CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21427 S-41
Priority or Standard	Priority
Submit Date(s)	4/19/2012
Received Date(s)	4/19/2012
PDUFA Goal Date	10/19/2012
Division / Office	DPP/ODE1/OND
Reviewer Name(s)	Christina P. Burkhart, M.D.
Review Completion Date	10/2/2012
Established Name	Duloxetine
(Proposed) Trade Name	Cymbalta
Therapeutic Class	SNRI
Applicant	Eli Lily and Company
Formulation(s)	Capsules
Dosing Regimen	Duloxetine 30 mg, 60 mg, 90 mg, or 120 mg daily
Indication(s)	Major Depressive Disorder
Intended Population(s)	Children and Adolescents (ages 7-17)

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Eli Lilly and Company has fairly responded to the Pediatric Written Request for Cymbalta issued by the Agency on 23 June 2006, and subsequently amended on 22 September 2009 and 02 November 2009. The sponsor has conducted two adequate and well-controlled trials to assess the safety and efficacy of Cymbalta in children and adolescents (ages 7 to 17) with the diagnosis of Major Depressive Disorder (MDD). The designs of these trials were consistent with those agreed upon with the Division of Psychiatry Products. Both trials were inconclusive as neither Cymbalta nor the active control (fluoxetine) demonstrated a statistically significant separation from placebo on the primary efficacy analysis. Therefore, the sponsor is not seeking an indication for the treatment of MDD in children and adolescents.

On 31 July 2012, the Pediatric Exclusivity Board conducted a hearing on the adequacy of these trials and granted an extension of the applicable Cymbalta patent and regulatory exclusivities for a period of six months in accordance with the Best Pharmaceuticals for Children Act (BPCA). On 12 September 2012, the Pediatric Review Committee (PeRC) met to consider the application. PeRC concluded that the pediatric studies were adequate and the sponsor had fulfilled the PREA requirements.

1.2 Risk Benefit Assessment

A risk benefit assessment was not conducted as the submitted studies were inconclusive with respect to the efficacy of duloxetine in the treatment of MDD in children and adolescents.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No new recommendations for postmarket risk evaluation and mitigation strategies are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The Agency required a study in pediatric patients to assess the safety and effectiveness of Cymbalta as a treatment for major depressive disorder (MDD) in pediatric patients ages 7 to 17 (children and adolescents) with the initial 03 August 2004 approval of Cymbalta for the treatment of MDD in adults. The final study reports contained within this application for Studies HMCK and HMCL fulfill this Phase 4 commitment

No new postmarket requirements or commitments are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Duloxetine hydrochloride (Cymbalta™) is a member of the serotonin and norepinephrine reuptake inhibitor (SNRI) class. It is currently approved in both the European Union (EU) and in the United States for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), and diabetic peripheral neuropathic pain (DPNP). Cymbalta™ was first approved in the United States in August 2004 and in the EU in December 2004. Duloxetine also is approved for the treatment of fibromyalgia in the US (approved June 2008) and for the treatment of moderate to severe stress urinary incontinence in women in the EU (Yentreve™ approved in August 2004). Duloxetine is not indicated for use in children and adolescents.

2.2 Tables of Currently Available Treatments for Proposed Indications

Fluoxetine (Prozac®) is the only antidepressant approved for use in children and adolescents for MDD. Escitalopram oxalate (Lexapro®) is approved for treatment of MDD in adolescents aged 12-17 years.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient of Cymbalta® (duloxetine hydrochloride) is readily available in the United States. Cymbalta® is currently approved for the treatment of MDD, GAD, diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain.

2.4 Important Safety Issues With Consideration to Related Drugs

Some safety issues associated with the use of SNRIs include elevated blood pressure, increased risk of bleeding in conjunction with the use of aspirin or nonsteroidal anti-inflammatory drugs, serotonin syndrome, withdrawal reactions, and increased risk of suicide in children/adolescents/young adults.

