

CLINICAL REVIEW

Application Type	NDA PREA Supplement
Application Number(s)	21520
Priority or Standard	Standard
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Division / Office	DPP/OND1
Reviewer Name(s)	Lucas Kempf, MD
Review Completion Date	
Established Name	Symbyax
(Proposed) Trade Name	Symbyax
Therapeutic Class	Antidepressant/antipsychotic
Applicant	Eli Lilly and Co.
Formulation(s)	Oral Capsule; 3/25 (initiation dose only), 6/25, 12/25 mg
Dosing Regimen	3/25 mg forced titration to 12/50 mg in one week then flexible dosing per investigators discretion (min: 6/25 mg)
Indication(s)	 (b) (4) associated with Bipolar I disorder

Intended Population(s) 10-17 years old

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Symbyax (OFC) is a compound medication for the acute treatment of (b) (4) depression episodes associated with bipolar depression in patient 10-17 years of age. The component medications olanzapine and fluoxetine have been previously studied in children and the combination has no evidence of significant increased safety risk.

The study submitted was adequately conducted and the data are reliable and support the application. The statistical 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 major depressive episodes associated with bipolar I disorder in patients 10 to 17 years of age. From a clinical and statistical perspective, there is no evidence against fulfilling the postmarketing commitment under the PREA.

1.2 Risk Benefit Assessment

Acute major depressive episodes in bipolar disorder have significant risk of suicide and impacts social, occupational and emotional development. Use of this medication carries risks for weight gain, metabolic syndrome, QTc prolongation, hyperprolactinemia, infarcts in the elderly, platelet inhibition, increased suicidal thoughts, mania/hypomania, NMS, EPS, and TD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS is recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are required at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Olanzapine and fluoxetine combination (OFC) is approved in the US as a capsule formulation (Symbyax®) prescribed for use in adult patients to treat depressive episodes associated with bipolar I disorder or treatment-resistant depression.

Olanzapine belongs to the thienobenzodiazepine class and is an antipsychotic and antimanic agent. Fluoxetine is a selective serotonin reuptake inhibitor and is an antidepressant.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently available drugs with indications for bipolar depression in children. Lithium Carbonate, Lamictal and Valproic Acid are commonly used in bipolar patients for mood stabilization. Symbyax and Seroquel have indications for acute bipolar depression. Antidepressants used alone frequently will cause switching to a mania or mixed states in bipolar patients.

2.3 Availability of Proposed Active Ingredient in the United States

Both olanzapine and fluoxetine are available in the USA and additionally the combination therapy is available since it is approved for adults.

2.4 Important Safety Issues with Consideration to Related Drugs

Antipsychotics have been associated with NMS, EPS, TD, metabolic syndrome, weight gain, QTc prolongation, hyperprolactinemia hypothyroidism, orthostatic hypotension, leukopenia, increases in blood pressure in children and adolescents, and infarcts. SSRIs have been associated with QTc prolongation, platelet inhibition, and increased suicidal thoughts.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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.

Additionally, 1 meeting was held on 8/28/2008 to waive the requirements to study patients from the age of 0-9 years due to impression of diagnosis in this age range. A second meeting was held on 7/30/2012 Lilly quality site assessments and to gain an agreement on a statistical plan to exclude sites with internal auditing GCP violations. Agreement was reached that Lilly may submit the mITT sample but the FDA will make the final determination of data quality violations based on our own auditing of sites.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Two sites for study HDAX were identified from internal audits to suffer from GCP quality issues as reported in pre-NDA meeting memo by Eli Lilly and Company digitally copied below:

On February 2 and 3, 2010, a Lilly Quality Site assessment was conducted at Site 215, Dr. Gurmeet Multani (Principal Investigator), Shanti Clinical Trials, Colton, California. This assessment revealed, per Lilly, “serious GCP noncompliance issues”. Enrollment was halted due to the assessment findings and Lilly issued a communication on February 17, 2010 notifying the Division of termination of Dr. Multani’s participation in Study HDAX due to these GCP issues. Lilly states that participation was ended for: inadequate documentation of PI oversight and assurance of patient safety; lack of documentation for PI oversight of study procedures and site personnel and; inadequate source documentation to support data as well as elements of subject inclusion criteria. On June 11, 2010, Lilly notified this site that all activities to resolve and rectify data will cease due to the “significant difficulties” experienced by monitors at the site.

On June 30, 2010, the IRB for Site 210 (Dr. Shishuka Malhotra, Neuro-Behavioral Clinical Research Incorporated, Canton, Ohio) issued a letter regarding Serious and Continuing Non- Compliance; this letter was also sent to Lilly and the Division. The letter addressed the reporting for Study HDAX where the site collected pharmacogenetic and sample banking without parental consent. Based on this IRB communication, Lilly issued a letter to Dr. Malhotra notifying the site that it was on “restricted enrollment” which limited the number of subjects the site was permitted to enroll and stipulated that monitoring activities occur sooner upon patient randomization. An audit conducted on November 29 and 30, 2010 revealed “major findings” related to multiple source document inconsistencies for the 2 patients reviewed. After the audit, the CRO formally instituted a site-specific monitoring plan for prompt monitoring after each subject was randomized into the trial. On May 8-10, 2012, based on information from the CRO, a site audit was conducted by Lilly due to “suspicion of misconduct across multiple trials”. Findings of this audit included: scientific misconduct in the form of falsified records, including documentation of the PI’s evaluation of key safety and efficacy study activities during times she was out of office and when the patient was not present and significant GCP noncompliance and source data discrepancies.

Four sites were inspected by the FDA. One with serious findings and three with varying degrees of apparently minor violations (EIRs still not received, preliminary results also scanty and incomplete).

Per Office of Scientific Investigations (OSI) communication electronically copied below;

1. Multani site is problematic for serious AE underreporting. The sponsor already knew this site to be problematic, noted as such in the NDA, and excluded the data from this site. The inspectional findings are consistent with the sponsor's assessment.
2. Malhotra site is not problematic for serious observations. This site was also reported by the sponsor to be problematic (similarly with the Multani site, site data also excluded from NDA). Our inspectional findings are NOT consistent with the sponsor assessment. This site looks OK with many but "acceptable" violations.
- 3 and 4. Tomasovic and Flaherty sites look OK with minor violations only.

3.2 Compliance with Good Clinical Practices

Only the Multani site investigation revealed significant GCP practices and the results are still significant when data from this site are excluded.

