Office of Clinical Pharmacology Review

NDA/Supplement/Serial #:	21,520/S039/0091
Brand Name:	SymByax
Generic Name:	Olanzapine/Fluoxetine Combination (OFC)
Dosage Form:	Capsule
Strengths:	3/25, 6/25, 12/25, 6/50 or 12/50 mg
Sponsor:	Eli Lilly
Indication:	Bipolar Depression
Submission Date:	9/28/2012, 4/4/2013
Review Type:	Pediatric sNDA
Review Team:	Huixia Zhang, Ph.D., Hao Zhu, Ph.D.

Table of Contents

1. Executive Summary

Eli Lilly and Company (Lilly) submitted this Supplemental New Drug Application (sNDA) in fulfillment of the post-marketing commitment under the Pediatric Research Equity Act (PREA), issued by the FDA in the Approval Letter dated on 09 April 2007 for supplements S-008 and S-010 of SymByax (OFC, Olanzapine/Fluoxetine Combination). The current submission included one efficacy and safety trial in pediatric patients 10-17 years of age (Study H6P-MC-HDAX), entitled "Study to Assess the Safety and Efficacy of Olanzapine and Fluoxetine Combination versus Placebo in Patients Ages 10-17 in the Treatment of Major Depressive Episodes Associated with Bipolar I Disorder".

The focus of the analyses performed by the Office of Clinical Pharmacology (OCP) is QTc interval prolongation, which is the main safety concern of SymByax and is thought to be mainly associated with fluoxetine/norfluoxetine (active metabolite of fluoxetine), in pediatric patients (10-17 years of age) with different body weight. The results demonstrated QTc prolongation following the treatment of Symbyax. However, the difference in QTc prolongation between high (12 ms of the one-sided upper 95%

confidence interval) and low body weight (15 ms of the one-sided upper 95% confidence interval) groups is not considered meaningful. Hence, no additional dose adjustment based on body weight is recommended in patients 10-17 years of age, given that there is already adequate warning language on QTc prolongation in the label.

1.1 Clinical Pharmacology Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology I has reviewed the submission and concludes that the submitted efficacy and safety study fulfills the Post-Marketing Commitment requested under PREA. In addition, OCP supports a recommendation of approval for SymByax in pediatric patients 10-17 years of age provided an agreement on the label can be reached with the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendation and Comments
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreement with the sponsor
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Study H6P-MC-HDAX
Proposed dose in pediatric patients 10 -17 years	☒ Yes ☐ No ☐ NA	Olanzapine/fluoxetine (6/25, 6/50, 12/25, 12/50 mg)
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor.

1.2 PMR/PMC Recommendation

No post-marketing studies are recommended by OCP.

1.3 Labeling Recommendation

Children and Adolescents (ages 10 to 17 years) — Based on the pediatric SYMBYAX study, average steady-state olanzapine, fluoxetine, and norfluoxetine concentrations were 42%, 55%, and 27% higher, respectively, in pediatric patients with lower body weights (less than 50 kg) than patients with high body weight (greater than or equal to 50 kg). Exposures in high body weigh patients were similar to those previously observed in adults.

1.4 Summary of Clinical Pharmacology Key Findings

The OCP analyzed the exposure and QTc interval data collected from the efficacy and safety trial (Study H6P-MC-HDAX) and found:

- Steady state concentrations of olanzapien, fluoxetine, and norfluoxetine in pediatric patients with high body weight (≥50kg) were similar to those previously observed in adult patients.
- By average, steady state plasma concentrations of olanzapine, fluoxetine, and norfluoxetine in pediatric patients were 42%, 55%, and 27% higher in patients with low body weight (<50 kg) than the concentrations observed in patients with high body weight (≥50 kg).
- Fluoxetine is a known QT prolonger with warnings in the label. Olanzapine is not considered as a QT prolonger even though no thorough QT study has been conducted. Patients with different body weight (< 50 kg vs. ≥ 50 kg) were grouped

by fluoxetine dose. It is shown that patients with different body weight received final fluoxetine doses in a reasonably similar pattern in Study H6P-MC-HDAX. Major moieties, such as fluoxetine and norfluoxetine, are expected to yield higher exposure in low body weight patients (< 50 kg) than in high body weight patients (≥ 50 kg). However, even with the different exposure levels in patients with different body weight (< 50 kg vs. ≥50 kg), the observed QT signals were similar between low body weight (<50kg) and high body weight (≥50kg) pediatric patients. Hence no additional dose adjustment is needed for patients based on body weight.

