# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 22331 |
| Priority or Standard | S |
| Submit Dates | 10/28/2013, 10/29/2013, 11/20/2013, 12/18/2013, 1/31/2014, 3/7/2014, 3/13/2014, 3/17/2014, 3/25/2014, 3/27/2014, 6/13/2014, 7/13/2014 |
| PDUFA Goal Date | November 30, 2014 |
| Division / Office | ODE-1/Division of Psychiatry Products |
| Reviewer Name | Roberta Glass, M.D. |
| Review Completion Date | October 20, 2014 |
| Established Name | Clonidine hydrochloride |
| Trade Name | Kapvay<br>[Jenloga: not marketed/hypertension] |
| Therapeutic Class | Alpha-2-adrenergic agonist |
| Applicant | Concordia Pharmaceuticals, Inc. |
| Formulation(s) | 0.1 mg & 0.2 mg extended release tablets |
| Dosing Regimen | 0.1 mg qd up to 0.2 mg BID |
| Indication(s) | ADHD |
| Intended Population(s) | Children and Adolescents |

# Table of Contents

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

(b) (4)

## 1.2 Risk Benefit Assessment

The sponsor recently added to their labeling that clonidine has the potential to cause cardiac conduction defects. However, the data base in this submission included evidence that clonidine may have the potential to cause QTc prolongation. The sponsor refers to the events of QTc prolongation as not unexpected events, yet the labeling does not mention QTc prolongation as an adverse event. It is recommended that the labeling mention the potential for Kapvay to cause QTc prolongation, even if it is merely mentioned in the post marketing data section of the label.

The currently approved labeling lists warnings of which somnolence, hypotension and cardiac conduction defects which were observed in this population.

The sponsor, did not, however, assess the effects Kapvay may have on longer term growth in this pediatric population. It is unclear if their data of 40 weeks could have detected a difference in growth potential, but it may be helpful to have the sponsor assess the z-scores for the pediatric population studied. Thus, taking into account the normal growth and development of each individual within their population norms, any change deviating from normal development may be detected.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

It would be helpful to have a clearer understanding Kapvay's effect on QTc prolongation. Given that clonidine is a drug that has been marketed for a long time, it appears to be less urgent a need to determine the exact effects it has on QTc intervals, as it appears to be widely recognized that the effects exist. At a minimum, the label needs to reflect clonidine's potential to prolong the QTc interval.

### 1.4 Recommendations for Postmarket Requirements and Commitments

It is recommended that the sponsor organize their data to better characterize the effects Kapvay has on growth (weight/height) of this pediatric population. Although clonidine's effects on appetite and growth may not be as dramatic or obvious as the effects of stimulants, it would be helpful information to characterize the effects on growth by determining the z-scores for this longer term trial.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Kapvay®, an extended release formulation of clonidine hydrochloride, is a centrally acting $\alpha_2$ adrenergic agonist. Since 2010, Kapvay® has been approved for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as an adjunctive therapy to stimulant medications. (b) (4) clonidine hydrochloride was currently approved under the name Jenloga for the treatment of hypertension, but Jenloga® has not been marketed yet in the US. Clonidine was originally approved for the treatment of hypertension in (b) (4) and is currently available as an immediate and extended release tablet, transdermal patch, and epidural injection.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

There are many medications marketed to treat ADHD. Stimulants, in various formulations of methylphenidate and amphetamine, continue to be the traditional first line choice. Non-stimulant medications indicated and labeled for ADHD are atomoxetine (Strattera®), guanfacine (Intuniv®) and clonidine (Kapvay®).

There are also an array of medications used off label to treat ADHD including tricyclic antidepressant (e.g. Elavil, Norpramin®, Pamelor®,Tofranil®), Wellbutrin®, and traditional anti-hypertensives such as Catapress®, Duraclon®, Nexiclon® and Tenex®.

Medications that are currently marketed and labeled for longer term maintenance treatment for ADHD in the pediatric population include Strattera® (atomoxetine) and Vyvanse® (lisdexafetamine). Drugs currently under reviewed for an ADHD long term maintenance claim include: Kapvay® (clonidine) and Intuniv® (guanfacine).

The following is a list of marketed drugs currently indicated for the treatment of ADHD:

*Stimulants: amphetamine product*

- Adderall® (amphetamine formulation) Tablets
- Adderall® XR (amphetamine formulation:extended release) Capsules
- Dexedrin® (dextroamphetamine)
- Desoxyn® (methamphetamine) Tablets
- Focalin® (dexmethylphenidate) Tablets
- Focalin® XR (dexmethylphenidate: extended-release) Capsules
- Vyvanse® (lisdexafetamine)

*Stimulants: methylphenidate product*

- Concerta® (methylphenidate formulation: extended release) Tablets
- Daytrana® (methylphnidate) Transdermal Patch
- Metadate® CD (methyphenidate: extended release) Capsule
- Metadate® ER (methylphenidate: extended release)
- Methylin® (methylphenidate) Oral Solution
- Methylin® (methylphenidate) Chewable Tablets
- Quillivant XR (methylphenidate) Oral Solution
- Ritalin® (methyphenidate) Tablets
- Ritalin® SR (methylphenidate: sustained release) Tablets
- Ritalin® LA (methylphenidate: extended relase) Capsules

*Non-stimulant products*

- Intuniv® (guanfacine)
- Kayvey® (clonidine: extended release)
- Strattera® (atomoxetine) Capsules

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

Clonidine was originally approved for the treatment of hypertension in (b) (4) Clonidine is currently available in forms of immediate and extended release tablet (indications: hypertension and ADHD), extended release patch (hypertension), and injection solution (cancer pain).

## 2.4 Important Safety Issues With Consideration to Related Drugs

Warnings for an alpha adrenergic drug agonist include hypotension/bradycardia, sedation/somnolence, withdrawal syndrome, potential worsening of cardiac conduction abnormalities such as sinus node dysfunction and atrio-ventricular block. These warnings are in the most recently approved Kapvay labeling.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

In September, 2010, Kapvay was approved for the treatment of ADHD as a supplement to Jenloga under the NDA 22-331. The approval letter (DAARTS: David: 9/28/10) sent to the sponsor included PREA responsibilities and PREA waivers.

According to the 9/28/10 FDA correspondence, the sponsor was waived from studying the pediatric population from ages 0-5 years based on clinical rationale that the "product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group".

The approval letter of 9/28/10 also states that the sponsor has the responsibility to conduct a clinical longer-term withdrawal maintenance study of efficacy and safety of clonidine as monotherapy or as adjunctive therapy in children and adolescents to service the ADHD population better, as likely patients will be treated for long term due to the chronic nature of ADHD.

Also under PREA, the sponsor was required to conduct further pre-clinical data assessing Kapvay co-administered with a stimulant.

