The results of the analysis on log-transformed LPS agree with the results from the primary analysis for suvorexant HD for each of the key timepoints; LPS was significantly reduced for suvorexant HD as compared with placebo at Night 1 and Month 1, but not at Month 3. Comparisons of suvorexant LD and placebo with respect to changes from baseline in log-transformed LPS were not significant at the key timepoints ( $p\text{-values} > 0.05$ ).

### 3.1.2.2 Reviewer's Results

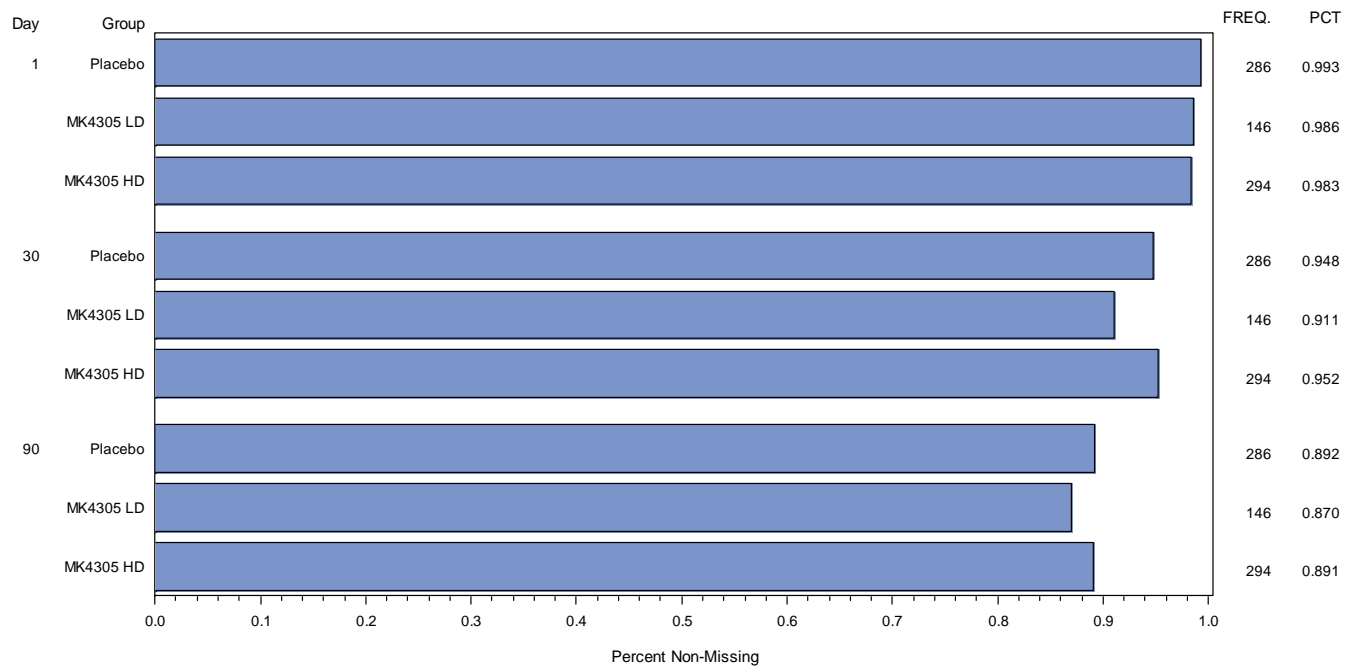
There were three multiple enrollees: one enrolled twice within study 029, another sequentially between study 28 and 29 and another had overlapping enrollments in study 28 and 29. These were handled as prespecified in the protocol clarification letter and described in section 3.1.1.1 on page 8.

Because of the prespecified order of testing the various timepoints and the lack of significance of LPS at Month 3 which was to be tested before Night 1 we cannot conclude efficacy in terms of LPS or (subjective TSO) on Night 1. In addition, any secondary endpoint results assessing onset must from a multiplicity perspective be viewed as exploratory at best, because of the lack of significance for LPS at month 3.

Figure 10 shows the percentages of randomized patients with non missing LPS data at each timepoint for each group. For the placebo and high dose groups between 5 and 6% had missing data at month 1 and about 11% had missing data at Month 3. The extent of missingness for the other primary efficacy measures was similar.



**Figure 10 Study 29: Percentages of Randomized Patients with non-Missing LPS data over Time**



An LOCF analysis of covariance for the Month 3 LPS gave  $p=0.0550$ , while an observed case analysis gave  $p=0.2838$ . So these additional analyses confirmed the sponsor's insignificant primary analysis result at Month 3 for LPS.

The somewhat strange phenomenon observed in study 28 of the low dose appearing markedly better in terms of sTSO in the subgroup of discontinued patients (Figure 6) compared to placebo or completers at times where they had data was not replicated in study 29 (nor was it seen for sTST or WASO either). Completers analyses of sTSO ( $N=862$ , Month 1 low diff:  $-9.7$ ,  $p=0.0019$ , high diff:  $-12.9$ ,  $p<0.0001$ ), sTST (Month 1 low diff:  $22.6$  and high diff:  $24.9$ , both  $p<0.0001$ ) and WASO ( $N=647$ , Month 1 low diff:  $23.6$ , high diff:  $30.8$ , both  $p<0.0001$ ) supported the primary analyses. The following additional sensitivity analyses initiated by the reviewer also supported the primary analysis for sTST and objective WASO: baseline carried forward in the event of missing data analyses and multiple ( $m=20$ ) imputation based on a placebo group based imputation model applied to impute missing data for all groups.

The sponsor prespecified excluding site 45490 from the primary analysis before unblinding the data because of protocol deviations they had discovered at that site. For completeness it is important to look at the results including the patients from this site since they were randomized and had post-baseline data. As it turns out the efficacy conclusions are unaffected by the inclusion or exclusion of data from this site as shown in Table 15.

**Table 15 Study 29: Efficacy Results for High Dose Including Site 45490**

| <b>Endpoint</b> | <b>Day</b> | <b>Estimate</b> | <b>Standard Error</b> | <b>Pr &gt;  t </b> |
|-----------------|------------|-----------------|-----------------------|--------------------|
| <b>sTSTm</b>    | <b>1</b>   | 26.43           | 3.40                  | <.0001             |
|                 | <b>30</b>  | 26.22           | 4.07                  | <.0001             |
|                 | <b>90</b>  | 25.06           | 4.62                  | <.0001             |
| <b>WASO</b>     | <b>1</b>   | -41.61          | 3.47                  | <.0001             |
|                 | <b>30</b>  | -29.54          | 3.58                  | <.0001             |
|                 | <b>90</b>  | -29.56          | 3.73                  | <.0001             |
| <b>sTSOm</b>    | <b>1</b>   | -13.01          | 2.37                  | <.0001             |
|                 | <b>30</b>  | -12.80          | 3.02                  | <.0001             |
|                 | <b>90</b>  | -13.19          | 3.14                  | <.0001             |
| <b>LPS</b>      | <b>1</b>   | -22.01          | 3.68                  | <.0001             |
|                 | <b>30</b>  | -12.92          | 3.04                  | <.0001             |
|                 | <b>90</b>  | -4.51           | 3.37                  | 0.1818             |

A sensitivity analysis with patients reporting more than 24 hours in a day's data unmodified (rather than excluded as prespecified) yielded the following results (Table 16). The exclusion of this questionable data did not seem to impact the results.

**Table 16 Study 29: Sensitivity Analysis for Primary Subjective Endpoints**

| <b>Endpoint</b> | <b>Day</b> | <b>Estimate</b> | <b>Standard Error</b> | <b>Pr &gt;  t </b> |
|-----------------|------------|-----------------|-----------------------|--------------------|
| <b>sTSOm</b>    | <b>1</b>   | -11.8           | 3.0                   | <.0001             |
|                 | <b>30</b>  | -12.7           | 3.1                   | <.0001             |
|                 | <b>90</b>  | -12.9           | 3.6                   | 0.0003             |
| <b>sTSTm</b>    | <b>1</b>   | 26.0            | 3.8                   | <.0001             |
|                 | <b>30</b>  | 26.1            | 4.3                   | <.0001             |
|                 | <b>90</b>  | 25.1            | 5.0                   | <.0001             |

### **3.1.3 Study P006**

#### **3.1.3.1 SUMMARY OF STUDY DESIGN**

This is a randomized, double-blind (with in-house blinding), placebo-controlled, 2-period cross-over PSG study to assess the safety, tolerability, and efficacy of four doses of MK-4305 (10, 20, 40, and 80 mg) in the treatment of patients with primary insomnia.

This design is equivalent to four separate 2-treatment 2-period crossover trials with patients in each trial receiving one of the four MK-4305 doses and placebo. The objectives of the study include demonstration of the effectiveness and dose response of MK-4305 and identification of an appropriate dose or doses for Phase III development. An interim analysis (IA) was to be employed to assess: (1) preliminary effectiveness of MK-4305 (futility of doses), and (2) safety and tolerability. A second IA was to be performed to aid in planning and/or acceleration of future studies. Each interim analysis was to include patients from the ex-Japan stratum only.

During the MK-4305 treatment period, patients were to receive one of four possible MK-4305 doses (10, 20, 40, or 80 mg). Assignment to dose of MK-4305 and treatment sequence (MK-4305/Placebo or Placebo/MK-4305) was to be randomly determined by a computer-generated random allocation schedule. The randomization was to be stratified by geographic region (Japan vs. ex-Japan).

Each 4-week treatment period was to consist of an overnight PSG visit on the first and last night of the treatment period, with an interim office visit at the Week-2 midpoint. Each treatment period was to consist of  $28 \pm 2$  days of treatment. A single-blind placebo washout interval of a minimum of 7 days was to separate the two treatment periods.

Additional treatment sequences might have been added to evaluate a 5-mg dose pending the results of an interim futility analysis when approximately 50% of the patients had completed the study.

#### **Objectives:**

1. To evaluate the efficacy of MK-4305 compared with placebo in improving sleep efficiency (SE) as measured by polysomnography (PSG) on Night 1 and at the end of 4 weeks of treatment, where SE is defined as 100 times total sleep time (minutes) divided by time in bed (minutes).

An interim analysis for identifying futile doses will be conducted after 50% of patients have completed their two 4-week treatment periods. A standing internal data monitoring committee (siDMC) will evaluate these interim data, encompassing evaluation of efficacy data in conjunction with evaluation of other data (e.g., adverse event data), to determine

what if any actions will be taken for the remainder of the study. Based upon this analysis, it is possible that a lower dose of MK-4305 (5 mg) may be added to the study; in this case, the sample size may increase by up to 52 patients (due to the addition of these lower dose sequences). A second interim analysis may be conducted when approximately 160 patients have completed both periods of the crossover study to help expedite Phase III planning. Each interim analysis will include patients from the ex-Japan stratum only.

### **Primary and Secondary Endpoints**

The co-primary endpoints that will be used in the evaluation of the primary efficacy hypothesis are sleep efficiency (SE) measurements at Night 1 and at the end of 4 weeks of treatment. SE is defined as total sleep time (TST) in minutes divided by time in bed (measured from lights off to lights on; fixed at 8 hours on each PSG night) in minutes, multiplied by 100, where TST is defined as the total time (minutes) in Stages 1, 2, 3, 4 and REM.

The secondary endpoints include Night 1 and end of Week 4 measurements for: 1) wakefulness after sleep onset (WASO) and 2) latency to persistent sleep (LPS). WASO is defined as the duration of wakefulness (any epoch of Stage 0) from persistent sleep onset (first epoch of the first twenty consecutive epochs of non-wake) to lights on and LPS is defined as the duration of time from lights off to persistent sleep onset. An epoch of non-wake is defined as a 30-second interval classified as either Stage 1, 2, 3, 4 or REM according to conventional Rechtschaffen and Kales (R&K) scoring.

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population is a subset of all randomized patients with patients excluded for the following reasons:  
failure to receive at least one dose of study treatment  
lack of any post-randomization efficacy data subsequent to at least one dose of study treatment.

The primary and secondary hypotheses will be evaluated using a mixed effects model including terms for baseline value, geographic region (Japan vs. ex-Japan), treatment, sequence, period, time (as a categorical variable), and treatment-by-time and period-bytime interactions. An unstructured covariance matrix will be used. If the model does not converge then a random effect for patient will be added to the model and an unstructured 2x2 covariance matrix within patient and time will be used. Note that the baseline value is only measured prior to randomization to a treatment sequence. The model will be used to provide an estimate of the treatment effect for the comparison of each MK-4305 dose with placebo.

Multiple imputation will be also used as a sensitivity analysis to approximate the missing value for the primary, secondary (and selected exploratory) endpoints.

### **Multiplicity**

An interim analysis for futility was to be conducted when approximately 50% of the patients had completed both treatment periods for the study; this analysis would ideally not affect

the Type I error. A second interim analysis was to possibly be conducted when approximately 160 patients completed both periods of the crossover study for planning future Phase III studies. If this analysis was performed, the method of Haybittle-Peto was to be used to control overall Type I error; this method uses an alpha of 0.001 at the interim and an alpha of 0.05 at the end of the study. The interim analyses were to include patients from the ex-Japan stratum only.

While, nominal p-values were to be computed for all comparisons of MK-4305 with placebo, statistical significance for the primary and secondary hypotheses was to be based on the following multiplicity strategy. To account for the multiple dose comparisons to placebo for the primary efficacy hypothesis, a fixed sequential testing procedure was to be used to assess statistical significance (for all doses not deemed futile at the interim analysis), beginning with the highest dose (i.e., 80 mg). The comparison of MK-4305 with placebo for SE had to be significant at  $\alpha=0.05$  at both time points (i.e., Night 1 and Week 4) in order to assess the statistical significance of the comparison of MK-4305 with placebo for the next highest dose (i.e., 40 mg), and so on. If a non-significant result was observed at either time point, the differences between MK-4305 and placebo for SE were to be considered nonsignificant at this and all lower doses. This procedure was to provide strong control for the multiple dose comparisons of MK-4305 with placebo for the primary efficacy endpoint. MK-4305 doses that were statistically significant for the primary hypothesis were to be tested in a similar fashion for the first secondary endpoint (WASO) at the 5% level of significance. Similarly, MK-4035 doses which are statistically significantly different from placebo for SE and WASO at both time points were to be tested in a similar fashion for the second secondary endpoint (LPS). This would provide control (not strong) of alpha for multiple dose comparisons of MK-4305 to placebo for multiple secondary endpoints.

### **Sample Size Determination**

Mean improvement in SE, WASO and LPS after 1 night of treatment are available from Actelion's orexin compound, almorexant. A total of 208 patients (i.e., 52 for each of the 4 doses) completing both periods of the study, including ~ 40 patients from Japanese ancestry, will be required to compare SE between all four MK-305 doses and placebo. Based upon this sample size, there is approximately 95% (73%) power to detect a difference of 8.33 (6.25) in SE at both time points for a particular MK-4305 dose. (Note that a difference of 8.33 (6.25) in SE corresponds to a 40 (30) minute difference in total sleep time (TST) when time in bed is fixed at 8 hours.) It is expected that approximately 10% of the patients randomized will discontinue treatment permanently during one of the two 4-week treatment periods; therefore, approximately 250 patients will be randomized to ensure 208 with complete data.

### **Interim Analyses**

An interim analysis for futility was to be conducted after 50% of patients had completed their two 4-week treatment periods. The following guidelines were to be used by a standing internal data monitoring committee (siDMC), encompassing evaluation of efficacy data in conjunction with evaluation of other data (e.g., adverse event data), to determine what if any actions were to be taken for the remainder of the study.

If the conditional probability of finding a significant difference from placebo for SE was <20% at either Night 1 or at the end of Week 4 for the lowest two doses, future

enrollment may have been stopped for the lower of the two doses. A similar analysis was to be performed for each higher MK-4305 dose pair, in order of increasing doses. If the conditional probability of finding a significant difference for a dose was 20% at Night 1 and at the end of Week 4, then the study was to continue with this dose pair and all higher doses unless the siDMC decided otherwise on the basis of safety and/or tolerability issues. Guidelines regarding the termination of a dose on the basis of safety and/or tolerability issues were to be provided in the siDMC charter. An MK-4305 dose which had 20% conditional probability of a significant difference in SE at both Night 1 and at the end of Week 4 but had a poor profile for safety and/or tolerability as compared with placebo was to not be continued. If, based upon the siDMC's review, the lower dose of MK-4305 (5 mg) was recommended for evaluation (e.g., if none of the MK-4305 doses were futile and/or there was poor tolerability) this dose may have been included for the remainder of the study. Such a decision could have increased the total patients completing the study by 26 to 52, depending upon the siDMC's recommendation. .

A second interim analysis was to potentially be conducted when approximately 160 patients had completed both periods of the crossover study. This analysis was to include patients in the ex-Japan stratum only. The purpose of this analysis was to expedite planning for Phase III studies; therefore both efficacy and safety were to be evaluated. The study was not to be stopped for superior efficacy on the basis of this analysis; however, the method of Haybittle-Peto was to be used to account for multiplicity related to this evaluation.

### **3.1.3.2 Patient Disposition**

Out of the 254 randomized patients, 249 received at least 1 dose of placebo and 243 received at least 1 dose of MK-4305. A total of 228 patients completed the study and 26 patients discontinued from the study (23 patients discontinued the study during Treatment Period 1 or 2 and 3 patients discontinued the study during the Washout period). The proportion of patients who discontinued during the treatment periods were similar between placebo and the MK-4305 total group. There were 3 patients who discontinued therapy in Treatment Period 1 but continued in the study by entering the Washout period (as allowed per protocol).

### **3.1.3.3 Patient Demographics**

The ages range from 18 to 64 years with the mean age of 44 years. The distribution of age was similar among the treatments and treatment sequences. A greater proportion of females were enrolled in this study; the total percent of females was 58.3%. While the gender distribution tended to range a bit for the treatment sequences, the distribution was similar for the treatments groups (ranging from 54.2% to 65.6% female).

**Table 17 Study 06: Baseline Demographics by Sequence**

| Arm            | Variable | Statistic or Sub Category | Statistic   |
|----------------|----------|---------------------------|-------------|
| 10 mg: Placebo | age      | Mean (SD)                 | 44.5 (11.2) |
| Placebo: 10 mg | age      | Mean (SD)                 | 46.0 (11.9) |
| 20 mg: Placebo | age      | Mean (SD)                 | 43.3 (11.4) |
| Placebo: 20 mg | age      | Mean (SD)                 | 44.4 (11.1) |
| 30 mg: Placebo | age      | Mean (SD)                 | 45.8 (10.0) |
| Placebo: 30 mg | age      | Mean (SD)                 | 43.7 (12.6) |
| 40 mg: Placebo | age      | Mean (SD)                 | 43.1 (12.0) |
| Placebo: 40 mg | age      | Mean (SD)                 | 44.1 (12.3) |
| All            | age      | Mean (SD)                 | 44.4 (11.5) |
| 10 mg: Placebo | race     | ASIAN N(%)                | 4 (12.9)    |
| Placebo: 10 mg | race     | ASIAN                     | 7 (21.9)    |
| 20 mg: Placebo | race     | ASIAN                     | 5 (15.2)    |
| Placebo: 20 mg | race     | ASIAN                     | 7 (21.9)    |
| 30 mg: Placebo | race     | ASIAN                     | 5 (15.6)    |
| Placebo: 30 mg | race     | ASIAN                     | 6 (18.8)    |
| 40 mg: Placebo | race     | ASIAN                     | 5 (16.1)    |
| Placebo: 40 mg | race     | ASIAN                     | 5 (16.1)    |
| All            | race     | ASIAN                     | 44 (17.3)   |
| 10 mg: Placebo | race     | WHITE N(%)                | 23 (74.2)   |
| Placebo: 10 mg | race     | WHITE                     | 22 (68.8)   |
| 20 mg: Placebo | race     | WHITE                     | 21 (63.6)   |
| Placebo: 20 mg | race     | WHITE                     | 21 (65.6)   |
| 30 mg: Placebo | race     | WHITE                     | 22 (68.8)   |
| Placebo: 30 mg | race     | WHITE                     | 23 (71.9)   |
| 40 mg: Placebo | race     | WHITE                     | 23 (74.2)   |
| Placebo: 40 mg | race     | WHITE                     | 23 (74.2)   |
| All            | race     | WHITE                     | 178 (70.1)  |
| 10 mg: Placebo | sex      | FEMALE N(%)               | 14 (45.2)   |
| Placebo: 10 mg | sex      | FEMALE                    | 21 (65.6)   |
| 20 mg: Placebo | sex      | FEMALE                    | 18 (54.5)   |
| Placebo: 20 mg | sex      | FEMALE                    | 25 (78.1)   |
| 30 mg: Placebo | sex      | FEMALE                    | 15 (46.9)   |
| Placebo: 30 mg | sex      | FEMALE                    | 21 (65.6)   |
| 40 mg: Placebo | sex      | FEMALE                    | 16 (51.6)   |
| Placebo: 40 mg | sex      | FEMALE                    | 18 (58.1)   |
| All            | sex      | FEMALE                    | 148 (58.3)  |
| 10 mg: Placebo | sex      | MALE N(%)                 | 17 (54.8)   |
| Placebo: 10 mg | sex      | MALE                      | 11 (34.4)   |
| 20 mg: Placebo | sex      | MALE                      | 15 (45.5)   |
| Placebo: 20 mg | sex      | MALE                      | 7 (21.9)    |
| 30 mg: Placebo | sex      | MALE                      | 17 (53.1)   |
| Placebo: 30 mg | sex      | MALE                      | 11 (34.4)   |
| 40 mg: Placebo | sex      | MALE                      | 15 (48.4)   |
| Placebo: 40 mg | sex      | MALE                      | 13 (41.9)   |
| All            | sex      | MALE                      | 106 (41.7)  |

\*The other races represented in the study: African American and Multi-Racial are not shown in this table as the numbers were very small

There did not appear to be any significant baseline differences between assigned treatment sequences in terms of WASO or LPS.

**Table 18 Study 06: Baseline Disease Characteristics by Sequence**

| Arm            | Baseline Variable | N  | Mean (Std. Dev.) |
|----------------|-------------------|----|------------------|
| 10 mg: Placebo | waso1             | 31 | 107.8 (53.3)     |
| Placebo: 10 mg | waso1             | 32 | 97.9 (34.3)      |

|                |       |     |              |
|----------------|-------|-----|--------------|
| 20 mg: Placebo | waso1 | 33  | 95.7 (36.8)  |
| Placebo: 20 mg | waso1 | 32  | 99.5 (43.5)  |
| 30 mg: Placebo | waso1 | 32  | 109.7 (50.9) |
| Placebo: 30 mg | waso1 | 32  | 104.8 (60.6) |
| 40 mg: Placebo | waso1 | 31  | 93.7 (31.6)  |
| Placebo: 40 mg | waso1 | 31  | 92.3 (41.7)  |
| All            | waso1 | 254 | 100.2 (44.9) |
| 10 mg: Placebo | lps   | 31  | 65.8 (44.3)  |
| Placebo: 10 mg | lps   | 32  | 74.9 (38.0)  |
| 20 mg: Placebo | lps   | 33  | 75.5 (34.3)  |
| Placebo: 20 mg | lps   | 32  | 65.0 (33.6)  |
| 30 mg: Placebo | lps   | 32  | 71.9 (61.1)  |
| Placebo: 30 mg | lps   | 32  | 59.0 (37.2)  |
| 40 mg: Placebo | lps   | 31  | 66.5 (37.8)  |
| Placebo: 40 mg | lps   | 31  | 70.4 (36.6)  |
| All            | lps   | 254 | 68.7 (41.0)  |

### 3.1.3.4 Sponsor's Results

#### Changes to the Analysis Plan

The protocol stated that a mixed model which included terms for: baseline value, region (Japan, ex-Japan), treatment, sequence, period, time (as a categorical variable), treatment by-time and period-by-time interactions, would be used for the evaluation of the primary and secondary endpoints. A decision was made prior to unblinding the data for the first interim analysis to multiply all terms in the model, with the exception of the treatment and treatment-by-time terms, by an indicator variable for 2-period crossover study (e.g. the MK-4305 10 mg: placebo and placebo:MK-4305 10 mg sequences comprised the 2-period crossover study for the MK-4305 10 mg dose). This change to the model still allowed placebo information to be pooled across the four 2-period crossover studies while estimating all other effects separately for each 2-period study. This may be important since these other terms could potentially vary with dose.

#### Interim Analyses

An interim analysis for futility of the MK-4305 doses was conducted when approximately 50% of patients completed the study. The analysis included only patients from the US cohort; no patients of Japanese heritage were included. Only an unblinded statistician and a standing internal data monitoring committee (siDMC) were unblinded for this analysis. Guidelines which documented the procedures, methods, and criteria for actions were prespecified in the siDMC charter for this interim analysis.

A second interim analysis was planned and conducted when there was approximately 80% power for the primary efficacy hypothesis (i.e., when approximately 160 patients completed both periods of the crossover study). The purpose of this analysis was to expedite planning of the Phase III program. Both efficacy and safety were evaluated and the analysis included patients from the US cohort only. Guidelines for the procedures, methods and criteria for action were also prespecified in the same siDMC charter used for the 50% interim analysis. At the conclusion of this interim analysis, the siDMC directed the release of group-level information to the Merck team responsible for planning Phase III to select doses and begin preparation of the Phase III program; the team was not given access to the individual patient data. No other individuals within or outside of Merck were informed of the results of this interim analysis until the last patient had completed



the study. There was no plan to end the trial for superior efficacy on the basis of this analysis and the method of Haybittle-Peto was used to account for multiplicity related to this evaluation.

### Efficacy Summary for Periods 1 and 2 Combined

Based on the testing strategy:

1. All doses of MK-4305 (i.e., 80 mg, 40 mg, 20 mg and 10 mg) were more effective than placebo in improving insomnia as measured by the primary efficacy endpoint, sleep efficiency (SE), at Night 1 and at the end of Week 4.
2. All doses of MK-4305 were more effective than placebo in improving sleep maintenance as measured by the secondary efficacy endpoint, wakefulness after persistent sleep onset (WASO), at Night 1 and at the end of Week 4.
3. No doses of MK-4305 were more effective than placebo in improving sleep onset as measured by the secondary efficacy endpoint, latency to onset of persistent sleep (LPS), at Night 1 and at the end of Week 4, according to the multiplicity testing strategy. However, all doses of MK-4305 had numeric decreases in LPS and multiple MK-4305 doses had nominal p-values for comparisons versus placebo which were < 0.001: namely, 80 mg and 40 mg on Night 1 and 20 mg at Week 4.