2. Question-Based Review

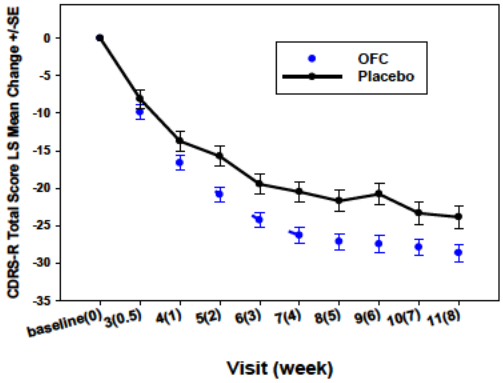
2.1 Is there evidence of effectiveness for SymByax in pediatrics aged 10-17 years (prescribability)?

Yes. The efficacy of SymByax in patients aged 10-17 years old was demonstrated in Study H6P-MC-HDAX.

Study H6P-MC-HDAX was a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of OFC for the treatment of major depressive episodes associated with bipolar I disorder in patients 10 to 17 years of age. Eligible patients were randomized in a 2:1 ratio to OFC or placebo for up to 8 weeks of double-blind treatment. Dosing was initiated with forced titration at 3 mg olanzapine/25 mg fluoxetine (3/25) per day and titrated up to 12/50 by the end of Week 2, with flexible dosing thereafter (6/25, 6/50, 12/25, or 12/50). The dose titration and reduction were not determined by QTc interval change.

The primary efficacy endpoint of the study was the mean change from baseline to Week 8 (Visit 11) in Children's Depression Rating Scale-Revised (CDRS-R) total score, and this endpoint was met (Figure 1). At Week 8, the OFC group had a mean decrease of 28.4 points on the CDRS-R, while the placebo group had a mean decrease of 23.4 points, indicating significant and superior improvement in the OFC group (p=.003). The OFC group showed statistically significantly greater improvement relative to placebo at Week 1 (p=.02) and at all subsequent visits (all p-values <.01).

Figure 1: Mean CDRS-R Total Score Change from Baseline by Treatment Group in Pediatric Patients (10-17 Years).



-Source: Table HDAX.11.16.(Clinical Study Report, pg.109-110)

2.2 Is dose adjustment needed for children with low body weight based on QT prolongation?

No, dose adjustment is not needed for pediatric patients with different body weight based on the QT and PK observations from study HDAX.

Patients, with body weight ranging from 24 kg up to 116.5 kg enrolled in Study HDAX study, received different doses of SymByax (6/25, 6/50, 12/25, 12/50 mg combination of olanzapine/fluoxetine). To determine if there is a need for body weight-based dosing, several analyses were performed.

1)Plasma concentration and body weight relationship: Steady state (Visit 11) plasma concentrations of olanzapine, fluoxetine and norfluoxetine were plotted against patient body weight. The steepest relationship between body weight and plasma concentration was observed for fluoxetine after OFC treatment (Figure 2). With fluoxetine, the relationship appears to be flattened in patients with body weight greater than 50 kg. The similar pattern was observed for norfluoxetine and olanzapine (Figure 2, 3, 4). Hence, 50 kg was chosen as an empirical cut-off point.

Figure 2. Observed Fluoxetine Plasma Concentration at Steady State (Visit 11) vs Baseline Body Weight in Pediatric Patients Following Oral Administration of OFC Once Daily.

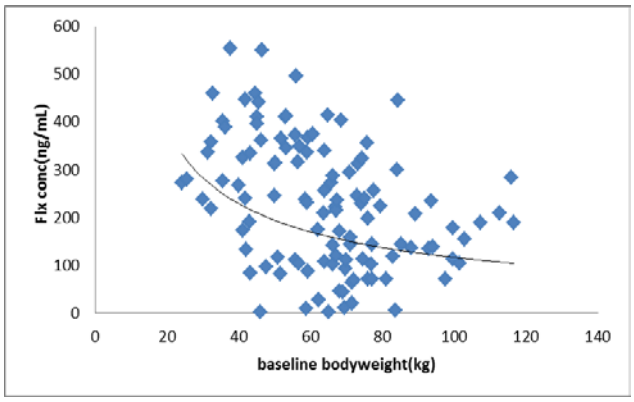


Figure 3. Observed Norfluoxetine Plasma Concentration at Steady State (Visit 11) vs Base Line Body Weight in Pediatric Patients Following Oral Administration of OFC once daily.

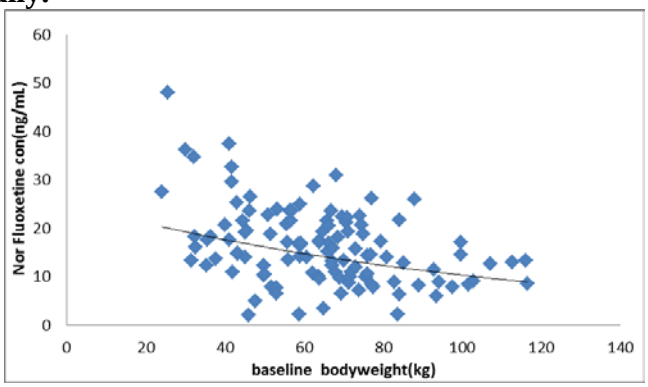
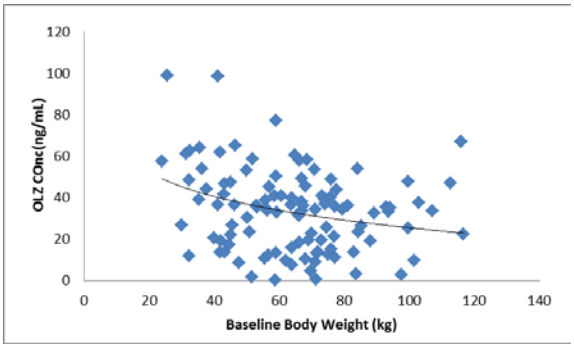