The sponsor first submitted their protocol for Study 401, this longer term withdrawal study, in April and August, 2011 as a paper submission (paper versus electronic submissions are on different delivery systems to FDA reviewers), and the sponsor began their study in August, 2011. Unfortunately, the sponsor did not get FDA reviewer feedback on their clinical design in time for the initiation of Study 401 until the correspondence dated February 7, 2012 after Study 401 had begun with enrollment completed by March 27, 2012. The FDA correspondence of February 7, 2012 recommended that the sponsor amend the Protocol for Study 401 to include at least a 12 week period of clinical stability prior to randomization (i.e. that Period 2 be 12 weeks instead of the proposed 6 weeks). In their response to FDA (March 29, 2012), the sponsor points out that it is too late to amend the protocol, but that between Phase 1 and Phase 2, many patients had a consecutive 9 weeks on maintenance treatment prior to randomization to Phase 3, the double blind portion of the study.

The other key FDA recommendation was that the time to treatment failure be used as the primary efficacy endpoint for Phase 3 (a better measure of maintenance efficacy), in place of the sponsor's choice of percent of treatment failures. The sponsor points out that in their response letter of March 29, 2012 that the time to treatment failure was set as a secondary efficacy variable. The sponsor also points out that they had a higher responder rate than expected resulting in more patients being randomized. Thus, the results should be powered well to detect a difference for either time to treatment failure or percent of treatment failures.

The sponsor submitted their final study report for Study 401 on October 28, 2013 without a user fee. Correspondences between FDA and the sponsor clarified that the review of Study 401 required a user fee was two fold: 1) the findings from study 401 is considered a post marketing commitment as the original NDA for Kapvay did not include any longer-term controlled efficacy and safety data in pediatric patients ages 6-17 yo., and 2) the sponsor is requesting that the label be modified to include safety and efficacy data from Study 401. FDA sent a letter to the sponsor (2/13/14) acknowledging receipt of a user fee, and thus this submission qualified for review for labeling changes.

### 2.6 Other Relevant Background Information

According to the approval letter for Kapvay, dated 9/28/10, this current study was requested under the Pediatric Research Equity Act (PREA) as a required study for the marketing of Kapvay. The requirement of submission of this longer-term maintenance study of efficacy and safety was deferred until December, 2013.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

There were several items not in the original submission that needed to be requested at filing and during the review period which were key items related to both efficacy and safety. The sponsor was able to provide them in time so that the review did not need to be delayed.

### 3.2 Compliance with Good Clinical Practices

According to the OSI (Office of Scientific Investigations), two of the three sites inspected resulted in an adequate data audit with no significant deficiencies. However, there was one site that could not be inspected, as the site had closed (Site 512: which had a very high response rate). There was insufficient data that was available from the sponsor to audit and to confirm the data reported. An analysis leaving results from Site 512 out showed that this site had no significant impact of the overall study outcome (See DAARTS: Lee:9/15/14 for full Clinical Inspection Summary).

### 3.3 Financial Disclosures

The Managing Director of Concordia Pharmaceuticals, Inc, John McCleery, CPA,CA, signed the Form 3454 testifying that, to his knowledge, there were no financial

arrangements made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f) for the listing of investigators attached to each 3454.

On Forms 3455, the sponsor reports the following nine investigators as having relevant financial disclosures:

1. (b) (6), investigator for Study SHN-KAP-401 (b) (6) received $114,000. In Honorarium.
2. (b) (6) investigator for Study SHN-KAP-401 (b) (6) received $91,000 in Honorarium as a speaker. ).
3. (b) (6) investigator for Study SHN-KAP-401 (b) (6) received $79,500 in Honorarium.
4. (b) (6) investigator for Study SHN-KAP-401 (b) (6) received $51,000. In Honorarium.
5. (b) (6), investigator for Study SHN-KAP-401 (b) (6) received $37,000 In Honorarium.
6. (b) (6), investigator for Study SHN-KAP-401 (b) (6) received $37,000 In Honorarium.
7. (b) (6), investigator for Study SHN-KAP-401 (b) (6) received $35,000. In Honorarium.
8. (b) (6) investigator for Study SHN-KAP-401 (b) (6) received $32,000. In Honorarium.
9. (b) (6), investigator for Study SHN-KAP-401 (b) (6) received $27,000. In Honorarium.

The sponsor states that the following steps taken minimize the potential for any data bias of Study 401 resulting from honoraria paid to any single investigator:

1. Randomization scheme
2. Study design included double blind and placebo control
3. Protocol included raters doing endpoints that were independent of the site investigator, and
4. 40 study sites participating in the U.S.

It is also noted that all sites had small enrollments with no site enrolling more than ten patients.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

No new information was submitted in this supplemental NDA.

## 4.2 Clinical Microbiology

No new information was submitted in this NDA.

## 4.3 Preclinical Pharmacology/Toxicology

No animal studies were submitted with this NDA.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

The exact mechanism of how Kapvay (clonidine) treats ADHD is unknown. It is known that clonidine stimulates the $\alpha_2$-adrenergic receptors in the brain, but it Is not a central nervous system stimulant.

### 4.4.2 Pharmacodynamics

In addition to being marketed to treat ADHD, clonidine has long been marketed as an antihypertensive agent. It is thought that by stimulating the $\alpha_2$-adrenergic receptors in the brain stem, clonidine reduces sympathetic outflow from the central nervous system resulting in decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

### 4.4.3 Pharmacokinetics

There was no new pharmacokinetic data included in this submission. The following information below is extracted from the current label for Kapvey and based on the original NDA submission for Kapvey to treat ADHD in the pediatric population.

Plasma clonidine concentrations in children and adolescents (0.1 mg bid and 0.2 mg bid) with ADHD are greater than adults with hypertension with children and adolescents receiving higher doses on a mg/kg basis. Normalized for body weight, clearance in children and adolescents was higher than observed in adults with hypertension. Clonidine clearance appears to decrease slights with increases in age over the range of 6-17 years, and females had a 23% lower clearance than males. Somnolence and fatigue was independent of dose or concentration in doses studied in the original NDA submission data.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

This submission relies solely on the data from one 40 week relapse prevention study, namely Study SHN-KAP-401 (referred to as Study 401 in this review). Please see the table below for a summary of Study 401 which is broken up into the following four periods or phases:

Phase 1: open-label optimization (4 weeks)
Period 2: open-label dose maintenance (6 weeks)
Period 3: double-blind randomized placebo withdrawal (26 weeks)
Period 4: taper-down and follow-up (4 weeks)

Table 5.1.1: Summary of Study 401

| Study | Design | Population | Efficacy variables | results |
|---|---|---|---|---|
| 401 | 40 week multicenter 4 phase study Phase 1 | Children and adolescents 6-17 with ADHD | Starting at Phase 3 (Visit 9)<br>$1^{o}$ efficacy variable:<br>% to treatment failure<br>$2^{o}$ variable:<br>Time to relapse | Kapvay group had lower percentagle of subjects reporting treatment failure (p-0.454) (31 (45.6%) subjects for Kapvay compared to n=42 (62.7%0 for placebo |