The sponsor submitted a statement of compliance indicating that all clinical trials were conducted in accordance with the Helsinki declaration and all applicable good clinical practices except 2 clinical sites that were discovered to deviate from good clinical practices after an internal audit. Further verification of these sites was done in an investigation by Office of Scientific Investigations (OSI) and 2 additional sites were investigated. The results of the investigations are detailed above in section 3.1.

Additionally, the sponsor submitted a memo signed September 9th, 2012 certifying that Eli Lilly and Company did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with the application.

3.3 Financial Disclosures

A 3554 form was attached with only 2 investigators with disclosable information.

-  (b) (6)

A 3455 supplemental form states he received \$75,000 for Honorarium. (b) (6) enrolled (b) (6) subjects of which one was randomized. Sponsor states that they performed the analysis with and without this patient and it was unchanged.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new CMC data in this submission.

4.2 Clinical Microbiology

There is no new microbiology data

4.3 Preclinical Pharmacology/Toxicology

There is no new preclinical pharmacology/toxicology data.

4.4 Clinical Pharmacology

Please see OCP full review for findings.

4.4.1 Mechanism of Action

Although the exact mechanism of SYMBYAX is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. In animal studies, ZYPREXA and fluoxetine in combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

4.4.2 Pharmacodynamics

The pharmacodynamics of Olanzapine and fluoxetine combination was evaluated at the time of the original NDA by the review team then (including DPP and OCP) and is described in the currently approved labeling.

Olanzapine binds with high affinity to the following receptors: serotonin 5HT_{2A/2C}, 5HT₆ (K_i=4, 11, and 5 nM, respectively), dopamine D₁₋₄ (K_i=11 to 31 nM),

histamine H1 ($K_i=7$ nM), and adrenergic α_1 receptors ($K_i=19$ nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT3 ($K_i=57$ nM) and muscarinic M1-5 ($K_i=73, 96, 132, 32,$ and 48 nM, respectively). Olanzapine binds weakly to GABAA, BZD, and β -adrenergic receptors ($K_i>10$ μ M). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and 5HT2 may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M1-5 receptors may explain its anticholinergic-like effects. The antagonism of histamine H1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1 -adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1 -adrenergic, and histamine H1 receptors.

4.4.3 Pharmacokinetics

The summary of findings related to olanzapine, fluoxetine, and norfluoxetine steady-state concentrations in pediatric patients included the following:

- As olanzapine and fluoxetine doses increased from 6-mg to 12-mg and from 25-mg to 50-mg, olanzapine, fluoxetine, and norfluoxetine plasma concentration appeared to increase in a linear manner.

Electronically copied from Table HDAX.11.32 for olanzapine concentrations

Table 1. OFC Pharmacokinetics

OLZ (mg)/FLX (mg) OFC Treatment	3/25 ^b (N = 1) (n = 1)	6/25 (N = 35) (n = 65)	6/50 (N = 54) (n = 92)	12/25 (N = 27) (n = 47)	12/50 (N = 78) (n = 152)
Concentration (ng/mL)	5.48	19.1 ± 9.99 (0.26 – 48.7)	20.5 ± 11.3 (0.32 – 66.3)	47.5 ± 24.6 (1.82 – 113)	37.7 ± 17.9 (0.27 – 83.0)

Electronically copied from Table HDAX 11.33 for Fluoxetine concentrations

OLZ (mg)/FLX (mg) OFC Treatment	3/25 ^b (N = 1) (n = 1)	6/25 (N = 34) (n = 64)	6/50 (N = 53) (n = 93)	12/25 (N = 28) (n = 49)	12/50 (N = 77) (n = 149)
Concentration (ng/mL)	17.1	117 ± 58.5 (10.2 – 345)	237 ± 130 (13.8 – 549)	169 ± 102 (1.33 – 364)	238 ± 119 (1.75 – 586)

Electronically copied from Table HDAX 11.33 for norfluoxetine concentrations

OLZ (mg)/FLX (mg) OFC Treatment	3/25 ^b (N = 1) (n = 1)	6/25 (N = 35) (n = 65)	6/50 (N = 54) (n = 94)	12/25 (N = 28) (n = 50)	12/50 (N = 78) (n = 152)
Concentration (ng/mL)	18.6	140 ± 59.3 (17.0 – 333)	193 ± 79.8 (16.5 – 436)	150 ± 79.1 (15.9 – 381)	177 ± 84.3 (1.24 – 395)

- Consistent with the known PK of both compounds, olanzapine and fluoxetine concentrations were higher in patients with lower body weights.
- Olanzapine and fluoxetine/norfluoxetine steady-state concentrations in pediatric patients were similar when treated with OFC or the respective monotherapies.
- When treated with OFC, steady-state olanzapine plasma concentrations in pediatric patients were slightly higher than the concentrations observed in adults; however, fluoxetine and norfluoxetine concentrations were similar for pediatric and adult patients.
- These results are consistent with comparisons between pediatric and adult populations previously reported for olanzapine and fluoxetine monotherapies.

Previously known PK data is electronically copied from current label below.

Fluoxetine (administered as a 60 mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5 mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

SYMBYAX — Following a single oral 12 mg/50 mg dose of SYMBYAX, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of SYMBYAX has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of SYMBYAX.

Olanzapine — Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine — Following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Food does not appear to

affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution

SYMBYAX — The in vitro binding to human plasma proteins of olanzapine and fluoxetine in combination is similar to the binding of the individual components.

Olanzapine — Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α 1-acid glycoprotein.

Fluoxetine — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α 1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. clinical trial

Type of trial	Protocol No. (country)	Trial Design and Objective	Treatment Groups	Number of Subjects/Healthy Subjects of Diagnosis of Subjects	Demographics by treatment Group (No. of Subjects)	Duration of Treatment	Trial Status; Type of Report
E, S	H6P-MC-HDAX(a) USA, 29 sites Mexico, 4 sites Russia, 8 sites	A Phase 4 randomized, multicenter, double-blind, placebo-controlled, parallel group with one drug and one placebo arm.	Placebo Route: oral capsule <u>OFC</u> Route: Oral capsule	Placebo Randomized: 97 Treated: 85 Completed: 60 OFC Randomized: 194 Treated: 191 Completed: 116	Placebo Gender: 46M,39F Mean age (min/max):15.3 (10.03/17.98) Race: W/B/A/O 61/11/0/12 OFC Gender: 84M,86F Mean age (min/max):14.59 (10.04/17.90) Race: W/B/A/O 119/23/0/25	8 weeks	Start March 17, 2009; completed Feb. 2, 2012

5.2 Review Strategy

The single HDAX phase 4 study was reviewed for safety and efficacy for the treatment of major depression in bipolar pediatric patients. The submitted synopsis, HDAX body,

addendums and labeling files were reviewed. Additionally, patient narratives were reviewed for serious SAEs, discontinuations, and deviations were examined for additional information. The applicant was requested to send additional information about PK, weight and side effects interactions.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Acute Bipolar type-I depression in children ages 10-17 years old.