**Table 19 Study 06: P-value Summary of Sponsor's Primary and Key Secondary Analyses**

| Comparison   | Primary Endpoints |        | Secondary Endpoints |        |         |        |
|--|-------------------|--------|---------------------|--------|---------|--------|
|  | SE                |        | WASO                |        | LPS     |        |
|  | Night 1           | Week 4 | Night 1             | Week 4 | Night 1 | Week 4 |
| MK-4305 80 mg vs. Placebo  | <.001             | <.001  | <.001               | <.001  | <0.001  | 0.068  |
| MK-4305 40 mg vs. Placebo  | <.001             | <.001  | <.001               | <.001  | <0.001  | <0.459 |
| MK-4305 20 mg vs. Placebo  | <.001             | <.001  | <.001               | <.001  | 0.130   | <0.001 |
| MK-4305 10 mg vs. Placebo  | 0.002             | 0.003  | <.001               | 0.001  | 0.577   | 0.644  |
| P-values in bold are significant according to the multiplicity testing strategy. |                   |        |                     |        |         |        |

Note: this table was copied from page 121 of sponsor's study report

### SE on Night 1 (Periods 1 and 2 Combined)

At baseline, the mean for SE was between 65 and 67 for all treatments. The estimated differences in SE between Night 1 and baseline were: 10.9, 17.8, 17.4, 23.7 and 21.8, for placebo, MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively. These changes from baseline correspond to percent increases in SE relative to baseline of 17% for placebo ( $= 100 \times 10.9/65.9$ ), and 27%, 26%, 37%, and 32% for MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively.

The differences in Least Squares (LS) means for SE between MK-4305 and placebo on Night 1 were all significant (p-value < 0.002); the placebo-subtracted differences were 5.2, 7.6, 10.8 and 12.9 for 10 mg, 20 mg, 40 mg and 80 mg, respectively.

### SE at Week 4 (Periods 1 and 2 Combined)

The estimated differences in SE between Week 4 and baseline were: 12.3, 18.7, 19.1,

20.4 and 19.8, for placebo, MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively. These changes from baseline correspond to percent increases in SE relative to baseline of 19% for placebo ( $= 100 \times 12.3/65.4$ ), and 28%, 29%, 32%, and 30% for MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively.

The differences in LS means for SE between MK-4305 and placebo at Week 4 were all significant ( $p\text{-value} \leq 0.003$ ); the differences were 4.7, 10.4, 7.8 and 7.6 between 10 mg, 20 mg, 40 mg and 80 mg and placebo, respectively, indicating that patients had significantly greater improvements in SE at Week 4 while on MK-4305 than while on placebo.

### **WASO**

The differences in LS means for WASO between MK-4305 and placebo were all significant ( $p\text{-value} < 0.001$ ); the differences were -21.2, -24.7, -33.9 and -36.8 minutes between 10 mg, 20 mg, 40 mg, 80 mg and placebo, respectively. Thus, all doses of MK-4305 were superior to placebo with respect to sleep maintenance as measured by WASO.

The differences in LS means for WASO between MK-4305 and placebo were all significant ( $p\text{-value} < 0.001$ ); the placebo-subtracted differences were -21.4, -28.1, -33.2, and -28.9 minutes between 10 mg, 20 mg, 40 mg and 80 mg, respectively, indicating that patients had significantly greater improvement in sleep maintenance while on MK-4305 than while on placebo (see Table 20).

Table 20 Study 06: Sponsor's Analysis of WASO Based on Both Periods

| Treatment  | N   | Baseline<br>Mean (SD)                    | Treatment<br>Mean (SD) | Change from Baseline |                |
|--|-----|--|------------------------|----------------------|----------------|
|  |     |  |                        | Mean (SD)            | 95% CI         |
| Night 1  |     |  |                        |                      |                |
| Placebo  | 249 | 100.7 (43.11)                            | 70.6 (33.77)           | -30.1 (38.25)        | (-37.3, -22.8) |
| MK4305 10 mg   | 62  | 103.4 (44.70)                            | 54.5 (37.86)           | -48.9 (32.94)        | (-62.3, -35.5) |
| MK4305 20 mg   | 61  | 97.7 (41.10)                             | 46.6 (42.62)           | -51.2 (38.42)        | (-61.0, -41.3) |
| MK4305 40 mg   | 59  | 107.3 (37.58)                            | 35.4 (20.51)           | -71.8 (32.79)        | (-85.6, -58.1) |
| MK4305 80 mg   | 61  | 93.9 (36.24)                             | 27.3 (17.14)           | -66.6 (36.04)        | (-75.9, -57.4) |
| Week 4   |     |  |                        |                      |                |
| Placebo  | 232 | 101.7 (43.74)                            | 73.7 (34.73)           | -28.1 (32.81)        | (-36.2, -19.9) |
| MK4305 10 mg   | 59  | 101.1 (41.40)                            | 51.2 (31.91)           | -49.9 (31.19)        | (-63.2, -36.6) |
| MK4305 20 mg   | 57  | 97.1 (41.82)                             | 47.0 (33.18)           | -50.1 (37.53)        | (-60.1, -40.2) |
| MK4305 40 mg   | 57  | 109.0 (37.84)                            | 49.1 (40.43)           | -59.9 (38.97)        | (-78.2, -41.6) |
| MK4305 80 mg   | 55  | 94.5 (34.97)                             | 40.5 (27.22)           | -53.9 (43.15)        | (-65.6, -42.3) |
| Pairwise Comparison  |     | Differences in LS Mean (SE) <sup>†</sup> |                        | 95% CI               | p-Value        |
| Night 1  |     |  |                        |                      |                |
| MK4305 10 mg   |     | -21.2 (6.27)                             |                        | (-33.5, -8.8)        | <.001          |
| MK4305 20 mg   |     | -24.7 (6.31)                             |                        | (-37.1, -12.3)       | <.001          |
| MK4305 40 mg   |     | -33.9 (6.33)                             |                        | (-46.4, -21.5)       | <.001          |
| MK4305 80 mg   |     | -36.8 (6.36)                             |                        | (-49.4, -24.3)       | <.001          |
| Week 4   |     |  |                        |                      |                |
| MK4305 10 mg   |     | -21.4 (6.48)                             |                        | (-34.2, -8.7)        | 0.001          |
| MK4305 20 mg   |     | -28.1 (6.58)                             |                        | (-41.0, -15.1)       | <.001          |
| MK4305 40 mg   |     | -33.2 (6.61)                             |                        | (-46.3, -20.2)       | <.001          |
| MK4305 80 mg   |     | -28.9 (6.70)                             |                        | (-42.1, -15.7)       | <.001          |
| <sup>†</sup> Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., crossed with indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies. |     |  |                        |                      |                |
| N = Number with measurement at time point.   |     |  |                        |                      |                |

Note: This Table was copied from page 126 of sponsor's study report

Table 21 Study 06 Sponsor's exploratory Analysis of WASO for first period only

| Treatment           | N   | Baseline<br>Mean (SD)                    | Treatment<br>Mean (SD) | Change from Baseline |                |
|---------------------|-----|--|------------------------|----------------------|----------------|
|                     |     |  |                        | Mean (SD)            | 95% CI         |
| Night 1             |     |  |                        |                      |                |
| Placebo             | 127 | 98.7 (45.76)                             | 76.6 (59.07)           | -22.1 (62.86)        | (-33.1, -11.0) |
| MR4305 10 mg        | 31  | 107.8 (53.28)                            | 61.0 (40.80)           | -46.9 (57.99)        | (-68.1, -25.6) |
| MR4305 20 mg        | 33  | 95.7 (36.80)                             | 51.7 (50.57)           | -44.0 (36.61)        | (-57.0, -31.0) |
| MR4305 40 mg        | 32  | 109.7 (50.93)                            | 40.8 (23.54)           | -69.0 (44.78)        | (-85.1, -52.8) |
| MR4305 80 mg        | 31  | 93.7 (31.60)                             | 28.5 (18.13)           | -65.2 (34.80)        | (-78.0, -52.5) |
| Week 4              |     |  |                        |                      |                |
| Placebo             | 116 | 100.2 (46.91)                            | 74.8 (54.53)           | -25.4 (61.55)        | (-36.7, -14.1) |
| MR4305 10 mg        | 29  | 104.4 (47.91)                            | 56.2 (38.21)           | -48.2 (58.72)        | (-70.5, -25.9) |
| MR4305 20 mg        | 31  | 95.7 (37.86)                             | 43.2 (30.06)           | -52.5 (35.16)        | (-65.4, -39.6) |
| MR4305 40 mg        | 30  | 113.1 (50.76)                            | 61.4 (48.41)           | -51.7 (75.83)        | (-80.0, -23.4) |
| MR4305 80 mg        | 28  | 97.9 (30.29)                             | 39.8 (21.71)           | -58.1 (38.86)        | (-73.2, -43.0) |
| Pairwise Comparison |     | Differences in LS Mean (SE) <sup>†</sup> |                        | 95% CI               | p-Value        |
| Night 1             |     |  |                        |                      |                |
| MR4305 10 mg        |     | -18.1 (9.36)                             |                        | (-36.5, 0.4)         | 0.055          |
| MR4305 20 mg        |     | -24.2 (9.12)                             |                        | (-42.2, -6.2)        | 0.008          |
| MR4305 40 mg        |     | -38.8 (9.25)                             |                        | (-57.0, -20.5)       | <.001          |
| MR4305 80 mg        |     | -46.7 (9.35)                             |                        | (-65.2, -28.3)       | <.001          |
| Week 4              |     |  |                        |                      |                |
| MR4305 10 mg        |     | -18.8 (9.46)                             |                        | (-37.4, -0.2)        | 0.048          |
| MR4305 20 mg        |     | -30.2 (9.21)                             |                        | (-48.4, -12.0)       | 0.001          |
| MR4305 40 mg        |     | -16.7 (9.36)                             |                        | (-35.1, 1.8)         | 0.076          |
| MR4305 80 mg        |     | -34.2 (9.58)                             |                        | (-53.0, -15.3)       | <.001          |

<sup>†</sup> Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., crossed with indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.

N = Number with measurement at time point.

Note: this table was copied from page 331 of sponsor's study report

*Reviewer's Comment:*

*There was no first period only analysis prespecified for WASO. For the first period only analysis the sponsor chose not to include the dose by covariate interactions that were prespecified for the*

analysis of both periods. WASO was significant at Day 1  $p=.036$  but strictly not at Day 28  $p=0.066$  if interactions like those used in the primary analysis of both periods were included in the first period only model. Note that the analysis of both periods (Table 20) is the preferred analysis by this reviewer since it was prespecified and there was no treatment group by period interaction apparent.

## LPS

As shown in Table 22 the differences in LS means for LPS between MK-4305 and placebo at Week 4 were -2.3, -22.3, -3.8, and -9.5 minutes for 10 mg, 20 mg, 40 mg and 80 mg and placebo, respectively, but none was significant according to the multiplicity testing strategy. MK-4035 20 mg was nominally significant ( $p$ -value < 0.001).

**Table 22 Study 06: Sponsor's Analysis of Latency to Persistent Sleep Based on Both Periods**

| Treatment           | N   | Baseline Mean (SD)                       | Treatment Mean (SD) | Change from Baseline |                |
|---------------------|-----|--|---------------------|----------------------|----------------|
|                     |     |  |                     | Mean (SD)            | 95% CI         |
| Night 1             |     |  |                     |                      |                |
| Placebo             | 249 | 69.3 (41.13)                             | 46.2 (50.32)        | -23.0 (55.14)        | (-29.9, -16.1) |
| MK4305 10 mg        | 62  | 69.9 (41.23)                             | 33.5 (25.86)        | -36.4 (46.39)        | (-48.2, -24.6) |
| MK4305 20 mg        | 61  | 70.8 (33.12)                             | 36.3 (31.62)        | -34.5 (42.61)        | (-45.4, -23.6) |
| MK4305 40 mg        | 59  | 66.8 (52.22)                             | 23.7 (16.08)        | -43.1 (50.80)        | (-56.3, -29.8) |
| MK4305 80 mg        | 61  | 69.1 (36.80)                             | 28.8 (22.31)        | -40.3 (37.59)        | (-50.0, -30.7) |
| Week 4              |     |  |                     |                      |                |
| Placebo             | 232 | 70.2 (41.51)                             | 38.4 (44.84)        | -31.8 (55.60)        | (-39.0, -24.6) |
| MK4305 10 mg        | 59  | 69.7 (41.55)                             | 28.0 (26.97)        | -41.7 (45.41)        | (-53.5, -29.8) |
| MK4305 20 mg        | 57  | 72.2 (33.62)                             | 28.0 (18.21)        | -44.2 (35.97)        | (-53.7, -34.7) |
| MK4305 40 mg        | 57  | 66.2 (51.82)                             | 28.0 (25.08)        | -38.2 (51.12)        | (-51.8, -24.6) |
| MK4305 80 mg        | 55  | 72.8 (36.43)                             | 29.8 (29.44)        | -43.0 (38.67)        | (-53.4, -32.5) |
| Pairwise Comparison |     | Differences in LS Mean (SE) <sup>†</sup> |                     | 95% CI               | p-Value        |
| Night 1             |     |  |                     |                      |                |
| MK4305 10 mg        |     | -3.4 ( 6.16)                             |                     | (-15.6, 8.7)         | 0.577          |
| MK4305 20 mg        |     | -9.4 ( 6.17)                             |                     | (-21.5, 2.8)         | 0.130          |
| MK4305 40 mg        |     | -23.1 ( 6.20)                            |                     | (-35.3, -10.9)       | <.001          |
| MK4305 80 mg        |     | -25.4 ( 6.23)                            |                     | (-37.7, -13.1)       | <.001          |
| Week 4              |     |  |                     |                      |                |
| MK4305 10 mg        |     | -2.3 ( 4.99)                             |                     | (-12.2, 7.5)         | 0.644          |
| MK4305 20 mg        |     | -22.3 ( 5.08)                            |                     | (-32.3, -12.3)       | <.001          |
| MK4305 40 mg        |     | -3.8 ( 5.09)                             |                     | (-13.8, 6.3)         | 0.459          |
| MK4305 80 mg        |     | -9.5 ( 5.17)                             |                     | (-19.7, 0.7)         | 0.068          |

<sup>†</sup> Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., crossed with indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.

N = Number with measurement at time point.

Note: This table was copied from page 129 of sponsor's study report

## Consideration of Carryover

Evidence of a potential carryover effect was observed for LPS in this 2-period crossover study. Patients who received placebo in Period 1 had further improvement in LPS when

they received MK-4305 in Period 2; however, for patients who received MK-4305 in Period 1 improvement in LPS did not diminish in Period 2, even though patients received placebo in Period 2 (see Figure 11 on page 60). To further evaluate the efficacy of MK-4305 on LPS without the influence of carryover, an ad hoc analysis of LPS restricted to Period 1 was also performed.

#### **LPS on Night 1 (Period 1 Only)**

The estimated differences in LPS between Night 1 in Period 1 and baseline were: -14.4, -32.2, -38.2, -49.2 and -36.0 minutes for placebo, MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively. These changes from baseline correspond to percent decreases in LPS relative to baseline of 21% for placebo ( $= 100 \times 14.3/67.3$ ), and 49%, 51%, 68% and 54% for MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively.

The differences in LS means for LPS between MK-4305 10 mg, 20 mg, 40 mg, 80 mg and placebo in Period 1 were: -19.1, -17.4, -31.0, and -22.3 minutes, respectively. The difference between MK-4305 80 mg and placebo at Night 1 was significant ( $p$ -value = 0.007) according to the multiplicity testing strategy, indicating that MK-4305 80 mg significantly improved sleep onset on Night 1 in Period 1 as compared to placebo. There was also evidence of improvement of sleep onset with MK-4305 10 mg, 20 mg and 40 mg on Night 1 in Period 1, since the nominal  $p$ -values for comparison of these MK-4305 doses with placebo were all  $\leq 0.03$ .

#### **LPS at Week 4 (Period 1 Only)**

The estimated differences in LPS between Week 4 in Period 1 and baseline were: -19.2, -37.1, -52.0, -38.1 and -40.9 minutes for placebo, MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively (Table 11-6, Figure 11-4). These changes from baseline correspond to percent decreases in LPS relative to baseline of 28% for placebo ( $= 100 \times 19.2/67.8$ ), and 58%, 67%, 54% and 58% for MK-4305 10 mg, 20 mg, 40 mg and 80 mg, respectively.

The differences in LS means for LPS between MK-4305 10 mg, 20 mg, 80 mg and placebo in Period 1 were -20.2, -24.6, -15.7, and -19.6 minutes, respectively. Only the difference between MK-4305 80 mg and placebo at Week 4 in Period 1 was significant ( $p$ -value = 0.024) according to the multiplicity testing strategy. This indicates that MK-4305 80 mg significantly improved sleep onset at Week 4 in Period 1 as compared to placebo. There was also possible evidence of improvement of sleep onset with the lower doses of MK-4305 at Week 4 in Period 1 as well, since the nominal  $p$ -values were both  $\leq 0.019$  for comparisons of 10 mg and 20 mg with placebo and the nominal  $p$ -value for MK-4305 40 mg versus placebo was nearly significant ( $p = 0.063$ ).

#### **Efficacy Summary of LPS for Period 1**

Evidence of a potential carryover effect for LPS was observed in this 2-period crossover study. Patients who received placebo in Period 1 did demonstrate further improvement in LPS when they received MK-4305 in Period 2; however, for patients who received MK-4305 in Period 1, improvement in LPS did not appear to diminish in Period 2 even though they received placebo in Period 2.

An ad hoc analysis of LPS for Period 1 data only (i.e., eliminating the potential influence of carryover effects) applying the prespecified multiplicity testing strategy showed that based on this alternative analysis (see Table 23):

1. MK-4305 80 mg significantly improved sleep onset as compared to placebo.
2. While not statistically significant according to the multiplicity testing strategy, all doses of MK-4305 had numeric decreases in LPS which were greater in magnitude than those observed for placebo. The nominal p-values were  $< 0.05$  for nearly all comparisons of MK-4305 versus placebo; the only exception was the comparison of MK-4305 40 mg versus placebo at Week 4, which was nearly nominally significant (p-value = 0.063).

**Table 23 Study 06: Sponsor's Analysis of Latency to Persistent Sleep Based on First Period Only**

| Treatment   | N   | Baseline Mean (SD)                       | Treatment Mean (SD) | Change from Baseline |                |
|---|-----|--|---------------------|----------------------|----------------|
|   |     |  |                     | Mean (SD)            | 95% CI         |
| Night 1   |     |  |                     |                      |                |
| Placebo   | 127 | 67.3 (36.45)                             | 53.0 (51.20)        | -14.3 (57.02)        | (-24.3, -4.3)  |
| MK4305 10 mg  | 31  | 65.8 (44.29)                             | 33.6 (26.85)        | -32.2 (49.84)        | (-50.5, -14.0) |
| MK4305 20 mg  | 33  | 75.5 (34.33)                             | 37.3 (37.03)        | -38.2 (45.93)        | (-54.5, -21.9) |
| MK4305 40 mg  | 32  | 71.9 (61.05)                             | 22.7 (14.65)        | -49.2 (59.32)        | (-70.6, -27.8) |
| MK4305 80 mg  | 31  | 66.5 (37.77)                             | 30.5 (23.99)        | -36.0 (40.67)        | (-51.0, -21.1) |
| Week 4  |     |  |                     |                      |                |
| Placebo   | 116 | 67.8 (36.55)                             | 48.6 (53.96)        | -19.2 (58.31)        | (-30.0, -8.5)  |
| MK4305 10 mg  | 29  | 64.3 (44.58)                             | 27.2 (27.58)        | -37.1 (46.83)        | (-54.9, -19.2) |
| MK4305 20 mg  | 31  | 77.8 (34.13)                             | 25.8 (17.99)        | -52.0 (37.24)        | (-65.7, -38.4) |
| MK4305 40 mg  | 30  | 71.2 (61.05)                             | 33.0 (29.90)        | -38.1 (59.92)        | (-60.5, -15.8) |
| MK4305 80 mg  | 28  | 70.8 (37.20)                             | 29.9 (25.68)        | -40.9 (37.63)        | (-55.5, -26.3) |
| Pairwise Comparison   |     | Differences in LS Mean (SE) <sup>†</sup> |                     | 95% CI               | p-Value        |
| Night 1   |     |  |                     |                      |                |
| MK4305 10 mg  |     | -19.1 ( 8.14)                            |                     | (-35.1, -3.0)        | 0.020          |
| MK4305 20 mg  |     | -17.4 ( 7.96)                            |                     | (-33.1, -1.7)        | 0.030          |
| MK4305 40 mg  |     | -31.0 ( 8.04)                            |                     | (-46.9, -15.2)       | <.001          |
| MK4305 80 mg  |     | -22.3 ( 8.14)                            |                     | (-38.3, -6.2)        | 0.007          |
| Week 4  |     |  |                     |                      |                |
| MK4305 10 mg  |     | -20.2 ( 8.52)                            |                     | (-37.0, -3.4)        | 0.019          |
| MK4305 20 mg  |     | -24.6 ( 8.31)                            |                     | (-41.0, -8.3)        | 0.003          |
| MK4305 40 mg  |     | -15.7 ( 8.41)                            |                     | (-32.3, 0.8)         | 0.063          |
| MK4305 80 mg  |     | -19.6 ( 8.62)                            |                     | (-36.6, -2.6)        | 0.024          |
| <sup>†</sup> Results based on a mixed effects model with terms for baseline value, region, treatment, time, and treatment-by-time interactions. |     |  |                     |                      |                |
| N = Number with measurement at time point.  |     |  |                     |                      |                |

Note: Copied from page 132 of sponsor's study report

**Reviewer's Comment:** For this analysis of LPS in the first period only, the sponsor removed the interactions between dose and time, dose and baseline score, and dose and country from the model for some unexplained reason. The results for the first period only appear somewhat less favorable based on the analyses including these interactions in the model as the sponsor prespecified and did for the analysis of both periods. This is particularly true for 10 mg on both days and 40 mg at Day 28 where the LPS results are no longer significant when the interactions are involved (10 mg: -11.8,  $p=0.256$  at Day 1 and -6.1,  $p=0.554$  at Day 28; 40 mg at Day 28: -4.7,  $p=0.65$ ).

Table 24 illustrates some unexpected significant variability between placebo groups associated with different treatment sequences in terms of mean LPS in the first period.

**Table 24 Study 06: Summary Statistics for Latency to Persistent Sleep in First Period**

| Treatment                               | N   | Baseline<br>Mean (SD) | Treatment<br>Mean (SD) | Change from Baseline |                |
|---|-----|-----------------------|------------------------|----------------------|----------------|
|   |     |                       |                        | Mean (SD)            | (95% CI)       |
| <b>Period 1</b>                         |     |                       |                        |                      |                |
| <b>Night 1</b>                          |     |                       |                        |                      |                |
| Placebo for sequences with MK4305 10 mg | 32  | 74.9 (38.00)          | 46.8 (40.44)           | -28.1 (54.24)        | (-47.7, -8.5)  |
| Placebo for sequences with MK4305 20 mg | 32  | 65.0 (33.64)          | 58.7 (52.95)           | -6.2 (59.98)         | (-27.8, 15.4)  |
| Placebo for sequences with MK4305 40 mg | 32  | 59.0 (37.23)          | 53.4 (57.06)           | -5.6 (61.91)         | (-27.9, 16.7)  |
| Placebo for sequences with MK4305 80 mg | 31  | 70.4 (36.55)          | 52.8 (54.61)           | -17.5 (50.74)        | (-36.1, 1.1)   |
| Placebos pooled over all sequences      | 127 | 67.3 (36.45)          | 53.0 (51.20)           | -14.3 (57.02)        | (-24.3, -4.3)  |
| MK4305 10 mg                            | 31  | 65.8 (44.29)          | 33.6 (26.85)           | -32.2 (49.84)        | (-50.5, -14.0) |
| MK4305 20 mg                            | 33  | 75.5 (34.33)          | 37.3 (37.03)           | -38.2 (45.93)        | (-54.5, -21.9) |
| MK4305 40 mg                            | 32  | 71.9 (61.05)          | 22.7 (14.65)           | -49.2 (59.32)        | (-70.6, -27.8) |
| MK4305 80 mg                            | 31  | 66.5 (37.77)          | 30.5 (23.99)           | -36.0 (40.67)        | (-51.0, -21.1) |
| <b>Week 4</b>                           |     |                       |                        |                      |                |
| Placebo for sequences with MK4305 10 mg | 31  | 73.9 (38.22)          | 35.5 (31.48)           | -38.4 (49.23)        | (-56.4, -20.3) |
| Placebo for sequences with MK4305 20 mg | 28  | 65.2 (31.32)          | 74.5 (81.00)           | 9.3 (68.65)          | (-17.3, 35.9)  |
| Placebo for sequences with MK4305 40 mg | 29  | 59.7 (38.60)          | 36.4 (42.42)           | -23.3 (57.80)        | (-45.3, -1.3)  |
| Placebo for sequences with MK4305 80 mg | 28  | 72.0 (37.44)          | 49.7 (42.70)           | -22.4 (48.18)        | (-41.1, -3.7)  |
| Placebos pooled over all sequences      | 116 | 67.8 (36.55)          | 48.6 (53.96)           | -19.2 (58.31)        | (-30.0, -8.5)  |
| MK4305 10 mg                            | 29  | 64.3 (44.58)          | 27.2 (27.58)           | -37.1 (46.83)        | (-54.9, -19.2) |
| MK4305 20 mg                            | 31  | 77.8 (34.13)          | 25.8 (17.99)           | -52.0 (37.24)        | (-65.7, -38.4) |
| MK4305 40 mg                            | 30  | 71.2 (61.05)          | 33.0 (29.90)           | -38.1 (59.92)        | (-60.5, -15.8) |
| MK4305 80 mg                            | 28  | 70.8 (37.20)          | 29.9 (25.68)           | -40.9 (37.63)        | (-55.5, -26.3) |

Note: This table was copied from page 324 of the sponsor's study report

### Subjective Sleep Endpoints

Patients reported significantly better total sleep time, time to sleep onset, wake after sleep onset and subjective sleep quality for the two higher doses of MK-4305 (40 mg and 80 mg) than for placebo on most weeks.

*Reviewer's note:* 10 and 20 mg doses did not show nominal significance compared to placebo on sTST or sTSO at any week except for 20 mg at week 2 for sTSO ( $p=0.0423$  however, 80 mg which had precedence in the hierarchy did not show nominal significance at that time  $p=0.0780$ ).