Table 5.1.2 Summary of Study 401 and the Four Phases identified by the sponsor

| Phase | Duration/design | Dosing | N completing | p-value |
|---|---|---|---|---|
| Phase 1 | 4 week open label Dose Optimization | Weekly titration starting 0.1mg To Maximum 0.4 mg | Entering N=253 Completed N=225 (88.9%) | |

| Phase | Duration/design | Dosing | N completing | p-value |
|---|---|---|---|---|
| Phase 2 | 6 week open label Dose Maintenance | Optimal dose identified in Phase 1 is maintained (range 0.1-0.4 mg/day) | Entering:<br><br>Completed:<br><br>N=136 (53.8%) | |
| Phase 3 | 26 week Randomized double blind placebo controlled relapse prevention | Optimal dose identified in Phase 1 is maintained (range 0.1-0.4 mg/day) | Entering:<br>Kapvay:N=68<br>Placebo: n=67<br><br>Completing:<br>Kapvay; N=37 (54.5%)<br>Placebo: n=25 (37.3%) | P=0.0454 |
| Phase 4 | 4 week taper | | | |

### 5.2 Review Strategy

This review used the following sponsor submission submitted to NDA 22331: 10/28/2013, 10/29/2013, 11/20/2013, 12/18/2013,1/31/2014, 3/7/2014, 3/13/2014, 3/17/2014, 3/25/2014, 3/27/2014, 6/13/2014, 7/13/2014.

Clinical Inspection Summary, by John Lee, MD dated 9/15/2014.

Statistical Review and Evaluation by Yang Wang, Ph.D., draft.

# 6 Review of Efficacy

## *Efficacy Summary*

## *6.1 Indication*

The sponsor's data was submitted to (b) (4)

### 6.1.1 Methods

The sponsor has submitted the current submission in which Phase 3, the placebo controlled 26 week relapse prevention study, (b) (4)

(b) (4). The safety was reviewed for the entire study with special emphasis to this Phase 3 placebo controlled portion of the study.

### 6.1.2 Demographics

The majority of patients in this study are Caucasian males with a mean age of 10.6 years old (range 6 to 17). The population consists of 177 males (70%) and 76 (30%) females of which there are 166 (65.6%) Caucasian, 67 (26.5) African American, 1 (0.4%) Asian, 1 (0.4) Native American, 1 (0.4) Native Hawaiian or Other Pacific Islander and 17 (6.7%) mixed. The sponsor reports that there are no statistically significant differences between the treatment groups with respect to demographics.

### 6.1.3 Subject Disposition

Of the 324 patients screened, 253 patients were enrolled in Phase One of Study 401. Twenty-eight (11%) of patients withdrew during the dose optimization phase (phase 1) of study 401. Please refer to Table 6.1.3.1 below for summary of reasons for withdrawal during Phase 1. Of the 225 patients enrolled into dose Maintenance phase ( Phase 2), 136 (53.8%) completed Phase 2. Please refer to Table 6.1.3.2 below for summary of reasons for withdrawal during Phase 2.

Although 136 patients completed Phase 2, 135 were considered randomized as one patient continued to take the open label medication rather than the randomized medication and was considered disqualified for Phase 3 of the study. Of the 135 patients, 68 were randomized to Kapvey treatment, and 67 were randomized to the placebo treatment group. For Phase 3, 73 patients (or 54.1%) completed Phase 3; this included 37 (or 54.4%) of Kapvey patients and 25 (37%) placebo patients. Please refer to the sponsor's table (Table 6.1.3.3) below for reason for withdrawal during Phase 3, the 26 week double blind placebo controlled portion of Study 401.

The sponsor further elaborates on who is eligible for efficacy analysis citing that some patients' data was not able to be used because of issues of non-compliance, drugs screen positive , failed randomization criteria and BMI out o frange at screening . Please refer to Figure 6.1.3 for further details of patients completing Phase 3 who were determined to be ineligible for efficacy data. The sponsor states that after ineligible patients are excluded, there were a total of n=117 patients who efficacy data was used to determine the final results for the study with n=58 for Kapvay treatment and n=59 for placebo treatment.

Table 6.1.3.1 Reasons for Withdrawal during Phase 1, dose optimization period (information obtained from Study Report 401 p. 55)

| | |
|---|---|
| Total Number of patients withdrawn | 28 (11.1%) |
| Adverse Events | 10 (4.0) |
| Withdrew consent | 6 (2.4) |

| | |
|---|---|
| Protocol deviations | 5 (2.0) |
| Prohibited treatment | 4 (1.6%) |
| Lost to follow up | 2 (0.8%) |
| Other (could not swallow pill). | 1 (0.4%) |

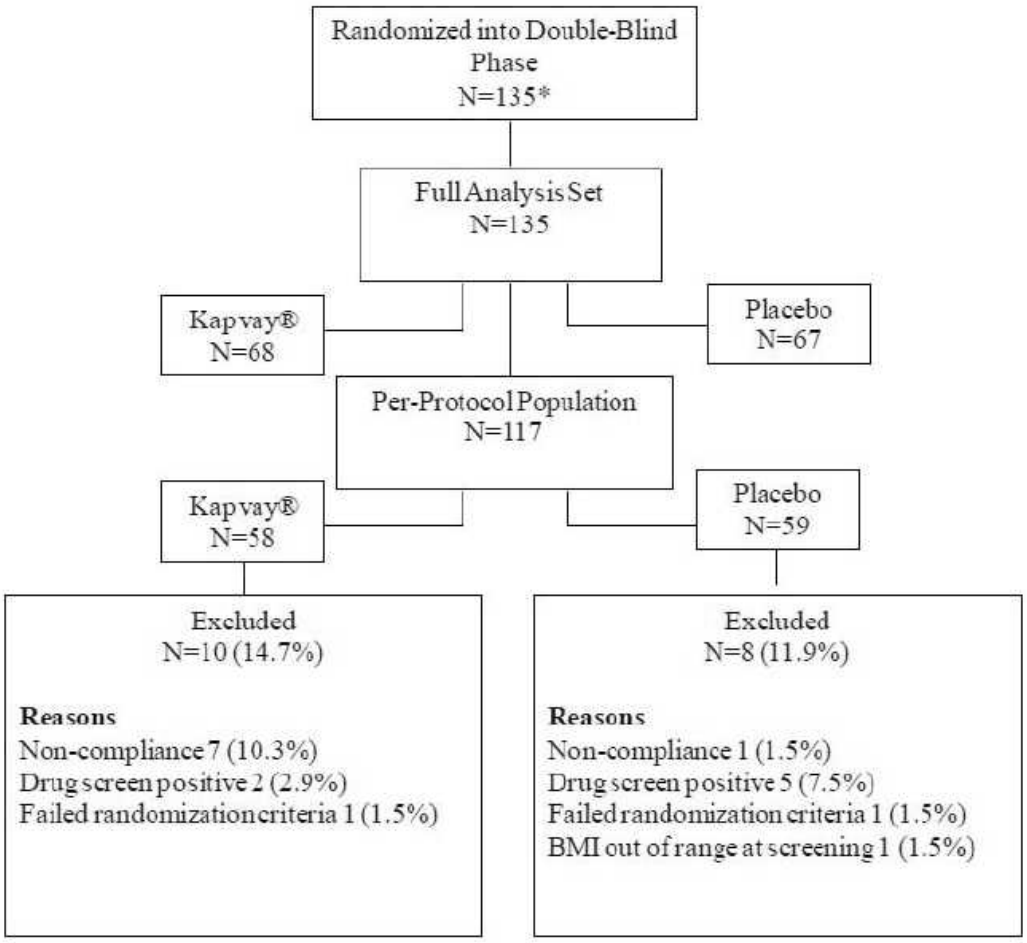
Table 6.1.3.2 Reasons for Withdrawal during Phase 2, dose maintenance period (information obtained from Study Report 401 p. 55)