6.1.1 Methods

Primary and secondary endpoints appear satisfactory for determining safety and efficacy. Primary objective was to assess the superiority of Olanzapine and fluoxetine HCl combined therapy compared with placebo in patients from the age 10-17 years old with a current bipolar I-depression episode assessed by baseline-to-endpoint mean change on the Children's Depression Rating Scale-revised (CDRS-R) total score using mixed model with repeat measured (MMRM) analysis.

Secondary objectives: Study reported multiple secondary objectives but none were identified as **key secondary** endpoints. They fall in 3 categories. The first is correlated measures of clinical improvement and time to response/ remission, second were safety measures of metabolic changes, QTc measures, AEs, vital signs, suicidal thoughts, EPS, and mania induction, third were effects on comorbid ADHD. They were as follows.

1. Study-defined rates of response and time to response as determined by $\geq 50\%$ reduction from baseline on CDRS-R total score AND a score of ≤ 2 on Young Mania Rating Scale (YMRS) item 1 (Elevated Mood).
2. Study-defined rates of remission and time to remission as determined by a CDRS-R total score of 28 or less, YMRS total score of 8 or less, AND Clinical Global Impression Scale-Bipolar Version (CGI-BP) total score of ≤ 3 .

3. Study-defined level of improvement (no/low, mild, moderate, or major) of bipolar disorder as determined by percentage reduction from baseline on CDRS-R total score and YMRS item 1 (Elevated Mood) score.
 4. Mean change from baseline to the end of 8 weeks of therapy using MMRM analyses in the following measures: YMRS total score and CGI-BP Severity of Depression, Severity of Mania, and Severity Overall.
 5. The last-observation-carried-forward (LOCF) change from baseline to endpoint on the CDRS-R total score and individual items.
 6. Assess the health-related quality of life using the Quality of Life Questionnaire for Children and Adolescents: parent and patient forms (Kiddo-KINDL® for ages 12 to 16; Kid-KINDL® for ages 8 to 11), and assess hospitalization rates using the Lilly Healthcare Services Information Module.
- Assess the safety and tolerability of OFC compared with placebo during 8 weeks of double-blind treatment by:
 1. Comparing the incidence of serious and non-serious AEs, changes in vital signs, electrocardiogram (ECG), and changes in laboratory analytes.
 2. Comparing the incidence of extrapyramidal symptoms (EPS) using Barnes Akathisia Rating Scale (Barnes 1989), Abnormal Involuntary Movements Scale (AIMS), Simpson-Angus Scale (Simpson and Angus 1970).
 3. Comparing the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the treatment period using Columbia-Suicide Severity Rating Scale (C-SSRS).
 4. Evaluating the difference in the incidence of worsening of manic symptoms as measured by YMRS total score (≥ 20) and CGI-BP Severity of Mania score (≥ 5).

10. Assess plasma concentration data for olanzapine and fluoxetine/norfluoxetine.

- Assess the treatment effects associated with the comorbidity of attention-deficit/hyperactivity disorder (ADHD) as determined by Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-PI)

Overall Study Design:

The study is for oral once-daily doses of olanzapine and fluoxetine HCl in a randomized, multicenter, double-blind, placebo-controlled, parallel group with one drug and one placebo arm.

- A 2- to 30-day screening period is followed by an 8-week double blind placebo controlled treatment phase.
- Dosing begins at 3/25 mg, with forced titration to achieve 12/50 mg once daily dosing within 1 weeks of randomization.
- Flexible dosing is incorporated such that patients must be maintained on a minimum daily dose of 6/25 mg.
- Randomization will be 2:1 drug: placebo, with n = 340 target number. Actual analyzed (OFC n = 170; placebo n = 85).

Subject Selection:

Enrolled patients met the diagnostic criteria for a current major depressive episode of bipolar I disorder according to DSM-IV-TR and had their diagnosis confirmed by the K-SADS-PL.

The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to the DSM-IV-TR criteria

Inclusion Criteria

- 10 to 17 years of age (who had not met their 18th birthday prior to Visit 1)
- DSM-IV-TR diagnostic criteria for bipolar I disorder, current episode depressed, as confirmed by the KSADS-PL at Visits 1 and 2, with a history of at least one manic episode.
- All patients had to have a CDRS-R score of ≥ 40 at both visits 1 and 2, and a YMRS total score of ≤ 15 with a YMRS item 1 (Elevated Mood) score of ≤ 2 at Visits 1 and 2.
- Patients had to weigh at least 20 kg at visit 1 (due to blood collection volume)

- Be able to swallow pills whole (without crushing or dissolving).
- Females of childbearing potential could not be pregnant and had to abstain from sexual activity or be using a medically accepted method of contraception for the duration of study participation as well as for an additional 4 to 5 weeks following study discontinuation.
- All patients and their legal guardians had to have a level of understanding sufficient to perform all tests and examinations required by the protocol, had

