**Statistical Review and Evaluation**

Clinical Studies

<table>
<thead>
<tr>
<th>NDA#</th>
<th>21,520 (S-091)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplement #</td>
<td>39</td>
</tr>
<tr>
<td>Drug Name</td>
<td>SYMBYAX (Olanzapine and Fluoxetine HCL)</td>
</tr>
<tr>
<td>Indication(s)</td>
<td>(b) (4) Depressive Episodes Associated with Bipolar I Disorder</td>
</tr>
<tr>
<td>Applicant</td>
<td>Eli Lilly and Co.</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>9/28/12</td>
</tr>
</tbody>
</table>

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics I  
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**Keywords:**  
NDA review, mixed models, multi-center, pediatric exclusivity, intent-to-treat
# Table of Contents

1 EXECUTIVE SUMMARY ................................................................................................................................. 5

2 INTRODUCTION ............................................................................................................................................... 6
   2.1 OVERVIEW ...................................................................................................................................................... 6
   2.2 DATA SOURCES .............................................................................................................................................. 6

3 STATISTICAL EVALUATION ........................................................................................................................ 7
   3.1 DATA AND ANALYSIS QUALITY ..................................................................................................................... 7
   3.2 EVALUATION OF EFFICACY ............................................................................................................................ 7
      3.2.1 Study Design and Endpoints .................................................................................................................... 8
      3.2.2 Statistical Methodologies ....................................................................................................................... 8
      3.2.3 Patient Disposition, Demographic and Baseline Characteristics .......................................................... 9
      3.2.4 Sponsor’s Results and Conclusions ..................................................................................................... 10
      3.2.5 Results Verification by the Reviewer ................................................................................................... 11

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS ............................................................................. 12
   4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION ........................................................................................ 12
   4.2 OTHER SPECIAL/SUBGROUP POPULATIONS .................................................................................................. 13

5 SUMMARY AND CONCLUSIONS ................................................................................................................ 14
   5.1 STATISTICAL ISSUES ..................................................................................................................................... 14
   5.2 COLLECTIVE EVIDENCE ............................................................................................................................... 14
   5.3 CONCLUSIONS AND RECOMMENDATIONS ............................................................................................ 14

APPENDIX .......................................................................................................................................................... 15
LIST OF TABLES

Table 1. List of all studies included in analysis. ................................................................. 6
Table 2. Summary of the sites with GCP violations. .............................................................. 8
Table 3. Patients’ disposition during the trial. ........................................................................ 9
Table 4. Baseline demographic characteristics of the patients in the mITT population. ........ 9
Table 5. Discontinuation reasons for patients in the mITT population..................................... 10
Table 6. CDRS-R total score change from baseline to Week 8 MMRM analysis results (mITT set). 11
Table 7. LS Mean Differences for the Primary Efficacy Endpoint (ITT and mITT sets). ............. 11
Table 8. Primary efficacy endpoint analysis by subgroup (ITT set). ......................................... 12
Table 9. Primary efficacy endpoint analysis by subgroup (mITT set). .................................... 13
Table 10. Change from the baseline to Week 8 in CDRS-R total score for each treatment arm by study site. 15
LIST OF FIGURES

Figure 1. Study design for Protocol H6P-MC-HDAX(a) ................................................................. 7
Figure 2. Change from baseline in CDRS-R total score for patients grouped by drop-out date (ITT set) ............... 12
Figure 3. Change from baseline to Week 8 in CDRS-R total score for patients by country and study site .............. 14
1 EXECUTIVE SUMMARY

Based on the MMRM analysis results, the reviewer confirms sponsor’s findings that Symbyax (Olanzapine and fluoxetine combination) administered orally, once a day 6/25, 12/25, 6/50, or 12/50 mg was statistically significantly superior to placebo in the acute treatment of depressive episodes associated with bipolar I disorder in patients 10 to 17 years of age. From the statistical perspective, the study fulfills the Post-Marketing Commitment requested under the Pediatric Research Equity Act (PREA).
2 INTRODUCTION

2.1 Overview

Symbyax (Olanzapine and fluoxetine combination, OFC) has already been approved for use in adult patients to treat depressive episodes associated with bipolar I disorder or treatment-resistant depression. OFC has not been studied in younger patients; however, the individual components have been evaluated:

- Olanzapine is approved for treatment of schizophrenia and manic or mixed episodes of bipolar I disorder in adolescents.
- Fluoxetine is approved for treatment of MDD and obsessive compulsive disorder (OCD) in children.