Table 25 summarizes the sponsor's analysis of subjective TSO

**Table 25 Study 06: Sponsor's Analysis of Subjective TSO**

| Pairwise Comparison  | Differences in LS Mean <sup>†</sup> (95% CI)       | p-Value        |
|--|--|----------------|
| <b>Week 1</b>  |  |                |
| MK4305 10 mg   | -2.4 (-8.8, 4.0)                                   | 0.4592         |
| MK4305 20 mg   | -4.2 (-10.8, 2.3)                                  | 0.2057         |
| MK4305 40 mg   | -12.8 (-19.5, -6.0)                                | 0.0002         |
| MK4305 80 mg   | -5.0 (-11.7, 1.7)                                  | 0.1396         |
| <b>Pairwise Comparison</b>   | <b>Differences in LS Mean<sup>†</sup> (95% CI)</b> | <b>p-Value</b> |
| <b>Week 2</b>  |  |                |
| MK4305 10 mg   | 1.9 (-4.5, 8.3)                                    | 0.5630         |
| MK4305 20 mg   | -6.8 (-13.3, -0.2)                                 | 0.0423         |
| MK4305 40 mg   | -12.2 (-19.0, -5.5)                                | 0.0005         |
| MK4305 80 mg   | -6.0 (-12.7, 0.7)                                  | 0.0780         |
| <b>Week 3</b>  |  |                |
| MK4305 10 mg   | -0.7 (-6.8, 5.3)                                   | 0.8121         |
| MK4305 20 mg   | -5.8 (-12.0, 0.4)                                  | 0.0688         |
| MK4305 40 mg   | -13.2 (-19.6, -6.8)                                | <.0001         |
| MK4305 80 mg   | -11.1 (-17.5, -4.8)                                | 0.0007         |
| <b>Week 4</b>  |  |                |
| MK4305 10 mg   | -3.0 (-9.3, 3.3)                                   | 0.3523         |
| MK4305 20 mg   | -4.3 (-10.8, 2.2)                                  | 0.1946         |
| MK4305 40 mg   | -17.4 (-24.1, -10.7)                               | <.0001         |
| MK4305 80 mg   | -7.7 (-14.3, -1.1)                                 | 0.0219         |
| <sup>†</sup> Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., crossed with indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.<br>N = Number with measurement at time point. |  |                |

Note: This table was copied from page 412 of the sponsor's study report

This reviewer also conducted first period only analyses for subjective Time to Sleep Onset (see Table 26) using the same model used by the sponsor for the objective endpoint first period only analyses.

**Table 26 Study 06: Analysis of sTSO in first period only**

| <b>Dose Day</b> | <b>Estimate</b> | <b>Std. Err.</b> | <b>p-value</b> |
|-----------------|-----------------|------------------|----------------|
| <b>10 1</b>     | -3.7189         | 4.1225           | 0.3680         |
| <b>10 28*</b>   | -10.4748        | 5.2403           | 0.0468         |
| <b>20 1</b>     | -4.0995         | 4.0950           | 0.3179         |
| <b>20 28</b>    | -5.4338         | 5.2913           | 0.3056         |
| <b>40 1</b>     | -12.7047        | 4.1970           | 0.0028         |
| <b>40 28</b>    | -13.8431        | 5.3507           | 0.0103         |
| <b>80 1</b>     | -7.6403         | 4.2265           | 0.0720         |
| <b>80 28</b>    | -13.7256        | 5.4729           | 0.0129         |

\*This was not nominally significant  $p=0.14$ , when dose by covariate interactions as used in the prespecified analysis were added

. Table 27 summarizes the sponsor's analysis of subjective TST.

**Table 27 Study 06: Sponsor's Analysis of Subjective TST**

| Pairwise Comparison  | Differences in LS Mean <sup>†</sup> (95% CI) | p-Value |
|--|--|---------|
| <b>Week 1</b>  |  |         |
| MK4305 10 mg   | 3.0 (-10.4, 16.4)                            | 0.6607  |
| MK4305 20 mg   | -3.1 (-16.8, 10.6)                           | 0.6570  |
| MK4305 40 mg   | 22.8 (8.6, 36.9)                             | 0.0018  |
| MK4305 80 mg   | 20.8 (6.8, 34.8)                             | 0.0039  |
| <b>Week 2</b>  |  |         |
| MK4305 10 mg   | 0.6 (-12.2, 13.3)                            | 0.9302  |
| MK4305 20 mg   | 10.5 (-2.5, 23.6)                            | 0.1137  |
| MK4305 40 mg   | 18.6 (5.1, 32.1)                             | 0.0072  |
| MK4305 80 mg   | 22.5 (9.3, 35.8)                             | 0.0010  |
| <b>Week 3</b>  |  |         |
| MK4305 10 mg   | 1.2 (-11.6, 14.0)                            | 0.8584  |
| MK4305 20 mg   | 5.4 (-7.7, 18.5)                             | 0.4171  |
| MK4305 40 mg   | 21.4 (7.9, 34.9)                             | 0.0020  |
| MK4305 80 mg   | 22.5 (9.1, 35.8)                             | 0.0011  |
| <b>Week 4</b>  |  |         |
| MK4305 10 mg   | 5.5 (-6.3, 17.3)                             | 0.3578  |
| MK4305 20 mg   | -1.8 (-13.9, 10.4)                           | 0.7741  |
| MK4305 40 mg   | 29.6 (17.1, 42.1)                            | <.0001  |
| MK4305 80 mg   | 19.4 (7.1, 31.7)                             | 0.0022  |
| <sup>†</sup> Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., crossed with indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.<br>N = Number with measurement at time point. |  |         |

Note: This table was copied from page 410 of sponsor's study report

This reviewer also conducted first period only analyses for subjective Total Sleep Time (see Table 28).

**Table 28 Study 06: Analysis of sTST in first period only**

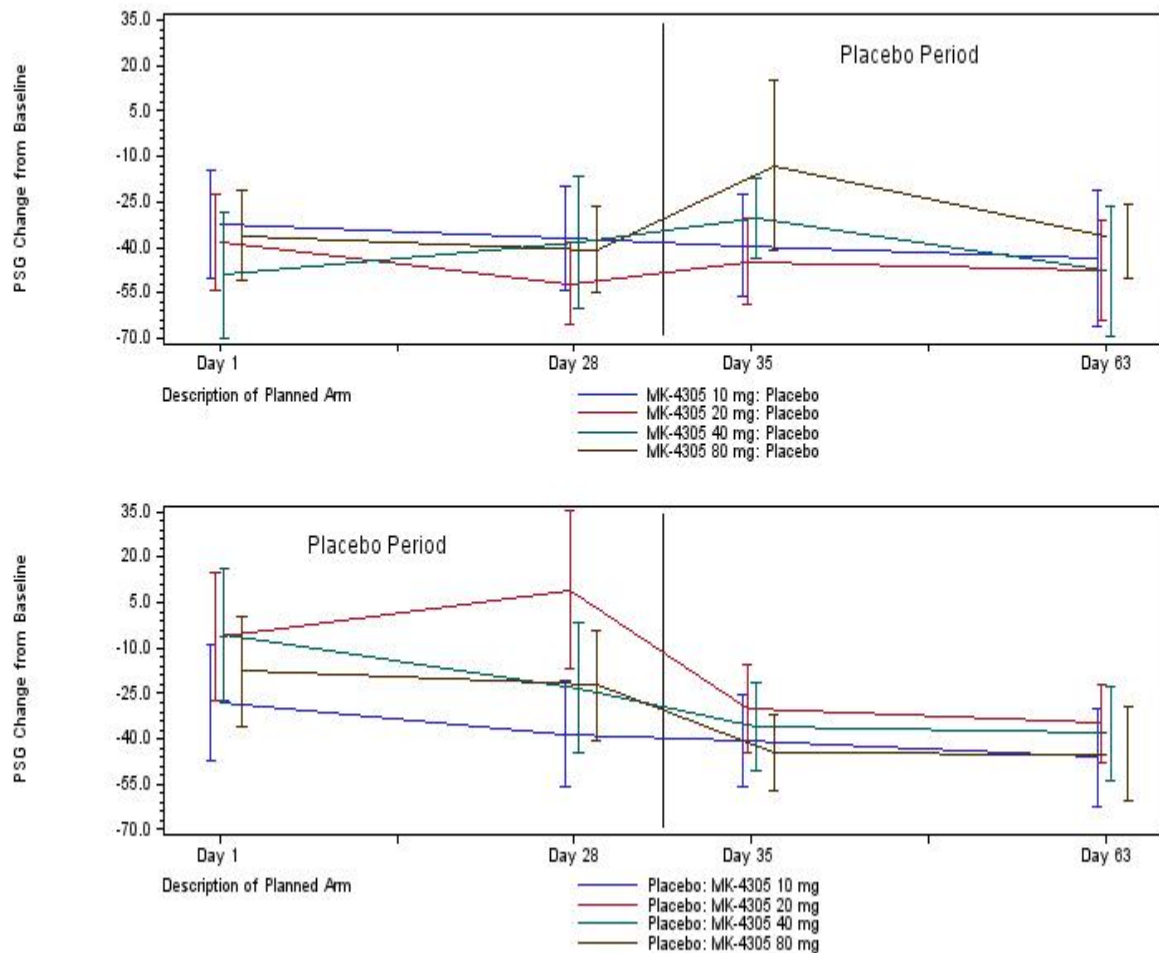
| Dose Day     | Estimate | Std. Err. | p-value |
|--------------|----------|-----------|---------|
| <b>10 1</b>  | 5.5400   | 8.2282    | 0.5015  |
| <b>10 28</b> | 15.4204  | 9.3958    | 0.1022  |
| <b>20 1</b>  | 5.1740   | 8.1668    | 0.5270  |
| <b>20 28</b> | 4.9265   | 9.4701    | 0.6034  |
| <b>40 1</b>  | 19.8850  | 8.4068    | 0.0189  |
| <b>40 28</b> | 12.6206  | 9.6240    | 0.1911  |
| <b>80 1</b>  | 18.9382  | 8.4577    | 0.0261  |
| <b>80 28</b> | 21.5596  | 9.8083    | 0.0290  |

### **3.1.3.5 Reviewer's Results**

As discussed by the sponsor there is evidence of a carryover effect from period 1 into period 2 for LPS. The interaction effect between period and treatment had a p-value of 0.0118, suggesting that the LPS's of some treatments arms varied significantly across the two periods.

This reviewer found that based only on the 2 sequences involving 10 mg, the 10 mg effects at Day 1 and Day 28 on LPS were not nominally significant:  
-3.45 +/- 4.68 (S.E.),  $p=.4633$  at Day 1 and -1.35 +/- 3.43(S.E.),  $p=.6945$  at Day 28. Also, based only on these 2 sequences there was no evidence of a carryover effect on LPS.

**Figure 11 Study 06: Mean Change from Baseline in LPS by Sequence and Period**

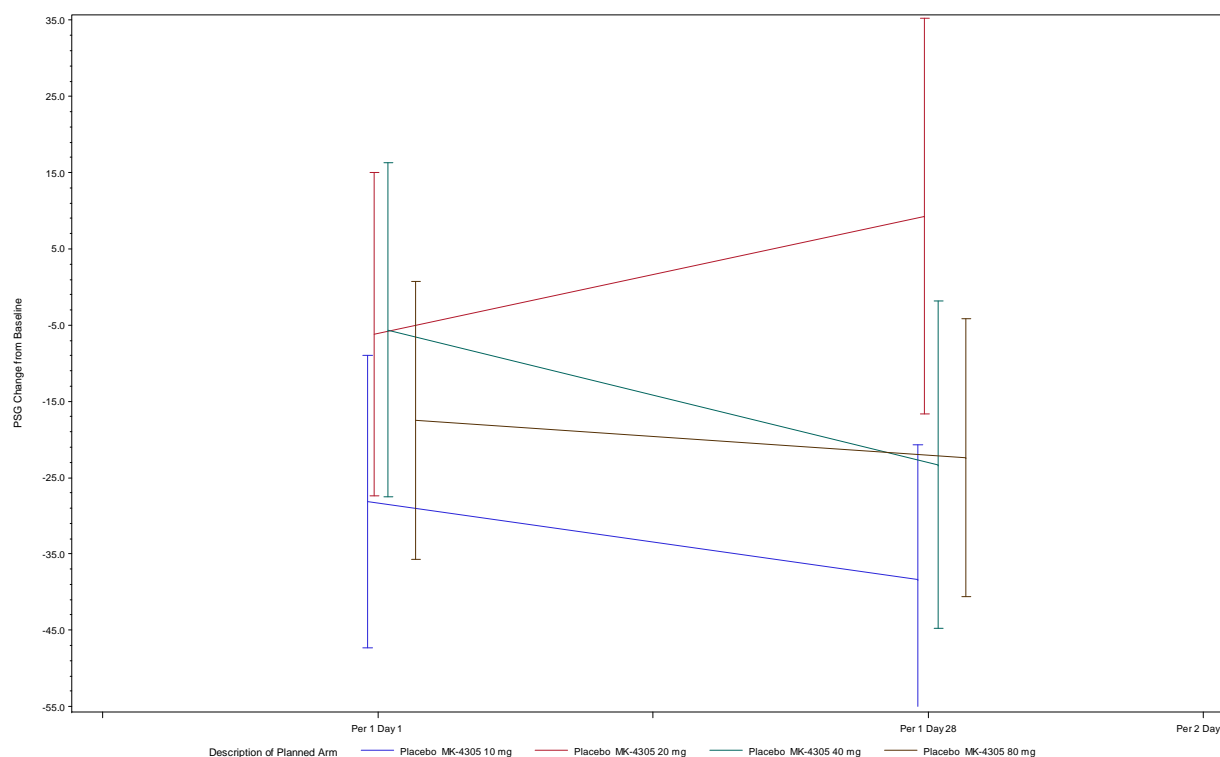


For LPS there was a nominally significant difference between the sequences assigned placebo in the first period (see the lower left side of Figure 11 or see Figure 12). There was no nominally significant difference between these groups in terms of mean baseline LPS. The post-baseline difference was most apparent at the day 28 timepoint, ( $p=0.0003$  for day 28 only and  $p=0.0033$  over both days). This may be due to chance alone but while there was no similar effect on WASO there was a similar trend in Sleep Efficiency but it was less significant ( $p=0.0665$  at day 28 and  $p=0.2788$  over both days).

The LPS effect of 10 mg on Day 1 was estimated to be  $-11.1 \pm 10.3$  (S.E.) minutes ( $p=0.2806$ ) based on substudy 1 only (10 mg/placebo and placebo/10 mg sequences) first period. The LPS

effect of 10 mg on Day 1 estimated based on pooling the placebo from all substudies was  $-21.7 \pm 8.4$  (S.E.) ( $p=0.0107$ ). The effect of LPS of 10 mg on Day 28 was estimated as  $-5.3867 \pm 10.3$ ,  $p=0.6007$  based on substudy 1 only and was  $-20.6 \pm 8.2423$ ,  $p=0.0131$  based on pooled placebo. If the placebo corresponding to 20 mg was left out of the comparison the estimated effect of 10 mg at day 28 was  $-11.7$  ( $p=0.169$ ) and if placebo groups corresponding to both 10 mg and 20 mg were left out the estimated effect of 10 mg compared to the remaining placebos at day 28 was  $-14.9$  ( $p=0.101$ ). This highlights the sensitivity of the 10 mg effect to the placebo groups involved in the comparison.

**Figure 12 Study 06: Mean Change from Baseline in LPS during first period for the placebo first sequences**



A Wilcoxon rank sum test done as a post-hoc sensitivity analysis which may lessen the impact of any outliers gave a result of  $p=0.276$  for 10 mg vs. pooled placebo in the first period on Day 1 and  $p=0.075$  for Day 28.

Twenty (8%) of 254 randomized patients had missing data at Week 4 in the first period (10/P:  $N=2$ , P/10: 1, 20/P: 2, P/20: 4, 40/P:2, P/40:3, 80/P 3, P/80: 3) In the second period the numbers missing (11%) at Week 4 were: (10/P:  $N=2$ , P/10: 2, 20/P: 3, P/20: 6, 40/P:3, P/40:5, 80/P 3, P/80: 4).

This reviewer also performed sensitivity analyses for missing data using multiple imputation. The sponsor had prespecified such a model for their sensitivity analysis for missing data.

The results are very similar to those for the observed data analyses, suggesting a limited impact of missing data on the results. The results of these analyses are shown for the 10 mg vs. placebo comparison in Table 29. I focus more on 10 mg here because 20 mg and 40 mg have more extensive data in the phase 3 studies but this is the only study involving 10 mg.

**Table 29 Study 06: Reviewer's Multiple Imputation Sensitivity Analyses for Missing Data**

| Efficacy Measure | Dose | Night | Difference from Placebo | Std. Error of Diff. | P-value  |
|------------------|------|-------|-------------------------|---------------------|----------|
| LPS              | 10   | 1     | -19.04                  | 8.15                | 0.0194 - |
| LPS              | 10   | 28    | -22.04                  | 8.80                | 0.0123 - |
| WASO             | 10   | 1     | -18.01                  | 9.37                | 0.0545   |
| WASO             | 10   | 28    | -19.71                  | 9.85                | 0.0459   |

### 3.2 Evaluation of Safety

General Safety is not reviewed in this document. Please see the medical officer's review for the evaluation of safety.

#### Effects of Suvorexant on Driving Performance

The effects of night time administration of suvorexant on next-morning driving performance were evaluated in two similarly designed highway driving studies in 24 healthy elderly ( $\geq 65$  years old, P039) and 28 healthy non-elderly (21-64 years old, P035) subjects. In both studies, driving performance was evaluated following single (on Day 2) and 8 consecutive nights (on Day 9) of suvorexant at low dose (15 mg in elderly and 20 mg in non-elderly) and high dose (30 mg in elderly and 40 mg in non-elderly) with the driving tests being conducted at ~9 hours post-dose. The primary endpoint was standard deviation of lane position (SDLP) which was used as a measure of driving performance. Zopiclone was used as active control in both studies. A published on-the-road highway driving study comparing the impairment caused by zopiclone in healthy subjects versus insomnia patients indicated that healthy subjects may be an appropriate population to evaluate effects of hypnotics on driving performance.

In both studies, zopiclone demonstrated assay sensitivity on both Day 2 and Day 9. In the elderly subjects, suvorexant (15 or 30 mg) did not result in impairment on next-day driving performance as assessed by mean SDLP (primary endpoint) and symmetry analysis of SDLP (secondary). In the non-elderly subjects, in the sponsor's opinion there was no clinically meaningful impairment of next-day driving performance at either dose level (20 and 40 mg) since the 90% CI of SDLP was  $< 2.4$  cm (pre-specified clinical significance bound). However, except for 20 mg at Day 9 all were significantly worse than placebo. In addition, the symmetry analysis of SDLP revealed a statistically greater number of subjects with SDLP treatment difference of  $> 2.4$  cm (indicating impairment) than those with SDLP  $< -2.4$  cm on Day 2 for both suvorexant doses, and on Day 9 for 40 mg. The treatment effect was apparently less with the low dose than high dose of suvorexant. The treatment difference on SDLP was smaller on Day 9 as compared to Day 2, suggesting to the sponsor the possibility of some tolerance effects after repeated dosing.

Plasma concentrations at 11 hr postdose were measured in both driving studies and the PKPD

relationship was explored for SDLP. There was an apparent dose response on SDLP.

Study 35 had some conduct irregularities. One subject, AN0005, was missing Day 9 following placebo treatment (period 3). This subject left the CRU the evening before testing due to a panic attack. Subject AN0004 was missing SDS data for the 20 mg suvorexant treatment (Period 1) due to a technical failure. Three subjects repeated one treatment period of the study. The repeated period data were used for each subject and the original period data were not used in the pharmacodynamics analysis due to an incomplete data set. The 3 subjects affected were (AN0011 (in Period 1, due to a technical failure of the car driving procedure); AN0016 (the subject was unable to return to the CRU on Day 8, Period 2 due to personal issues); and AN 0021 (in Period 4, due to a hardware issue occurring at the beginning of the driving assessment. Five subjects had prematurely stopped car driving test data. Of these 5 subjects, the car driving test data for 4 subjects (AN0002, AN0006, AN0007, and AN0021) were used in the analysis. AN0016 prematurely stopped the driving test during Day 2 Period 2; however, this subject repeated Period 2 as he was unable to attend Day 8. Only data from the repeated period was included in the analysis.

Table 30 summarizes the sponsor's analyses of mean SDLP in the non-elderly study. These results were verified by this reviewer.

**Table 30 Study 35: Non-Elderly Driving Study Analysis of Mean SDLP**

| Day  | Treatment        | N  | LS Mean |               | Difference From Placebo |              |
|--|------------------|----|---------|---------------|-------------------------|--------------|
|  |                  |    | Mean    | 95% CI        | Mean                    | 90% CI       |
| 2  | Placebo          | 28 | 15.53   | (14.53,16.53) |                         |              |
|  | Zopiclone 7.5 mg | 28 | 17.66   | (16.66,18.66) | 2.14                    | (1.49,2.79)  |
|  | Suvorexant 20 mg | 28 | 16.54   | (15.54,17.54) | 1.01                    | (0.36,1.66)  |
|  | Suvorexant 40 mg | 28 | 17.19   | (16.19,18.19) | 1.66                    | (1.01,2.31)  |
| 9  | Placebo          | 27 | 15.47   | (14.46,16.47) |                         |              |
|  | Zopiclone 7.5 mg | 28 | 16.91   | (15.91,17.91) | 1.45                    | (0.79,2.10)  |
|  | Suvorexant 20 mg | 28 | 15.94   | (14.94,16.94) | 0.48                    | (-0.18,1.13) |
|  | Suvorexant 40 mg | 28 | 16.77   | (15.77,17.77) | 1.31                    | (0.65,1.96)  |
| Original Period 2, Day 2 data for AN0016 was not included in the analysis (the subject had a premature stop due to somnolence). The subject could not return for the Period 2, Day 8 visit and repeated this period. Only the repeat period is included in the analysis. |                  |    |         |               |                         |              |

Note: This table was copied from page 60 of the sponsor's study report

*Reviewer's Comment:*

*At Day 2 both doses were significantly worse than placebo but the upper limits of the 90% C.I.s were below 2.4. At Day 9, the Mean SDLP was nominally significantly worse in the high dose than in the low dose as well as placebo ( $p=0.0006$ ). On day 9 the 40 mg mean SDLP was nominally significantly worse than that for 20 mg,  $0.83$   $p=0.036$ . Also, the 40 mg 95%*



*C.I.(.89,2.44) , just included the cutpoint of interest 2.40. On day 2, the 40 mg mean SDLP comparison to 20 mg had an estimated difference of 0.65 with a p-value of 0.101.*

Table 31 summarizes the symmetry analysis of subjects with differences from placebo  $> 2.40$  or  $< -2.40$  in the non-elderly study.

**Table 31 Study 35: Non-Elderly Driving Study Symmetry Analysis**

| Treatment                             | Day=2               |                     |                     | Day=9               |                     |                     |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                                       | Suvorexant<br>20 mg | Suvorexant<br>40 mg | Zopiclone<br>7.5 mg | Suvorexant<br>20 mg | Suvorexant<br>40 mg | Zopiclone<br>7.5 mg |
| $n+1$ <sup>†</sup>                    | 6                   | 10                  | 14                  | 2                   | 6                   | 8                   |
| $n-1$ <sup>‡</sup>                    | 0                   | 2                   | 1                   | 1                   | 0                   | 0                   |
| $m = n+1 + n-1$                       | 6                   | 12                  | 15                  | 3                   | 6                   | 8                   |
| Test Statistic <sup>§</sup>           | 2.45                | 2.31                | 3.36                | 0.58                | 2.45                | 2.83                |
| Reject Null Hypothesis? <sup>  </sup> | Yes                 | Yes                 | Yes                 | No                  | Yes                 | Yes                 |

<sup>†</sup> $n+1$  = number of subjects with treatment difference (from placebo)  $\geq 2.4$  cm.  
<sup>‡</sup> $n-1$  = number of subjects with treatment difference (from placebo)  $\leq -2.4$  cm.  
<sup>§</sup>Test Statistic =  $(n+1 - n-1) / \sqrt{m}$ .  
<sup>||</sup>Reject Null hypothesis if test statistic  $> 1.74$ , which is the critical value for general sign test with exact unconditional approach for sample size  $N=28$  and  $N=27$ .  
 Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.  
 Original Period 2, Day 2 data for A10016 was not included in the analysis (the subject had a premature stop due to nonadherence). The subject could not return for the Period 2, Day 8 visit and repeated this period. Only the repeat period is included in the analysis.

Note: This table was copied from page 61 of the sponsor's study report

Table 32 summarizes the sponsor's analysis of mean SDLP for the elderly study. The results were verified by this reviewer.

**Table 32 Study 39: Elderly Driving Study Analysis of Mean SDLP**

| Day | Treatment        | N  | LS Mean |               | Difference from PBO |              |
|-----|------------------|----|---------|---------------|---------------------|--------------|
|     |                  |    | Mean    | 95% CI        | Mean                | 90% CI       |
| 2   | Placebo          | 24 | 16.67   | (15.48,17.86) |                     |              |
|     | Zopiclone 7.5 mg | 24 | 18.56   | (17.37,19.75) | 1.89                | (1.22,2.55)  |
|     | MK-4305 15 mg    | 24 | 16.24   | (15.05,17.43) | -0.43               | (-1.10,0.23) |
|     | MK-4305 30 mg    | 24 | 17.04   | (15.85,18.23) | 0.37                | (-0.30,1.03) |
| 9   | Placebo          | 24 | 15.41   | (14.22,16.60) |                     |              |
|     | Zopiclone 7.5 mg | 24 | 16.58   | (15.39,17.78) | 1.17                | (0.51,1.84)  |
|     | MK-4305 15 mg    | 24 | 15.50   | (14.31,16.69) | 0.09                | (-0.58,0.76) |
|     | MK-4305 30 mg    | 24 | 16.01   | (14.82,17.20) | 0.60                | (-0.06,1.27) |

Note: This table was copied from page 59 of the sponsor's study report

An exploratory comparison of 40 vs 20mg on day 2 gave an estimate of 0.7992 (0.4027 S.E.)  $p=0.0489$ . On day 9 the estimated difference between 40 mg and 20 mg was 0.51,  $p=0.205$ .