Exclusion Criteria

- Schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, delirium of any type, amnestic disorder, any substance-induced disorder, or any psychotic disorder due to a general medical condition.
- History of mental retardation or a current diagnosis of autism or pervasive developmental disorder
- DSM-IV-TR diagnosis of substance dependence other than nicotine or caffeine within the 30 days prior to Visit 2.
- Actively suicidal (for example, no suicide attempts within the past month or having current suicidal intent including plan).
- history of allergic reaction or hypersensitivity to OFC or any of its components, had previously been withdrawn from OFC or any of its components due to clinically significant adverse effects, or were considered to be treatment-resistant to OFC or any of its components.
- Could not have been treated with an investigational or unapproved medication within 30 days prior to Visit 1, with electroconvulsive therapy within 3 months prior to Visit 2, with clozapine within 3 months prior to Visit 1, with a monoamine oxidase inhibitor within 14 days prior to Visit 2, with remoxipride within 6 months prior to Visit 2, with a depot antipsychotic within 1 dosing interval prior to Visit 2 or within 2 dosing intervals for risperidone long-acting injection.
- All other medications with primary central nervous system activity had to be discontinued at least 25 hours prior to Visit 2 unless otherwise allowed per protocol.
- Patients were also excluded if they had any of the following medical conditions: unstable thyroid disorder, uncorrected narrow-angle glaucoma, 1 or more seizures without a clear and resolved etiology, any acute, serious, or unstable medical conditions, current leukopenia or

history of leukopenia without a clear and resolved etiology, known history of agranulocytosis (absolute neutrophil count $<500 \text{ mm}^3$ or $<0.5 \text{ GI/L}$), any serious unstable illnesses such that death is anticipated within 1 year or intensive care unit hospitalization is anticipated within 6 months, any laboratory results at visit 1 that indicate clinically significant abnormalities that would preclude safe participation in the study in the opinion of the investigator (e.g., prolactin $>200 \text{ ng/mL}$ at Visit 1, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] values ≥ 2 times the upper limit of normal [ULN], or total bilirubin values ≥ 1.5 times the ULN), or QTc Bazett's >450 milliseconds for males or >460 milliseconds for females.

- Patients could not participate if they were immediate family of investigator site personnel directly affiliated with the study.

Criteria for discontinuing subjects:

The criterion for discontinuation appears to be standard and safe. There were appropriate attempts to follow-up with patient if discontinuation was due to AEs. Criteria are listed below.

- Found not to fit diagnosis
- Couldn't tolerate minimal dose of medicine on or after visit 3
- Investigator decided
- Patient, family or attending request
- Needed another treatment with therapeutic drug
- Investigator or Lilly stopped the patients participation
- Withdrew consent
- Pregnancy
- Prolactin level $> 200 \text{ ng/ml}$
- QTc Bazett's $>500 \text{ msec}$

Selection of doses:

Dose selection was appropriate due to unknowns about PK data, individual tolerability and perceived efficacy based on previous mean modal dose efficacy study in adults and in agreement in pre-NDA meetings but maybe problematic for labeling since patients were forced titrated to 6/50 mg but PK exposure was higher and side effects were higher in children.

- OFC (list olanzapine/fluoxetine in mgs) forced titration period: patients took doses of 3/25 mg from visit 2-visit 3: 6/25 mg from visit 3-visit 4, 6/50 mg from visit 4-visit 5, and 12/50 mg at visit 5.
- Flexible dosing adjusting doses for tolerability within approved doses at investigator's discretion followed through the rest of the study period.

Details of Study drug treatments:

Drug and placebo were appropriately blinded and packaged in blister packs that were uniquely identifiers per report. Two pills were taken nightly per protocol. Table electronically copied from study report.

Table 3. Treatment Regimens

Treatment Group Daily Dose	Treatment Group Daily Dose Description ^b
3/25 mg ^a OFC	One 3/25 mg OFC capsule and one placebo capsule
6/25 mg OFC	One 6/25 mg OFC capsule and one placebo capsule
6/50 mg OFC	Two 3/25 capsules
12/25 mg OFC	One 12/25 mg OFC capsule and one placebo capsule
12/50 mg OFC	Two 6/25 capsules
Placebo ^b	Two placebo capsules

Prior and Concomitant Medications (permitted and prohibited):

Prior and concomitant medications permitted and prohibited was rational and reflected current practices. No mood stabilizers or antidepressants were allowed. ADHD medications, benzodiazepines and anticholinergic medications were allowed. These medications would be the most common medications coadministered in practice considering the OFC medication side effects and most common comorbid disorders.

Assessment of subjects' compliance with treatment

Assessment of compliance appears to be standard.

- It was assessed at each visit by direct questioning and counting of returned capsules.
- Patients who were significantly noncompliant were discontinued from the study; however, these patients' data were included in the study database.

- A patient was considered significantly noncompliant if he or she missed more than 5 consecutive days of study medication (full doses), or more than 10 cumulative days of study medication (full doses) during the study.
- A patient was considered significantly noncompliant if he or she intentionally or repeatedly took more than the prescribed amount of medication.

Primary efficacy measure and Key secondary and other secondary measures

Primary efficacy endpoint

The primary efficacy measure was the CDRS-R designed for assessing presence and severity of depression in children 6 to 12 years of age, and it has also been used for adolescents.

Secondary endpoint

- Adolescent-Structured Young Mania Rating Scale
- Clinical Global Impression Scale-Bipolar Version Severity of Illness
- Bipolar Depression Rating Scale (BDRS)

Health Outcome Measures

- parent-rated KINDL® and the patient-rated Kiddo-KINDL (for patients aged 12-16) and Kid-KINDL (for patients aged 8-11), and the rate and duration of any treatment-emergent hospitalization during the study.

Planned safety assessments

- AEs elicited every visit in regular terms and coded in MedDRA
- Concomitant Therapies were recorded
- Standard labs were taken at regular intervals along with thyroid function tests and pregnancy testing
- Vital signs with orthostatic measurements and weight
- ECK and visit 1,6,11 12 leads and in triplicate
- Extrapyrimal symptoms with Simpson-Angus scale, AIMS, and Barnes Akathisia scale.
- Suicidality with C-SSRS
- Comorbid ADHD was assessed with ADHDRS-IV-PI

Description of planned statistical analysis

Efficacy, safety, and health outcomes analyses were done using a mITT analyses. The mITT population consisted of all randomized patients who had taken at least 1 confirmed dose of study drug. Data from the 2 sites with data integrity problems were excluded from the analysis.

For the primary efficacy measure, MMRM analysis was conducted to evaluate mean change from baseline to Week 8 on the CDRS-R total score. Kaplan-Meier methodology and the log-rank test were used to assess time to events. Changes from baseline to endpoint for continuous data were analyzed using a last-observation-carried-forward (LOCF) method, with treatment comparisons based on analysis of covariance (ANCOVA) models; the models generally included terms for treatment and baseline. Fisher's exact test was used for analysis of categorical data. All tests of hypotheses were 2-sided with a type I error of 0.05. There were no adjustments for multiple testing as only the primary efficacy analysis was confirmatory while all other tests were only suggestive.