On April 09, 2007 the Agency sent the Approval Letter, indicating that the sponsor needs to complete a post-marking commitment study under Pediatric Research Equity Act (PREA). In the current submission the sponsor submits the study H6P-MC-HDAX (HDAX) to fulfill this commitment.

This is a Phase 4 multicenter, randomized, placebo-controlled, parallel-group study designed to demonstrate the efficacy and safety of OFC in the pediatric patient population (ages 10 to 17 years) with bipolar I disorder with a current major depressive episode compared to placebo during 8 weeks of double-blind treatment. Patients were randomized in 2:1 ratio to OFC or placebo, respectively. A total of 291 patients were enrolled with 190 patients completing this study at 41 sites in the United States, Puerto Rico, Mexico and Russia. The summary of the study is presented in Table 1.

Table 1. List of all studies included in analysis.

<table>
<thead>
<tr>
<th>Phase and Design</th>
<th>Treatment Period</th>
<th>Follow-up Period</th>
<th># of Subjects per Arm (ITT)</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>H6P-MC-HDAX</td>
<td>Phase 4</td>
<td>8 Weeks</td>
<td>none</td>
<td>194 OFC 97 placebo Bipolar I Disorder in pediatric patients</td>
</tr>
</tbody>
</table>

Source: Computed by the reviewer.

During the course of the trial the sponsor proposed to reverse the prioritization so that the ITT population (randomized patients who received at least one drug dose) would be used for sensitivity analyses, while mITT (modified ITT population excluding the patients from two sites with GCP violation) would be used as the primary dataset for analyses. Further details clarifying this issue are provided in Section 3.2.2.

2.2 Data Sources

The sponsor’s electronic submission was stored in the FDA network with the following Electronic Document Room (EDR) location: \CDSESUB1\EVSPROD\NDA021520\0091
3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data satisfying and acceptable for the analysis. The reviewer was able to reproduce the primary analysis dataset from the raw data and trace how the primary endpoint was derived.

The sponsor noted that “minor raw data errors” were discovered in the reporting database after it was locked (13/04/12). These errors remain in the reporting database that was used for all analyses in the submitted clinical study report. The sponsor believes these errors are not clinically significant and do not affect any conclusions in the submitted clinical study report. The most notable error was that one patient who was intentionally listed as a screen failure on the eCRF was unintentionally randomized in IVRS. This patient (Patient ID 2308) did not undergo any study procedures for Study Period II and never received study drug.

3.2 Evaluation of Efficacy

This was a Phase IV, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of OFC versus placebo in patients aged 10 to 17 years meeting the diagnostic criteria for a current major depressive episode of bipolar I disorder according to the DSM-IV-TR. Patients were randomized 2:1 to OFC or placebo arms. Following a 2- to 45-day screening period (Study Period I), qualified patients were randomized and entered a 2-week forced-titration period followed by a 6-week flexible dosing period (total 8 weeks, Study Period II). Patients were evaluated for safety and efficacy at each visit. The study design is visually represented on Figure 1.

Figure 1. Study design for Protocol H6P-MC-HDAX(a).

Source: Figure HDAX.1 (Protocol H6P-MC-HDAX(a), pg. 22).
3.2.1 Study Design and Endpoints

The primary objective of this study was to assess the superiority of olanzapine and fluoxetine combination (OFC) therapy compared with placebo in the treatment of patients with a current major depressive episode of bipolar I disorder in improving overall symptomatology based on mean change from baseline to Week 8 on the Children’s Depression Rating Scale-Revised (CDRS-R) total score, using mixed-model repeated measures (MMRM) analysis.

The primary efficacy measure was the change from baseline to Week 8 in Children’s Depression Rating Scale-Revised (CDRS-R) total score. The CDRS-R is modeled after the Hamilton Depression Rating Scale for adults, but also includes questions about school. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 scale. The null hypothesis was that no difference exists between patients receiving OFC and patients receiving only placebo in change from Baseline to Week 8 in CDRS-R total score.

No key secondary endpoints were prespecified.