| | |
|---|---|
| Number of patients withdrawn | 89 (35.2) |
| Non-responders | 33 (13.0) |
| Withdrew consent | 23 (9.1) |
| Protocol deviation | 11 (4.3) |
| Prohibited treatment | 2 (0.8%) |
| other (4 treatment failure, 1 hospitalized, 1 increased symptoms and refused to taper, 1 parent decreased medication) | 7 (2.8) |
| Adverse Events | 6 (2.4) |

Table 6.1.3.3 Reasons for Withdraw during Phase 3, 26 week double blind placebo controlled phase (table extracted from Study Report 401: Table 10-2)

| | Double-Blind Full Analysis Set | | |
|---|---|---|---|
| **Reason for Withdrawal** | **Kapvay® (n=68)** | **Placebo (n=67)** | **Overall (N=135)** |
| Number of subjects withdrawn | 31 (45.6%) | 42 (62.7%) | 73 (54.1%) |
| Adverse event | 2 (2.9%) | 0 (0%) | 2 (1.5%) |
| Withdrawal of informed assent/consent | 5 (7.4%) | 21 (31.3%) | 26 (19.3%) |
| Protocol deviation | 6 (8.8%) | 4 (6.0%) | 10 (7.4%) |
| Use of prohibited treatment | 0 (0%) | 2 (3.0%) | 2 (1.5%) |
| Lost to follow-up | 6 (8.8%) | 3 (4.5%) | 9 (6.7%) |
| Other | 12 (17.6%) | 12 (17.9%) | 24 (17.8%) |

Figure 6.1.3 Sponsor figure showing reasons why patients were excluded from the final efficacy analysis (From Study Report 401: Figure 10-1)




## 6.1.4 Analysis of Primary Endpoint

The primary efficacy variable in the IND was chosen by the sponsor to be the percentage of treatment failures during the double-blind randomized-withdrawal period (Period 3). "Treatment Failure" was defined as satisfying the following 2 criteria:

1. ≥30% increase (worsening) in ADHD-RS-IV (clinician version) total score in two consecutive visits when comparing visits during Period 3 to Visit 9 (when randomization to the controlled withdrawal period began).
2. ≥2 point increase (worsening) in the CGI-S at any 2 consecutive visits during Period 3 compared to Visit 9 (the point of randomization).

Any patient who terminated the study prematurely for any reason during Period 3 (Visit 9 through Visit 20) was considered treatment failure for the purposes of analysis. Reasons for withdrawal included not only treatment failure, but also patients withdrawing prematurely for lack of consent, non-compliance, protocol deviation, lost to follow up, etc.

During Period 3, the sponsor stratified by age utilizing the following two groups:

1. 6-12 years old
2. 13-17 years old

Results showed that for the primary endpoint, a statistically significant difference was found comparing the % of patients with treatment failure comparing the treatment failure rate of the Kapvay and the placebo groups (p=0.0454). In the Kapvay group, there were a total of 31 (45.6%) patients who experienced treatment failure during Phase 3, compared to 42 (62.7%) placebo patients.

When separating out the two stratified age groups for Phase 3, the findings were as follows:

1. 6-12 yo: 24 of 53 (45%) patients taking Kapvay had treatment failure
   32 of 49 (65.3%) placebo

2. 13-17: 7 of 15 (46%) Kapvay treatment failure
   10 of 18 (55.6%) placebo

The following sponsor table was confirmed by the FDA statistical report, and summarizes the sponsor's findings.

Table 6.1.4 The primary efficacy variable: Treatment Failures in Phase 3 (26 week placebo controlled relapse prevention phase) of Study 401.
(Extracted from sponsor's Study Report 401: Table 11-3.)

| Reason for Withdrawal | Double-Blind Full Analysis Set | | p-value from CMH test stratified by age (6-12, 13-17) |
|---|---|---|---|
| | Kapvay® | Placebo | |
| **Primary Analysis** | | | |
| Number of subjects | 68 | 67 | |
| Number of treatment failures | 31 (45.6%) | 42 (62.7%) | 0.0454* |
| **Basis of Treatment Failure** | | | |
| Clinical criteria[a,b] | 11 (16.2%) | 9 (13.4%) | |
| Lack of efficacy[c] | 1 (1.5%) | 3 (4.5%) | |
| Withdrawal of informed assent/consent | 4 (5.9%) | 20 (29.9%) | |
| Other early terminations | 15 (22.1%) | 10 (14.9%) | |
| | | | |
| **Clinical Criteria or Lack of Efficacy** | | | |
| Number of subjects | 49 | 37 | |
| Number of treatment failures | 12 (24.5%) | 12 (32.4%) | 0.4077 |
| **Basis of Treatment Failure** | | | |
| Clinical criteria[a,b] | 11 (22.4%) | 9 (24.3%) | |
| Lack of efficacy[c] | 1 (2.0%) | 3 (8.1%) | |
| | | | |
| **Clinical Criteria, Lack of Efficacy, Withdrawal of Informed Assent/Consent** | | | |
| Number of subjects | 53 | 57 | |
| Number of treatment failures | 16 (30.2%) | 32 (56.1%) | 0.0056** |
| **Basis of Treatment Failure** | | | |
| Clinical criteria[a,b] | 11 (20.8%) | 9 (15.8%) | |
| Lack of efficacy[c] | 1 (1.9%) | 3 (5.3%) | |
| Withdrawal of informed assent/consent | 4 (7.5%) | 20 (35.1%) | |