Duloxetine has also been associated with rare cases of hepatic failure and Stevens - Johnson syndrome (SJS).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Following approval of Cymbalta for the treatment of adults with MDD, Lilly submitted a Proposed Pediatric Study Request to FDA on October 7, 2005. The Pediatric Written Request (WR) for Cymbalta was issued by the Agency on 23 June 2006, and subsequently amended on 22 September 2009 and 02 November 2009. The WR included the following elements:

- Pediatric Pharmacokinetic study in MDD
- Pediatric Safety Study
- Nonclinical toxicology study
- Submission of the reports by March 31, 2013

The following sponsor table lists key communications between Lilly and FDA that served to amend and/or clarify the intent of the original WR dated June 23, 2006:

Table of Key Communications between Lilly and FDA to clarify and/or modify the WR

Date	Description of Correspondence
October 7, 2005	Lilly Proposed Pediatric Study Request
June 23, 2006	FDA WR
September 20, 2006	Lilly Briefing Document - Nonclinical Study Proposal
October 4, 2006	Lilly Briefing Document - Clinical Development Plan
November 7, 2006	FDA-Lilly Face-to-Face Meeting (FDA Minutes)
September 6, 2007	Lilly Protocol – PK Study HMFN
September 5, 2008	Lilly Nonclinical Study Reports (Studies 014R06PK, 901198, 901221, 901347)
September 18, 2008	Lilly HMFN PK Results and Draft Protocols HMCK and HMCL
October 17, 2008	Lilly Request for Amendments to WR
February 3, 2009	FDA Response on HMCK and HMCL Protocol Reviews
February 23, 2009	Lilly HMCK and HMCL Protocols
April 2,2009	FDA Advice Letter HMCK and HMCL
April 6, 2009	Lilly HMFN PK Study Report
May 4, 2009	FDA-Lilly Teleconference Statistical Power for HMCL 30 mg Fixed-Dose Arm
May 27, 2009	Lilly Response HMCK HMCL Statistics
June 17, 2009	FDA Comments HMCK HMCL Statistics and Randomization
June 26, 2009	Lilly Response HMCK HMCL Statistics and Randomization
August 14, 2009	Lilly HMCL Protocol Amendment (a)
September 23, 2009	FDA WR Amendment #1
September 30, 2009	FDA Notification that WR to be Amended with BPCA 2002 Timing
October 16, 2009	Lilly HMCK Investigator Discontinued
November 2, 2009	FDA WR Amendment #2
December 3, 2009	Lilly Acceptance WR Amendment #2
December 9, 2009	Lilly Request for PK and Stats Clarification
January 26, 2010	Lilly Notification of EU PIP Decision
September 20, 2010	Lilly Pediatric Update, WR Clarification, and Type A Meeting Request
October 26, 2010	FDA Type A Meeting Preliminary Comments (meeting subsequently cancelled)
January 18, 2011	Lilly HMCK Protocol Amendment (a)
April 26, 2011	Lilly HMCL Investigator Discontinued
May 19, 2011	Lilly HMCK, HMCL, Population Pharmacokinetics Statistical Analysis Plans
June 22, 2011	FDA Acceptance of the Proposed Pop PK Analysis Plan
October 13, 2011	Lilly Pre-NDA Meeting Request
January 18, 2012	FDA Confirmation of Pre-NDA Meeting Cancellation by Lilly

2.6 Other Relevant Background Information

Lilly submitted a Pediatric Investigation Plan (PIP) to the European Medicines Agency (EMEA) in October 2009. According to the sponsor, the proposals made within the PIP were similar to studies already committed to or proposed to the FDA. The EMEA's pediatric committee (PDCO) assessed the proposals and decided that there was no

need to study duloxetine in pediatric patients. On January 21, 2010, the EMEA informed Lilly that the decision had been made that no pediatric requirements were needed on the grounds that duloxetine *"is likely to be unsafe in the pediatric population."*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was organized and electronic navigation was not difficult.

Dr. John Lee, a medical officer in the Division of Good Clinical Practice Compliance in the Office of Scientific Investigations, submitted the Clinical Inspection Summary on August 15, 2012. This summary is based on preliminary communications with the field investigator. Four study sites were inspected. At all four study sites, no significant deficiencies were observed.

At Sites 102 and 106 of Study HMCL and at Site 710 of Study HMCK, a Form FDA 483 was not issued. The study protocol and all applicable GCP regulations were followed at these three sites.