6.1.2 Demographics

Patients were approximately evenly divided between males (51%) and females (49%) and were predominantly white (71%), with a mean age of 14.7 years.

There were no statistically significant differences between groups with respect to baseline demographic and illness characteristics. Patients were moderately depressed with a mean baseline CDRS-R total score of 54.3 (standard deviation [SD] 9.4) and CGI-BP of 4.4 (SD 0.7). Also patients had a mean baseline YMRS total score of 6.1 (SD 3.8) indicating an exclusion of mania symptoms in the current episode.

6.1.3 Subject Disposition

A total of 176 of 255 (69%) patients completed the study (68% OFC; 71% placebo; $p=.77$).

There were no statistically significant differences between treatment groups for reasons for discontinuation, although a larger number of OFC-treated patients discontinued due to an AE than did placebo patients (14% vs. 6%, $p=.06$). The most

common AEs leading to discontinuation in the OFC group were weight increased (n = 5), suicidal ideation (n = 3), somnolence (n = 2), and bipolar disorder (n = 2).

6.1.4 Analysis of Primary Endpoint

The study met the primary endpoint. At Week 8, the OFC group had a least squares mean decrease of 28.4 points (standard error [SE] 1.1) on the CDRS-R, while the placebo group had a mean decrease of 23.4 points (SE 1.5), indicating significant improvement in both groups, but superior improvement in the OFC group (p=.003), with an effect size of .46. Sensitivity analysis using the full intent-to-treat population also indicated superiority of OFC versus placebo (p=.003). The OFC group showed statistically significantly greater improvement relative, i.e. reduction in depression scores to placebo at Week 1 (p=.02) and at all subsequent visits (all p-values <.01).

6.1.5 Analysis of Secondary Endpoints

The HDAX reported multiple secondary objectives but none were identified as **key secondary** endpoints. They fall in 3 categories; first is correlated measures of clinical improvement and time to response/ remission, second were safety measures of metabolic changes, QTc measures, AEs, vital signs, suicidal thoughts, EPS, and mania induction (which will be reviewed below in Safety), third were effects on comorbid ADHD.

Rate of response to treatment was statistically significantly higher in the OFC group (78%) than in the placebo group (59%; p=.003), with the OFC group demonstrating a significantly shorter time to response than placebo (p=.001).

Rate of remission was statistically significantly greater in the OFC group (59%) than in placebo (43%; p=.035), with the OFC group experiencing a significantly shorter time to remission than placebo (p=.028).

Categorical analysis of levels of improvement on the CDRS-R indicated that patients in the OFC group were approximately twice as likely to achieve greater improvement than patients in the placebo group (odds ratio 2.04; p=.007).

The rate of treatment-emergent mania was not significant as measured by the Adolescent-Structured YMRS (OFC 1%, placebo 0%, p=1.0).

The other secondary measures of efficacy, the BDRS, CGI-BP-overall, and CGI-Depression scores were statistically significant.

The last observation-carried-forward analysis from baseline to endpoint on the CDRS-R total scale was significant.

Both patients and their parents rated quality of life measures on the Kiddo-KINDL were performed but only the patient's self-rating was significantly different on the overall quality of life measure.

Mean change from baseline to endpoint (LOCF) in ADHD-RS score was not significant.

6.1.6 Other Endpoints

Treatment emergent hospitalizations for psychiatric reasons were not significantly different between groups. There was a baseline rate of 5% for patients and duration of 5 days for OFC group and 6 days for the placebo group. Six in the OFC group were for agitated depression with or without suicidal intentions and one for an ovarian surgery. 3 were in the placebo group for depression with and without suicidal ideations. One hospitalization was for pyoderma.

6.1.7 Subpopulations

This study was not powered to detect subpopulation effects but analysis of age (<12 years and >12 years), gender, race (white and non-white), and diagnostic subtype of psychotic or non-psychotic did not demonstrate significant differences for the primary outcome measure.

Table 4. subpopulations

Tables excerpt from the statistical review below

Table 8 and 9 from statistical review Primary efficacy endpoint analysis by subgroup (ITT set).

	N	LS difference (SE)	95% CI	p-value
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Full ITT dataset	286	-4.80 (1.60)	(-7.95, -1.65)	0.0030
Gender				
Male	144	-6.49 (2.28)	(-11.02, -1.96)	0.0055
Female	142	-3.27 (2.25)	(-7.73, 1.20)	0.1500
Age category				
7-11 years	42	-4.88 (6.54)	(-18.96, 9.20)	0.4684
12-17 years	244	-4.56 (1.71)	(-7.94, -1.17)	0.0086
Weight category				
≤ 50 kg	74	-8.33 (3.77)	(-16.00, -0.66)	0.0343
> 50 kg	212	-3.77 (1.82)	(-7.38, -0.17)	0.0404
Race/Ethnicity				
Black	37	-1.81 (4.65)	(-11.38, 7.76)	0.7002
White	205	-5.73 (1.91)	(-9.51, -1.94)	0.0033
Multiple	24	-1.49 (5.38)	(-12.87, 9.88)	0.7848
Hispanic/Latino	65	-1.86 (2.53)	(-7.00, 3.29)	0.4689
Not Hispanic/Latino	220	-5.89 (1.93)	(-9.70, -2.08)	0.0027
Country				
Mexico	23	-0.75 (6.26)	(-14.65, 13.14)	0.9066
Russia	44	-10.73 (2.42)	(-15.76, -5.71)	0.0002
USA	209	-4.43 (1.92)	(-8.22, -0.63)	0.0226

Source: computed by the reviewer.