Table 33 summarizes the symmetry analysis of subjects with differences from placebo  $> 2.40$  or  $< -2.40$  in the elderly driving study.

**Table 33 Study 39: Elderly Driving Study Symmetry Analysis**

| Treatment                             | Day=2            |                  |                     | Day=9            |                  |                     |
|---------------------------------------|------------------|------------------|---------------------|------------------|------------------|---------------------|
|                                       | MK-4305<br>15 mg | MK-4305<br>30 mg | Zopiclone<br>7.5 mg | MK-4305<br>15 mg | MK-4305<br>30 mg | Zopiclone<br>7.5 mg |
| n+1 <sup>†</sup>                      | 0                | 3                | 8                   | 0                | 5                | 6                   |
| n-1 <sup>‡</sup>                      | 3                | 1                | 0                   | 0                | 1                | 1                   |
| m = n+1 + n-1                         | 3                | 4                | 8                   | 0                | 6                | 7                   |
| Test Statistic <sup>§</sup>           | -1.73            | 1                | 2.83                | N.D.             | 1.63             | 1.89                |
| Reject Null Hypothesis? <sup>  </sup> | No               | No               | Yes                 | No               | No               | Yes                 |

<sup>†</sup> n+1 = number of subjects with treatment difference from placebo  $\geq 2.4$  cm.  
<sup>‡</sup> n-1 = number of subjects with treatment difference from placebo  $\leq -2.4$  cm.  
<sup>§</sup> Test Statistic =  $(n+1 - n-1)/\sqrt{m}$ .  
<sup>||</sup> Reject Null hypothesis if test statistic  $> 1.74$ , which is the critical value for general sign test with exact unconditional approach for sample size N=24.  
Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.

Note: This table was copied from page 59 of the sponsor's study report

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

#### 4.1.1 Gender

In study P028 North American sites accounted for 34% of all randomized patients, 42% were Elderly, 65% White and 26% Asian, 63% Female.

In P029 67% were female, 80% were White, 8% Asian, and 41% were Elderly.

Note that the p-values presented in section 4.1 and its subsections should be considered exploratory since they are not adjusted for the multiplicity of tests and in addition the

study was not powered for assessing effects in these subgroups. Pooled study results are only considered if the contributing studies are positive on their own. In such cases these results are provided, assuming consistency across studies, to get a more precise estimate of the effect in subgroups. The LPS results for high dose should be considered exploratory for Month 3 since study 29 was not positive in terms of LPS at month 3. Also, low dose results should be considered exploratory since the studies allocated all of the alpha (type I error) to testing the high dose.

Study 28 and 29 were pooled for gender subgroup analyses since they were of very similar design. There was no compelling evidence of differential efficacy for Males and Females in terms of LPS, WASO, sTST, or sTSO (see Table 34, Table 35, Table 36, and Table 37).

**Table 34** Change from Baseline in LPS by Gender in P28/P29 Pooled

| <b>Gender</b>      | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Female             | 90          | -5.2814                  | 3.0223                  | 0.0808                 | -7.6442                  | 2.6106                  | 0.0035                 |
| Female             | 30          | -9.4241                  | 2.8334                  | 0.0009                 | -12.6431                 | 2.4187                  | <.0001                 |
| Female             | 1           | -13.2441                 | 3.0688                  | <.0001                 | -17.5972                 | 2.6243                  | <.0001                 |
| Male               | 90          | -3.4120                  | 4.1610                  | 0.4124                 | -4.4094                  | 3.5207                  | 0.2106                 |
| Male               | 30          | -8.6088                  | 3.8437                  | 0.0253                 | -9.6025                  | 3.2989                  | 0.0037                 |
| Male               | 1           | -7.6409                  | 4.1203                  | 0.0639                 | -12.6783                 | 3.5571                  | 0.0004                 |
| Male vs.<br>Female | 90          | 1.8694                   | 5.1410                  | 0.7162                 | 3.2348                   | 4.3869                  | 0.4610                 |
| Male vs.<br>Female | 30          | 0.8153                   | 4.7733                  | 0.8644                 | 3.0406                   | 4.0949                  | 0.4579                 |

**Table 35 Change from Baseline in WASO by Gender in P28/P29 Pooled**

| <b>Gender</b>      | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Female             | 90          | -17.6079                 | 5.2170                  | 0.0008                 | -24.5786                 | 4.8225                  | <.0001                 |
| Female             | 30          | -26.0302                 | 5.0257                  | <.0001                 | -26.0964                 | 4.6486                  | <.0001                 |
| Female             | 1           | -31.5294                 | 4.3235                  | <.0001                 | -33.5833                 | 3.9419                  | <.0001                 |
| Male               | 90          | -14.6121                 | 7.1993                  | 0.0428                 | -20.1741                 | 6.2150                  | 0.0012                 |
| Male               | 30          | -26.9247                 | 6.9177                  | 0.0001                 | -26.2577                 | 5.9591                  | <.0001                 |
| Male               | 1           | -34.5159                 | 5.8526                  | <.0001                 | -46.2136                 | 5.0503                  | <.0001                 |
| Male vs.<br>Female | 90          | 2.9957                   | 8.8987                  | 0.7365                 | 4.4045                   | 7.8763                  | 0.5762                 |
| Male vs.<br>Female | 30          | -0.8944                  | 8.5561                  | 0.9168                 | -0.1612                  | 7.5662                  | 0.9830                 |

**Table 36 Change from Baseline in sTSO by Gender in P28/P29 Pooled**

| <b>Gender</b>      | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Female             | 90          | -4.6446                  | 2.7227                  | 0.0882                 | -11.5033                 | 2.4059                  | <.0001                 |
| Female             | 30          | -3.8226                  | 2.7690                  | 0.1676                 | -11.3188                 | 2.4485                  | <.0001                 |
| Female             | 1           | -6.6865                  | 2.2562                  | 0.0031                 | -9.4449                  | 1.9942                  | <.0001                 |
| Male               | 90          | -8.3626                  | 3.6853                  | 0.0234                 | -9.5179                  | 3.2091                  | 0.0031                 |
| Male               | 30          | -8.7585                  | 3.7227                  | 0.0187                 | -7.8697                  | 3.2663                  | 0.0161                 |
| Male               | 1           | -4.9561                  | 3.0244                  | 0.1014                 | -9.0074                  | 2.6601                  | 0.0007                 |
| Male vs.<br>Female | 90          | -3.7180                  | 4.5824                  | 0.4173                 | 1.9854                   | 4.0140                  | 0.6209                 |
| Male vs.<br>Female | 30          | -4.9360                  | 4.6403                  | 0.2876                 | 3.4491                   | 4.0852                  | 0.3986                 |

**Table 37 Change from Baseline in sTST by Gender in P28/P29 Pooled**

| <b>Gender</b>      | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Female             | 90          | 16.3379                  | 4.3180                  | 0.0002                 | 26.0808                  | 3.8157                  | <.0001                 |
| Female             | 30          | 19.0584                  | 3.9626                  | <.0001                 | 26.0755                  | 3.5029                  | <.0001                 |
| Female             | 1           | 16.1804                  | 3.2194                  | <.0001                 | 25.0402                  | 2.8458                  | <.0001                 |
| Male               | 90          | 15.0096                  | 5.8447                  | 0.0103                 | 15.1642                  | 5.0897                  | 0.0029                 |
| Male               | 30          | 16.7534                  | 5.3248                  | 0.0017                 | 16.6413                  | 4.6734                  | 0.0004                 |
| Male               | 1           | 12.4592                  | 4.3166                  | 0.0039                 | 21.3010                  | 3.7968                  | <.0001                 |
| Male vs.<br>Female | 90          | -1.3283                  | 7.2669                  | 0.8550                 | -10.9166                 | 6.3654                  | 0.0865                 |
| Male vs.<br>Female | 30          | -2.3050                  | 6.6379                  | 0.7284                 | -9.4342                  | 5.8449                  | 0.1067                 |

In the crossover study (P06) 58% of the 254 randomized patients were Female. Although the difference between Males and Female estimated 10 mg effects on WASO at Day 1 of the first period is noticeably large it is not significant considering the standard error of the estimates. Overall, there was no compelling evidence of differential estimated effects between genders for WASO or LPS in study 6 first period.

**Table 38 Study 06 First Period Only Analyses of Change from Baseline in WASO and LPS by Gender**

| <b>Endpoint</b> | <b>Gender</b> | <b>Day</b> | <b>Estimate</b> | <b>Standard<br/>Error</b> | <b>DF</b> | <b>t Value</b> | <b>Pr &gt;<br/> t </b> |
|-----------------|---------------|------------|-----------------|---------------------------|-----------|----------------|------------------------|
| <b>WASO</b>     | <b>Female</b> | <b>1</b>   | -25.9918        | 13.5315                   | 251       | -1.92          | 0.0559                 |
|                 | <b>Female</b> | <b>28</b>  | -20.1399        | 14.1788                   | 251       | -1.42          | 0.1567                 |
|                 | <b>Male</b>   | <b>1</b>   | -4.8758         | 13.4528                   | 251       | -0.36          | 0.7173                 |
|                 | <b>Male</b>   | <b>28</b>  | -16.6700        | 13.3522                   | 251       | -1.25          | 0.2130                 |
| <b>LPS</b>      | <b>Female</b> | <b>1</b>   | -19.1324        | 11.8231                   | 251       | -1.62          | 0.1069                 |
|                 | <b>Female</b> | <b>28</b>  | -27.4794        | 12.7650                   | 251       | -2.15          | 0.0323                 |
|                 | <b>Male</b>   | <b>1</b>   | -17.0123        | 11.7838                   | 251       | -1.44          | 0.1501                 |
|                 | <b>Male</b>   | <b>28</b>  | -13.0058        | 12.0424                   | 251       | -1.08          | 0.2812                 |

### 4.1.2 Race

In study P28 overall proportions of randomized patients a given race were: 65% white, 26% Asian, 6% Black, 3% Multi-Racial, and .1% Pacific Islander. Although a considerable overall proportion of patients were Asian they were almost exclusively enrolled in the Q only cohort so that while for subjective endpoints the proportion Asian was 26%, for PSG endpoints the proportion Asian was only 2%.

There was no suggestion of an interaction in study 28 for sTSO, while for sTST the ‘Other’ category was numerically in the wrong direction so there was a suggestion of an interaction at Month 1. However, at month 3 as well as Night 1 the ‘Other’ category was numerically better than placebo thereby diminishing the credibility of the interaction at 1 Month.

**Table 39 Study 28 Differences in Change from Baseline in sTSO High Dose vs. Placebo at Month 1 by Race**

| <b>Subgroup<br/>or Contrast</b> | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Asian</b>                    | -6.9274         | 4.9357                | 849       | -1.40          | 0.1608         |
| <b>Other</b>                    | -4.0025         | 8.1062                | 838       | -0.49          | 0.6216         |
| <b>White</b>                    | -8.1375         | 3.1227                | 855       | -2.61          | 0.0093         |
| <b>Asian vs. White</b>          | 1.2102          | 5.8453                | 851       | -0.21          | 0.8360         |

There was no compelling evidence of a difference in effect of the high dose at 1 Month on sTSO between Whites and Asians ( $p=0.836$ ) or Whites and ‘Others’ ( $p=0.886$ ).

Table 40 shows Race subgroup analyses for subjective Total Sleep Time at 1 Month for the high dose. There was a suggestion of differential efficacy between Whites and Asians ( $p=0.0277$ ) and Whites and ‘Others’ ( $p=.0162$ ) at Month 1 for the high dose in the subjective Total Sleep Time. However, the estimated effect was still numerically in the right direction for Asians, the ‘Other’ subgroup was small, and this pattern was not exhibited on the other efficacy measures. Therefore, this pattern may be due to chance.

**Table 40 Study 28: Differences in Change from Baseline in sTST High Dose vs. Placebo at Month 1 by Race**

| <b>Subgroup<br/>or Contrast</b> | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Asian</b>                    | 7.7452          | 7.5200                | 948       | 1.03           | 0.3033         |
| <b>Other</b>                    | -2.2489         | 12.3660               | 938       | -0.18          | 0.8557         |
| <b>White</b>                    | 27.3731         | 4.7610                | 955       | 5.75           | <.0001         |
| <b>Asian vs. White</b>          | 19.6279         | 8.9013                | 950       | 2.21           | 0.0277         |

Table 41 shows Race subgroup analyses for objective LPS at Month 1 and Month 3 for the high dose. Note that the Q only cohort in study 28 consisted of only Japanese patients which reduces the PSG Asian cohort significantly enough to make it more appropriate to combine Asians with Others for race subgroup analyses involving PSG endpoints (only 2% were Asian in the PQ cohort).

**Table 41 Study 28: Differences in Change from Baseline in LPS High Dose vs. Placebo at Month 1 by Race**

| <b>Subgroup<br/>or Contrast</b> |    | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|----|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Other</b>                    | 90 | -3.8785         | 6.7906                | 676       | -0.57          | 0.5681         |
| <b>Other</b>                    | 30 | 8.3294          | 6.7368                | 729       | 1.24           | 0.2167         |
| <b>White</b>                    | 90 | -11.0910        | 2.8294                | 677       | -3.92          | <.0001         |
| <b>White</b>                    | 30 | -14.6979        | 2.7945                | 729       | -5.26          | <.0001         |
| <b>Other vs. White</b>          | 90 | -7.2124         | 7.3520                | 675       | -0.98          | 0.3269         |
| <b>Other vs. White</b>          | 30 | -23.0274        | 7.2873                | 727       | -3.16          | 0.0016         |

Table 42 shows Race subgroup analyses for objective WASO at Month 1 and Month 3 for the high dose. Effects were bigger in the ‘Other’ subgroup but were in the right direction and nominally significant for both subgroups.

**Table 42 Study 28: Differences in Change from Baseline in WASO High Dose vs. Placebo at Month 1 by Race**

| <b>Subgroup<br/>or Contrast</b> |    | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|----|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Other</b>                    | 90 | -41.4422        | 9.8198                | 680       | -4.22          | <.0001         |
| <b>Other</b>                    | 30 | -41.9337        | 9.4761                | 718       | -4.43          | <.0001         |
| <b>White</b>                    | 90 | -19.3328        | 4.0977                | 684       | -4.72          | <.0001         |
| <b>White</b>                    | 30 | -23.4159        | 3.9377                | 722       | -5.95          | <.0001         |
| <b>Other vs. White</b>          | 90 | 22.1094         | 10.6353               | 680       | 2.08           | 0.0380         |
| <b>Other vs. White</b>          | 30 | 18.5178         | 10.2545               | 718       | 1.81           | 0.0714         |

In study P29 proportions of randomized patients a given race were: 80% white, 8% Asian, 5% Black, 7% Multi-Racial.

Table 43 shows subgroup estimates of the high dose effect on subjective TSO for race at Month 1 and Month 3. Both subgroups (White and Other) had high dose vs. placebo differences in the right direction and there was no compelling evidence of differential effect by subgroup (e.g., sTSOm interaction  $p=.51$  at Day 30).

**Table 43 Study 29: sTSO Differences at Month 1 High Dose vs Placebo by Race**

| <b>Subgroup<br/>or Contrast</b> |    | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|----|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Other</b>                    | 90 | -14.6758        | 7.0811                | 775       | -2.07          | 0.0385         |
| <b>Other</b>                    | 30 | -8.4170         | 6.8416                | 923       | -1.23          | 0.2189         |
| <b>White</b>                    | 90 | -12.2893        | 3.4659                | 755       | -3.55          | 0.0004         |
| <b>White</b>                    | 30 | -13.4379        | 3.3910                | 921       | -3.96          | <.0001         |
| <b>Other vs. White</b>          | 90 | 2.3865          | 7.8819                | 772       | 0.30           | 0.7621         |
| <b>Other vs. White</b>          | 30 | -5.0209         | 7.6332                | 923       | -0.66          | 0.5108         |



Table 44 shows subgroup estimates of the high dose effect on subjective TSO for race at Month 1 and Month 3.

**Table 44 Study 29: sTST Differences at Month 1 High Dose vs Placebo by Race**

| <b>Subgroup<br/>or Contrast</b> |    | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|----|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Other</b>                    | 90 | 15.5220         | 10.4627               | 904       | 1.48           | 0.1383         |
| <b>Other</b>                    | 30 | 25.9098         | 9.1709                | 949       | 2.83           | 0.0048         |
| <b>White</b>                    | 90 | 26.9093         | 5.1278                | 882       | 5.25           | <.0001         |
| <b>White</b>                    | 30 | 26.1581         | 4.5475                | 948       | 5.75           | <.0001         |
| <b>Other vs. White</b>          | 90 | 11.3874         | 11.6498               | 900       | 0.98           | 0.3286         |
| <b>Other vs. White</b>          | 30 | 0.2482          | 10.2333               | 949       | 0.02           | 0.9807         |

Table 45 shows subgroup estimates of the high dose effect on objective WASO for race at Month 1 and Month 3.

**Table 45 Study 29: WASO Differences at Month 1 High Dose vs Placebo by Race**

| <b>Subgroup<br/>or Contrast</b> |    | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|----|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Other</b>                    | 90 | -18.4149        | 12.2228               | 661       | -1.51          | 0.1324         |
| <b>Other</b>                    | 30 | -28.9747        | 11.6989               | 676       | -2.48          | 0.0135         |
| <b>White</b>                    | 90 | -30.5603        | 3.9081                | 653       | -7.82          | <.0001         |
| <b>White</b>                    | 30 | -29.4636        | 3.8335                | 677       | -7.69          | <.0001         |
| <b>Other vs. White</b>          | 90 | -12.1454        | 12.8323               | 660       | -0.95          | 0.3443         |
| <b>Other vs. White</b>          | 30 | -0.4889         | 12.3113               | 677       | -0.04          | 0.9683         |

Table 46 shows subgroup estimates of the high dose effect on objective LPS for race at Month 1 and Month 3.

**Table 46 Study 29: LPS Differences at Month 1 High Dose vs. Placebo by Race**

| <b>Subgroup<br/>or Contrast</b> |    | <b>Estimate</b> | <b>Standard Error</b> | <b>DF</b> | <b>t Value</b> | <b>p-value</b> |
|---------------------------------|----|-----------------|-----------------------|-----------|----------------|----------------|
| <b>Other</b>                    | 90 | 10.0428         | 10.5963               | 641       | 0.95           | 0.3436         |
| <b>Other</b>                    | 30 | -11.3683        | 9.3443                | 675       | -1.22          | 0.2242         |
| <b>White</b>                    | 90 | -5.0456         | 3.4344                | 642       | -1.47          | 0.1423         |
| <b>White</b>                    | 30 | -12.1714        | 3.0798                | 678       | -3.95          | <.0001         |
| <b>Other vs. White</b>          | 90 | -15.0885        | 11.1401               | 642       | -1.35          | 0.1761         |
| <b>Other vs. White</b>          | 30 | -0.8032         | 9.8398                | 675       | -0.08          | 0.9350         |

In study P06 70% of randomized patients were White. Because of the small overall size of the study and the crossover design not much can be said about race subgroup effects from this study. Race was also mostly confounded with Country in this study (see regional estimates at the end of section 4.1.4).

### 4.1.3 Age

In studies 28 and 29 the mean age was 55 to 56 and about 58 to 60% were non-elderly.

Table 47 shows the results for mean change from baseline in LPS by Age group (Age<65 and Age  $\geq$  65). There was some suggestion of lower effects on LPS for Elderly at 1 month.

This was true both in the pooled analysis as well as for study 29 analyzed separately. For the study 29 only analysis the LPS month 1 apparent interaction between age groups for high dose alone vs. placebo had a p-value of 0.0071 or across both hi and low dose comparisons (p=0.0257). However, this may be a quantitative interaction though since the effect in the elderly subgroup was still numerically in the right direction (-2.99, p=.5031).

**Table 47 Change from Baseline in LPS by Age Group in P28/P29 Pooled**

| <b>Age Group</b>  | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|-------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Elderly           | 90          | -6.3985                  | 3.6977                  | 0.0838                 | -7.8343                  | 3.1984                  | 0.0144                 |
| Elderly           | 30          | -5.2240                  | 3.4796                  | 0.1335                 | -6.9298                  | 2.9737                  | 0.0199                 |
| Elderly           | 1           | -10.1704                 | 3.7511                  | 0.0068                 | -17.6958                 | 3.2263                  | <.0001                 |
| Non-Eld.          | 90          | -3.2936                  | 3.2468                  | 0.3106                 | -5.4343                  | 2.7649                  | 0.0496                 |
| Non-Eld.          | 30          | -12.1545                 | 3.0090                  | <.0001                 | -15.1004                 | 2.5723                  | <.0001                 |
| Non-Eld.          | 1           | -12.0673                 | 3.2611                  | 0.0002                 | -14.5087                 | 2.7907                  | <.0001                 |
| Eld. Vs. Non-Eld. | 90          | 3.1050                   | 4.9189                  | 0.5280                 | 2.4001                   | 4.2296                  | 0.5705                 |
| Eld. Vs. Non-Eld. | 30          | -6.9305                  | 4.5985                  | 0.1320                 | -8.1705                  | 3.9337                  | 0.0380                 |

Table 48, Table 49, and Table 50 show the results by Age group for WASO, sTST, and sTSO, respectively. There was no compelling evidence of differential effects by Age group on these endpoints.

**Table 48 Change from Baseline in WASO by Age Group in P28/P29 Pooled Studies**

| <b>Age Group</b>  | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|-------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Elderly           | 90          | -14.9477                 | 6.4178                  | 0.0201                 | -16.8556                 | 5.8105                  | 0.0038                 |
| Elderly           | 30          | -26.6104                 | 6.2086                  | <.0001                 | -26.3445                 | 5.5506                  | <.0001                 |
| Elderly           | 1           | -39.7014                 | 5.3117                  | <.0001                 | -45.4524                 | 4.7546                  | <.0001                 |
| Non-Eld.          | 90          | -17.9340                 | 5.5967                  | 0.0014                 | -27.4945                 | 5.0231                  | <.0001                 |
| Non-Eld.          | 30          | -26.0884                 | 5.3627                  | <.0001                 | -26.3299                 | 4.8434                  | <.0001                 |
| Non-Eld.          | 1           | -27.1623                 | 4.5850                  | <.0001                 | -33.1765                 | 4.0860                  | <.0001                 |
| Eld. Vs. Non-Eld. | 90          | -2.9862                  | 8.5167                  | 0.7260                 | -10.6389                 | 7.6854                  | 0.1667                 |
| Eld. Vs. Non-Eld. | 30          | 0.5221                   | 8.2027                  | 0.9493                 | 0.0146                   | 7.3693                  | 0.9984                 |

**Table 49 Change from Baseline in sTST by Age Group in P28/P29 Pooled**

| <b>Age Group</b>  | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|-------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Elderly           | 90          | 18.9499                  | 5.3771                  | 0.0004                 | 20.6024                  | 4.7279                  | <.0001                 |
| Elderly           | 30          | 15.5224                  | 4.9435                  | 0.0017                 | 20.8347                  | 4.3480                  | <.0001                 |
| Elderly           | 1           | 16.7522                  | 4.0110                  | <.0001                 | 25.1524                  | 3.5307                  | <.0001                 |
| Non-Eld.          | 90          | 13.4874                  | 4.5557                  | 0.0031                 | 23.2304                  | 3.9986                  | <.0001                 |
| Non-Eld.          | 30          | 20.1079                  | 4.1599                  | <.0001                 | 23.9585                  | 3.6685                  | <.0001                 |
| Non-Eld.          | 1           | 13.4727                  | 3.3777                  | <.0001                 | 22.6294                  | 2.9783                  | <.0001                 |
| Eld. Vs. Non-Eld. | 90          | -5.4625                  | 7.0395                  | 0.4379                 | 2.6280                   | 6.1943                  | 0.6714                 |
| Eld. Vs. Non-Eld. | 30          | 4.5855                   | 6.4523                  | 0.4774                 | 3.1238                   | 5.6913                  | 0.5832                 |

**Table 50 Change from Baseline in sTSO by Age Group in P28/P29 Pooled**

| <b>Age Group</b>  | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|-------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| Elderly           | 90          | -6.8121                  | 3.3914                  | 0.0447                 | -9.2371                  | 2.9814                  | 0.0020                 |
| Elderly           | 30          | -3.8744                  | 3.4583                  | 0.2627                 | -8.7419                  | 3.0409                  | 0.0041                 |
| Elderly           | 1           | -6.7878                  | 2.8099                  | 0.0158                 | -9.6849                  | 2.4733                  | <.0001                 |
| Non-Eld.          | 90          | -5.5008                  | 2.8735                  | 0.0558                 | -11.9246                 | 2.5215                  | <.0001                 |
| Non-Eld.          | 30          | -6.9660                  | 2.9091                  | 0.0167                 | -11.0524                 | 2.5664                  | <.0001                 |
| Non-Eld.          | 1           | -5.7715                  | 2.3659                  | 0.0148                 | -9.0448                  | 2.0860                  | <.0001                 |
| Eld. Vs. Non-Eld. | 90          | 1.3113                   | 4.4389                  | 0.7677                 | -2.6875                  | 3.9063                  | 0.4916                 |
| Eld. Vs. Non-Eld. | 30          | -3.0915                  | 4.5133                  | 0.4934                 | -2.3106                  | 3.9807                  | 0.5617                 |

Note: using studyid\*cohort interaction

Study 06 was completely non-elderly so the above subgroup comparisons were not possible for study 06.

#### 4.1.4 Region

In this section regional subgroup effects (North America vs. non-North America) are investigated. These subgroup estimates were determined by augmenting the primary analysis model with interactions between region and visit and treatment group as well as visit\*treatment.