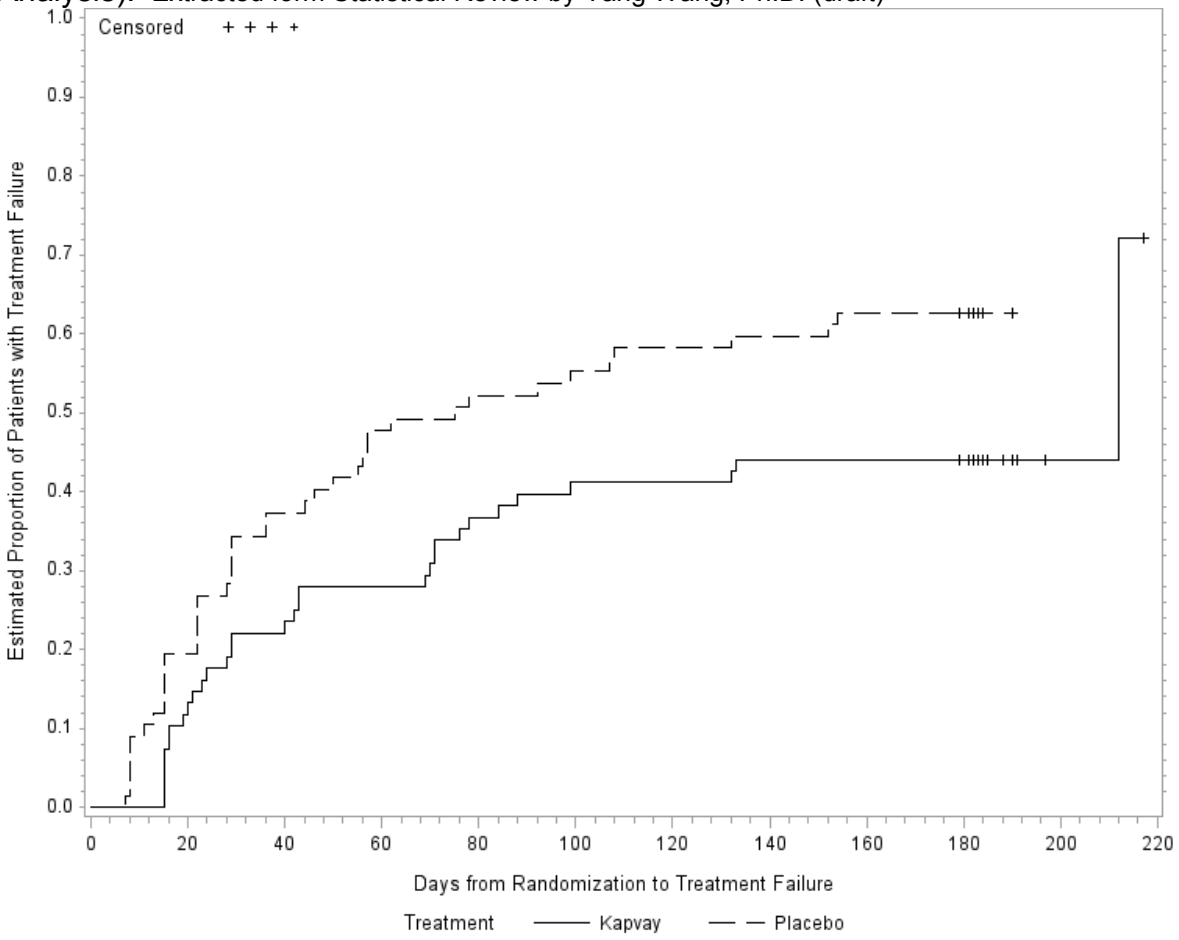
## 6.1.5 Analysis of Secondary Endpoints(s)

The time to relapse, or treatment failure, during the double blind placebo randomization withdrawal period is the standard measure of primary efficacy for most maintenance studies. However, the sponsor had already begun the study when they received this feedback from FDA. The sponsor responded that, although they had designated percent of treatment failure as the primary efficacy variable, they reasoned that the study was sufficiently powered to assess and detect a significant difference also in time to treatment failure. (see correspondences between FDA and sponsor dated 3/29/12 and 5/15/12)

The sponsor shows that there is a statically significant treatment group difference in time to treatment failure comparing the Kapvay (212 days) and placebo (75 day) groups in the primary analysis (p=0.024). These findings were confirmed by FDA statistician

(Wang: draft) and demonstrated in the graph below 6.1.5.1. The sensitivity analysis confirmed the findings that Kapvay appeared to be a superior treatment over time compared to placebo (for further details, see: Wang: draft)

Figure 6.5.1 Cumulative proportion of Patients with Treatment Failure over Time (Full Analysis). Extracted form Statistical Review by Yang Wang, Ph.D. (draft)




## 6.1.6 Subpopulations

Please refer to the statistical review for a fuller discussion of subgroups. It appears that the study was insufficiently powered to see a difference between males and females, as a large majority of patients were male. Also, a significant majority of patients were Caucasian compared to any other racial subgroup, and no conclusions can be made from the data collected regarding efficacy response by race.

### 6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Optimal dosing for each individual was assessed during Phase 2 of the submitted study 401. Table6.8.1, below, is a summary of the doses that were determined as clinically optimal for the enrolled patients who continued onto Phase 3. As can be seen from Table6.8.1, the doses were all within the range of the labeled recommended doses, 0.1 mg/day to 0.4 mg/day. Therefore, it appears from this table that the currently recommended doses derived from the shorter term studies have been effective in this longer term dosing study.

Table 6.1.7: Duration of exposure by dose group during Study 401, based on optimal dose achieved during Phase 2. (table extracted from sponsor submission of 7/9/2014).

| Kapvay Subjects | Total N=68 | Time (days) spent on this dose in Period 3** | | |
|---|---|---|---|---|
| Dose Group (mg/day)* | N | Mean | Median | Range |
| 0.1 | 5 | 150.8 | 184 | 15-190 |
| 0.2 | 14 | 88.8 | 60.5 | 15-184 |
| 0.3 | 25 | 136.8 | 182.0 | 13-216 |
| 0.4 | 24 | 120.9 | 155.5 | 15-195 |

### 6.1.8 Additional Efficacy Issues/Analyses

The results suggest that there is a statistically significant difference in both the primary and secondary efficacy variables. The concern identified during the review is how the sponsor has defined their population of treatment failures. Their definition for treatment failures not only included worsening on two efficacy scales (ADHD-RS-IV and CGI-S), but it also included subjects who terminated the study prematurely for any reason. Any reason included any of the following: adverse events, consent withdrawal, protocol deviation, lost to follow-up and “other” (see Table 6.1.4 above for further details).