	N	LS difference (SE)	95% CI	p-value
Full mITT dataset	254	-5.04 (1.64)	(-8.29, -1.79)	0.0026
Gender				
Male	130	-7.52 (2.37)	(-12.22, -2.81)	0.0021
Female	124	-2.60 (2.28)	(-7.14, 1.94)	0.2574
Age category				
7-11 years	39	-3.12(7.75)	(-20.51, 14.27)	0.6964
12-17 years	215	-4.98 (1.77)	(-8.48, -1.49)	0.0056
Weight category				
≤ 50 kg	65	-8.28 (4.54)	(-17.59, 1.02)	0.0789
> 50 kg	189	-3.89 (1.87)	(-7.59, -0.19)	0.0396
Race/Ethnicity				
Black	34	0.73 (4.26)	(-8.07, 9.53)	0.8655
White Multiple	180	-5.83 (1.98)	(-9.76, -1.90)	0.0040
Hispanic/Latino	21	-8.17 (6.28)	(-21.68, 5.35)	0.2153
Not Hispanic/Latino	61	-2.06 (2.65)	(-7.45, 3.33)	0.4430
Country	192	-6.31 (2.01)	(-10.30, -2.32)	0.0022
Mexico				
Russia	23	-0.75 (6.26)	(-14.65, 13.14)	0.9066
USA	44	-10.73 (2.42)	(-15.76, -5.71)	0.0002
	177	-4.87 (2.04)	(-8.90, -0.84)	0.0183

Source: computed by the reviewer.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In this study it is difficult to comment on the optimum dosing recommendations. Unfortunately, the study design was with a forced titration from the dose 3/25 mg to a fixed maximum dose 12/50 mg of which was then allowed to be adjusted down based

on clinician’s impressions of side effects. The minimum dose was not allowed to go below 6/25 mg. This titration schedule would likely not reflect what would be done in clinical practice except in the most acute setting. Most child psychiatrists would slowly titrate to a dose by both analyzing efficacy and tolerability. Evidence of this problem is that only 39% of the patients were able to tolerate the maximum dose of 12/50 mg. The average daily dose of OFC during the study was 7.7 mg olanzapine (SD 2.1) and 37.6 mg fluoxetine (SD 8.4). Also this study demonstrated that the PK data for this combination drug varies based on the patient’s weight and therefore weight may be a factor in determining the recommended dosing.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This is an acute study and this combination has not been studied in the persistence of efficacy and/or tolerance of effects beyond 8 weeks.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The single HDAX phase 4 PREA study was reviewed for safety for the treatment of major depression in bipolar pediatric patients. Supplied study documents were reviewed including the HDAX synopsis, body, discontinuations, ae listings, protocol deviations, and lab listings.

Table 6. Study schedule

Study Schedule											
Visit	1	2	3	4	5	6	7	8	9	10	11 or final
Clinical chemistry, lipids, hematology, and prolactin	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	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	X	X	X	X	X	X	X	X	X	X	X
Efficacy Scales:											
YMRS (Young Mania Rating	X	X	X	X	X	X	X	X	X	X	X
CDRS-R (Children's Depression	X	X	X	X	X	X	X	X	X	X	X
BDRS (Bipolar Depression	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
Kiddo-KINDL (patient-rated; for patients ages 12-16); Kid-		X									X
Healthcare Services Information	X	X	X	X	X	X	X	X	X	X	X

7.1.2 Categorization of Adverse Events

Adverse events for all the studies were coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This study is the sole pediatric study of OFC.

7.2 Adequacy of Safety Assessments

This study provides adequate safety assessments of known risks for medications in their class. The sponsors monitors vital signs every visit. Baseline ECG and 2 additional ECGs were taken over the course of the study.

Physical and psychiatric symptoms including the C-SSRS for suicidality and laboratory tests were taken at every visit. AIMS and Simpson-Angus were performed 4 times over the course of the study including the baseline assessment. Two scales for monitoring for manic switching were used; YMRS and CGI-BP Severity of Mania score.

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

Due to the fixed titration protocol there was adequate exposure of patients to the maximum daily dose. A total of 170 patients were exposed to OFC. The most frequent modal daily dose during the study was the 12/50-mg capsule (12-mg olanzapine/50-mg fluoxetine) and the mean daily dose of olanzapine was 7.7mg (SD=2.1), and the mean daily dose of fluoxetine was 37.6mg (SD=2.1). For the maximum daily dose of 12/50 mg 39% of the patients were exposed for a mean duration of 32 days. The other standard daily doses, 6/25, 6/50, and 12/25 mg, were the modal daily dose for 26%, 22%, and 10% of OFC patients, respectively. Median duration of exposure was 56 days.

7.2.2 Explorations for Dose Response

While there was an initial forced titration, there was an adequate exploration of all doses in flexible dosing.

7.2.3 Special Animal and/or In Vitro Testing

No new animal or in vitro data.

7.2.4 Routine Clinical Testing

For HDAX, the type and frequency of vital sign, clinical laboratory, and ECG monitoring seems adequate given the known safety profile of olanzapine and fluoxetine.

7.2.5 Metabolic, Clearance, and Interaction Workup

The study contained an adequate study of the metabolism in the pediatric population. Additionally, given the high comorbidity, there are an adequate number of patients with comorbid ADHD and on stimulant medication to test for safety.

Since OFC is a combination product, adequate analysis of interacting blood levels of component compounds and efficacy and safety measures were analyzed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse effects based on those for similar drugs in the drug class are outlined in Section 2.4. These were evaluated as part of the original NDA review. The currently approved labeling includes class warnings as appropriate.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this study.

7.3.2 Nonfatal Serious Adverse Events

In the mITT population (255 patients total), 15 patients reported SAEs. The incidence of SAEs was similar between the groups, with 9 (5.3%) patients in the OFC group and 6 (7.1%) patients in the placebo group reporting SAEs. A total of 11.4% of patients discontinued from the study due to AEs, 14.1% in the OFC group and 5.9% in the placebo group; although this difference in incidence between the groups was not statistically significant ($p=.060$), the percentage of discontinuations due to AEs in the OFC group was greater than 2 times the percentage observed in the placebo group

Patients in the OFC group had a higher incidence of TEAEs: 73.5% in the OFC group and 57.6% in the placebo group ($p=.015$). Patients in the OFC group also had a higher incidence of TEAEs judged by the investigator to be possibly related to study drug; 62.9% in the OFC group and 38.8% in the placebo group ($p<.001$).