Table 51 Study 29: Regional Subgroup Analyses for LPS

| Region                    | Time    | Lo Diff. Est. | Lo Std. Err. | Lo p-value | Hi Diff. Est. | Hi Std. Err. | Hi p-value |
|---------------------------|---------|---------------|--------------|------------|---------------|--------------|------------|
| North Am                  | Month 1 | -2.8517       | 4.7425       | 0.5478     | -7.6357       | 3.7187       | 0.0404     |
| Non-North Am              | Month 1 | -14.6974      | 12.4632      | 0.2387     | -24.6394      | 9.3317       | 0.0085     |
| North Am vs. non-North Am | Month 1 | -11.8458      | 13.3330      | 0.3746     | -17.0037      | 10.0471      | 0.0910     |
| North Am                  | Month 3 | 1.1308        | 5.2819       | 0.8306     | -3.6565       | 4.1703       | 0.3809     |
| Non-North Am              | Month 3 | 7.7795        | 15.4501      | 0.6148     | -0.5123       | 10.4061      | 0.9608     |
| North Am vs. non-North Am | Month 3 | -6.6487       | 16.3252      | 0.6839     | -3.1442       | 11.2128      | 0.7793     |

Table 52 Study 29 Regional Subgroup Analyses for WASO

| Region                    | Time    | Lo Diff. Est. | Lo Std. Err. | Lo p-value | Hi Diff. Est. | Hi Std. Err. | Hi p-value |
|---------------------------|---------|---------------|--------------|------------|---------------|--------------|------------|
| North Am                  | Month 1 | -21.6962      | 5.8802       | 0.0002     | -34.7564      | 4.5887       | <.0001     |
| Non-North Am              | Month 1 | -19.0745      | 15.4411      | 0.2171     | -1.2321       | 11.7438      | 0.9165     |
| North Am vs. non-North Am | Month 1 | 2.6217        | 16.5212      | 0.8740     | 33.5243       | 12.6063      | 0.0080     |
| North Am                  | Month 3 | -33.0982      | 6.0060       | <.0001     | -32.9251      | 4.7571       | <.0001     |
| Non-North Am              | Month 3 | -28.6841      | 17.2760      | 0.0973     | -10.3186      | 11.7657      | 0.3808     |
| North Am vs. non-North Am | Month 3 | -4.4141       | 18.2876      | 0.8093     | -22.6065      | 12.6892      | 0.0753     |

**Table 53 Study 28 Regional Subgroup Analyses for LPS**

| <b>Label</b>                         | <b>Time</b>        | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------------------------|--------------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| <b>North Am</b>                      | <b>Month<br/>1</b> | -8.2783                  | 4.2446                  | 0.0515                 | -12.2996                 | 3.8838                  | 0.0016                 |
| <b>Non-North Am</b>                  | <b>Month<br/>1</b> | -5.8140                  | 7.2390                  | 0.4221                 | -1.5975                  | 5.6410                  | 0.7771                 |
| <b>North Am vs.<br/>non-North Am</b> | <b>Month<br/>1</b> | 2.4643                   | 8.3915                  | 0.7691                 | 10.7022                  | 6.8454                  | 0.1184                 |
| <b>North Am</b>                      | <b>Month<br/>3</b> | -10.8238                 | 4.2780                  | 0.0116                 | -10.9020                 | 3.9093                  | 0.0054                 |
| <b>Non-North Am</b>                  | <b>Month<br/>3</b> | -1.6839                  | 7.2920                  | 0.8174                 | -4.1835                  | 5.6430                  | 0.4587                 |
| <b>North Am vs.<br/>non-North Am</b> | <b>Month<br/>3</b> | 9.1399                   | 8.4544                  | 0.2800                 | 6.7185                   | 6.8619                  | 0.3279                 |

**Table 54 Study 28 Regional Subgroup Analyses for WASO**

| <b>Region</b>                        | <b>Time</b>        | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------------------------|--------------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| <b>North Am</b>                      | <b>Month<br/>1</b> | -37.7779                 | 5.9557                  | <.0001                 | -35.4144                 | 5.4580                  | <.0001                 |
| <b>Non-North Am</b>                  | <b>Month<br/>1</b> | -19.6475                 | 10.1875                 | 0.0542                 | -24.3390                 | 7.9152                  | 0.0022                 |
| <b>North Am vs.<br/>non-North Am</b> | <b>Month<br/>1</b> | 18.1304                  | 11.8061                 | 0.1251                 | 11.0754                  | 9.6196                  | 0.2500                 |
| <b>North Am</b>                      | <b>Month<br/>3</b> | -22.0289                 | 6.1558                  | 0.0004                 | -28.1706                 | 5.6365                  | <.0001                 |
| <b>Non-North Am</b>                  | <b>Month<br/>3</b> | -20.7892                 | 10.5205                 | 0.0486                 | -26.0219                 | 8.1967                  | 0.0016                 |
| <b>North Am vs.<br/>non-North Am</b> | <b>Month<br/>3</b> | 1.2397                   | 12.1972                 | 0.9191                 | 2.1487                   | 9.9530                  | 0.8291                 |

sTST results for High Dose minus placebo at 1 month for North America and non-North America were as follows.

**Table 55 Study 28 Regional Subgroup Analyses for sTST**

| <b>Region</b>                        | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| <b>North Am</b>                      | Month<br>1  | 22.5926                  | 7.2159                  | 0.0018                 | 23.6983                  | 6.6089                  | 0.0004                 |
| <b>Non-North Am</b>                  | Month<br>1  | 18.9616                  | 9.7241                  | 0.0515                 | 6.3231                   | 7.5127                  | 0.4002                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>1  | -3.6310                  | 12.1092                 | 0.7644                 | -17.3752                 | 10.0065                 | 0.0828                 |
| <b>North Am</b>                      | Month<br>3  | 17.0706                  | 7.4735                  | 0.0226                 | 26.4447                  | 6.8328                  | 0.0001                 |
| <b>Non-North Am</b>                  | Month<br>3  | 10.1800                  | 10.0306                 | 0.3104                 | 6.9730                   | 7.7541                  | 0.3687                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>3  | -6.8906                  | 12.5087                 | 0.5819                 | -19.4717                 | 10.3357                 | 0.0599                 |

**Table 56 Study 28 Regional Subgroup Analyses for sTSO**

| <b>Region</b>                        | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| <b>North Am</b>                      | Month<br>1  | 8.7769                   | 4.7820                  | 0.0667                 | -4.7262                  | 4.3771                  | 0.2805                 |
| <b>Non-North Am</b>                  | Month<br>1  | -4.7922                  | 6.4404                  | 0.4570                 | -8.2226                  | 4.9773                  | 0.0988                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>1  | 3.9847                   | 8.0207                  | 0.6194                 | -3.4964                  | 6.6288                  | 0.5980                 |
| <b>North Am</b>                      | Month<br>3  | -9.0915                  | 3.7102                  | 0.0144                 | -12.1773                 | 3.3904                  | 0.0003                 |
| <b>Non-North Am</b>                  | Month<br>3  | -3.1593                  | 4.9681                  | 0.5250                 | -6.7427                  | 3.8639                  | 0.0812                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>3  | 5.9322                   | 6.1992                  | 0.3388                 | 5.4346                   | 5.1416                  | 0.2907                 |

Note: Arh1 covariance structure used because unstructured failed to converge

In study P029 about 48% of all randomized patients were associated with North American sites. Regional treatment effects for the key efficacy variables are provided in the following tables.

**Table 57 Study 29 Regional Subgroup Analyses for sTST**

| <b>Region</b>                        | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| <b>North Am</b>                      | Month<br>1  | 18.4111                  | 6.9755                  | 0.0084                 | 20.8290                  | 5.7079                  | 0.0003                 |
| <b>Non-North Am</b>                  | Month<br>1  | 26.9385                  | 7.3475                  | 0.0003                 | 29.2487                  | 6.9217                  | <.0001                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>1  | 8.5275                   | 10.1176                 | 0.3995                 | 8.4198                   | 8.9711                  | 0.3482                 |
| <b>North Am</b>                      | Month<br>3  | 17.1261                  | 7.8194                  | 0.0288                 | 18.3977                  | 6.3935                  | 0.0041                 |
| <b>Non-North Am</b>                  | Month<br>3  | 24.3438                  | 8.3824                  | 0.0038                 | 28.0552                  | 7.8412                  | 0.0004                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>3  | 7.2177                   | 11.4511                 | 0.5286                 | 9.6575                   | 10.1173                 | 0.3400                 |

**Table 58 Study 29 Regional Subgroup Analyses for sTSO**

| <b>Region</b>                        | <b>Time</b> | <b>Lo Diff.<br/>Est.</b> | <b>Lo Std.<br/>Err.</b> | <b>Lo p-<br/>value</b> | <b>Hi Diff.<br/>Est.</b> | <b>Hi Std.<br/>Err.</b> | <b>Hi p-<br/>value</b> |
|--------------------------------------|-------------|--------------------------|-------------------------|------------------------|--------------------------|-------------------------|------------------------|
| <b>North Am</b>                      | Month<br>1  | -9.0090                  | 5.1865                  | 0.0827                 | -14.1000                 | 4.2469                  | 0.0009                 |
| <b>Non-North Am</b>                  | Month<br>1  | -4.0846                  | 5.4731                  | 0.4557                 | -9.9009                  | 5.1574                  | 0.0552                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>1  | 4.9244                   | 7.5323                  | 0.5134                 | 4.1991                   | 6.6798                  | 0.5297                 |
| <b>North Am</b>                      | Month<br>3  | -8.7637                  | 5.2850                  | 0.0976                 | -9.8881                  | 4.3203                  | 0.0223                 |
| <b>Non-North Am</b>                  | Month<br>3  | -2.9587                  | 5.6708                  | 0.6020                 | -15.9360                 | 5.3021                  | 0.0027                 |
| <b>North Am vs.<br/>non-North Am</b> | Month<br>3  | 5.8050                   | 7.7438                  | 0.4537                 | -6.0479                  | 6.8386                  | 0.3767                 |



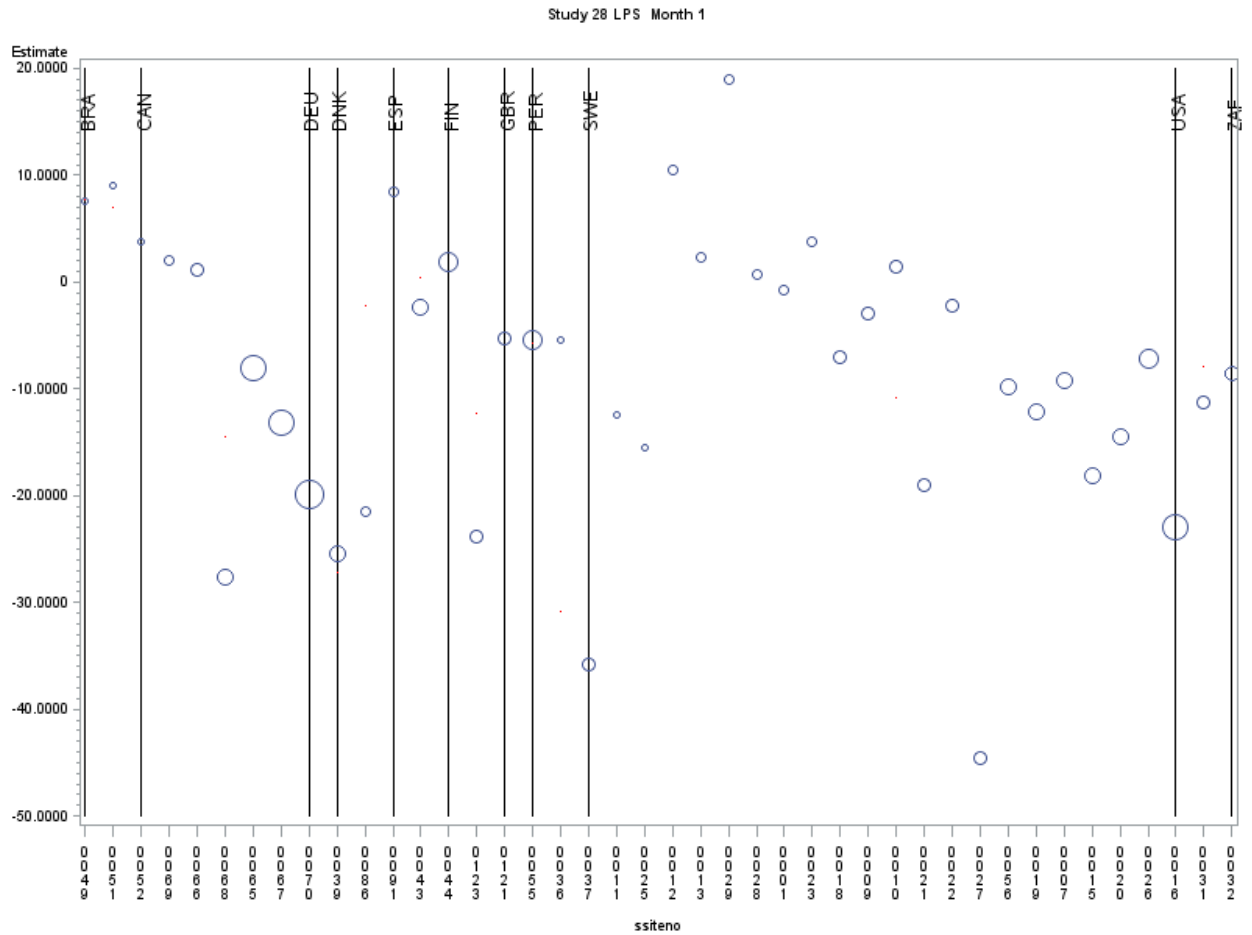
In study P06 there were two regions: North America (87%) and Japan (13%). There were significant regional differences in the 10 mg effect on WASO in the first period, with the effects in Japan being numerically in the wrong direction (Day 1: 8.6318 [26.0732 S.E.] ; Day 28: 18.3524 [25.3512 S.E.] as compared to North America: Day 1: -22.0518 [10.0736 S.E.] ; Day 28: -24.5936 [ 10.1558 S.E.]). However, the 10 mg estimated effects on LPS in the first period were consistent across the two regions(-18.9 ; -16.4 ; -19.1; -20.7 for Japan Day 1 and Day 28 and North Am. Day 1 and Day 28, respectively).

#### **4.1.5 Site Effects**

The primary was adjusted for prespecified Regions rather than individual sites. However, it is important to examine the estimated treatment effects by site to see if any sites had a major impact on the results.

Figure 14 shows estimated LPS mean treatment group differences from placebo for the high dose by individual sites in study 28. The size of the plotting symbol in the figure is proportional to the number of patients randomized in the site and the sites are ordered from smallest to largest from left to right within each country. Negative differences favor the high dose group. There were 79 sites in study 28.

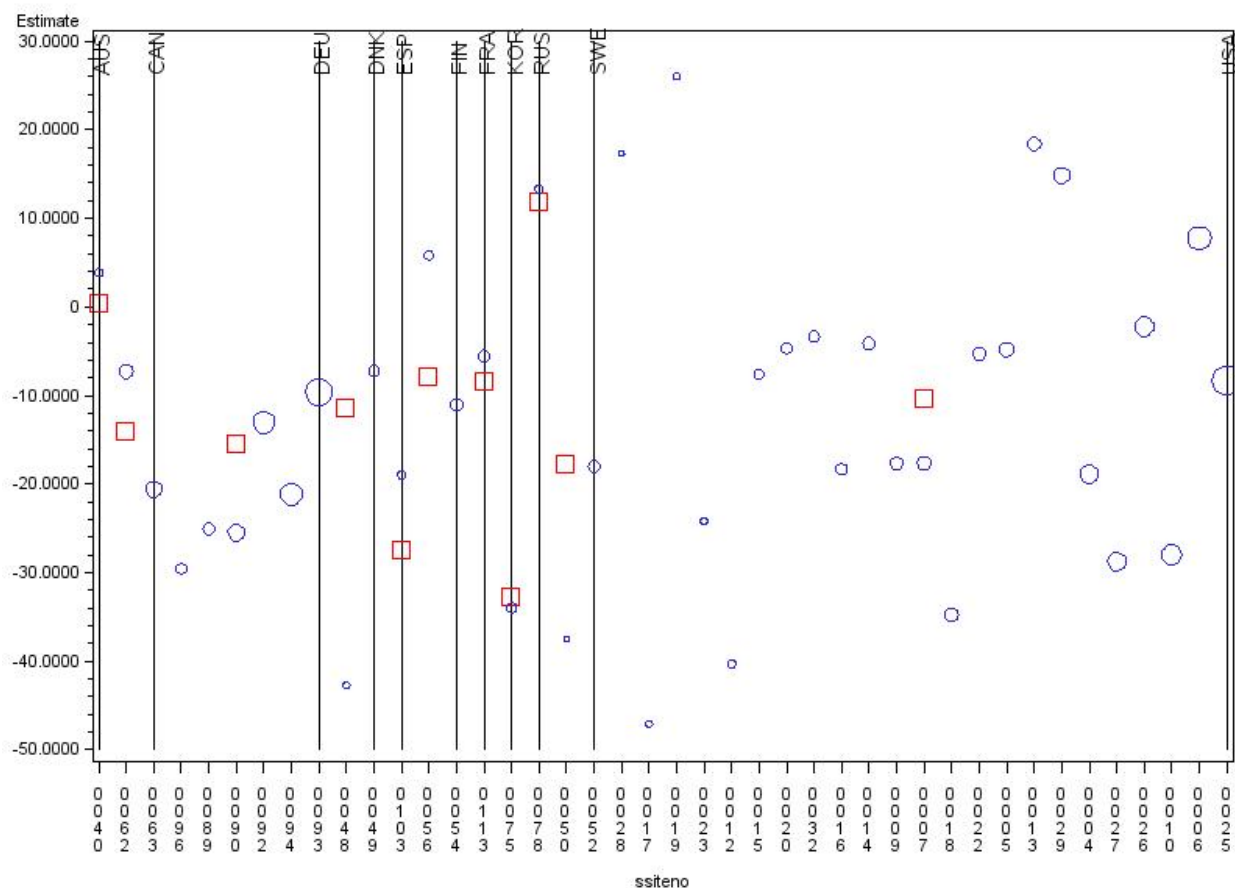
**Figure 13 Study 28: Differences of Placebo from High Dose in Mean Change in LPS at Month 1 by Site**



For study 28, exclusion of any one site had no effect on the significance of the high (or low) dose comparison to placebo in terms of mean change from baseline in LPS at Day 30, 90, or 1.

Figure 14 shows estimated LPS mean treatment group differences from placebo for the high dose by individual sites grouped by country in study 29. There were 90 sites overall in study 29 but only 45 were big enough to have estimates for PSG endpoints. The square plotting symbol gives the estimated difference for the country as a whole.

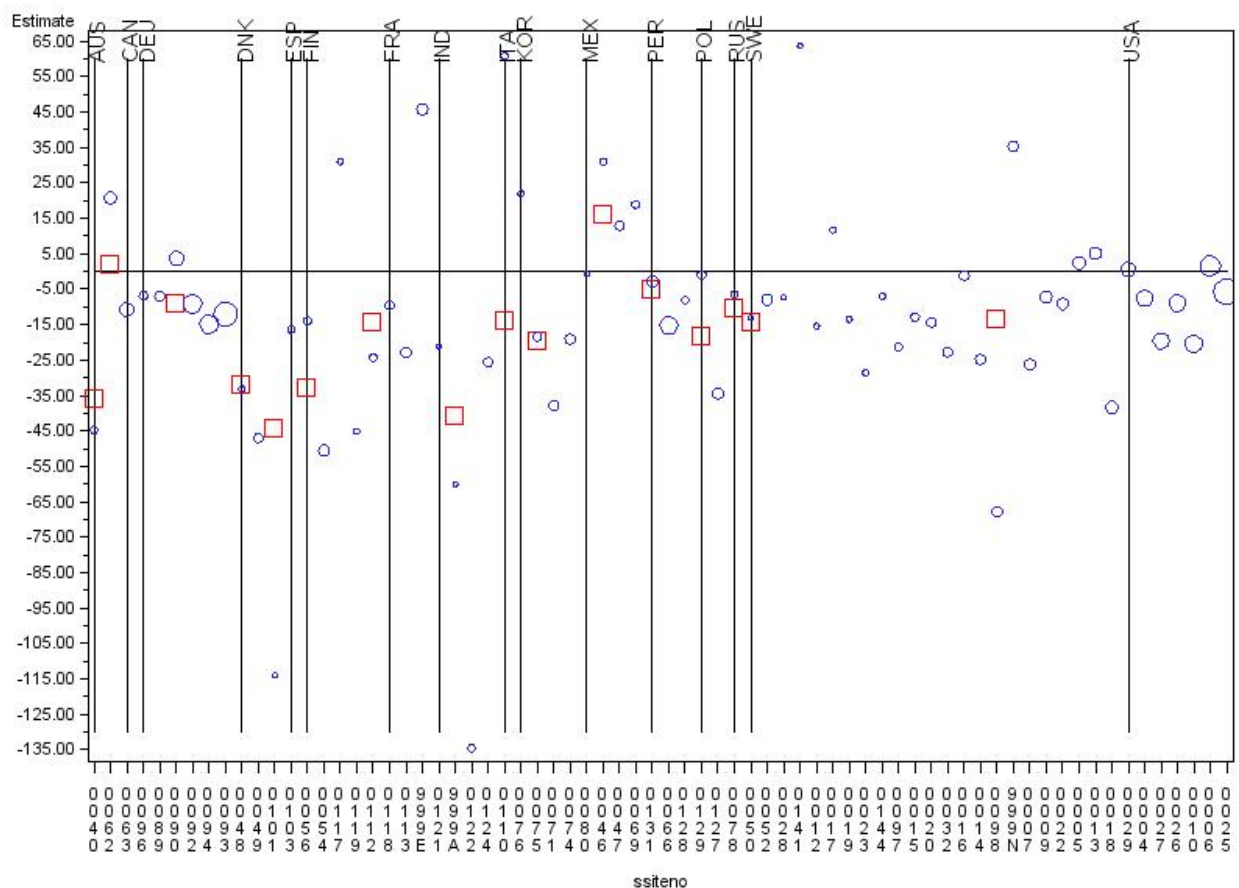
**Figure 14 Study 29: Differences of Placebo from High Dose in Mean Change in LPS at Month 1 by Site**  
P29 LPS Month 1



Exclusion of site 0004, resulted in a loss of nominal significance for the low dose ( $p=0.060$  but not for the high dose) at day 30 in terms of LPS. But this was not true for any other site for the low or high dose at day 30. Of course, as seen previously in this document, neither the low nor the high dose was significant compared to placebo in terms of mean change in LPS at day 90.

Figure 15 shows the results for the related subjective diary based endpoint, Time to Sleep Onset, at Month 1. In contrast to the objective LPS results, the high dose effect on subjective TSO was statistically significant at Month 3 (as well as at Month 1). The square plotting symbol gives the mean effect for the country.

**Figure 15 Study 29: Differences of Placebo from High Dose in Mean Change in Subj. TSO at Month 1 by Site**  
P29 sTSO 1 Month



## 4.2 Other Special/Subgroup Populations

### 4.2.1 Cohort

Cohort Q (Questionnaire only) or PQ (Questionnaire and PSG) was a randomization stratification factor.

In study P28 24% were Q cohort (no PSG assessments). Estimated differences of high dose from placebo were numerically smaller in the Q only, but the difference (interaction) was not significant for sTSTm or sTSOm.

**Table 59 Study 28: Cohort Differences for Subjective Endpoints for High Dose vs. Placebo**

| <b>Endpoint</b> | <b>Contrast</b>         | <b>Estimate</b> | <b>Std. Err.</b> | <b>p-value</b> |
|-----------------|-------------------------|-----------------|------------------|----------------|
| <b>sTST</b>     | <b>Q vs. PQ Month 3</b> | -12.6896        | 9.2632           | 0.1711         |
|                 | <b>Q vs. PQ Month 1</b> | -11.8005        | 8.9614           | 0.1882         |
| <b>sTSO</b>     | <b>Q vs. PQ Month 3</b> | 6.9505          | 5.2149           | 0.1830         |
|                 | <b>Q vs. PQ Month 1</b> | 0.6071          | 5.8353           | 0.9172         |

In study P29 26% were Q cohort (no PSG assessments). The cohort differences between the high dose effect were not significant.

**Table 60 Study 29: Cohort Differences for Subjective Endpoints for High Dose vs. Placebo**

| <b>Endpoint</b> | <b>Contrast</b>         | <b>Estimate</b> | <b>Std. Err.</b> | <b>p-value</b> |
|-----------------|-------------------------|-----------------|------------------|----------------|
| <b>sTST</b>     | <b>Q vs. PQ Month 3</b> | -0.1235         | 11.1874          | 0.9912         |
|                 | <b>Q vs. PQ Month 1</b> | -0.08504        | 9.7935           | 0.9931         |
| <b>sTSO</b>     | <b>Q vs. PQ Month 3</b> | -1.2402         | 7.5644           | 0.8698         |
|                 | <b>Q vs. PQ Month 1</b> | 8.4376          | 7.2890           | 0.2473         |

Thus, overall there was no compelling indication that the high dose effects differed substantially by cohort.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

As the sponsor stated in their integrated summary of efficacy patients in P006 who were randomized to 20 and 40 mg suvorexant, tended to have a somewhat less severe insomnia at baseline as judged by subjective reports with longer sTSTm (>340 minutes) and shorter sTSOm values (<69 minutes) at baseline compared with the Phase 3 trials (<330 minutes and >69 minutes for sTSTm and sTSOm). With regards to PSG parameters, patients in P006 had a shorter mean WASO duration compared to the Phase 3 efficacy trials (P028 and P029).

Overall, patients in the confirmatory trials (P028 and P029) had substantial impairment with regards to onset and maintenance with less than 5.5 hours of sTSTm, more than 1 hour of time to sleep onset as measured by both sTSOm and LPS and nearly 2 hours of WASO. Slightly higher severity of symptoms was observed in P029 compared to P028 as judged by the subjective assessments (sTSTm,

sTSOm, and sWASOm), but not based on PSG measured sleep onset and maintenance (WASO and LPS). Table 61 shows summary statistics for efficacy measures at Baseline by trial in the Phase 2b/3 Trials.