Figure 4. Observed Olanzapine Plasma Concentration at Steady State (Visit 11) vs Base Line Body Weight in Pediatric Patients Following Oral Administration of OFC once daily.



The observed mean plasma concentration at Visit 11 after OFC treatment was shown in Table 1. Compared with the mean concentration in pediatric patients with high body weight (≥50 kg), the mean concentration in patients with low body weight (<50kg) was about 42%, 55%, and 27% higher for olanzapine, fluoxetine, and norfluoxetine, respectively.

Table 1: Mean Observed Plasma Concentration (ng/mL) Of Olanzapine, Fluoxetine, And Norfluoxetine At Week 8 (Visit 11) After OFC Once Daily Treatment Regardless Of OFC Dose.

	Olanzapine	Fluoxetine	Norfluoxetine
Base line body weight<50kg	43.2	308.3	231.7
Base line body weight ≥50kg	30.4	198.8	182.5
All pediatric subjects	33.8	227.9	195.6
%difference between low body weight and high body weight pediatric patients	+42	+55	+27

2) Final dose and body weight relationship: Patients with different body weight (< 50 kg vs. ≥50 kg) received final fluoxetine doses in a reasonably similar pattern in Study H6P-MC-HDAX. Fluoxetine is a known QT prolonger with warnings in the label. Olanzapine is not currently considered as a QT prolonger even though no thorough QT study has been conducted. Therefore, patients in Study HDAX were grouped by fluoxetine doses. As shown in Table 2, even though not totally balanced, the highest dose of fluoxetine (50 mg) was administered to most patients (~ 70%) in each body weight group.

Table 2: Distribution of Low (<50kg) and High (≥50kg) Body Weight Patients by Fluoxetine Dose

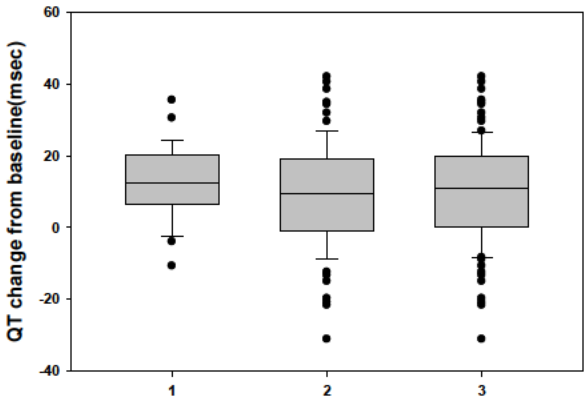
# Patients	Fluoxetine 25 mg	Fluoxetine 50 mg	Total
BW <50kg	10	20	30
BW>=50kg	21	62	83
%			
BW <50kg	33.3	66.6	100
BW>=50kg	25.3	74.7	100

3)Final QT interval observations: The final QTc interval change from baseline, as summarized by categorical analysis and distribution pattern (Table 3 and Figure 5), showed no meaningful difference between the high and low body weight groups. The mean QTc changes from baseline were about 12.3msec and 9.0msec for the low and high body weight group, respectively, and the upper bounds of one-sided 95% confidence intervals of QTc changes from baseline for the low and high body weight groups were 15.5msec and 11.8msec, respectively.

Table 3: Distribution of QT Change from Baseline in Visit 11 in Pediatric Patients

	# (%) of Subjects	
QT Prolongation Category	Low Body Weight Group (<50kg)	High Body Weight Group (≥50kg)
30-45 msec	2(6.9%)	6(7.6%)
0-30 msec	22(75.9%)	52(65.8%)
<0 msec	5(17.2%)	21(26.6%)
Total	29(100%)	79(100%)

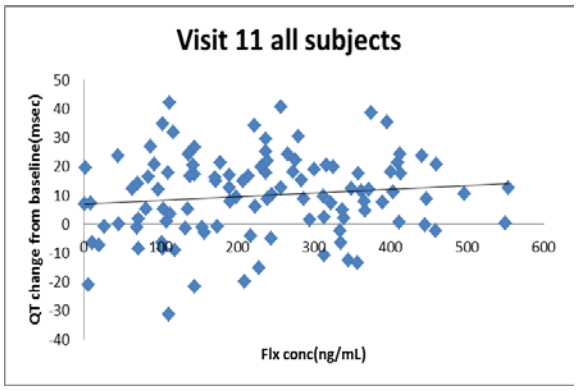
Figure 5: QTc Prolongation vs Body Weight