At Site 708 of Study HMCK, a Form FDA 483 was issued for “two minor, apparently isolated deficiencies in recordkeeping that are not expected to impact subject safety or the study results.” This site otherwise conducted the study in accordance with the study protocol and applicable GCP regulations. The Form FDA 483 was issued for the following two deficiencies:

- The study protocol specifies that the electrocardiogram (ECG) is to be interpreted initially by the clinical investigator for subject selection and management, and subsequently by a central cardiologist for data interpretation and analysis. For four subjects, the central cardiologist's interpretation was not documented in the subject case history file.
- For five subjects (six visits), the CDRS-R score on the eCRFs did not match exactly the score on the source document. The reviewer noted that the minor discrepancies in CDRS-R total scores as noted on source documents and eCRFs presumably resulted from errors in manually adding the individual item scores at eCRF data entry and that the errors did not appear to have occurred with a preference to any treatment arm and that the small differences in scores would not be expected to have a significant impact on data reliability.

The inspection report concluded that the study data from all four sites appear reliable as reported in the NDA supplement.

3.2 Compliance with Good Clinical Practices

Studies HMFN, HMCK, and HMCL were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (GCPs) and the applicable laws and regulations.

Lilly certifies that none of the investigators have been debarred under 21 U.S.C. 335a(a) or (b).

3.3 Financial Disclosures

Following Lilly's submission on 19 April 2012, Lilly identified errors with the Financial Disclosure (FD) statements. The column entitled "Certification and/or Disclosure for each Investigator" was only marked 'yes' if there was an update to the initially reported FD information during the final site close-out. So while FD information was collected for all investigators, the document made it appear as though only a few investigators reported this information. Lily notified the Agency of the error on 27 April 2012 and submitted an amendment containing the updated Financial Disclosure statements on 10 May 2012.

For (b) (6), 4 investigators reported receiving significant payments from Lily with a market value from $25,000 to $130,625. Lily completed a sensitivity analysis to assess the effect of individual sites with disclosable financial interests and arrangements, as well as the combination of investigators above suggested limits. Neither the individual site nor the combination had an effect on the outcome of the study.

For (b) (6), 8 investigators reported receiving significant payments from Lily with a market value from $25,000 to $77,520. Lily completed a sensitivity analysis to assess the effect of individual sites with disclosable financial interests and arrangements, as well as the combination of investigators above suggested limits. No individual investigator affected the study outcome. When the 53 patients (11.4% of the total patients randomized) from these eight sites were removed and the primary MMRM analysis re-run, it showed a statistically significant improvement in patients treated with Duloxetine 30 mg compared with patients treated with placebo at the week 10 endpoint (p-value=0.039). However, no adjustment was made for multiplicity.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new information on the chemistry, manufacturing, and controls of duloxetine was submitted to this sNDA.

4.3 Preclinical Pharmacology/Toxicology

In response to the WR, Lilly completed 4 nonclinical juvenile animal toxicology studies. In a 12/21/2011 review, Dr. Linda Fossom and Dr. Arippa Ravindran reviewed these nonclinical studies and concluded that the studies were adequate to fulfill the nonclinical toxicology study requirement in the Pediatric Written Request.

These 4 nonclinical juvenile animal toxicology studies are listed below in Table 1.

Table 1: Completed Juvenile Animal Toxicology Studies

Study Title	Study Description
Study 014R06PK	Pharmacokinetics of Duloxetine in Juvenile and Adult Sprague Dawley Rats Following Single Oral Dose Administration of 2, 10, or 45 mg/kg Duloxetine as the Hydrochloride Salt
Study 901198	A General Toxicity Repeat Dose Study in Rats Administered LY248686 Hydrochloride (Compound 246916) Orally by Gavage from Postnatal Day 21 Through 70
Study 901221	A 70- Day Oral Gavage Combined Repeat Dose, Neurobehavioral and Fertility Study of LY248686 Hydrochloride (Compound 246916) in the Young Albino Rat
Study 901347	A Pilot Juvenile Study in Rats Administered LY248686 Hydrochloride (Compound 246916) Orally by Gavage from Postnatal Day 21 Through 34

The protocols for these juvenile toxicity studies were submitted to the Division for comment prior to their initiation. These studies utilized rats from postnatal day (PND) 21 through PND 90 (comparable to humans aged 2 through maturity to adulthood). These studies evaluated the effects of Cymbalta on growth, reproductive development, and neurological and neurobehavioral development. The same group of animals was used to evaluate neurobehavioral effects during treatment and the effects on reproductive parameters. The neurobehavioral tests assessed sensory function, motor function, and learning and memory. Neuropathological evaluation included examination of all major brain regions and cellular elements, with particular attention to alterations indicative of developmental insult. In comments dated 26 Oct 2010, the FDA agreed that these 4 completed toxicology studies fulfilled the nonclinical toxicology requirements set forth in the WR.