Table 7. Nonfatal SAE

System organ preferred term	OFC (n=170) N (%)	Placebo (n=85) N (%)	Total (N=255) N (%)	p-value *a
Psychiatric Disorders	8 (4.7)	6 (7.1)	12 (4.7)	.581
Aggression	2 (1.2)	1 (1.2)	3 (1.2)	1.00
Suicidal ideation	2 (1.2)	1 (1.2)	3 (1.2)	1.00
Agitation	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Bipolar disorder	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Homicidal ideation	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Self-injurious behavior	1 (0.6)	0(0.0)	1 (0.4)	1.00
Suicide attempt	1(0.6)	0 (0.0)	1 (0.4)	1.00
Depression	0 (0.0)	1 (1.2)	1 (0.4)	.333
Psychotic disorder	0 (0.0)	1 (1.2)	1 (0.4)	.333
Reproductive system and	1 (0.6)	0 (0.0)	1 (0.4)	1

breast disorders				
Ovulation disorder**	1 (1.2)	0 (0.0)	1 (0.8)	1
Immune system disorders	0 (0.0)	1 (1.2)	1 (0.4)	.333
Anaphylactic reaction	0 (0.0)	1 (1.2)	1 (0.4)	.333
Infections and infestations	0 (0.0)	1 (1.2)	1 (0.4)	.333
Pyoderma	0 (0.0)	1 (1.2)	1 (0.4)	.333

** gender specific events

7.3.3 Dropouts and/or Discontinuations

Discontinuations and drop outs do not appear to deviate from expected from the side effect profile of the compounds.

Summarizing from the application:

In the Safety population, a total of 33 (11.5%) patients discontinued the study due to AEs; 26 (13.6%) in the OFC group and 7 (7.3%) in the placebo group, representing 2 additional patients in each group relative to the mITT population. In the OFC group, the most frequently reported AE that led to discontinuation was weight increased (5 patients [2.9%]), followed by suicidal ideation (3 patients [1.8%]) and bipolar disorder and somnolence (2 patients each [1.2%]). Other AEs that led to discontinuation in the OFC group (1 patient each) were related to abnormal hepatic enzymes, decreased white blood cell count, psychiatric AEs, increased triglycerides, headache, and galactorrhea. In the OFC safety group that includes the 2 sites with alleged GCP errors, the AEs leading to discontinuation for those 2 additional patients were clavicle fracture for 1 patient and blood creatine phosphokinase and alkaline phosphatase increased in the other patient.

In the placebo group, AEs that led to discontinuation were: neutrophil count decreased, hepatic enzyme increased, suicidal ideation, depression, and anaphylactic reaction (1 patient each [1.2%]). In the placebo group, the AEs leading to discontinuation for the 2 additional patients not reported in the mITT population were suicidal ideation and depression for 1 patient and self-injurious behavior in the other patient.

Table 8. Discontinuations due to AEs from the application:

Table HDAX.12.9. Adverse Events Leading to Discontinuation by Decreasing Frequency Modified Intention-to-Treat Set

System Organ Class Preferred Term	OFC (N=170) n (%)	Placebo (N=85) n (%)	Total (N=255) n (%)	p-value* ^a
Patients with at least one AE leading to discontinuation	24 (14.1)	5 (5.9)	29 (11.4)	.060
Investigations	10 (5.9)	2 (2.4)	12 (4.7)	.347
Weight increased	5 (2.9)	0 (0.0)	5 (2.0)	.173
Neutrophil count decreased	1 (0.6)	1 (1.2)	2 (0.8)	1.00
Alanine aminotransferase increased	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Aspartate aminotransferase increased	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Blood triglycerides increased	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Liver function test abnormal	1 (0.6)	0 (0.0)	1 (0.4)	1.00
White blood cell count decreased	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Hepatic enzyme increased	0 (0.0)	1 (1.2)	1 (0.4)	.333
Psychiatric disorders	10 (5.9)	2 (2.4)	12 (4.7)	.347
Suicidal ideation	3 (1.8)	1 (1.2)	4 (1.6)	1.00
Bipolar disorder	2 (1.2)	0 (0.0)	2 (0.8)	.554
Abnormal behaviour	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Agitation	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Anxiety	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Homicidal ideation	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Self injurious behaviour	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Suicide attempt	1 (0.6)	0 (0.0)	1 (0.4)	1.00
Depression	0 (0.0)	1 (1.2)	1 (0.4)	.333

Abbreviations: MedDRA = medical dictionary for regulatory activities; N = number of patients in this analysis set; n = number of

7.3.4 Significant Adverse Events

In review of the study, significant adverse events were relatively low and mostly covered by the above sections and narratives were reviewed by the undersigned.

As summarized in the application:

In the mITT population, 6 (2.4%) patients were reported with PCS AEs; 4 (2.4%) in the OFC group and 2 (2.4%) in the placebo group. In the OFC group these events were: chronic pancreatitis (1), syncope (1), and self-injurious behavior (2), and in the placebo group these were: syncope (1) and suicide attempt (1). For the OFC patients, only 1 of these (self-injurious behavior/“scratches on wrist”) was reported as related to study drug, and 1 (syncope/“faint in draw samples”) was reported as related to study procedures. For the placebo patients, suicide attempt was reported as related to study drug.

In the safety population, 1 more patient was included (Site 210, Patient 2110). This patient was assigned to placebo and had an AE of self-injurious behavior, which was reported as unrelated to study drug.

7.3.5 Submission Specific Primary Safety Concerns

There are no specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent adverse events reported at a rate of $\geq 5\%$ in the OFC group and at a rate of >2 times placebo are the following: weight increase (20% vs. 1.2%), increased appetite (16.5% vs. 1.2%), headache (15.9% vs. 14.1%), somnolence (15.9% vs. 2.4%), tremor (8.8% vs. 1.2%), blood triglycerides increased (7.1% vs. 2.4%), and sedation (6.5% vs. 0.0).

7.4.2 Laboratory Findings

Laboratory findings confirm known risks of increases of liver enzymes with OFC and the risk for metabolic syndrome but interestingly fasting sugars were not changed over this short time frame. Additionally there is a small decrease in RBC measures, small increases in eosinophil counts and increases in prolactin levels.

In the OFC group, there were significant LS mean increases from baseline to endpoint in liver enzymes ALT (OFC: 7.6 U/L, placebo: 0.5 U/L), AST (OFC: 4.1 U/L, placebo: 1.0 U/L), gamma glutamyl-transferase (GGT) (OFC: 2.3 U/L, placebo: -1.7 U/L), and in serum lipids, fasting cholesterol (OFC: 0.42 mmol/L, placebo: -0.11 mmol/L), fasting low-density lipoprotein (LDL) cholesterol (OFC: 0.25 mmol/L, placebo: -0.09 mmol/L), and fasting triglycerides (OFC: 0.4 mmol/L, placebo: -0.04 mmol/L), as well as prolactin (OFC: 8.7 $\mu\text{g/L}$, placebo: 0.7 $\mu\text{g/L}$). In all cases except for AST, the difference of change from baseline was statistically significant compared with the change in the placebo group. While there was also a statistically significant difference detected between groups for alkaline phosphatase, this difference was driven by the significant decrease observed in the placebo group. A statistically significantly greater percentage of patients in the OFC group compared with the placebo group were reported as shifting from within the normal limit at baseline to above the normal limit post-baseline on ALT (48% vs. 3%) and AST (37% vs. 10%). Five patients in the OFC group had ALT shift from normal to $\geq 3\text{x}$ ULN, and 2 of these increased to $\geq 5\text{x}$ ULN.