# 7 Review of Safety

***Safety Summary***

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review discusses Study 401, the longer term withdrawal study design. Study 401 has four periods identified, three of which were open label. In the study

report for Study 401, the sponsor pools together Phase 1, 2 and 4, the three open label portions of the study. For Phase 3, the 26 week placebo controlled study, the sponsor reports events separately for the Kapvay and placebo group, and offers comparison data. This review will focus on safety data obtained in Phase 3, which offers a placebo controlled group for comparison. It is important to be kept in mind that by the time the study progressed to Phase 3, many patients had already withdrawn, possibly due to intolerable adverse events. Therefore, the population described in Phase 3 was an enriched group that was able to tolerate Kapvay for at least for the ten weeks of Phase 1 and 2 combined.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The sponsor's Table 7.2.1, below, summarizes the days of exposure during Phase 3, the 26 placebo controlled portion of Study 401. As summarized, 68 patients were exposed to Kapvay at their own individual optimal dose (between 0.1-0.4 mg/day) for a mean of 122.3 days.

Table 7.2.1. Number of Days Exposure to Double blind Medication (26 weeks) from p.84 of Study report (measured in days).
(Extracted from Sponsor's table from submission of 7/9/2014)

| Treatment | N | Mean | Median | Range |
|---|---|---|---|---|
| Kapvay | 68 | 122.3 | 181 | 13, 216 |
| Placebo | 67 | 94.0 | 63 | 2, 190 |

### 7.2.2 Explorations for Dose Response

Period 1 explored optimal dosing at the labeling recommended dose within the range of 0.1-0.4 mg/day. Table 7.2.2, below, summarizes the optimal dosing observed that was the planned dosing for Period 3, but the sponsor states that there may have been deviations around this dose. It appears that the majority of patients gravitated to the doses of 0.3-0.4 mg Kapvay as their optimal treatment dose during Phase 2 as summarized in Table 7.2.2. Because the sponsor did not report any adverse events by dose group, it is not possible to explore a dose response and associated adverse events profile from the data submitted by the sponsor for this supplement.

Table 7.2.2. Duration of exposure by dose group during Study 401, based on optimal dose achieved during Phase 2. (table extracted from Sponsor submission of 7/9/2014).

| Kapvay Subjects | Total N=68 | Time (days) spent on this dose in Period 3** | | |
|---|---|---|---|---|
| Dose Group (mg/day)* | N | Mean | Median | Range |
| 0.1 | 5 | 150.8 | 184 | 15-190 |
| 0.2 | 14 | 88.8 | 60.5 | 15-184 |
| 0.3 | 25 | 136.8 | 182.0 | 13-216 |
| 0.4 | 24 | 120.9 | 155.5 | 15-195 |

### 7.2.4 Routine Clinical Testing

During Phase 3 of Study 401, the sponsor monitored routine laboratory test, including CBC, LFTs, urinalysis, urine drug screens, serum and urine pregnancy tests, ECGs and suicide monitoring (C-SSRS).

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The approved labeling summarizes the findings from earlier submissions. There were no new findings in this current submission.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths in this study.

### 7.3.2 Nonfatal Serious Adverse Events

Table 7.3.2, below, summarizes the incidence of serious adverse events occurring in Study 401. There were two serious events occurring in the open label portion of the study (Subject 530-002 (irritability) and Subject 512-004 (sickle cell anemia with crisis). During the double blind portion (Phase 3), Subject 512-004 had a second sickle cell crisis while taking placebo, and Subject 527-003 reported suicidal ideation while taking placebo. The sponsor reports that there were no serious adverse events occurring in patients taking Kapvay during the double blind placebo controlled portion of the study (Phase 3).

Table 7.3.2. Serious Adverse Events in Study 401 during the open label and double-blind phases (Sponsor's Table 12-8 Study report 401)

| Subject | Preferred Term | Open-Label Full Analysis Set (N=253) | Double-Blind Full Analysis Set | |
|---|---|---|---|---|
| | | | Kapvay® (n=68) | Placebo (n=67) |
| | | Number of Subjects Reporting | | |
| 530-002 | Irritability | 1 | 0 | 0 |
| 527-003 | Suicidal ideation | 0 | 0 | 1 |
| 512-004 | Sickle cell anemia with crisis | 1 | 0 | 1 |
| **Number of Subjects Reporting SAEs** | | n% | | |
| | | 2 (0.8%) | 0 (0%) | 2 (3.0%) |

### 7.3.3 Dropouts and/or Discontinuations

During the open label portions of the study (Phases 1/2/4), there were 16 (6.3%) patients who withdrew from the study for an adverse event. Of these 16 patients, 9 (3.6) withdrew due to somnolence, 2 (0.8%), 1 reported (0.4) loss of consciousness (unclear what the cause from sponsor's submission), and 1 (0.4) withdrew due to hypersomnia. The majority of these withdrawals during the open label portion of the study appear to be related to the sedating properties of Kapvey.

During the double blind portion of the study (Phase 3), 2 (or 2.9%) patients taking Kapvay withdrew from the study from the study. The sponsor reported that one patient (518-005) withdrew due to QTc prolongation and one patient (515-008) because of depressed mood; however, it is noted that the withdrawal summary for patient 515-008 also reported QTc prolongation during the period of the study prior to withdrawal (submission for 7/9/14).

Please refer to Table 7.3.3 below for the sponsor's summary of adverse events leading to withdrawal

Table 7.3.3 Treatment emergent adverse events leading to withdrawals: (excerpt from sponsor's table p.95 of study report)

| System Organ Class<br>Preferred Term | Open-Label Full Analysis Set | | Double-Blind Full Analysis Set | | | |
|---|---|---|---|---|---|---|
| | | | Kapvay® | | Placebo | |
| | Number of subjects reporting[a] (%) | Number of reports | Number of subjects reporting[a] (%) | Number of reports | Number of subjects reporting[a] (%) | Number of reports |
| n | 253 | | 68 | | 67 | |
| Any | 16 (6.3) | 17 | 2 (2.9) | 2 | 0 (0) | 0 |
| **Investigations** | 1 (0.4) | 1 | 1 (1.5) | 1 | 0 (0) | 0 |
| Electrocardiogram QT prolonged | 1 (0.4) | 1 | 1 (1.5) | 1 | 0 (0) | 0 |
| **Nervous System Disorders** | 13 (5.1) | 13 | 0 (0) | 0 | 0 (0) | 0 |
| Hypersomnia | 1 (0.4) | 1 | 0 (0) | 0 | 0 (0) | 0 |
| Loss of Consciousness | 1 (0.4) | 1 | 0 (0) | 0 | 0 (0) | 0 |
| Sedation | 2 (0.8) | 2 | 0 (0) | 0 | 0 (0) | 0 |
| Somnolence | 9 (3.6) | 9 | 0 (0) | 0 | 0 (0) | 0 |
| **Psychiatric Disorders** | 2 (0.8) | 3 | 1 (1.5) | 1 | 0 (0) | 0 |
| Affect lability | 1 (0.4) | 1 | 0 (0) | 0 | 0 (0) | 0 |
| Depressed mood | 0 (0) | 0 | 1 (1.5) | 1 | 0 (0) | 0 |
| Depression | 1 (0.4) | 1 | 0 (0) | 0 | 0 (0) | 0 |
| Morbid thoughts | 1 (0.4) | 1 | 0 (0) | 0 | 0 (0) | 0 |

AE = adverse event; TEAE = treatment-emergent AE
[a] Within a given level of summarization, if a subject had multiple TEAEs they were counted only once.