3.2.2 Statistical Methodologies

The primary efficacy analysis was restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM) with unstructured covariance. The model includes treatment, visit, treatment-by-visit, country as fixed categorical effects; and baseline CDRS-R as a covariate. Initially, the primary analysis set was on the ITT population (defined as all randomized patients who received at least one drug dose), and analysis performed on the mITT population was considered as sensitivity analysis. The mITT population is the ITT population with the exclusions of patients from the sites prematurely closed due to the GCP violations. During the course of this trial (first patient enrolled on 03/17/2009, last patient completed on 02/02/2012), the sponsor conducted audits for a few sites and found serious CGP violations in two of them (sites 210 and 215, see Table 2 for details).

Table 2. Summary of the sites with GCP violations.

<table>
<thead>
<tr>
<th>Site</th>
<th>GCP issues revealed</th>
<th>Actions taken</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symbyax (OFC)</td>
</tr>
<tr>
<td>215</td>
<td>02/02/2010</td>
<td>Enrollment halted on 02/17/2010</td>
<td>7</td>
</tr>
<tr>
<td>210</td>
<td>06/30/2010</td>
<td>Enrollment restricted</td>
<td>14</td>
</tr>
</tbody>
</table>

Source: Summarized by the reviewer.

As a result, sponsor requested to reverse the prioritization such that the mITT, not ITT, population will be the primary analysis set (refer to meeting minutes dated 08/01/2012 under IND 103074). We commented that in principle the primary analysis set should be performed on the ITT analysis regardless of protocol violations, in addition that FDA had not yet confirmed the violations from these two sites. We noted that it was an unusual circumstance to request revision of the primary analysis set before the sNDA submission and recommended that the sponsor keep ITT as the primary analysis set and what analysis results will be included in the labeling description will eventually be a matter of review. However, the sponsor justified the seriousness
of violations that data from these two sites appear to be problematic. We accepted the sponsor’s proposal to use the mITT as the primary set for the efficacy analysis, but noted that we would also review the primary analysis performed with the ITT population.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients’ disposition between the treatment arms during the trial is summarized in Table 3.

Table 3. Patients’ disposition during the trial.

<table>
<thead>
<tr>
<th>Patients disposition</th>
<th>Symbyax (OFC)</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned</td>
<td>200</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Randomized (in 2:1 ratio)</td>
<td>194</td>
<td>97</td>
<td>291</td>
</tr>
<tr>
<td>ITT (received at least 1 dose)</td>
<td>191</td>
<td>96</td>
<td>287</td>
</tr>
<tr>
<td>mITT (excluding sites 210 and 215)</td>
<td>170</td>
<td>85</td>
<td>255</td>
</tr>
<tr>
<td>Completed the study</td>
<td>116</td>
<td>60</td>
<td>176</td>
</tr>
</tbody>
</table>

Source: summarized by the reviewer from the Clinical Study Report data.

There was also one patient (PID 2308) who was listed as a screen failure on the eCRF, but was unintentionally randomized. This patient did not undergo any study procedures for Study Period II and never received study drug. The data that was provided by the sponsor contains no records of this patient, which makes the total numbers of ITT and mITT patients 286 and 254 respectively.

The demographic and baseline characteristics for the mITT patients are summarized in Table 4.

Table 4. Baseline demographic characteristics of the patients in the mITT population.

<table>
<thead>
<tr>
<th></th>
<th>Symbyax (OFC)</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 170</td>
<td>N = 85</td>
<td>N = 255</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.59 (2.30)</td>
<td>15.03 (2.13)</td>
<td>14.74 (2.25)</td>
</tr>
<tr>
<td>Min – Max</td>
<td>10.04 – 17.90</td>
<td>10.03 – 17.98</td>
<td>10.03 – 17.98</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 (49.4)</td>
<td>46 (54.1)</td>
<td>130 (51.0)</td>
</tr>
<tr>
<td>Female</td>
<td>86 (50.6)</td>
<td>39 (45.9)</td>
<td>125 (49.0)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>38 (22.4)</td>
<td>23 (27.1)</td>
<td>61 (23.9)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>132 (77.6)</td>
<td>61 (71.8)</td>
<td>193 (75.5)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>9 (5.3)</td>
<td>5 (5.9)</td>
<td>14 (5.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>23 (13.5)</td>
<td>11 (12.9)</td>
<td>34 (13.3)</td>
</tr>
<tr>
<td>Native Hawaiian/Pacific Islander</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>White</td>
<td>119 (70.0)</td>
<td>61 (71.8)</td>
<td>180 (70.6)</td>
</tr>
<tr>
<td>Multiple</td>
<td>15 (8.8)</td>
<td>7 (8.2)</td>
<td>22 (8.6)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>62.74 (19.01)</td>
<td>65.27 (19.33)</td>
<td>63.59 (19.12)</td>
</tr>
<tr>
<td>Min – Max</td>
<td>24.00 – 119.00</td>
<td>31.30 – 133.60</td>
<td>24.00 – 133.60</td>
</tr>
</tbody>
</table>
The disposition of the mITT patients with respect to the reasons for discontinuation is summarized in Table 5.