The mean increase in fasting glucose was clinically insignificant (<1 mg/dL), with no difference between treatment groups.

Treatment-emergent abnormal prolactin level lead to clinically relevant TEAEs in five female patient (3%) of OFC patients; 6% of OFC females. Prolactin increased significantly for the OFC group relative to placebo across all subgroup analyses, with no clinically meaningful differences between subgroups in most categories. The one exception was for age category, as the OFC treated pre-adolescent patients (≤ 12 years of age) had a mean increase in prolactin almost twice the magnitude of that observed in the OFC-treated adolescents, while the change in placebo remained virtually the same in both age groups. This finding was supported by the overall model which showed a significant interaction between treatment and age for prolactin.

7.4.3 Vital Signs

There were no significant changes in VS or orthostatic changes between groups.

7.4.4 Electrocardiograms (ECGs)

12 lead-lead ECG was obtained in triplicate at baseline, week 6, and at week 11 (or final visit if discontinued early). The HDAX study showed a statistically significant greater mean increase in heart rate (4.5 vs 1.0 BPM) and QTcF 8.2 vs -1.1 msec) for OFC vs. placebo. The increase in QTC interval was twice as large as what was found in adult patients. There was also a higher incidence of QTc increases greater than ≥ 30 msec (12% vs 1%) and QTc ≥ 430 for males or ≥ 450 msec for females (8% vs. 1%) for OFC vs. placebo. There is a significant relationship between QTc change and norfluoxetine plasma levels. This poses specific increased risk for patient's at lower weights because of their to the increased plasma concentrations.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Only one incident of anaphylaxis happened in the placebo group.

7.5 Other Safety Explorations

OFC was associated with greater mean change in weight compared to placebo (4.4 kg vs. 0.5 kg, respectively). The percentages of children and adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with 8-week exposure were 52%, 14%, and 1%, respectively. The proportion of patients who had clinically significant weight gain was greater in children and adolescent patients compared to short-term data in adults.

7.5.1 Dose Dependency for Adverse Events

There was a small but statistically significant relationship between change in QTcF and norfluoxetine plasma concentration ($p=.001$) such that a 3.9 msec increase in QTcF might be expected to be observed with each 100 ng/mL of norfluoxetine.

7.5.2 Time Dependency for Adverse Events

Somnolence as a treatment emergent adverse event was significantly increased at the begin visit 5 of treatment through the 8th visit but then was no longer significant for the remaining time points.

Weight increase was significant by visit 4 and throughout the end of the study. 5.9% of the OFC population was affected at visit 4 increasing to 13.5% by the final visit 11. Increased appetite followed a similar timing but was significant starting at week 5 but stable varying at 10-15% of the OFC population.

7.5.3 Drug-Demographic Interactions

There were no significant differences for any safety indicators based on demographics or age race, gender and illness severity.

7.5.4 Drug-Disease Interactions

There was no significant difference for any safety indicators for subtypes of the disease.

7.5.5 Drug-Drug Interactions

There was no evidence of clinically significant drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new data on human carcinogenicity are available.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies with OFC in pregnant women. It is not known whether OFC or its metabolites are excreted in human breast milk. There were no pregnancies in this study.

7.6.3 Pediatrics and Assessment of Effects on Growth

Mean increase in weight was significantly greater for the patients in the OFC group (4.4 kg) relative to the placebo group (0.5 kg, $p < .001$). Mean increase in BMI was also significantly greater for the patients in the OFC group (1.5 kg/m²) relative to the placebo group (0.1 kg/m², $p < .001$). MMRM findings for weight and BMI were also statistically significant, with the OFC group having a mean body weight increase of 5.1

kg at Week 8 compared with 0.6 kg for the placebo group ($p < .001$), and a mean BMI increase of 1.7 mm/kg² compared with 0.1 mm/kg² for the placebo group ($p < .001$). For both weight and BMI, differences between the OFC and placebo groups were statistically significant at all visits (all p 's $< .001$). There were no between-group differences on any of the potentially clinically significant vital sign parameters. However, incidence of patients gaining $\geq 7\%$ of baseline body weight was significantly greater for the OFC group relative to placebo (52% vs. 4%, $p < .001$), as was incidence of gaining $\geq 15\%$ of baseline body weight (14% vs. 0%, $p < .001$). Two patients in the OFC group gained $\geq 25\%$ of their baseline body weight.

Significant weight gain is a commonly known side effect for olanzapine.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is limited data on overdose since only 6 patients took more than the recommended dose. 5 were accidental and the sixth was unclear if it was intentional or accidental. In 5 cases, the patient took a double dose of study drug on 1 day; in the sixth case, an extra half dose was taken over 2 days. Sequelae were mild drowsiness reported for 1 patient, mild headache reported for another, and mild vomiting reported 4 days later for another.

Table 9. Overdoses

Table HDAX.14.12. Listing of Patients Taking More Than the Prescribed Dose
Patients Exposed to Study Medication

Investigator	Patient #	Visit	Prescribed Dose	Dose Taken	Start Date	End date
130	1302	8.00	6/50 OFC	12/100 OFC	19AUG2009	20AUG2009
	1305	8.00	12/50 OFC	18/75 OFC	20JUN2011	22JUN2011
150	1504	9.00	6/25 OFC	12/50 OFC	19JUL2010	20JUL2010
205	2060	5.00	6/50 OFC	12/100 OFC	18JUL2009	19JUL2009
	2067	5.00	6/50 OFC	12/100 OFC	28JUL2009	29JUL2009
255	2551	4.00	6/25 OFC	12/50 OFC	05AUG2011	06AUG2011

No new data on drug abuse potential and withdrawal/rebound are available.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

There is no postmarketing experience information

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

/s/

LUCAS B KEMPF
06/24/2013

ROBERT L LEVIN
06/24/2013
See Cross-Discipline Team Leader Review Memo to follow.