## 7.3.4 Significant Adverse Events

Events were broken down separating out Open label (Period 1/2/4) and Period 3 (placebo controlled).

In summary of the non-serious, but significant adverse events in the open label portions of the study (Phases 1/2/4), there were 11 patients described with vital sign abnormalities and three patients described with QTc prolongation as follows:

1. blood pressure decreased n=3
2. heart rate increase: n=1
3. heart rate decreased: n=1
4. weight increased: n=6
5. QTc prolongation: n=3

a) Subject 518-010: discontinued due to QTc prolongation with QTcF=504msec and QTcB=532 msec.
b) Subject 515-008: listed as discontinued for depressed mood; requested CRF shows QTc prolongation with QTcF=441.
c) Subject 505-017: listed as withdrawal of informed consent; requested CRF showed ECG abnormalities including QTc prolongation with QTcF=443.

In summary of the double-blind phase (period 3), the sponsor offers Table 7.3.4 below. In this summary table, it is reported that n=30 (or 50%) of Kapvay patients reported adverse events compared to n=31 (or 46.3%) of patients in the placebo group. At Visit 20 (completion of Phase 3), 11 of 57 (19.3%) Kapvay treated subjects compared to 5 of 56 (8.9%) had abnormal ECG.

During this double blind portion of Study 401, the sponsor reports that the most significant adverse events were ECG abnormalities, somnolence, dizziness (thought to be postural and depressed mood (note: summaries included QTc prolongation for this patient reported to have depressed mood). The sponsor attributed all of these as not unexpected effects of Kapvay.

Table 7.3.4: Adverse events identified by the sponsor to be definitely related to effects of Kapvay (extracted from Study Report for 401 Table 12-7).

| Severity<br>Subject Number | MedDRA Preferred Term |
|---|---|
| **Mild** | |
| 505-017 | Electrocardiogram QT prolonged |
| | Sinus bradycardia |
| 507-005 | Dizziness postural |
| 507-010[a] | Somnolence (2 reports mild) |
| 507-011 | Dizziness postural (6 reports) |
| **Moderate** | |
| 507-010[a] | Somnolence |
| 518-005 | Electrocardiogram QT prolonged |
| **Severe** | |
| 515-008 | Depressed mood |

### 7.3.5 Submission Specific Primary Safety Concerns

In all the references to the QTc prolongation observed in three identified patients in this study, the sponsor refers to these events as not unexpected and definitely drug related. There perspective that QTc is an expected adverse event is (b) (6) The sponsor has proposed to (b) (4)

The other prominent adverse event observed in this study are the AEs related to the sedating properties of Kapvay. Sedation and somnolence were also observed with frequency and intensity during the earlier short-term studies, and is described in labeling.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

According to the the sponsor's summary table of treatment-emergent adverse events in ≥2.5% of patients (Table 7.4.1 below), the most frequently reported adverse event during the open label portions of the study were somnolence, headache, sedation (which doul be lumped with somnolence), fatigue, and abdominal pain. It is noted that somnolence, sedation and fatigue are all AEs related to the sedating properties of Kapvay. Comparing Kapvay and placebo groups in the placebo controlled portion of the study, it appears from Table 7.4.1 that the most common AE observed for Kapvay were upper respiratory infection, headache and somnolence and abdominal pain. All of these findings in this longer term study are consistent with the common adverse events observed in the previous short term studies which supported the original marketing of Kapvay and are described in the currently approved Kapvay label with the exception of the (b) (6)

Table 7.4.1 Sponsor summary of Treatment Emergent Adverse Events in ≥2.5% of patients (table extracted from Study Report 401 Table 12-3)

| System Organ Class<br>Preferred Term | Open-Label Full Analysis Set (N=253) | Double-Blind Full Analysis Set | |
|---|---|---|---|
| | | Kapvay® (n=68) | Placebo (n=67) |
| | Number of subjects reporting (%) | | |
| **Nervous System Disorders** | | | |
| Somnolence | 106 (41.9%) | 3 (4.4%) | 0 (0%) |
| Headache | 29 (11.5%) | 2 (2.9%) | 3 (4.5%) |
| Sedation | 27 (10.7%) | 1 (1.5%) | 1 (1.5%) |
| Dizziness | 12 (4.7%) | 0 (0%) | 0 (0%) |
| Dizziness postural | 7 (2.8%) | 2 (2.9%) | 2 (3.0%) |
| **Gastrointestinal Disorders** | | | |
| Abdominal pain upper | 13 (5.1%) | 1 (1.5%) | 1 (1.5%) |
| **General Disorders and Administration Site Conditions** | | | |
| Fatigue | 22 (8.7%) | 1 (1.5%) | 0 (0%) |
| Irritability | 14 (5.5%) | 0 (0%) | 0 (0%) |
| **Investigations** | | | |
| Electrocardiogram QT prolonged | 1 (0.4%) | 2 (2.9%) | 0 (0%) |
| Weight increased | 4 (1.6%) | 2 (2.9%) | 0 (0%) |
| **Psychiatric Disorders** | | | |
| Affect lability | 11 (4.3%) | 1 (1.5%) | 0 (0%) |

## 7.4.2 Laboratory Findings

Laboratory test included testing at Visit 1 Screening, Visit 9 (Week 9-the beginning of Phase 3), and Visit 20 (Week 37 and termination of Phase 3). The mean changes for parameters tested appeared to have unremarkable differences when comparing the placebo and Kapvay group for mean laboratory changes for the parameters tested. The sponsor points out the following two patients who had clinically significant abnormalities:

1. Patient 538-077 had elevated hepatic enzymes in Period 3. The most significant elevation was ALT=171 U/L (reference range 5-30 U/L). The patient remained on the medication with elevated ALT, which did not resolve until the patient completed the study.
2. Patient 516-003 was noted to have elevated hepatic enzyme. This patient had an ALT=78 (reference range 5-20) at Visit 20 (end of Phase 3). A retest showed ALT=122 U/L, suggesting that the elevated enzyme did not resolve once the drug

was removed, but the sponsor did conclude that this AE was possibly drug related and considered mild.