Table 5. Discontinuation reasons for patients in the mITT population.

<table>
<thead>
<tr>
<th>Patients Disposition</th>
<th>Symbyax (OFC)</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 170</td>
<td>N = 85</td>
<td>N = 255</td>
</tr>
<tr>
<td>Number of Completers</td>
<td>116 (68.2)</td>
<td>60 (70.6)</td>
<td>176 (69.0)</td>
</tr>
<tr>
<td>Number of Dropouts</td>
<td>54 (31.8)</td>
<td>25 (29.4)</td>
<td>79 (31.0)</td>
</tr>
<tr>
<td>Dropout Reasons:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>24 (14.1)</td>
<td>5 (5.9)</td>
<td>29 (11.4)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Sponsor’s Decision</td>
<td>1 (0.6)</td>
<td>1 (1.2)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Physician Decision</td>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Parent/Caregiver Decision</td>
<td>6 (3.5)</td>
<td>2 (2.4)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Subject Decision</td>
<td>8 (4.7)</td>
<td>7 (8.2)</td>
<td>15 (5.9)</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>6 (3.5)</td>
<td>0 (0.0)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>5 (2.9)</td>
<td>5 (5.9)</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Clinical Relapse</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Entry Criteria Not Met</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Lost to Follow Up</td>
<td>2 (1.2)</td>
<td>3 (3.5)</td>
<td>5 (2.0)</td>
</tr>
</tbody>
</table>

Source: Table HDAX.10.1 (Clinical Study Report, pg. 68)

3.2.4 Sponsor’s Results and Conclusions

The sponsor found statistically significant difference (p-value = 0.003) between OFC and placebo in the acute treatment of major depressive episodes associated with bipolar I disorder in patients 10 to 17 years of age. The results of the primary efficacy analysis (MMRM analysis using contrast between OFC and placebo on mean change from baseline in the CDRS-R total score at the Week 8) are presented in Table 6.
3.2.5 Results Verification by the Reviewer

The reviewer confirm the sponsor’s analysis results for the primary efficacy endpoint using both ITT and mITT datasets. The reviewer’s results of the MMRM analysis are summarized in Table 7.

Table 7. LS Mean Differences for the Primary Efficacy Endpoint (ITT and mITT sets).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Effect</th>
<th>Visit</th>
<th>Difference (SE)</th>
<th>DF</th>
<th>t-Value</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>OFC vs. Placebo</td>
<td>11</td>
<td>-5.0388 (1.6439)</td>
<td>158</td>
<td>-3.07</td>
<td>0.0026</td>
<td>(-8.2856, -1.7919)</td>
</tr>
<tr>
<td>ITT</td>
<td>OFC vs. Placebo</td>
<td>11</td>
<td>-4.8018 (1.5954)</td>
<td>187</td>
<td>-3.01</td>
<td>0.0030</td>
<td>(-7.9491, -1.6545)</td>
</tr>
</tbody>
</table>

Source: Computed by the reviewer

The reviewer explored the potential impact of the dropouts on the efficacy results by comparing the average change from the baseline in CDRS-R total score in treatment arm versus placebo for each drop-out date (see Figure 2). The two graphs (one for each treatment arm) show the average change from baseline in the primary efficacy measure (CDRS-R total score) computed for the patients, after they were grouped according to the date of their drop-out. Each curve is labeled with the number of patients in the group. The visual analysis of the data did not appear to indicate an obvious deviation from missing at random (MAR) assumption.
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This section contains the reviewer’s results of the exploratory analysis for Study H6P-MC-HDAX. The data were grouped by gender, age group, weight group, race, ethnicity, and country. The analyses were performed on both ITT and mITT datasets (see Table 8 and Table 9 respectively).