**Table 61 Summary Statistics for Efficacy Measures at Baseline by Trial in the Phase 2b/3 Trials**

| Protocol #                      | Endpoint | MK-4305 LD |       | MK-4305 HD |       | Placebo |       |
|---------------------------------|----------|------------|-------|------------|-------|---------|-------|
|                                 |          | N          | Mean  | N          | Mean  | N       | Mean  |
| Phase 2b – Dose-Finding         |          |            |       |            |       |         |       |
| 006 <sup>†</sup>                | sTSTm    | 56         | 340.6 | 51         | 349.7 | 221     | 342.1 |
|                                 | sTSOm    | 56         | 68.8  | 51         | 56.7  | 221     | 62.9  |
|                                 | sWASOm   | 49         | 81.9  | 42         | 84.6  | 191     | 76.6  |
|                                 | WASO     | 61         | 97.7  | 59         | 107.3 | 249     | 100.7 |
|                                 | LPS      | 61         | 70.8  | 59         | 66.8  | 249     | 69.3  |
| Phase 3 – Confirmatory Efficacy |          |            |       |            |       |         |       |
| 028                             | sTSTm    | 252        | 322.4 | 383        | 316.1 | 384     | 315.7 |
|                                 | sTSOm    | 252        | 63.3  | 383        | 68.0  | 384     | 66.9  |
|                                 | sWASOm   | 252        | 73.9  | 381        | 78.4  | 384     | 78.2  |
|                                 | WASO     | 193        | 119.2 | 291        | 117.7 | 290     | 114.9 |
|                                 | LPS      | 193        | 68.9  | 291        | 61.8  | 290     | 66.2  |
| 029                             | sTSTm    | 238        | 298.3 | 386        | 315.3 | 383     | 309.7 |
|                                 | sTSOm    | 238        | 86.0  | 386        | 74.4  | 383     | 81.3  |
|                                 | sWASOm   | 233        | 84.8  | 382        | 82.1  | 375     | 83.3  |
|                                 | WASO     | 150        | 119.6 | 299        | 119.4 | 295     | 118.4 |
|                                 | LPS      | 150        | 65.3  | 299        | 67.3  | 295     | 68.0  |
| Phase 3 – Long-Term Safety      |          |            |       |            |       |         |       |
| 009                             | sTSTm    | -          | -     | 492        | 319.5 | 245     | 330.0 |
|                                 | sTSOm    | -          | -     | 492        | 65.9  | 245     | 65.3  |
|                                 | sWASOm   | -          | -     | 488        | 79.6  | 241     | 71.2  |
|                                 | WASO     | -          | -     | -          | -     | -       | -     |
|                                 | LPS      | -          | -     | -          | -     | -       | -     |

<sup>†</sup> For Protocol 006, only data for the MK-4305 20 and 40 mg dose groups are included here since these correspond to LD and HD, respectively, for this non-elderly patient trial.  
MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.  
MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

Note: This table was copied from page 126 of the sponsor's integrated summary of efficacy

Because of the potential for next day driving impairment with 40 mg as seen in the non-elderly driving study there may be interest in lower doses. Table 62 summarizes results for the lowest dose in each study (10 mg in the non-elderly adult study 06 and 15 mg for the elderly in studies 28 and 29).

**Table 62 Summary of Efficacy Measures for Lowest Doses in Phase 2B/3 studies**

| Study | Dose            | Measure | Time     | Baseline<br>Placebo | Placebo<br>Mean<br>change<br>estimate | Baseline<br>MK4305 | Diff<br>Estimate | Diff<br>StdErr | Pvalue |
|-------|-----------------|---------|----------|---------------------|---------------------------------------|--------------------|------------------|----------------|--------|
| 6     | 10 <sup>#</sup> | LPS     | Night 1  | 67.3                | -12                                   | 65.8               | -19.1            | 8.14           | 0.0201 |
| 28/29 | 15*             | LPS     | Night 1  | 67.5                | -14.9                                 | 66.5               | -10.2            | 3.75           | 0.0068 |
| 6     | 10 <sup>#</sup> | sTSO    | Week 1   | 61.7                | -1.89                                 | 65.5               | -4.03            | 4.7            | 0.3919 |
| 28/29 | 15*             | sTSO    | Week 1   | 69.4                | -7.59                                 | 65.9               | -6.66            | 2.81           | 0.0176 |
| 6     | 10 <sup>#</sup> | WASO    | Night 1  | 98.7                | -21                                   | 108                | -18.1            | 9.36           | 0.0549 |
| 28/29 | 15*             | WASO    | Night 1  | 127                 | -2.66                                 | 133                | -39.3            | 4.07           | <.0001 |
| 6     | 10 <sup>#</sup> | LPS     | Night 28 | 67.3                | -16.7                                 | 65.8               | -20.2            | 8.5            | 0.0185 |
| 28/29 | 15*             | LPS     | Night 28 | 67.5                | -25.3                                 | 66.5               | -5.2             | 3.5            | 0.1335 |
| 6     | 10 <sup>#</sup> | sTSO    | Week 4   | 61.7                | -3.3                                  | 65.5               | -10.5            | 4.7            | 0.0254 |
| 28/29 | 15*             | sTSO    | Week 4   | 69.4                | -12.5                                 | 65.9               | -3.8             | 3.5            | 0.2776 |
| 6     | 10 <sup>#</sup> | WASO    | Night 28 | 98.7                | -23.4                                 | 107.8              | -18.8            | 9.5            | 0.0481 |
| 28/29 | 15*             | WASO    | Night 28 | 127.1               | -1.0                                  | 133.5              | -27.0            | 4.6            | <.0001 |

<sup>#</sup> Non-elderly only in study 6

\* Elderly only dose

An effect on Latency to Persistent Sleep as measured by Polysomnography was replicated for

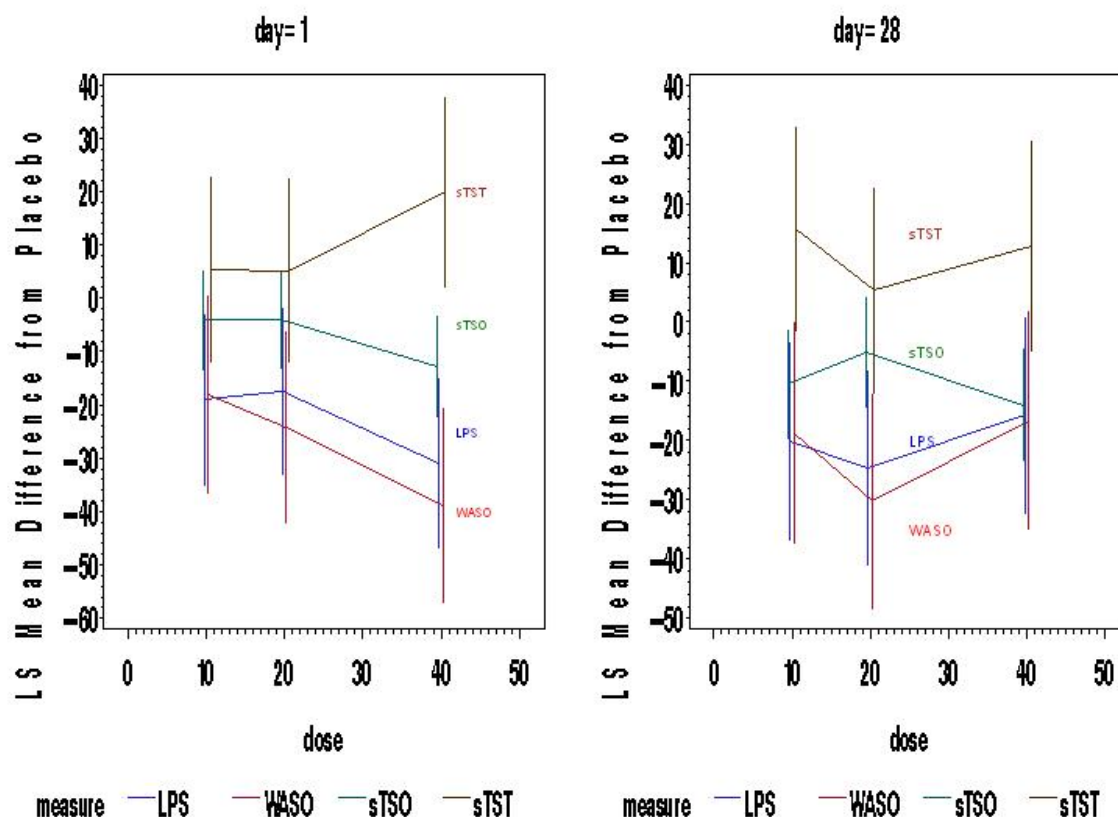
the Month 1 visit, the primary timepoint, but not at the final timepoint of Month 3. However, the corresponding subjectively measured item, Time to Sleep Onset, as determined from weekly averages of subjects' sleep ratings captured in diaries was statistically significant at Month 1 and Month 3 in both studies. The failure of LPS at Month 3 in study 29 means any secondary efficacy measures of Sleep Onset must be viewed as exploratory at best.

Some sponsors of investigational sleep drugs design separate studies for elderly and non-elderly and/or for demonstration of sleep maintenance and sleep onset effects. The Suvorexant phase 3 studies were ambitious in that they aimed to demonstrate effects for both elderly and non-elderly patients on both Sleep Maintenance and Onset, in terms of both an objective and a subjective assessment for each in the same study. They also put more weight on the high dose (the low dose had 30 to 40% less patients by design) and the multiplicity adjustment method tested the high dose first, such that the low dose could only be tested if the high dose was first significant at multiple timepoints on both subjective and objective assessments. Also, a Bonferroni adjustment was made so that Maintenance endpoints could be tested regardless of the significance of Onset endpoints or vice versa, but at the cost of the tests being done at the significance level of 0.025 rather than 0.05. There was also a Hochberg adjustment made because of testing both objective and subjective endpoints such that if, for example, the subjective onset endpoint was not significant at 0.025 then the objective onset endpoint needed to be significant at 0.0125. Under these circumstances the low dose was not statistically significant at the multiplicity adjusted level in study 29 at Month 1 or Month 3 for either of the primary sleep onset endpoints (objective LPS or subjective time to sleep onset) or for sTSO in study 28. Therefore, the statistically significant Onset effects of the low dose (15 mg for elderly and 20 mg for non-elderly) observed in study 28 for LPS were not strictly replicated in study 29. The low dose p-values in study 28 were 0.0004 and 0.0061 for LPS at month 1 and month 3 and 0.0519 and 0.0377 at month 1 and month 3 for sTSO. In study 29 the low dose p-values were 0.0306 and 0.9322 for LPS at month 1 and month 3 and 0.0498 and .0389 for sTSO at month 1 and month 3. The low dose was statistically significant at Month 1 and Month 3 for the primary maintenance endpoints in both study 28 and study 29.

**Figure 16** summarizes dose response at day 1 on the left and day 28 on the right for study 6 in terms of the key efficacy measures used later in the phase 3 studies.



Figure 16 Study 06: Dose Response in First Period for Various Efficacy Measures

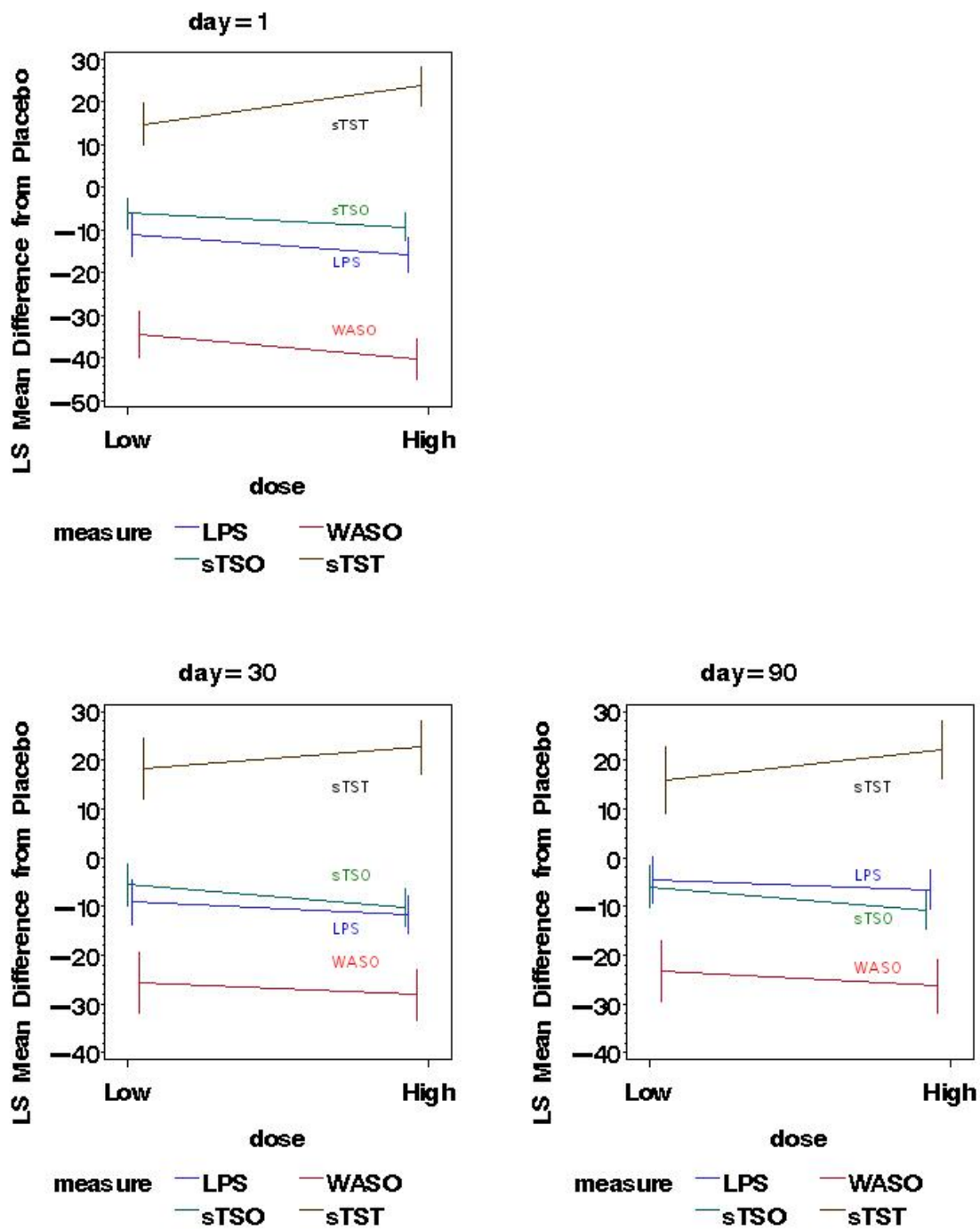


An exploratory test for linear trend among the doses 10 through 40 in the first period was not significant for sTST (.49,  $p=0.175$ ), sTSO (-.35,  $p=0.063$ ), or LPS (-.43,  $p=0.064$ ), but was for WASO (-.71,  $p=0.019$ ) at day 1.

A linear trend among the doses 10 through 40 in the first period was not significant for sTST (.03,  $p=0.941$ ), sTSO (-.21,  $p=.277$ ), LPS (0.22,  $p=0.308$ ), or WASO (0.31,  $p=0.362$ ) at day 28. The trend in WASO was not significant at day 28 even if the 80 dose was included (-.156,  $p=.225$ ). Including 80 mg data in fact did not change the nominal significance of any of the estimated linear trends. It should be noted that this was a small study though, so the power was not too high for detecting such a trend and only the first period data was used for this exploratory analysis because of the treatment by period interaction found for LPS. Overall, it seems that the dose response is uncertain based on study 6.

Figure 17 shows the results for the primary efficacy measures at each time point based on the pooled phase 3 data.

Figure 17 Study 28/29 Pooled Estimates for Primary Efficacy Measures



## 5.2 Conclusions and Recommendations

The clinical trial efficacy data provided in this application seems to clearly support the efficacy of Suvorexant for Sleep Maintenance. In the application there are two similarly designed 3 month placebo controlled phase 3 studies and one early phase 2B dose finding crossover study. The evidence for an effect on Sleep Onset was weaker than that for maintenance. In one study at the 3 month visit night the effect on latency as measured objectively by Polysomnography did not achieve statistical significance, thus failing to replicate the statistically significant effect demonstrated in the other study. However, the high dose effect at Month 1 was significant in both studies and there was replication of the effect on the corresponding subjective assessment, the patient reported weekly average of the Time to Sleep Onset, at Month 3 (as well as Month 1).

The Suvorexant phase 3 studies were ambitious in that they aimed to demonstrate effects for both elderly and non-elderly patients on both Sleep Maintenance and Onset, in terms of both an objective and a subjective assessment for each, in the same study. They also put more weight on the high dose (the low dose had 30 to 40% less patients by design) and the multiplicity adjustment method tested the high dose first, such that the low dose could only be tested if the high dose was first significant at multiple timepoints on both subjective and objective assessments. After taking into account the prespecified adjustments for multiple testing the low dose was only statistically significant for objective latency to persistent sleep in study 28 (not significant for objective latency in study 29 or for subjective time to sleep onset in study 28 or study 29). However, the low dose was statistically significant for objective and subjective primary endpoints for maintenance in both of these studies.

In the non-elderly next day driving safety study the 40 mg dose had significant asymmetry of differences from placebo with significantly more being positive and higher than the impairment threshold of interest (2.40) on both days 2 and 9. The low dose also was significant on day 2 in the symmetry analysis but not on day 9. There was also some other evidence that the driving effect might be dose related which would suggest a lower dose if it was still efficacious.

In a prior phase 2B crossover study in non-elderly adults a lower dose, 10 mg, as well as a higher dose, 80 mg, were studied in addition to the adult doses used later in Phase 3. There was a suggestion of efficacy of 10 mg, particularly for wake time after sleep onset, based on this study data but there is no existing means of replication for the 10 mg dose and no 10 mg data for the elderly. If the phase 3 doses are considered to have too much of a risk of next day driving impairment then in this reviewer's opinion another study may be needed.

## OVERALL SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The findings from overall clinical pharmacology are as follows:

The efficacy evaluation included analyses of improvement in sleep maintenance and sleep onset as evidenced by both objective assessments by polysomnography (PSG) and subjective patient reports. Wakefulness after persistent sleep onset (WASO) and latency to onset of persistent sleep (LPS) are considered the primary endpoints for the objective evaluation of sleep maintenance and onset, respectively, while weekly means (of the daily e-diary) for mean subjective total sleep time (sTSTm) and mean subjective time to sleep onset (sTSOm) are considered the primary endpoints for the subjective evaluation of sleep maintenance and onset, respectively. Supportive analyses of mean subjective wake time after sleep onset (sWASOm) were also provided, as further evidence for the efficacy of suvorexant in sleep maintenance.

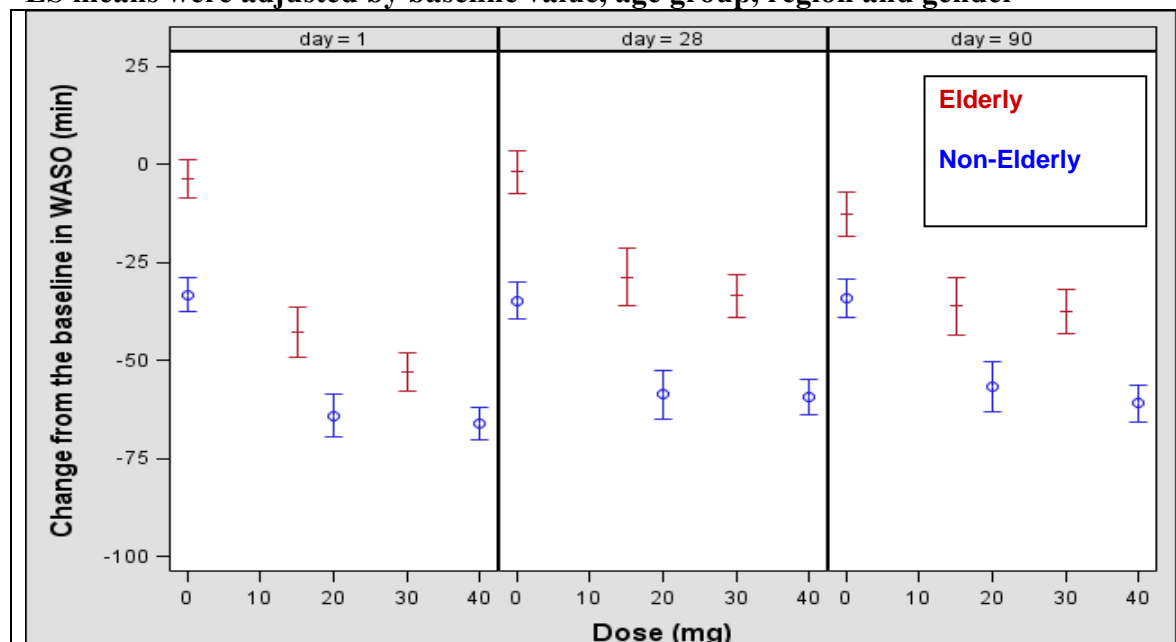
Key safety evaluations included Adverse Effects (AEs) analysis, next-day effects on digital symbol substitution test (DSST), an objective measure in Phase 3 studies.

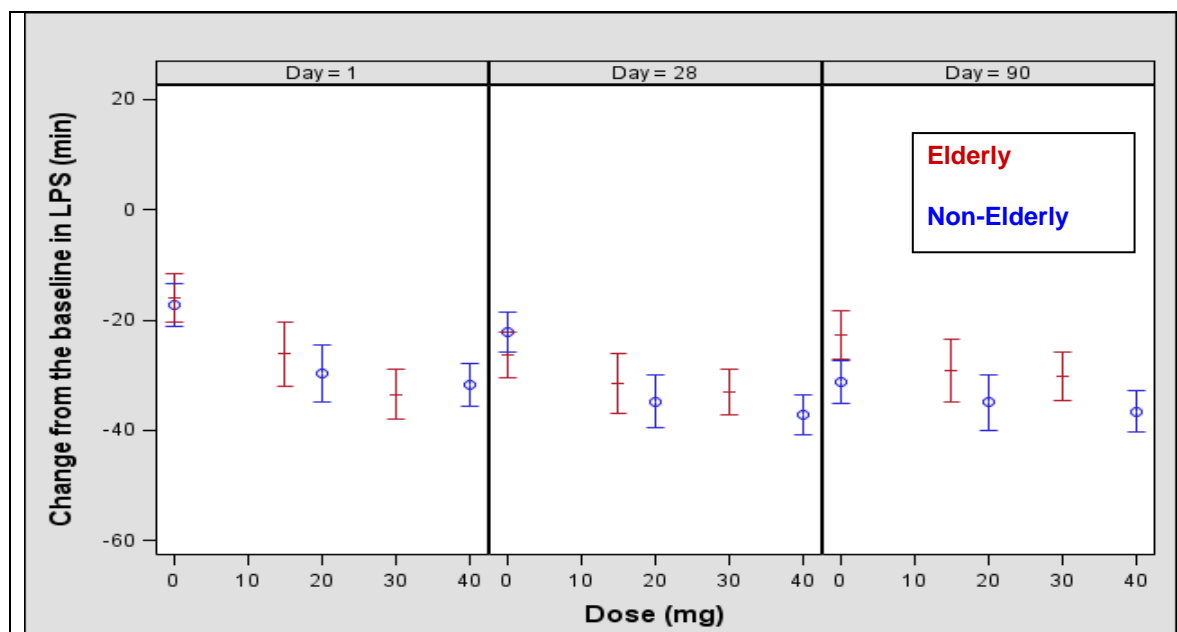
### What are the characteristics of exposure/effectiveness relationships?

Dose-response analyses were conducted on pooled data from the phase 3 trials 028 and 029. Both LD (15 mg for elderly patients and 20 mg for non-elderly patients) and HD (30 mg for elderly patients and 40 mg for non-elderly patients) showed significant effectiveness compared to placebo group. No apparent dose/exposure ( $AUC_{0-24}$ )-dependent improvement was observed in both sleep maintenance and onset measurements over the dose range of 15 mg to 40 mg, based on the independent analyses performed by the pharmacometrics reviewer.

Figure 1 presents the dose-response relationship for sleep maintenance ( $\Delta$ WASO) and onset ( $\Delta$ LPS) from the phase 3 trials. It shows little difference in effectiveness between the two dose groups for both elderly and non-elderly patients.

**Figure 1: LS mean with 95% CI for  $\Delta$  WASO (top) and  $\Delta$  LPS (bottom) vs. Dose by day. LS means were adjusted by baseline value, age group, region and gender**



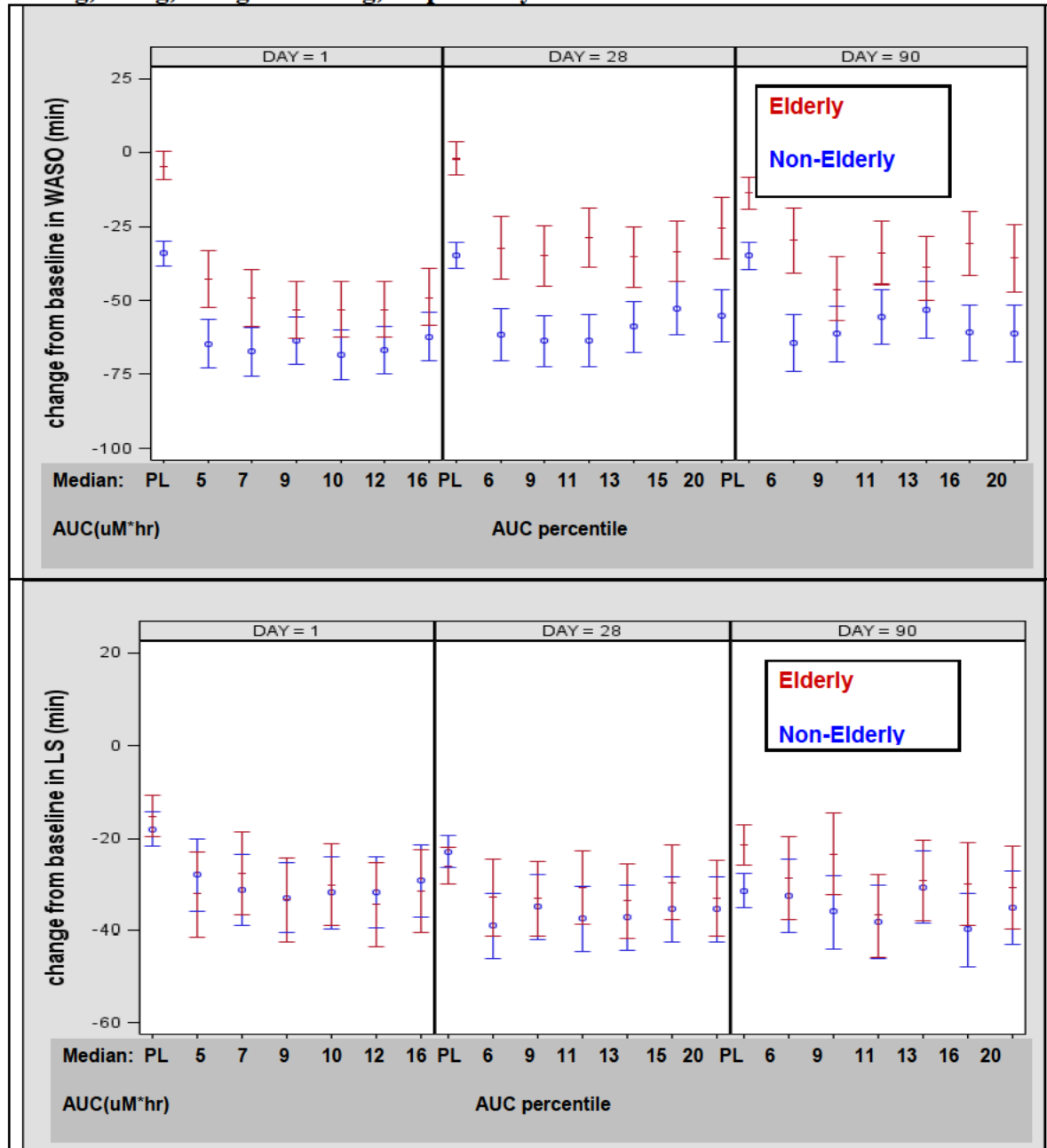


The pharmacometrics reviewer further looked into the relationship between the same endpoints and  $AUC_{0-24}$ ,  $AUC_{0-24}$  was categorized by 6 bins with same number of patients at each bin. All placebo patients were grouped in the first bin.