In his review, Dr. Arippa Ravindran concluded:

Oral administration of LY248686 (HCl) in juvenile Sprague-Dawley rats (50 days and 70 days) resulted in decreased food consumption, body weight and body weight gains relative to controls at the high dose of 45 mg/kg/d. In addition, treatment-related increase in the number of navigation errors in Cincinnati water maze, indicative of sequential learning deficits was observed at the high dose. However, the navigation errors were no longer observed following discontinuation of the treatment indicating that the treatment-related learning deficits may be transient in nature. There were no indications of treatment related adverse effects on fertility parameters at doses up to 45 mg/kg/d. The studies submitted by the Sponsor in response to the PWR appear to be adequate.

Dr. Linda Fossom, the Pharmacology/Toxicology Team Leader, added the following additional comments:

I agree that the studies reviewed here are adequate to fulfill the nonclinical toxicology study requirement in the Pediatric Written Request (as originally issued 6/13/2006 and revised 9/22/2009).

Because of the nature of the findings (limited to a slight delay in sexual maturation in female rats, without effects on fertility, and delayed learning in the reversal arm of the Cincinnati water maze during drug treatment, which was not observed after drug discontinuation) and because these findings were only seen at the high dose, which produced substantial decrease in food consumption and body weight gain, I believe that the findings do not indicate any particular safety concerns for use of duloxetine for the clinical trials in pediatric patients (with major depressive disorder) ages 7 years and greater that are required under the WR.

For further details of these studies, please see the pharmacology/toxicology review (12/21/2011) by Dr. Arippa Ravindran (IND 38,838).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new information on mechanism of action was submitted to this sNDA. According to Cymbalta's label, the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown. However, these mechanisms of actions are believed to be related to Cymbalta's potentiation of serotonergic and noradrenergic activity in the CNS.

4.4.2 Pharmacodynamics

No new information on the pharmacodynamics of duloxetine was submitted to this sNDA.

4.4.3 Pharmacokinetics

The complete study report from Study HMFN was included in this sNDA submission. Study HMFN was an open-label, Phase 2, pharmacokinetic study. The safety, tolerability and pharmacokinetic data from this study supported dose selection and dosing regimen for the subsequent Phase 3 acute efficacy clinical trials (Studies HMCK and HMCL). A duloxetine dose range of 20 mg to 120 mg was evaluated in Study HMFN. The pharmacokinetics of oral duloxetine in pediatric patients in this dose range were found to be linear. Body weight and age did not have a statistically significant effect on duloxetine pharmacokinetic parameters. Overall, safety findings from this study were consistent with the known safety and tolerability profiles for duloxetine.

Dr. Islam Younis (Office of Clinical Pharmacology) reviewed Study HMFN. He concluded that the sponsor had met the clinical pharmacology requirements of the written request and that duloxetine steady state plasma concentration was comparable in children (7-12 years), adolescents (13-17 years), and adults.

The following is a brief summary of Study HMFN. Please see Dr. Younis' review for further details.

Title: "An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with Major Depressive Disorder"

Objectives

Primary Objective:

- To assess the safety and tolerability of duloxetine delivered orally, in children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who met criteria for MDD (DSM-IV-TR) and confirmed by the Kiddie-SADS-Lifetime Version (K-SADS-PL). The primary objective was evaluated by monitoring AEs, vital signs, labs, ECGs, suicidality (C-SSRS and by Item 13 of the Children's Depression Rating Scale-Revised [CDRS-R]).

Secondary Objective:

- To characterize the pharmacokinetics (PK) of duloxetine at steady-state in the treatment of children and adolescents with MDD.
- To compare the steady-state duloxetine PK in the treatment of children and adolescents with MDD with historical adult duloxetine PK

- To assess the efficacy of duloxetine at a proposed dose range of 20 to 120 mg QD by treatment response using CDRS-R and the Clinical Global Impression of Severity (CGI-S) scale
  Reviewer comment: Since this was an uncontrolled study, any efficacy conclusions would not be significant.

Design

This was a Phase 2, multicenter, open-label, single-arm study of the tolerability, safety, and pharmacokinetics of duloxetine in children and adolescents outpatients (aged 7 to 17 years) meeting criteria for MDD.

The study was conducted by 22 primary investigators, all psychiatrists, at 22 study centers in the United States.