Table 8. Primary efficacy endpoint analysis by subgroup (ITT set).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>LS difference (SE)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full ITT dataset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>144</td>
<td>-6.49 (2.28)</td>
<td>(-11.02, -1.96)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Female</td>
<td>142</td>
<td>-3.27 (2.25)</td>
<td>(-7.73, 1.20)</td>
<td>0.1500</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-11 years</td>
<td>42</td>
<td>-4.88 (6.54)</td>
<td>(-18.96, 9.20)</td>
<td>0.4684</td>
</tr>
<tr>
<td>12-17 years</td>
<td>244</td>
<td>-4.56 (1.71)</td>
<td>(-7.94, -1.17)</td>
<td>0.0086</td>
</tr>
<tr>
<td>Weight category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50 kg</td>
<td>74</td>
<td>-8.33 (3.77)</td>
<td>(-16.00, -0.66)</td>
<td>0.0343</td>
</tr>
<tr>
<td>&gt; 50 kg</td>
<td>212</td>
<td>-3.77 (1.82)</td>
<td>(-7.38, -0.17)</td>
<td>0.0404</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>37</td>
<td>-1.81 (4.65)</td>
<td>(-11.38, 7.76)</td>
<td>0.7002</td>
</tr>
<tr>
<td>White</td>
<td>205</td>
<td>-5.73 (1.91)</td>
<td>(-9.51, -1.94)</td>
<td>0.0033</td>
</tr>
<tr>
<td>Multiple</td>
<td>24</td>
<td>-1.49 (5.38)</td>
<td>(-12.87, 9.88)</td>
<td>0.7848</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>65</td>
<td>-1.86 (2.53)</td>
<td>(-7.00, 3.29)</td>
<td>0.4689</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>220</td>
<td>-5.89 (1.93)</td>
<td>(-9.70, -2.08)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>23</td>
<td>-0.75 (6.26)</td>
<td>(-14.65, 13.14)</td>
<td>0.9066</td>
</tr>
<tr>
<td>Russia</td>
<td>44</td>
<td>-10.73 (2.42)</td>
<td>(-15.76, -5.71)</td>
<td>0.0002</td>
</tr>
<tr>
<td>USA</td>
<td>209</td>
<td>-4.43 (1.92)</td>
<td>(-8.22, -0.63)</td>
<td>0.0226</td>
</tr>
</tbody>
</table>

Source: computed by the reviewer.
Table 9. Primary efficacy endpoint analysis by subgroup (mITT set)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>L̅S difference (SE)</th>
<th>95% CI</th>
<th>p-value</th>
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<td>254</td>
<td>-5.04 (1.64)</td>
<td>(-8.29, -1.79)</td>
<td>0.0026</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td>130</td>
<td>-7.52 (2.37)</td>
<td>(-12.22, -2.81)</td>
<td>0.0021</td>
</tr>
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<td>124</td>
<td>-2.60 (2.28)</td>
<td>(-7.14, 1.94)</td>
<td>0.2574</td>
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<tr>
<td>7-11 years</td>
<td>39</td>
<td>-3.12 (7.75)</td>
<td>(-20.51, 14.27)</td>
<td>0.6964</td>
</tr>
<tr>
<td>12-17 years</td>
<td>215</td>
<td>-4.98 (1.77)</td>
<td>(-8.48, -1.49)</td>
<td>0.0056</td>
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<td>Weight category</td>
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<tr>
<td>≤ 50 kg</td>
<td>65</td>
<td>-8.28 (4.54)</td>
<td>(-17.59, 1.02)</td>
<td>0.0789</td>
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<tr>
<td>&gt; 50 kg</td>
<td>189</td>
<td>-3.89 (1.87)</td>
<td>(-7.59, -0.19)</td>
<td>0.0396</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
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<td></td>
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<tr>
<td>Black</td>
<td>34</td>
<td>0.73 (4.26)</td>
<td>(-8.07, 9.53)</td>
<td>0.8655</td>
</tr>
<tr>
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<td>(-9.76, -1.90)</td>
<td>0.0040</td>
</tr>
<tr>
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<td>(-21.68, 5.35)</td>
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<tr>
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<td>(-7.45, 3.33)</td>
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<tr>
<td>Not Hispanic/Latino</td>
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<td>-6.31 (2.01)</td>
<td>(-10.30, -2.32)</td>
<td>0.0022</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>23</td>
<td>-0.75 (6.26)</td>
<td>(-14.65, 13.14)</td>
<td>0.9066</td>
</tr>
<tr>
<td>Russia</td>
<td>44</td>
<td>-10.73 (2.42)</td>
<td>(-15.76, -5.71)</td>
<td>0.0002</td>
</tr>
<tr>
<td>USA</td>
<td>177</td>
<td>-4.87 (2.04)</td>
<td>(-8.90, -0.84)</td>
<td>0.0183</td>
</tr>
</tbody>
</table>