Group 1: base line bw<50kg, n=29
Group 2: base line bw>=50kg, n=79
Group 3: all subjects, n=108

4)Concentration-QT relationship: In an effort to understand the similar QT effect observed in patients with different body weight groups, concentration-QT relationships using univariate analyses were explored. The assumption is the overall QT effect is driven by one moiety. The results indicated that no significant relationship between changes in QTcF and either fluoxetine (Figure 6) or olanzapine (Figure 7) concentrations, but a significant relationship between change in QTcF and norfluoxetine plasma concentration was noticed (Figure 8). However, norfloxetine, even though with a significant and relatively steep slope, is associated with only ~30% higher exposure in patients with low body weight than with high body weight. Hence the QT effect is not expected to be meaningfully different between patients with different body weight.

Figure 6: Scatter Plot of Change from baseline to Visit 11 in QTcF (msec) versus Fluoxetine Plasma Concentration (ng/mL).



Note: Parameters and P-values are shown in Table 5.

Figure 7: Scatter Plot of Change from baseline to Visit 11 in QTcF (msec) versus Olanzapine Plasma Concentration (ng/mL).

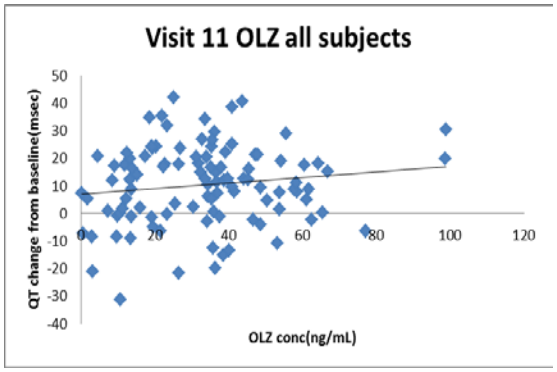


Figure 8: Scatter Plot of Change from baseline to Visit 11 in QTcF (msec) versus Norfluoxetine Plasma Concentration (ng/mL).

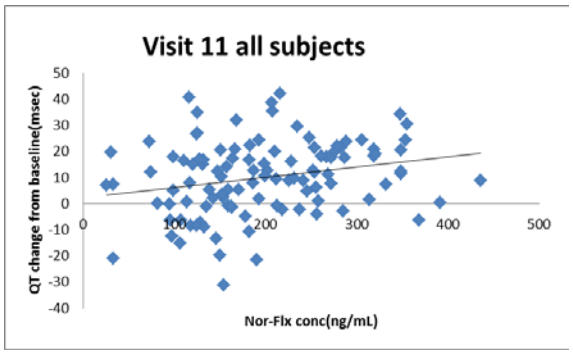


Table 5: QTcF Interval Change from Baseline to Week 8-Regression Against Study Drug Concentration

Model	Parameter	Parameter Estimate	Standard Error	95% CI	p-value *a
#1 (n=93)	Intercept	6.060	2.723	(0.650, 11.469)	.029
	Olanzapine Concentration	0.112	0.071	(-0.029, 0.253)	.118
#2 (n=96)	Intercept	5.383	2.745	(-0.067, 10.834)	.053
	Fluoxetine Concentration	0.018	0.010	(-0.003, 0.038)	.091
#3 (n=98)	Intercept	3.532	3.174	(-2.767, 9.831)	.269
	Norfluoxetine Concentration	0.030	0.015	(0.001, 0.060)	.044
#4 (n=92)	Intercept	1.849	3.802	(-5.707, 9.404)	.628
	Olanzapine Concentration	0.034	0.087	(-0.138, 0.206)	.698
	Fluoxetine Concentration	0.005	0.015	(-0.025, 0.035)	.739
	Norfluoxetine Concentration	0.027	0.021	(-0.016, 0.069)	.213

-Source: Table 1 in Regulatory Response (4/4/2013 sponsor submission)

Given that there is already adequate warning language in the labeling regarding QT prolongation associated with Symbyax use, and the analyses performed above, there is no strong evidence to suggest body weight based dosing for SymByax is necessary.