The top panel of Figure 2 shows the results by elderly and non-elderly patients where non-elderly patients seems to get better benefit in  $\Delta WASO$  compared to elderly patients but there appears to be still no clear exposure-dependent relationship in both populations.

The bottom panel of Figure 2 displays the exposure-response relationship for  $\Delta LPS$  for by elderly and non-elderly patients. No exposure dependent changes in sleep onset endpoint were observed.

**Figure 2: LS mean with 95% CI for  $\Delta$  WASO (top) and  $\Delta$  LPS (bottom) vs. exposure ( $AUC_{0-24}$ ) by day by elderly and non-elderly patients. LS means were adjusted by baseline value, age group, region and gender to be consistent with dose-response analysis. The median  $AUC_{0-24}$  at day 1 are 6  $\mu M \cdot hr$ , 7  $\mu M \cdot hr$ , 10  $\mu M \cdot hr$ , 11  $\mu M \cdot hr$  at 15mg, 20mg, 30mg and 40mg, respectively. As suvorexant PK reaches steady-state around day 15,  $AUC_{0-24}$  at day 28 and 90 appears to be similar: 8  $\mu M \cdot hr$ , 8  $\mu M \cdot hr$ , 14  $\mu M \cdot hr$ , 14  $\mu M \cdot hr$  at 15mg, 20mg, 30mg and 40mg, respectively.**

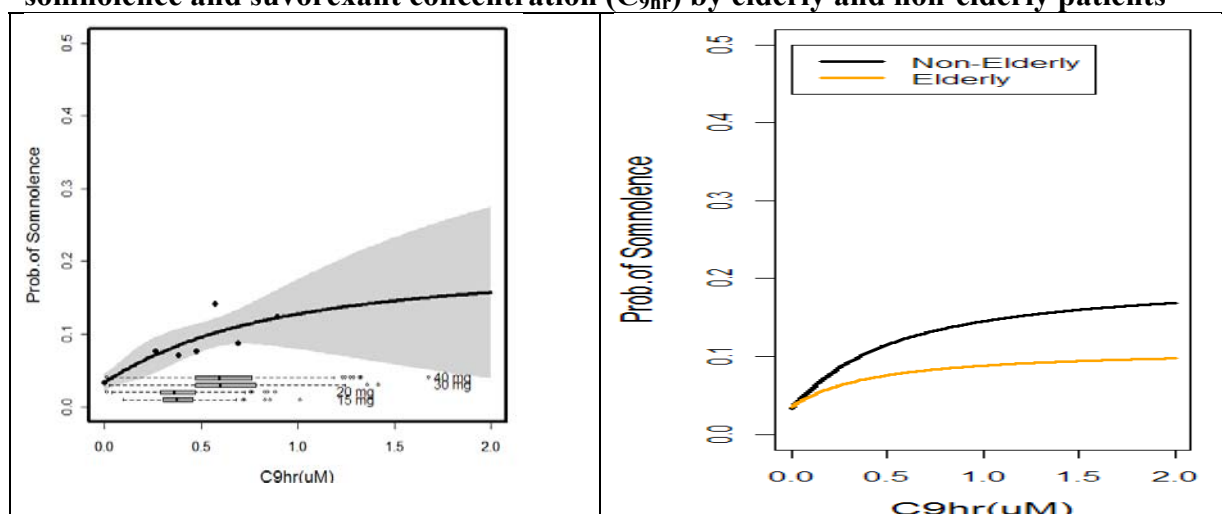


### What are the characteristics of exposure-safety relationships?

For the safety analysis, the pharmacometrics reviewer analyzed the relationship between  $C_{9hr}$  (Suvorexant concentrations at 9h post-dose) and incidence of somnolence (the most frequently reported AE) and digital symbol substitution test (DSST) score. The DSST was used to evaluate the next-day effects of suvorexant on psychomotor performance.

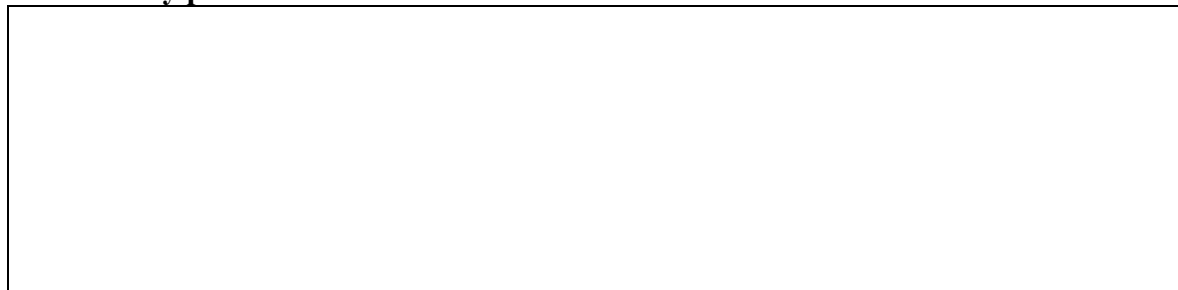
As shown in Figure 3, the probability of somnolence increases with increase of suvorexant concentrations. In addition, non-elderly patients showed higher risk of somnolence at the same concentration compared to elderly patients.

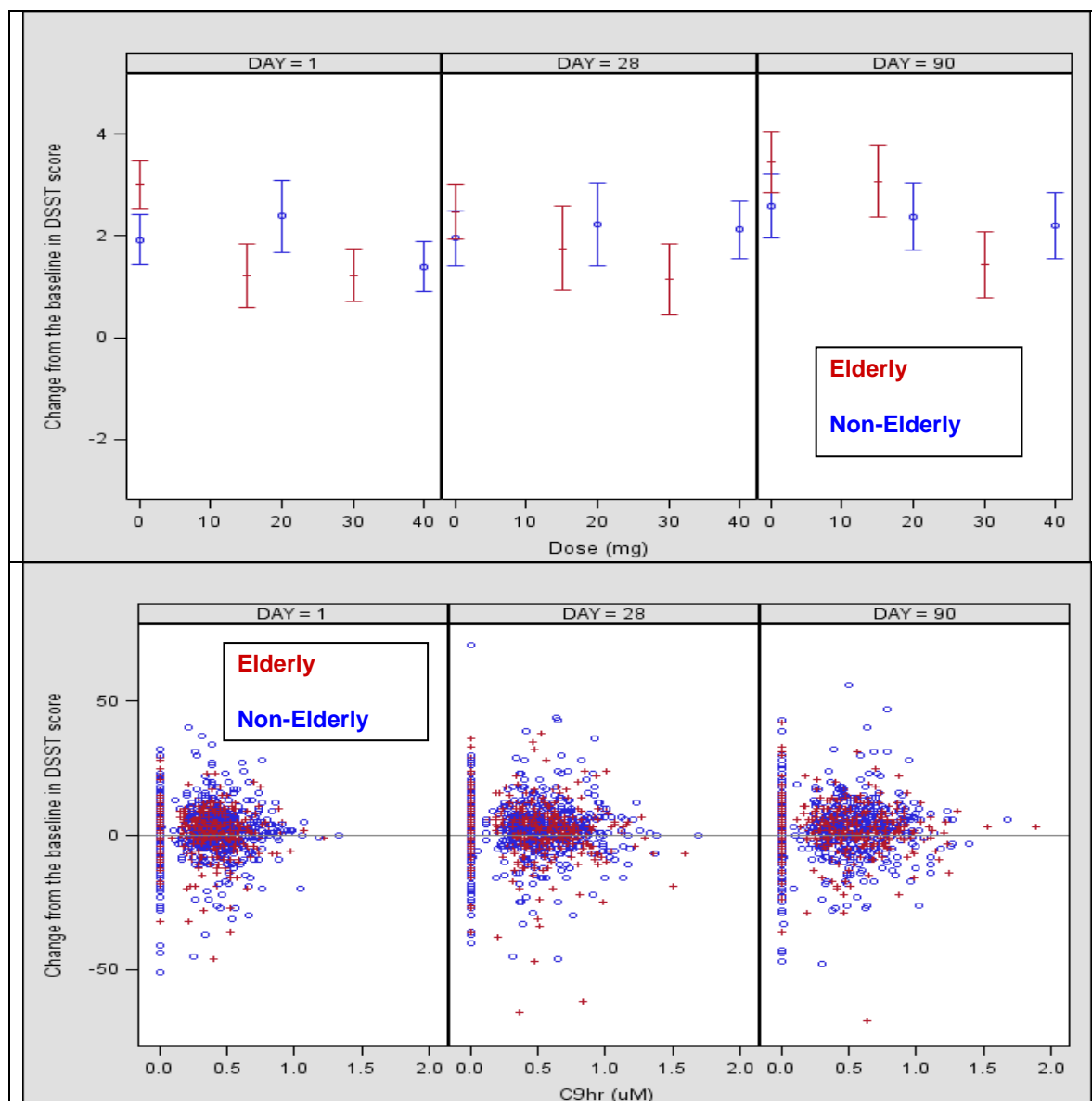
**Figure 3: Left: Overall model-predicted relationship for probability of somnolence and suvorexant concentration ( $C_{9hr}$ ). Right: model-predicted relationship for probability of somnolence and suvorexant concentration ( $C_{9hr}$ ) by elderly and non-elderly patients**



In elderly patients dose dependent (30 mg vs. 15 mg relative to placebo) decrease in DSST was observed (Figure 4). However, the magnitude of difference did not seem to be noticeable, and DSST score did not show clear concentration-dependent relationship.

**Figure 4: Dose vs.  $\Delta$ DSST (top) and  $C_{9hr}$  vs.  $\Delta$ DSST (bottom) relationship by elderly and non-elderly patients**





In conclusion, based on the reviewer's analyses, the dose of 15 mg would be reasonable starting dose for both elderly and non-elderly patients, although 15 mg was not studied in non-elderly patients.

### **General Pharmacokinetics (ADME characteristics) of Suvorexant**

#### **Absorption:**

Suvorexant is a Class 2 drug substance according to the Biopharmaceutics Classification System (high permeability, low solubility).

After oral administration of suvorexant, median peak plasma concentrations occur approximately 2 hours (range: 0.5 to 6.0 hours) after dosing of 40 mg under fasted conditions. The estimated absolute bioavailability (F) for 40 mg is approximately 47%.



**Distribution:**

The absolute volume of distribution was estimated to be 48.6 L following a 20-mg suvorexant IV dose. The total V/F was estimated to be 105.9 L following oral administration of suvorexant. Plasma protein binding for suvorexant is high (99.5%) and is independent of concentration over the range of 1 to 25  $\mu$ M. Suvorexant is highly bound to both human serum albumin and to  $\alpha$ 1-acid glycoprotein.

**Metabolism:**

Suvorexant is eliminated almost entirely through metabolism in humans, primarily by cytochrome P450 3A (CYP3A), with less contribution by CYP2C19. The predominant metabolic pathway of suvorexant in human is hydroxylation (formation of M9) followed by further oxidation to the carboxylic acid derivative (M4).

M9 was the major circulating metabolite, present to approximately equal concentrations to parent under steady-state conditions. However, unlike suvorexant, M9 is a substrate of P-gp and does not penetrate the brain. M9 is not expected to be active *in vivo* based on results from *in vitro* and EEG studies in dogs.

**Elimination:**

Suvorexant was eliminated primarily in the form of metabolites.

The primary route of excretion is through feces, approximately 66% of the suvorexant dose recovered in the feces and 23% recovered in the urine.

The mean terminal half-life ( $t_{1/2}$ ) for suvorexant is 12.2 hours. The terminal half-life for M9 is similar to that observed for suvorexant.

Steady-state of suvorexant was reached by 3 days of once-daily dosing, consistent with its terminal half-life. Estimates of suvorexant AUC and  $C_{max}$  accumulation, based on the increase from single to multiple-dose, approximates 1.2 to 1.6.

**Single dose and multiple dose pharmacokinetics:**

Suvorexant pharmacokinetics has been characterized in healthy men and women over a single-dose range of 4 mg to 240 mg. Additionally, the pharmacokinetics of suvorexant has been assessed in clinical trials of patients with insomnia following administration of multiple doses up to 80 mg administered once daily at bedtime.

A population approach was used to evaluate the pharmacokinetics of suvorexant in healthy subjects from 16 Phase 1 studies (12 single-dose and 4 multiple-dose) with dense pharmacokinetic sampling following doses ranging from 10 to 80 mg administered under fasted conditions. The population PK model that best characterized the Phase 1 data was a 3-compartment model with dose-dependent F1, sigmoidal absorption (with lag time), linear distribution into the first peripheral compartment ( $V_{p1}/F$ ) and first-order elimination from the central compartment ( $V_c/F$ ). The plasma clearance of suvorexant was estimated to 2.92 L/hour following an IV dose of 20 mg. Following oral administration of suvorexant, the typical CL/F is in general agreement with that following IV dosing adjusting for absolute bioavailability.

**Dose proportionality:**

Suvorexant pharmacokinetics are less than dose proportional over the 10 to 80-mg range, likely due to absorption limitations.

### **Pharmacokinetics in patients:**

The systemic exposure to suvorexant in patients is similar to that in healthy subjects.

### **Intrinsic Factors:**

#### **Gender**

Suvorexant exposure was higher in females than in males. The apparent oral clearance of suvorexant was 20.5% lower in females compared to males. No dose adjustment for suvorexant is needed based on gender only.

#### **Weight and Body Mass Index (BMI)**

Apparent oral clearance of suvorexant was inversely related to BMI. Population PK analysis showed that an approximate 2- to 3-fold reduction in CL/F is expected when comparing men with relatively low BMI versus obese women.

Suvorexant dose in obese females should be reduced, e.g. 10 mg starting dose.

If the recommended suvorexant dose is 15 mg, the sponsor needs to develop a lower strength tablet for this patient population. (PMC)

#### **Age**

The lower doses for the elderly in the phase 3 trials were selected based on the belief that elderly subjects may be more sensitive to hypnotics than non-elderly subjects. However, data from the phase 1 suvorexant driving studies and the sponsor's PK/PD Analysis of Adverse Effects (AEs) from the Phase 2 and 3 trials did not indicate that age has an effect on suvorexant PK and PD. Elderly patients are predicted to have ~15% increased  $C_{9hr}$  relative to non-elderly. In addition, the results from the highway driving studies suggested that elderly subjects may be slightly less sensitive than non-elderly subjects to the impairment on driving performance. No dose adjustment for suvorexant is recommended based on age.

#### **Pediatrics**

The safety and effectiveness of suvorexant in pediatric patients under 18 years of age have not been established.

#### **Race:**

There is no significant impact of race on the PK of suvorexant observed.

No dose adjustment for suvorexant is recommended based on race.

#### **Hepatic impairment**

Systemic exposure (expressed as unbound and bound) to suvorexant in subjects with moderate hepatic impairment was similar to that in matched healthy subjects. However, suvorexant half-life was increased (from 14.7 to 19.1 h) in subjects with moderate hepatic impairment.

Suvorexant pharmacokinetics were not evaluated in subjects with severe hepatic impairment.

Suvorexant is not recommended in subjects with severe hepatic impairment.

No dose adjustment for suvorexant is needed in subjects with moderate hepatic impairment.

#### **Renal impairment:**

Severe renal impairment does not have significant impact on the PK of suvorexant.

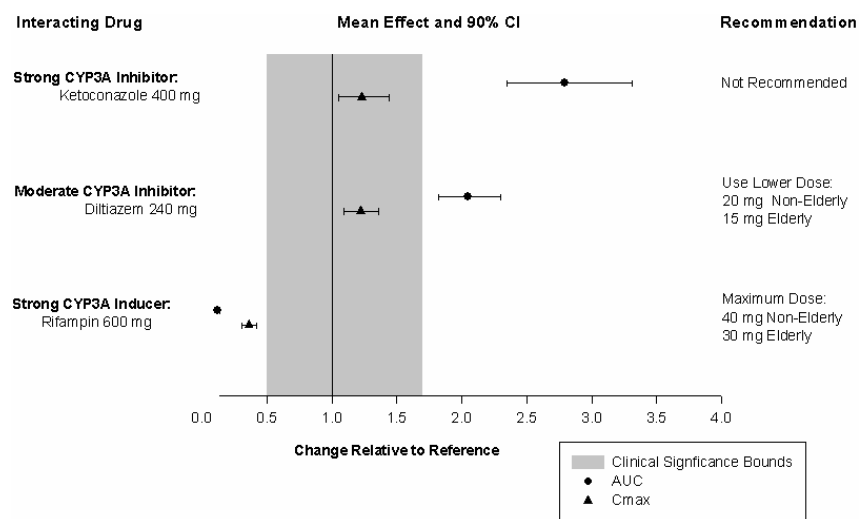
No dose adjustment is required in patients with renal impairment.

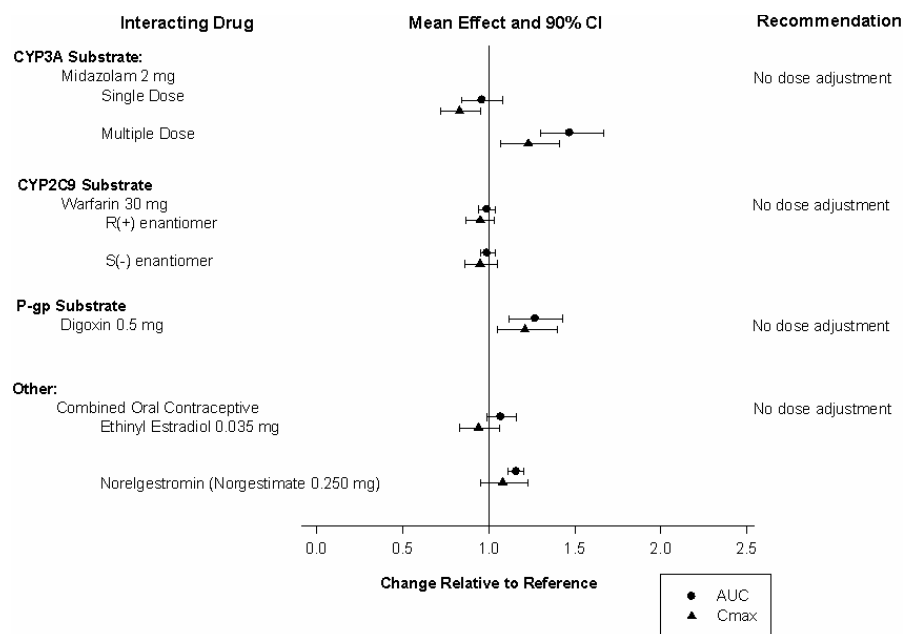
### **Extrinsic Factors:**

**In Vitro Studies:** *In vitro* metabolism studies demonstrate that suvorexant has a potential to inhibit CYP3A, intestinal P-gp and BCRP; however, suvorexant is unlikely to cause clinically significant inhibition of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. In addition, no clinically meaningful inhibition of OATP1B1 and OCT2 transporters is anticipated. At clinically recommended doses, suvorexant does not exhibit an induction potential for CYP3A4, CYP1A2, and CYP2B6. M9 did not show *in vitro* inhibition potential for any of the CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A). M9 is a P-gp substrate.

### **In Vivo Studies:**

*In Vivo* drug-drug interaction (DDI) studies have been conducted with ketoconazole (strong CYP3A and/or P-gp inhibitor), diltiazem (moderate CYP3A inhibitor) and rifampin (strong CYP3A inducer) to evaluate the DDI potential of other drugs on suvorexant PK. In addition, clinical PK studies were conducted to determine the DDI potential of suvorexant on midazolam (sensitive CYP3A substrate), oral contraceptives (CYP3A, UGT and SULT substrate), warfarin (CYP2C9 substrate), and digoxin (P-gp substrate). The results from these studies and the dose adjustments proposed by the sponsor are presented below.





Due to potential additive CNS effects, clinical studies have been conducted to evaluate the potential for PK and PD drug-drug interactions between suvorexant and CNS-active agents, including alcohol and paroxetine, a commonly prescribed selective serotonin reuptake inhibitor (SSRI).

The co-administration of suvorexant with alcohol produced additive impairment on psychomotor performance. There was no PK interaction between alcohol and suvorexant.

There was no PK or PD interaction between suvorexant and paroxetine.

#### Clinical Pharmacology DDI Studies Conclusions:

- Suvorexant should not be co-administered with strong CYP3A inhibitors.
- The suvorexant dose in subjects receiving moderate CYP3A4 inhibitors should be reduced by half. If the recommended suvorexant dose is 15 mg, the sponsor needs to develop a lower strength tablet for dose adjustment in patients receiving moderate CYP3A4 inhibitors. (PMR)
- The efficacy of suvorexant dose in subjects receiving CYP3A4 inducers may be decreased.
- No dose adjustment is needed for oral contraceptives when given in combination with suvorexant.
- No dose adjustment is needed for warfarin when given in combination with suvorexant.
- No dose adjustment is needed for digoxin when co-administered with suvorexant, however serum digoxin concentrations should be monitored as clinically indicated.
- Alcohol should not be co-administered with suvorexant due to the additive CNS effects.
- A general precaution should be advised when suvorexant is co-administered with drugs that produce CNS depressant effects due to potential additive effects.

#### Biopharmaceutics:

##### BCS Class:

Suvorexant can be considered a Biopharmaceutical Classification System (BCS) Class II drug (low solubility, high permeability).

*Bioequivalence:*

The Final Market Image (FMI), which is the intended commercial formulation, was used in the Phase 3 trials, therefore no bioequivalence study is required.

*Food Effect:*

Suvorexant can be administered without regards to meals or meal types. For faster onset of sleep suvorexant should not be administered with or immediately after a meal as Tmax is delayed ~1 hour by food.