Source: computed by the reviewer.

Based on this reviewer’s analysis, there does not appear to be substantial heterogeneity in treatment efficacy among the subgroups. The only subgroup that had opposite sign for numeric estimate for the efficacy effect was the Black subgroup in the mITT population. This was inconsistent with the rest of the subgroups, including the Black subgroup effect in the ITT population. The reason for that could possibly be attributed to the relatively large variance in quite a small subgroup.

4.2 Other Special/Subgroup Populations

The scatterplot of the primary endpoint data (change from baseline to Week 8 in CDRS-R total score) for each patient grouped by country and study site is presented on Figure 3. The visual analysis of the data for each site did not appear to indicate any suspicious patterns that could suggest data manipulation or unusual distribution. The primary endpoint data is also summarized in Table 10 for every study site.
5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In the original SAP, the sponsor planned to perform all analyses on the ITT population and only provide modified ITT (mITT) as a sensitivity analysis for the primary efficacy endpoint and three adverse event reports. The mITT population is the ITT population with the exclusion of sites with GCP violations. The sponsor proposed to reverse this prioritization so that the main analyses will be the mITT analyses; the ITT would be used for sensitivity analyses. The issue, however, seems to have no impact on the efficacy analysis results.

5.2 Collective Evidence

There is only one study reviewed in this submission. The primary analysis results of this study are statistically significant whether based on ITT or mITT populations. The exploratory subgroup analyses did not reveal noticeable heterogeneity with respect to the primary efficacy measure (change from baseline to Week 8 in CDRS-R total score).

5.3 Conclusions and Recommendations

The reviewer confirmed the sponsor’s analysis results that Symbyax (OFC) was statistically significantly superior to placebo (p-value = 0.003) in the acute treatment of depressive episodes associated with bipolar I disorder in patients 10 to 17 years of age. From the statistical perspective, there is no evidence against fulfilling the postmarketing commitment under the PREA.
## APPENDIX

Table 10. Change from the baseline to Week 8 in CDRS-R total score for each treatment arm by study site.

<table>
<thead>
<tr>
<th>Site</th>
<th>Country</th>
<th>N</th>
<th>Symbyax (OFC) Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>OFC–Placebo Difference</th>
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<tr>
<td>145</td>
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<td>28</td>
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<td>-23.60 (12.70)</td>
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<td>-24.42 (13.79)</td>
<td>-12.40 (11.48)</td>
<td>-12.02</td>
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<tr>
<td>195</td>
<td>USA</td>
<td>20</td>
<td>-25.46 (10.74)</td>
<td>-18.17 (8.47)</td>
<td>-7.29</td>
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<td>205</td>
<td>USA</td>
<td>16</td>
<td>-18.67 (11.13)</td>
<td>-22.67 (10.69)</td>
<td>4.00</td>
</tr>
<tr>
<td>405</td>
<td>Russia</td>
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<td>-16.00 (11.40)</td>
<td>-18.89</td>
</tr>
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<tr>
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<td>-23.50 (10.60)</td>
<td>-7.50</td>
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<tr>
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<td>-40.67 (11.50)</td>
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</table>

Source: computed by the reviewer. The missing data indicate that no patients were available by Week 8.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREJUS PARFIONOVAS
05/09/2013

PEILING YANG
05/09/2013
I concur with the review.

HSIEN MING J HUNG
05/09/2013