SIGNATURES

Huixia Zhang, Ph.D.
Reviewer, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

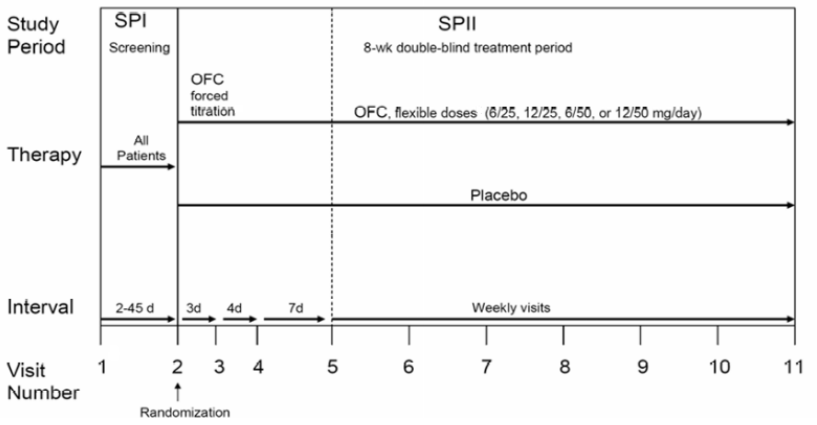
RD/FT, Initialized by Hao Zhu, Ph.D.
Team leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology
Cc: NDA 21,520 (Mehta, Uppoor, Zhu, Zhang)

3. Individual Study Report

Pediatric Efficacy and Safety Study

Report # H6P-MC-HDAX	**Study Period**: March 2009-Febrary 2012
EDR location: \\CDSESUB1\EVSPROD\NDA021520\0091	
Title: Study to Assess the Safety and Efficacy of Olanzapine and Fluoxetine Combination versus Placebo in Patients Ages 10 to 17 in the Treatment of Major Depressive Episodes Associated with Bipolar I Disorder.	
Objectives: To assess the superiority of olanzapine and fluoxetine combination (OFC) compared with placebo as measured by the mean change from baseline to Week 8 in the Children's Depression Rating Scale-Revised score (CDRS-R).	
Study Design: Study H6P-MC-HDAX was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of OFC versus placebo in patients (ages 10 to 17 years) meeting the diagnostic criteria for a current major depressive episode of Bipolar I disorder. The study design is represented in Figure 1.	

Figure 1: Study design for H6P-MC-HDAX



-Source: Figure HDAX.1 (Protocol H6P-MC-HDAX(a), pg. 22)

Primary efficacy endpoint: change from baseline to Week 8 (Visit 11) in Children's Depression Rating Scale-Revised (CDRS-R) total score.

Major safety measurements: vital signs, ECG, laboratory analytes, EPS, C-SSRS; worsening of mania based on YMRS and CGI-BP Severity of Mania; and comorbidity of ADHD measured with Attention- Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version.

Treatments:
Following a 2- to 45-day screening period (Study Period I, SP1), qualified patients were randomized (2:1 to OFC or placebo arms) and entered an 8-week double-blind treatment period (Study Period II, SPII) in which they received once-daily oral dosing with OFC or Placebo. Patients were dosed with an initial forced titration followed by flexible dosing.

All patients assigned to the OFC therapy arm were given an initial dose of 3/25 mg at Visit 2, which was increased to 6/25 mg at Visit 3, 6/50 mg at Visit 4, and 12/50 mg at Visit 5. After Visit 5, if there were no tolerability or safety issues, the patients were dosed at the maximum tolerable dose, not to exceed 12/50 mg, and not less than 6/25 mg. The allowed dosages were 6/25, 6/50, 12/25, and 12/50 mg. Patients were evaluated for safety and efficacy at each visit. The dose was to be taken once daily preferably in the evening.

Table 1: Study Schedule for Protocol H6P-MC-HDAX

Visit	1	2	3	4	5	6	7	8	9	10	11 or final visit
Weeks until next visit	2-45 d	3 d	4 d	1	1	1	1	1	1	1	
Visit window		±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	
Randomization		X									
Informed consent/assent[c]	X[c]										
Demographics, history and physical exam	X										
Historial illnesses and previous medications	X										
Psychiatric exam	X										
Height	X										X
Body weight and temperature	X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure and pulse rate) supine and standing	X	X	X	X	X	X	X	X	X	X	X
Electrocardiograms (triplicate)	X					X					X
Pre-existing conditions/adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X	X	X	X	X	X	X	X	X	
Study drug compliance			X	X	X	X	X	X	X	X	X
K-SADS-PL	X	X[a]									
ADHDRS-IV-PI		X									X
Healthy Lifestyle Concepts Information for Parent/Patient	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests											
HbA1c, hepatitis screen, urine drug screenb, and TSH	X										
Pregnancy testb	X	X									

Visit	1	2	3	4	5	6	7	8	9	10	11 or final visit
Clinical chemistry, lipids, hematology, and prolactin (fasting)	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X										
Pharmacokinetic Sampling						X				X	X
Cotinine assay						X					
Safety Scales:											
AIMS (Abnormal Involuntary Movement Scale)	X	X					X				X
Simpson-Angus	X	X					X				X
Barnes Akathisia	X	X					X				X
Columbia Suicide Severity Rating Scale (C-SSRS), including the Self-Harm Supplement Form and the Supplemental Self-Harm Follow-up Form if necessary	X	X	X	X	X	X	X	X	X	X	X
Efficacy Scales:											
YMRS (Young Mania Rating Scale)	X	X	X	X	X	X	X	X	X	X	X
CDRS-R (Children's Depression Rating Scale-Revised)	X	X	X	X	X	X	X	X	X	X	X
BDRS (Bipolar Depression Rating Scale)	X	X	X	X	X	X	X	X	X	X	X
CGI-BP	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Scales:											
KINDL® (parent-rated)		X									X