# Suvorexant Safety

Ronald Farkas MD PhD  
Lead Medical Officer  
Division of Neurology Products  
OND/CDER/FDA

# FDA Preliminary Conclusions

- Suvorexant is effective, but not safe at the higher doses mainly studied
- The lowest doses have similar efficacy and better safety, but because studied in fewer patients, rates of less common but potentially serious AEs not well understood

# Much less safety data at lower doses

## Phase 3

|                 | Patients | Days | Relative patient days |
|-----------------|----------|------|-----------------------|
| 40 mg (adult)   | 730      | 141  | 5                     |
| 30 mg (elderly) | 627      | 199  | 6                     |
| 20 mg (adult)   | 353      | 86   | 1.4                   |
| 15 mg (elderly) | 202      | 105  | 1                     |

## Phase 2

10 mg (adult), 62 patients, 4 weeks



# FDA Approach to Benefit/Risk:

***Consider actual, not just ideal use***

“Beyond the clinical study...must consider how people actually use...consider cognitive and behavioral factors affecting human judgment and decision-making”\*

\*Structured approach to benefit-risk assessment in drug regulatory decision-making: Draft PDUFA implementation Plan- Feb 2013

# Key Safety Concerns

- Daytime somnolence can be severe and worsen suddenly: patients drive while impaired
- Unconscious, intense nighttime activity resembling REM Sleep Behavior Disorder
- Suicidal ideation
- Narcolepsy-like syndrome

# Narcolepsy-like Syndrome

- Orexin antagonism by suvorexant did cause additional narcolepsy-like symptoms and signs
- Not clear how concerned should FDA be about these additional adverse effects
  - Sleep paralysis (N = 6)
  - Hypnagogic and hypnopompic hallucinations (N = 7)
  - Weakness in knees when laughing/**cataplexy**? (N ≈ 5)
  - Sleep-onset REM (common, 3-5%)

# Cases

- 58 year old women, 40 mg AN03123

Shortly after sleep onset, the patient had a dream that something dark approached her. The patient woke up several times and felt unable to move her arms and legs and unable to speak. Several hours later, she found herself standing at the window without knowing how she got there\*

\* Unconscious activity rarely observed in controlled trials;  
Concern about incidence, and what actually occurred

- 28 year old woman, 20 mg AN07058  
around time of sleep onset, inability to move, as if someone holding her down, as well as sensation of an individual in bed with her
- 68 year old women, 30 mg AN12896  
Laid down to sleep and had a feeling as if 'shocked' then felt paralyzed and heard vivid sounds of people coming up the stairs, with a sense of violent intent
- 58 year old man, 40 mg AN03039  
Feeling of shadow falling over his body, hunted by enemies, hearing extremely loud screams

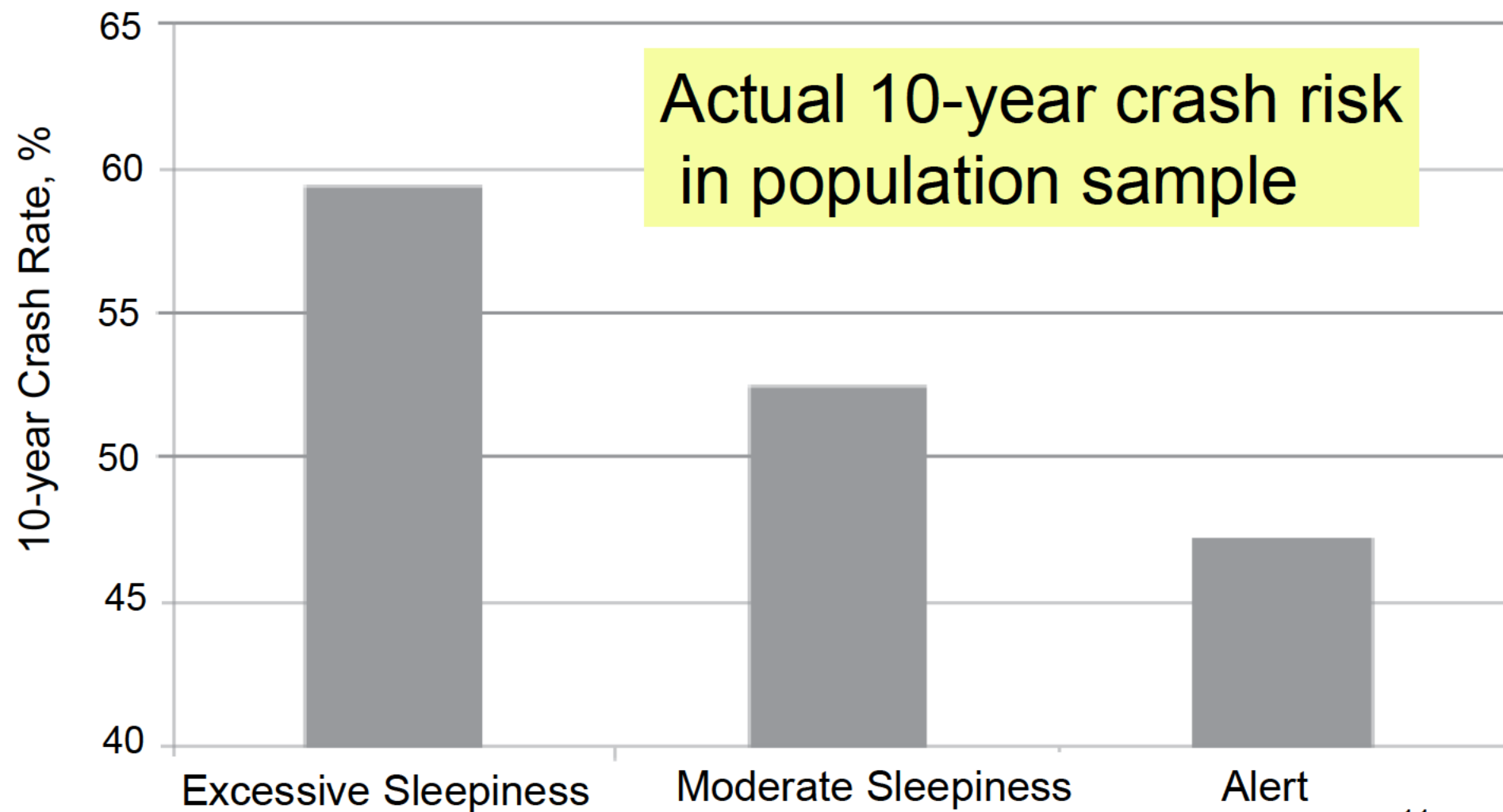


# Daytime Somnolence

Even though suvorexant increases sleep time,  
it makes many patients more sleepy,  
some much sleepier

|                          | Placebo<br>(N=1025) | Low Dose<br>(N=493) | High Dose<br>(N=1291) |
|--------------------------|---------------------|---------------------|-----------------------|
| Somnolence               | 3%                  | 7%                  | 11%                   |
| Severe Somnolence        | 0.1%                | 0.2%                | 0.6%                  |
| Somnolence by age        |                     |                     |                       |
| ≥65 y                    | 3%                  | 5%                  | 9%                    |
| <65 y <u>higher</u> dose | 3%                  | 8%                  | 13%                   |
| Somnolence by sex        |                     |                     |                       |
| F <u>higher</u> exposure | 2%                  | 9%                  | 11%                   |
| M                        | 4%                  | 3%                  | 10%                   |

# Driving while impaired by drowsiness is dangerous





# Suvorexant database suggests serious risk from drug-impaired driving

- Falling asleep while driving
- Driving out of lane
- Impaired ability to stay in driving lane during formal driving study

- 59 year old man, 40 mg suvorexant
  - *Nodded off* at a red light
  - Multiple episodes of *nodding off while driving*
  - Once *started to veer off road* until wife yelled
    - also experienced ‘*weak knees*’ when laughing – suggests ***cataplexy***\* AN02642

\*other patients with events that suggest cataplexy:  
‘attack of muscle weakness’, ‘weakness of knees’

- 72 year old women, 30 mg suvorexant
  - “subject caused several dangerous situations during the car driving assessment” AN0033
  
- 65 year old man, 40 mg AN 04579
  - Excessive sleepiness could happen at any time.  
***Started when the patient was driving***

- 61 year old man, 40 mg AN 07433
  - Difficulty staying awake *while driving*
- 58 year old man, 40 mg AN 03055
  - Strong urges to sleep *while driving*
- 27 year old man, 40 mg AN 03128
  - Severe sleepiness *while driving*
- 60 year old man, 40 mg AN 02615
  - Need to pull over to rest *while driving*

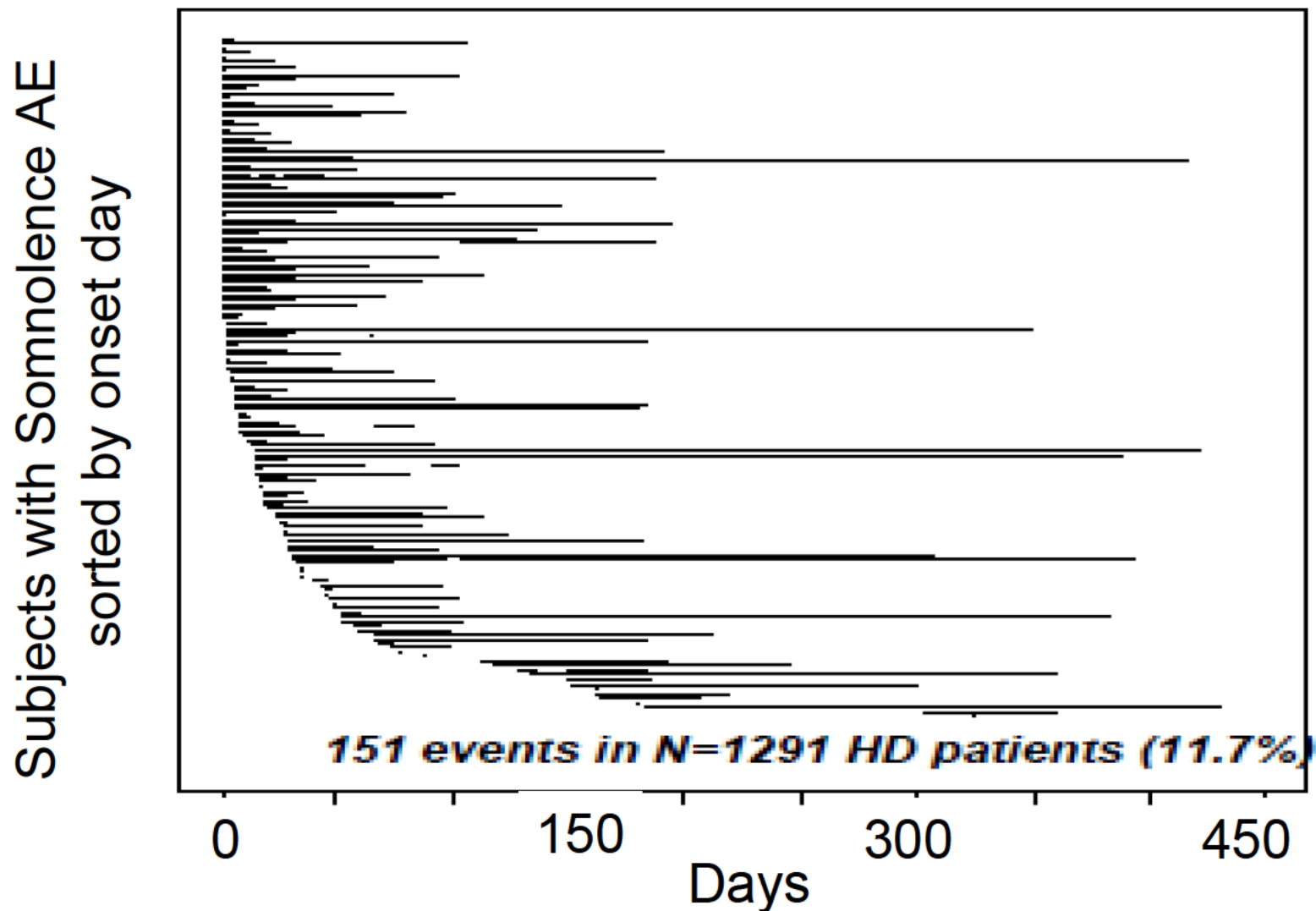
# Suvorexant Low Dose

- 57 year old female, **20 mg** AN0021, study 35
  - “Subject *fell asleep and drove across the middle line with her eyes closed*”
- 69 year old woman, **15 mg** AN11697
  - 2- to 3 hour daily naps; thought she could suffer an accident

# Placebo Drowsiness Cases

- Fewer and less severe – only these 3 events
  - 87 year old woman
    - Moderate intensity, started daily naps
  - 64 year old man
    - Moderate EDS remained constant through day
  - 36 year old man
    - Mild intensity throughout day

# Somnolence not limited to brief period after start drug



Patients were unable to drive safely in the suvorexant studies despite close clinical monitoring and warnings about impairment

- *“MK-4305 may make you sleepy”*
- *“Your ability to drive or operate other heavy machinery may be impaired after taking study drug”*



If instructions about safe driving not effective in highly supervised study, how will drug be safe in actual clinical use?

Increased FDA understanding that patients are not reliably aware of drug impairment...

...and even if aware, may not act as needed

# Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality

Joris C. Verster • Thomas Roth

Psychopharmacology 2011

“the general advice that ‘patients should listen to their body, and not drive if they feel their driving is impaired’ **should not be relied on** because patients may not be aware of their driving impairment”

Sponsor:

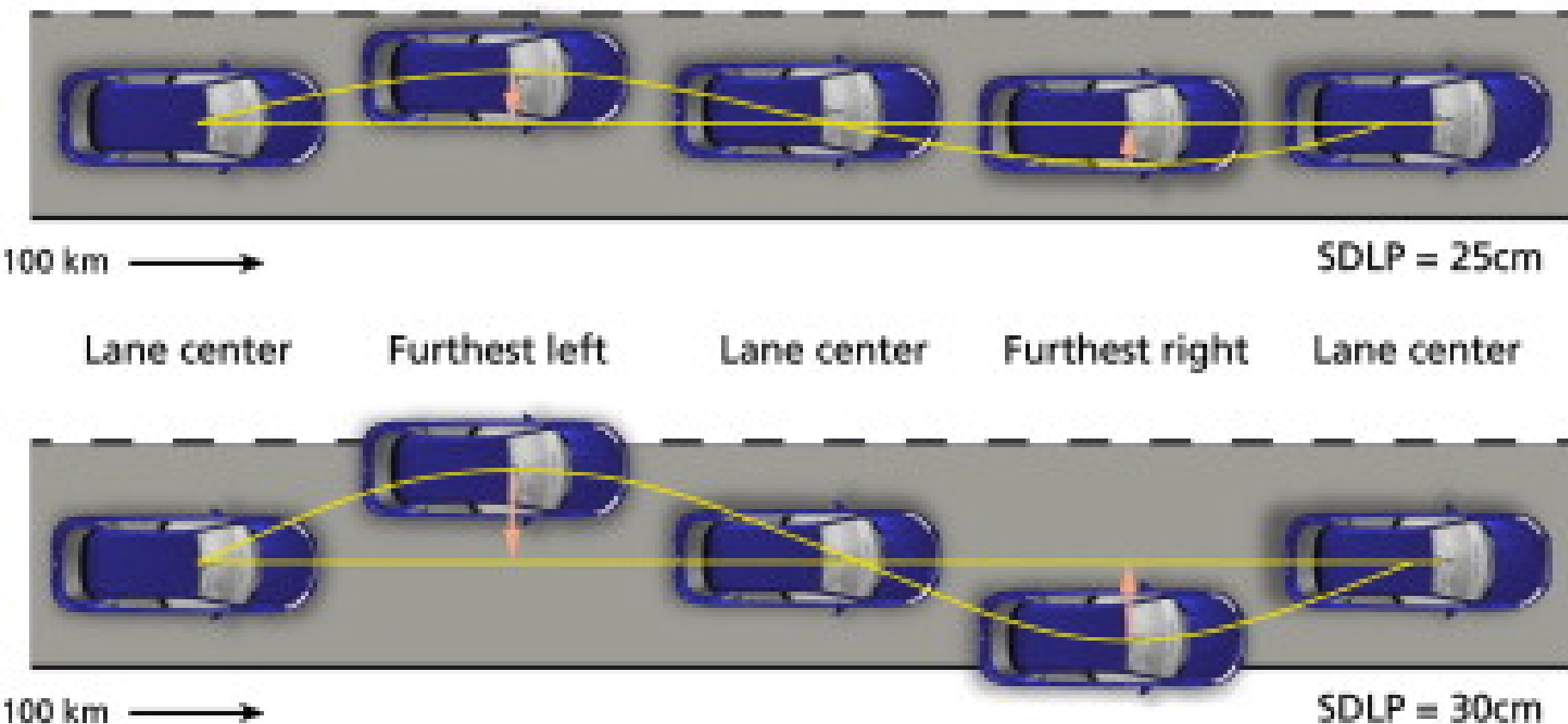
“The higher incidence of drug-related AEs with suvorexant is not associated with a higher rate of treatment discontinuation compared to placebo”

This seems like a problem, not evidence of safety

# Suvorexant Formal Driving Study

- On-road test of stability of lane position
  - ‘standard deviation of lane position’ (SDLP)
- On-face importance for safe driving
  - leaving lane (or roadway) clearly dangerous
- Usual interpretation
  - Individual patient has meaningful impairment when SDLP worsens by same amount as from alcohol at legal limit in many countries, 0.05%, corresponds to 2.5 cm worsening of SDLP

## Standard Deviation of Lateral Position (SDLP)



# Driving Study Endpoint

- In hindsight, *falling asleep and leaving road entirely* may be bigger risk than type of impairment causing 'weaving'
- SDLP does *not* measure risk of falling asleep
- SDLP still impaired by suvorexant

# Driving Study Endpoint

- Non-elderly study
  - 3 of 5 patients that prematurely stopped test for somnolence had worsened SDLP; other 2 had almost no change from placebo

NHTSA expert panel:

Sleepiness causes auto crashes because it impairs performance and can lead to inability to resist falling asleep at the wheel

# Driving Test Interpretation

- Evaluating average impairment of all patients in study is not sensitive to clinically important impairment in individuals
- For adverse effects, need to ask how many patients are affected, and how severely



# Driving Study Findings

| Adult (<65 years) |       | Elderly ( $\geq$ 65 years) |       |
|-------------------|-------|----------------------------|-------|
| First night/day   | 20 mg | First night/day            | 15 mg |
|                   | 40 mg |                            | 30 mg |
| After 1 week      | 20 mg | After 1 week               | 15 mg |
|                   | 40 mg |                            | 30 mg |

Statistically significant impairment

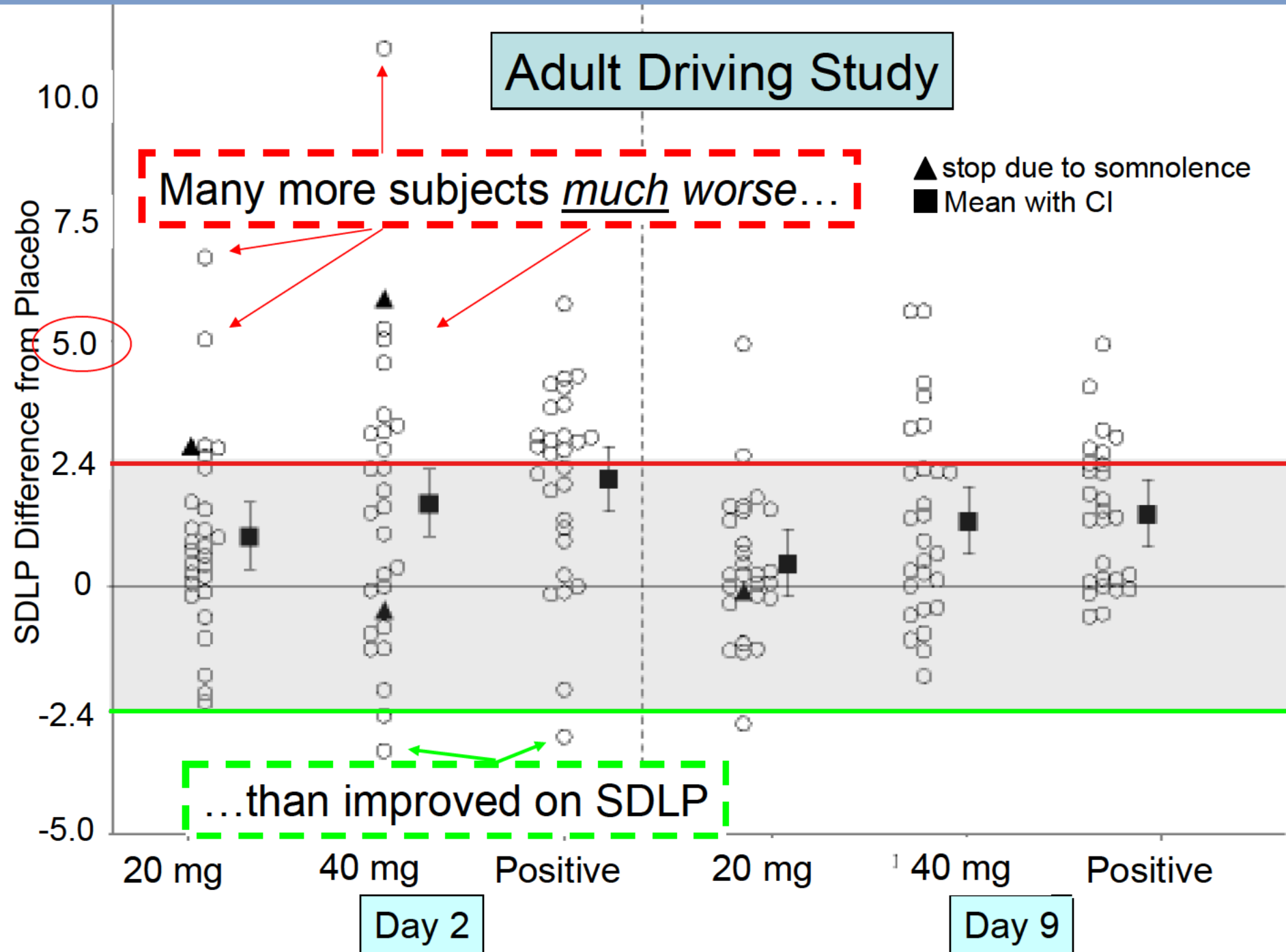
‘Lean’ towards significant impairment → worrisome in small safety study

By ‘symmetry analysis’: more patients impaired than improved

## Many patients impaired even at low dose

|                   |  |
|-------------------|--|
| Adult (<65 years) |  |
| First night/day   | 20 mg: $\approx$ <b>20%</b> of subjects impaired |
|                   | 40 mg: $\approx$ <b>30%</b> of subjects impaired |
| After 1 week      | 20 mg:   |
|                   | 40 mg: $\approx$ <b>20%</b> of subjects impaired |

# Adult Driving Study



# Driving Study in Elderly

- 30 mg
  - day 9 very close to statistically positive
  - day 2 trend to impairment
- 15 mg no impairment on SDLP reassuring...
  - but severe somnolence occurs at this dose, and incidence of falling asleep driving not studied
  - and positive 20 mg study indicates narrow therapeutic margin for driving impairment

# Elderly Driving Study Results

SDLP Difference from Placebo

○ Individual Values  
—■— Mean with 90% CI

worsened

improved

15 mg

30 mg

Positive

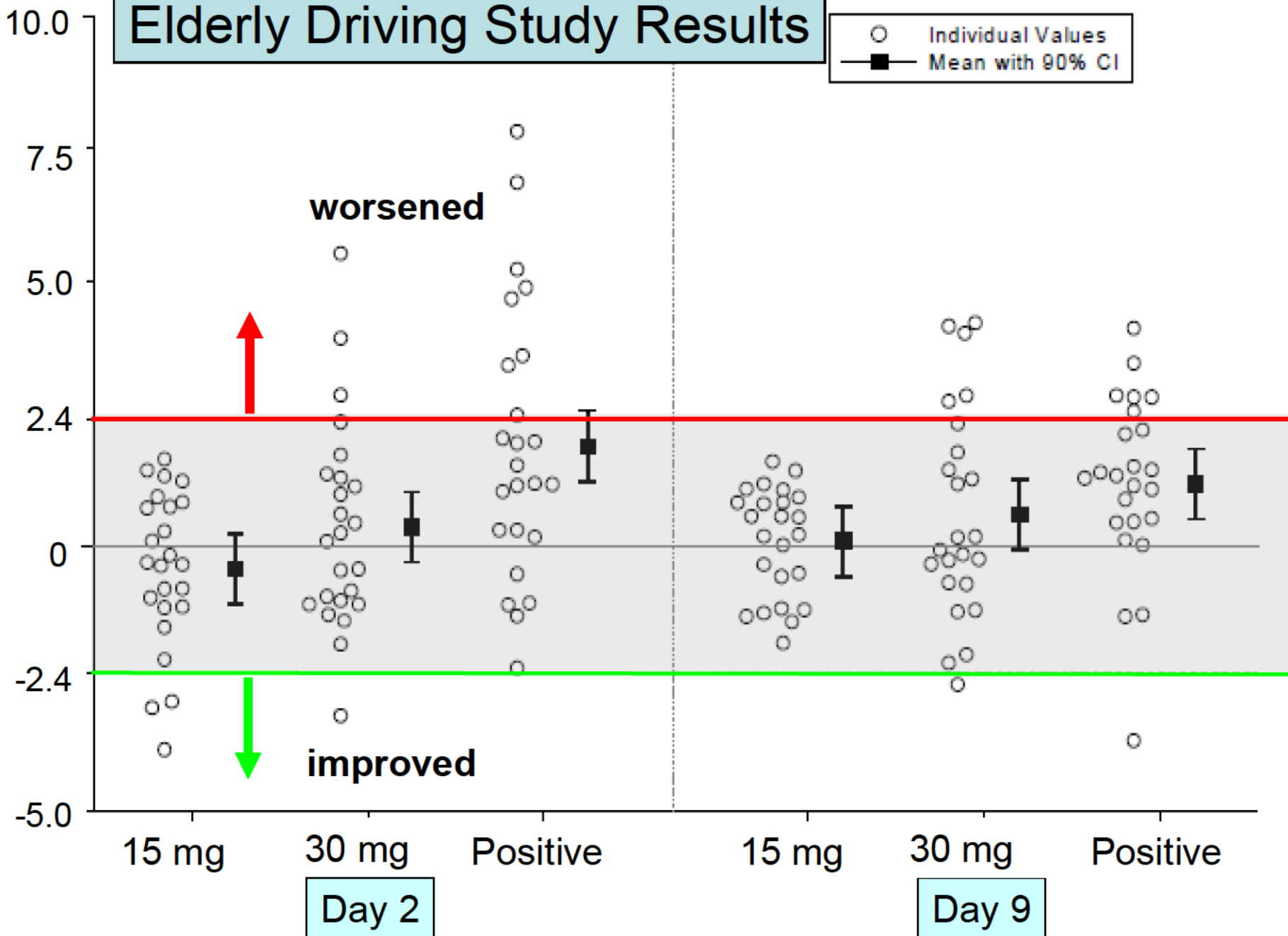
Day 2

15 mg

30 mg

Positive

Day 9



# Suvorexant and MVAs

- All MVA's not the same –
  - Almost all in database 'not at fault' → give little insight into safety of suvorexant
  - Drug/drowsy-related MVA's did not clearly occur; much less common and more serious than MVA's that were captured
  - Suvorexant database not large enough to capture MVA's of interest, like single car driving off road
- That said, ≈30% higher MVA incidence in suvorexant arm not reassuring



# REM Sleep Behavior Disorder-like Event

# REM Sleep Behavior Disorder (RBD)

- Occurs in narcolepsy and other disorders
- Characterized by intense motor or verbal paroxysmal dream-enacting episodes
- Can be aggressive, violent... Individuals act out dreams, sometimes with serious injury to self and others



## 65 year old man, 30 mg AN12939

- During PSG, 2.5 hours after dosing
- Talking in sleep, sat up in bed, went back to sleep
- ***Lunged out of bed, and hit his head and face against a wall***

Very concerning to see this type of event in relatively small number of exposed patients



# Suicide Risk

# Suicide Risk

- Suicidal ideation assessed with Columbia Suicidality Rating Scale
  - 8 patients, 0.6%, on suvorexant high dose
  - 0 patients on placebo (N = 1012)
  - 1 patient, 0.2%, on low dose
  - 0 patients on placebo (N = 763)

# Suicide Adverse Events

- Suicidal ideation as adverse event
  - 0.1% placebo
  - 0.2% low dose
  - 0.4% high dose
- Reported as suicidal ideation without intent to act



# Insomnia Efficacy Endpoints

# Efficacy Endpoints

- FDA requires both objective and subjective endpoints for various diseases

Objective: show change occurred

Subjective: show change *clinically meaningful*

# Subjective Insomnia Endpoints

- Known to be inaccurate and affected by patient beliefs
- Meaningful, but interpret with caution
- Subjective sleep might 'improve' due to non-beneficial or even adverse drug effect, e.g.
  - Daytime somnolence from residual drug might reassure the patient that drug is working
  - Or residual drug might even cloud thinking

# 10 mg Suvorexant

- Crossover study 006
  - 10 mg **Effective** at night 1 and week 4 by pre-specified efficacy analysis
    - sleep efficiency
    - sleep maintenance (WASO)
- Study 006 confounded by carryover effect of suvorexant between periods
  - Period 1 improvement in LPS did not diminish in period 2, even though patients on placebo



# 10 mg Suvorexant

- FDA analyzed LPS for *period 1*
  - by reasonable analyses, evidence of efficacy for 10 mg

## *Percent decrease in LPS*

|              | Night 1    |                  | Week 4     |                  |
|--------------|------------|------------------|------------|------------------|
| <b>10 mg</b> | <b>49%</b> | <b>p = 0.02*</b> | <b>58%</b> | <b>p = 0.02*</b> |
| 20 mg        | 51%        |                  | 67%        |                  |
| 40 mg        | 68%        |                  | 54%        |                  |
| 80 mg        | 54%        |                  | 58%        |                  |