### 7.4.3 Vital Signs

In the Open Label portion of the study, there were 11 patients reported to have vital sign abnormalities reported as follows:

- blood pressure decreased: n=3
- patients with heart rate increased: n=1
- patient with heart rate decreased: n=1
- patients with weight increased: n=6

In the double blind portion of Study 401 (Phase 3), the sponsor notes in the study report that there were 4 patients who had vital sign abnormalities

- Blood pressure increased: Subject 508-012
- Weight increased on Kapvay: Subject 531-002 and 525-001
- Weight increased on Placebo: Subject 531-005

According to Appendix Table 14.3.8.1 in the Study report for Study 401, the mean change of heart rate from baseline for the Kapvay group was lower than the mean change from baseline for the placebo group for Phase 3 of Study 401 in the summary as follows:

| Double-Blind Full Analysis Set KAPVAY N=68 | Change from Baseline N=68 | Double-Blind Full Analysis Set Placebo N=67 | Change from Baseline N=67 |
|---|---|---|---|
| 59 | 59 | 60 | 60 |
| 106.0 (10.12) | -0.1 (10.47) | 107.0 (10.21) | 2.1 (9.41) |
| 106 | 0 | 107 | 1 |
| 83 | -25 | 85 | -17 |
| 130 | 31 | 126 | 28 |

### 7.4.4 Electrocardiograms (ECGs)

In the study report for Study 401, the sponsor writes about the following 3 patients who demonstrated QTc prolongation during the study as follows:

a) Subject 518-010: discontinued due to QTc prolongation with QTcF=504msec and QTcB=532 msec.

b) Subject 515-008: listed as discontinued for depressed mood; requested CRF shows QTc prolongation with QTcF=441.
c) Subject 505-017: listed as withdrawal of informed consent; requested CRF showed ECG abnormalities including QTc prolongation with QTcF=443.

The following findings show that there were mean QTc changes observed in to be greater in the Kapvay group compared to the placebo group as seen from this following excerpt from Appendix Table 14.3.12.1 from the Study report for Study 401:

| | Double-Blind Full Analysis Set KAPVAY N=68 | Change from Baseline N=68 | Double-Blind Full Analysis Set Placebo N=67 | Change from Baseline N=67 |
|---|---|---|---|---|
| Visit 20 (Week 37)/Study Termination | | | | |
| n | 55 | 55 | 56 | 56 |
| Mean (SD) | 402.9 (17.98) | 3.9 (14.97) | 399.6 (16.79) | 1.9 (15.22) |
| Median | 401.0 | 2.0 | 398.5 | 3.0 |
| Minimum | 369 | -35 | 370 | -31 |
| Maximum | 453 | 32 | 438 | 38 |

### 7.5.1 Dose Dependency for Adverse Events

The sponsor did not provide a breakdown of adverse events by dosing.

### 7.5.2 Time Dependency for Adverse Events

As expected, there were fewer adverse events observed during Phase 3 of the study, as patients who cannot tolerate the study drug generally withdraw earlier in the study, and do not enter Phase 3 of the study.

### 7.5.3 Drug-Demographic Interactions

The sponsor did not submit summary safety data broken down by demographic groups.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

There are no human carcinogenicity studies in this submission.

### 7.6.2 Human Reproduction and Pregnancy Data

There is no data regarding human reproduction and pregnancy in this submission.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor did not calculate z-scores to offer a perspective of the effects of Kapvay on growth. The Study Report 401 lists that some patients had weight increases, but this information offers little to no perspective given that it is expected that weight increases will occur in the pediatric population in the normal course of development.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Although there was a week long period of withdrawal from study drug, the sponsor did not summarize these findings to support any label changes. The currently approved label for Kapvay already describes a withdrawal syndrome.

## 8 Postmarket Experience

In a recent annual report, the sponsor included a description of the two patients that showed QTc prolongation. These two cases of patients demonstating QTc prolongation while on Kapvay (Subjects 518-005 and 518-010). In their annual report for the year 2012, (b) (6) (b) (4)

## 9 Labeling

### Labeling Recommendations

There are two recommendations for labeling as a result of this review, one regarding how the efficacy results are presented, and the other regarding a safety issue.

a) Recommendations for efficacy

Regarding the efficacy data, according to the confirmatory FDA statistical review, the sponsor has demonstrated that Kapvay is superior to placebo in their 26 week treatment withdrawal design in both the primary variable (% of treatment failure) and the secondary viable (time to treatment failure). However, there is concern in the definition of “treatment failure” they have used.

Their definition for treatment failure not only included worsening on two efficacy scales (ADHD-RS-IV and CGI-S), but it also includes subjects who terminated the study prematurely for any reason. Any reason included any of the following: adverse events, consent withdrawal, protocol deviation, lost to follow-up and "other" (see Table 6.1.4, above, for further details).

Therefore, it is recommended that the description of results of this study include the entire definition of "treatment failure" and that the specific number (n) of each category of "withdrawals for any reason' (b) (4) the data and findings from Study 401 is better described with a clearer and more open presentation of how the efficacy results were obtained.

b. Recommendations for safety

In the study report for Study 401, there were several patients observed with QTc prolongation. In their write up of each of these cases, the sponsor added that this was a known and expected adverse event with clonidine. (b) (6) . In the original review of Kapvay, (DAARTS: Mathews: 7/16/10), Dr. Mathews describes several cases of QTc prolongation in the short term studies. Also, recently while approving a couple of 505(b) 2 clonidine NDAs (for hypertension), a postmarketing commitment was requested in the approval letter to do a "Thorough QT Study" (NDA 22499/22500: DARRTS: Stockbrideg:9/23/2010); however, the sponsor for these two NDAs has not followed through on their post marketing commitment to date.

In conclusion, it appears that QTc prolongation is a finding that is associated with the use of clonidine, a drug with a long marketing history, but the QTc prolongation with clonidine has not been characterized to date. QTc prolongation is a very specific finding and if a drug has the potential to cause QTc prolongation, it is not the best choice medication for an individual with a family history of QTc prolongation. It is unclear at this point, if other drug, such as certain antibiotics, need to be avoided as concomitant medications with Kapvay use.

At this junction in time, because the QTc prolongation effects are not well characterized, but have been observed in the Kapvay's data base, it is recommended that QTc prolongation be mentioned somewhere in the Kapvay labeling. One appropriate place could be in a labeling section that describes post marketing data.

## 9.2 Advisory Committee Meeting

There is no recommendation for an advisory committee meeting at this time.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ROBERTA L GLASS
10/20/2014

JING ZHANG
10/24/2014

1. I agree with Dr. Glass to recommend an approval action.
2. I agree with adding "Q-T prolongation" [redacted] (b) (6) because there were also case reports from annual reports.
3. Regarding Z-score data for weight again, I suggest that we request the data now. If we can't complete our review in this review cycle, it should not be a hold issue for taking action.