Visit	1	2	3	4	5	6	7	8	9	10	11 or final visit
Kiddo-KINDL® (patient-rated; for patients ages 12-16); Kid-KINDL® (patient-rated; for patients ages 8-11)		X									X
Healthcare Services Information Module	X	X	X	X	X	X	X	X	X	X	X

PK Sampling Times:

Heparinized blood samples for measurement of plasma olanzapine, fluoxetine and norfluoxetine concentrations were collected at Visits 6, 10 and 11 (or final).

Analytical Method:

Analyte	Olanzapine	Fluoxetine	Norfluoxetine
Method	HPLC	LC/MS/MS	LC/MS/MS
Matrix	plasma	plasma	plasma
LLOQ (ng/mL)	0.025-100	1.00-500	1.00-500
Performance	acceptable	acceptable	acceptable

Study Population: Overall, 291 patients were enrolled and 190 patients completed the study at 41 sites in the United States, Mexico, and Russia.

Table 2: Baseline Demographic Characteristics of the Patients in the mITT Population.

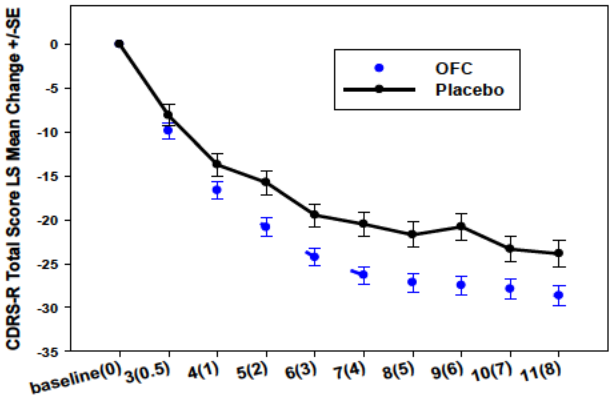
	SymByax (OFC) n=170	Placebo n=85
Age [Mean ±SD] Min-Max	14.6±2.3 10.04-17.90	15.0±2.13 10.03-17.98
Male/Female	84/86	46/39
Race (Caucasian/Black/Asian/other)	119/23/0/28	61/11/0/13
Weight (kg) [Mean ±SD] Min-Max	62.7±19.0 24-119	65.3±19.3 31.3-133.6

- *Source: Table HDAX.11.2 (Clinical Study Report, pg.80-81)*

Results

1. Efficacy

Figure 1: CDRS-R Total Score Mean Change from Baseline by Treatment Group in Pediatric Patients (10-17 Years).



-Source: Table HDAX.11.16.(Clinical Study Report, pg.109-110)

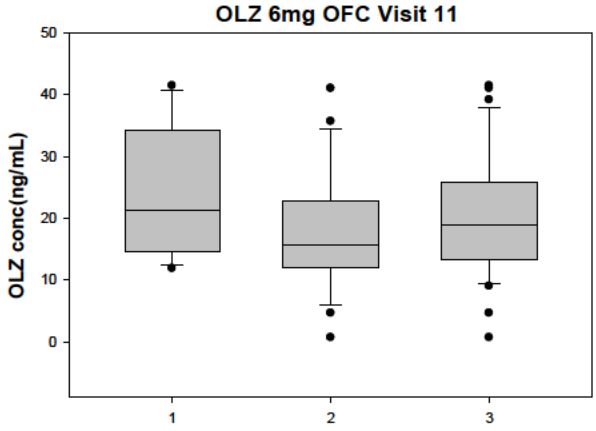
2. Plasma concentrations

In pediatric patients, observed plasma concentrations for olanzapine and fluoxetine increased in an approximate dose-proportional manner with increasing doses of OFC. However, norfluoxtine concentration increase was less than dose proportional after 25mg and 50mg fluoxetine OFC treatment.