Enrollment was tracked in 4 age strata (7 through 9 years, 10 through 12 years, 13 through 14 years, and 15 through 17 years), and enrollment in each age stratum was stopped when that age stratum was complete to avoid over-representation in the study sample.

The study consisted of 5 periods:
Period I: Screening (2 weeks)
Period II: Dose titration with PK Sampling (10 weeks)

- Objective of this period was to titrate each patient to the patient's highest clinically appropriate tolerable dose up to a maximum of 120 mg QD, based on safety, tolerability, and treatment response (CGI-S <3)
- Patients had weekly visits
- Patients in the lower body-weight group (20 to 40 kg) initiated duloxetine at 20 mg QD for 2 weeks.
- Patients in the higher body-weight group (>40 kg) were initiated at 30 mg QD for 2 weeks.
- At Visit 5/Week 2, patients who tolerated the initial dose and who had a CGI-Severity score ≥3 were escalated to the next planned increment.
- Patients who were unable to tolerate the initial dose or those who had a CGI Severity score of 1 or 2, remained at the initial dose.
- Subsequent dose increases occurred at 1- to 2-week intervals, based on investigator's assessment of safety and tolerability and treatment response (CGI-Severity score) in 30 mg QD increments up to a maximum dose of 120 mg QD.
- If a patient tolerated the dose and the CGI-Severity score was ≥3 for 2 consecutive visits, the patient's dose was escalated.

- If a patient was unable to tolerate a higher dose, the patient was placed on a lower previously tolerated dose, but not a lower dose than the patient's initial starting dose.
- If a patient was tolerating the current dose, as judged by the investigator and the CGI Severity score was <3, the patient continued the current dose with no dose escalation.
- At Visit 13/Week 10, a final dose adjustment was made as allowed.

Period III: Safety and Tolerability (8 weeks)

- Duloxetine dose remained fixed (at the same dose prescribed at Visit 13/Week 10) throughout this period to evaluate the safety and tolerability at a fixed dose.

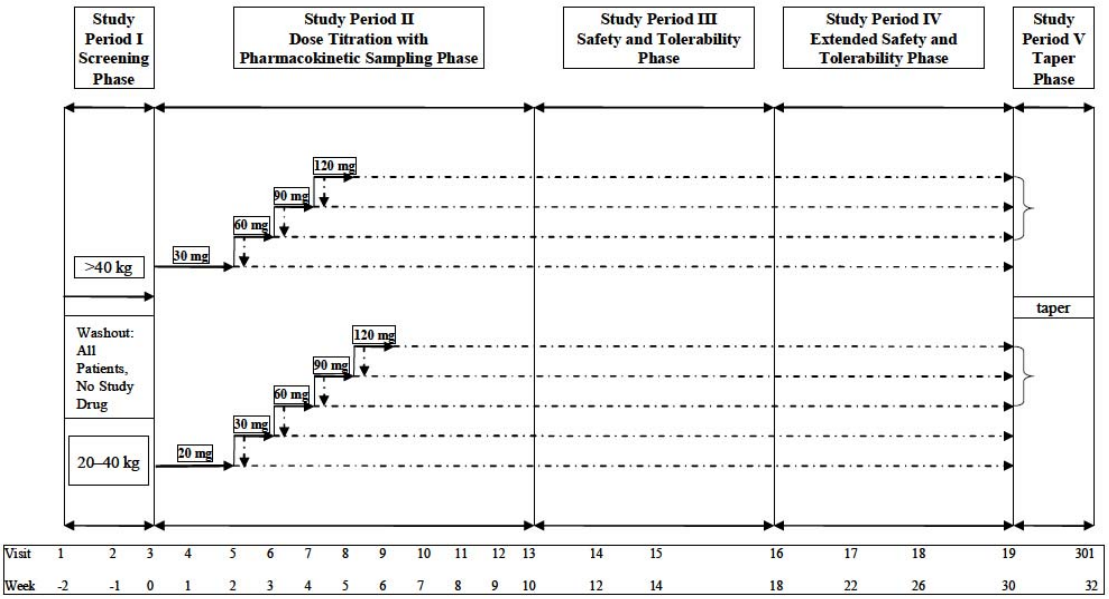
Period IV: Extended Safety and Tolerability (3 months)

- Patient's dose was escalated or decreased at the investigator's discretion throughout this period.
- Provided additional long-term safety and tolerability information

Period V: Taper Phase (2 weeks)