A. Olanzapine

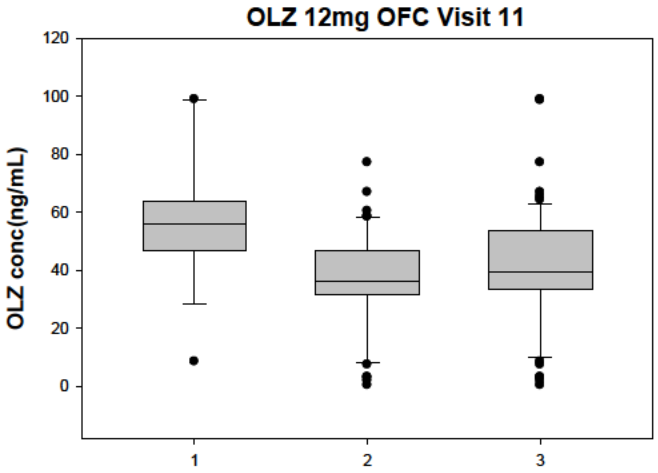
Pediatric patients with lower body weights (<50 kg) had mean olanzapine concentrations that were approximately 18.5% and 70.5%, respectively, higher than those pediatric patients with higher body weights (≥50 kg) in the 6mg, and 12mg olanzapine OFC groups (Figure 2, Figure 3).

Figure 2: Observed Olanzapine Plasma Concentrations at Steady-State in Pediatric Patients Following Oral Administration of 6mg Olanzapine OFC.



Group 1: base line bw<50kg, n=12
Group 2: base line bw>=50kg, n=22
Group 3: all subjects, n=34

Figure 3: Observed Olanzapine Plasma Concentrations at Steady-State in Pediatric Patients Following Oral Administration of 12mg Olanzapine OFC.

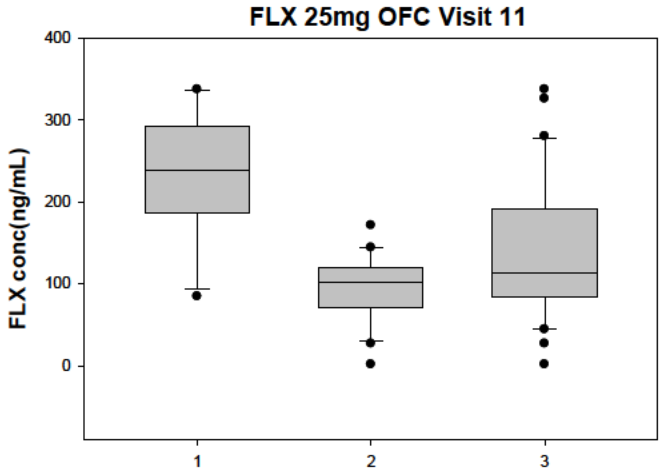


Group 1: base line bw<50kg, n=16
Group 2: base line bw>=50kg, n=52
Group 3: all subjects, n=68

B. Fluoxetine

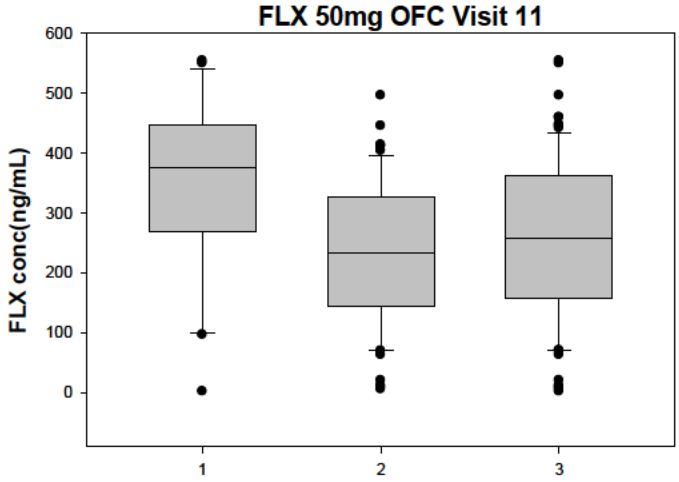
For fluoxetine, mean plasma concentrations in patients with lower body weights (<50kg) were 167% and 49.3% greater, respectively, compared with those observed in heavier patients (≥50 kg), for the 25-mg and 50-mg fluoxetine OFC treatment groups (Figure 4, Figure 5).

Figure 4: Observed Fluoxetine Plasma Concentrations at Steady-State in Pediatric Patients Following Oral Administration of 25mg Fluoxetine OFC.



Group 1: base line bw<50kg, n=10
Group 2: base line bw>=50kg, n=21
Group 3: all subjects, n=31

Figure 5: Observed Fluoxetine Plasma Concentrations at Steady-State in Pediatric Patients following Oral Administration of 50mg Fluoxetine OFC.

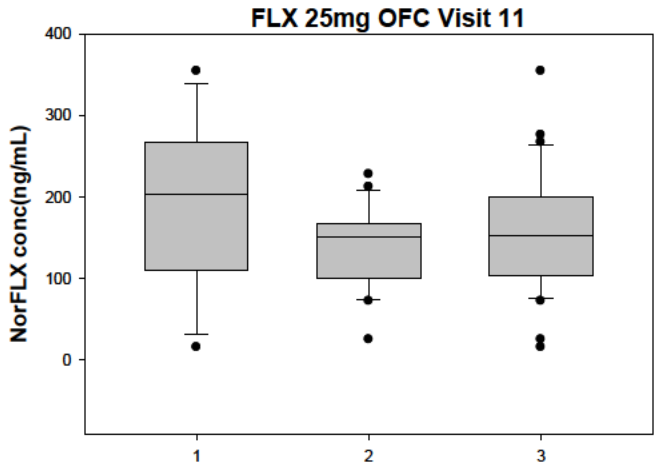


Group 1: base line bw<50kg, n=20
Group 2: base line bw>=50kg, n=62
Group 3: all subjects, n=82

C. Norfluoxetine

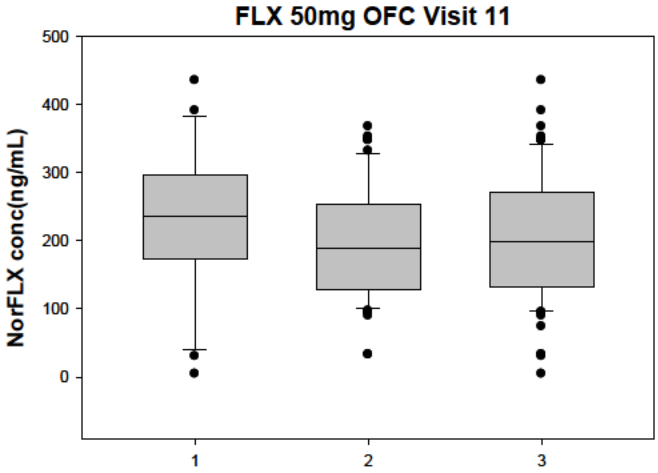
For norfluoxetine, mean plasma concentrations in patients with lower body weight (<50kg) were 78.8% and 30.1% greater, respectively, compared with those observed in heavier patients (≥50 kg), for the 25-mg and 50-mg fluoxetine OFC treatment groups (Figure 6, Figure 7).

Figure 6: Observed Norfluoxetine Plasma Concentrations at Steady-State in Pediatric Patients Following Oral Administration of 25mg Fluoxetine OFC.



Group 1: base line bw<50kg, n=11
Group 2: base line bw>=50kg, n=21
Group 3: all subjects, n=32

Figure 7: Observed Norfluoxetine Plasma Concentrations at Steady-State in Pediatric Patients Following Oral Administration of 50mg Fluoxetine OFC.



Group 1: base line bw<50kg, n=21
Group 2: base line bw>=50kg, n=62
Group 3: all subjects, n=83

Safety

- Was there any death or serious adverse events? ☐ Yes ☒ No ☐ NA

Conclusion

- Steady state plasma concentrations of olanzapine, fluoxetine, and norfluoxetine in pediatric patients aged 10-17 years old, were higher in patients with lower body weight

(<50kg) than patients with higher body weight. Concentrations in pediatric patients with high body weight (≥50kg) were similar to those previously observed in adult patients.

- QT signals were similar between low body weight (<50kg) and high body weight (≥50kg) pediatric patients. No dose adjustment is needed for patients with low body weight.

Comments

Sparse PK samples were collected at Visit 6 (week 3), Visit10 (week 7) and Visit 11 (Week 8) from patients in this trial. Due to the long half-lives of fluoxetine (about 3-4 days), norfluoxetine (about 9 days), and olanzapine (about 30 hours), samples collected at Visit 11(Week 8) were used to estimate steady state concentrations of the three moieties. According to the protocol, OFC doses were preferably taken in the evening, and clinical samples and measurements were collected during the day time. We directly compared the exposure differences by different body weight groups assuming PK samples were collected in a similar window from the previous dosing time. Even the PK samples were not collected in the same window, given the long half lives of fluoxetine (about 3-4 days) and norfluoxetine (about 9 days) and once daily dosing, the PK results are unlikely to be affected, especially for fluoxetine or norfluoxetine.

Observed concentration data from this HDAX study indicate that lighter pediatric patients (<50 kg) have a higher exposure to olanzapine, fluoxetine and norfluoxetine than heavier pediatric patients (≥50kg) after SymByax administration. The final dose distribution in each body weight group (<50 kg and ≥ 50kg) indicated similar percentage of patients received same doses of olanzapine or fluoxetine.

Although a significant relationship was observed between norfluoxetine concentration and QT prolongation, due to the weak (flat) relationship between norfluoxetine concentration and body weight (i.e., small increase in concentration with significant decrease in body weight), the relationship between QT prolongation and body weight was mitigated. For fluoxetine and olanzapine, though a stronger relationship was observed between body weight and their concentrations, a flat and non-significant relationship was observed for concentration and QT. A significant increase in concentration cannot be translated into significant increase in QT prolongation potential.

Combining all the analyses together and given there is already adequate QT warning language in the label, there is no strong evidence to suggest body weight based dosing for SymByax.

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/s/

HUIXIA ZHANG
07/01/2013

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07/01/2013