- Patients who had been administered duloxetine at a dose of at least 60 mg QD for 1 week gradually reduced their duloxetine dose

Figure 1: HMFN Study Design



(Source: HMFN Study Report, p. 836)

Subjects

- Outpatient children and adolescents aged 7 to 17 years
- Diagnosis of MDD as defined by the DSM-IV-TR and confirmed by the K-SADS-PL
- Diagnosis of moderate or greater severity of MDD as determined by CDRS-R with a total score ≥40 at Visits 1, 2, and 3 and a CGI-S rating of ≥4 at Visits 1, 2, and 3
- Genotyped to enroll both CYP2D6 poor and extensive metabolizers

Concomitant Medications

Any medication that was contraindicated for use with duloxetine or that may have caused a clinically important change in the pharmacokinetics of duloxetine was not allowed. In general, concomitant medications with primarily central nervous system (CNS) activity were not allowed.

Description of CDRS-R

According to the sponsor, the Children's Depression Rating Scale-Revised (CDRS-R) is a clinician-rated instrument designed to measure the presence and severity of depression in children. The scale was modeled after the Hamilton Depression Rating Scale (HAMD) for adults and includes questions about school. The scale consists of 17 items scored on a 1- to 5-point scale or 1- to 7-point scale. A rating of 1 indicates normal functioning. Total scores range from 17 to 113. In general, scores below 20 indicate an absence of depression, scores of 20 to 30 indicate borderline depression, and scores of 40 to 60 indicate moderate depression. Inclusion criteria for HMFN included a CDRS-R total score of ≥40.

Statistical Analyses

Pharmacokinetic:

- Steady-state duloxetine plasma concentration-time data was analyzed using the population pharmacokinetic modeling approach using the software NONMEM. Potentially important patient factors such as age, body weight, gender, nicotine exposure, CYP2D6 genotype status, creatinine clearance, and menarche status were investigated to assess their influence on the pharmacokinetic parameters (clearance [CL/F] and volume of distribution [V/F]).
- Duloxetine pharmacokinetics in pediatric patients compared with adults using observed steady state concentrations and population pharmacokinetic model parameters.

Safety:

- Percentages of patients that reported treatment-emergent adverse events (TEAEs), discontinuation-emergent AEs, serious adverse events (SAEs), discontinuations due to AEs, and suicidality

- Mean change in labs, height, weight, vital signs, and ECG intervals from baseline to endpoint
- Categorical analyses of potentially clinically significant (PCS) changes in vital signs and ECG
- Proportion of patients with treatment-emergent abnormal laboratory values or PCS changes

Results

Demographic and Baseline Characteristics

The number of males was roughly equivalent to the number of females. The majority of subjects were Caucasian.

Table 2: HMFN Patient Baseline Characteristics

All Enrolled Patients (N=72)

	Mean (SD)
Age (years)	12.5 (2.9)
Body Mass Index (kg/m^2)	23.7 (6.4)
CDRS-R total score	61.7 (9)
CGI-Severity	4.5 (0.6)
Categorical Demographics: n (%)	
Age distribution:	
≤12	31.(43.1)
>12	41 (56.9)
Gender	
Female	35 (48.6)
Male	37 (51.4)
Tobacco use:[a*]	
No	70 (97.2)
Yes	1 (1.4)
Origin:	
African	17 (23.6)
Caucasian	42 (58.3)
East Asian	1 (1.4)
Hispanic	11 (15.3)
Native American	1 (1.4)

(Source: HMFN Study Report, p.73)

Baseline Psychiatric History

The mean age at first episode of MDD was 10.75 years of age. The mean number of previous MDD episodes was < 1 (range of 0-6). Family history was significant for depression in > 50 % of enrolled subjects.

Disposition

Table 3: HMFN Patient Disposition

Parameter	n
Screened	101
Enrolled	72
Completed Study Period II	58
Completed Study Period III	48
Completed Study Period IV	41

(Source: HMFN Study Report, p.64)

Table 4: HMFN Summary of Study Period III Completers by Age and Gender

Age Category	Gender	Duloxetine (N = 55) n (%)
7-9 Years	Male	6 (10.91)
	Female	10 (18.18)
10-12 Years	Male	10 (18.18)
	Female	5 (9.09)
13-14 Years	Male	6 (10.91)
	Female	6 (10.91)
15-17 Years	Male	4 (7.27)
	Female	8 (14.55)

(Source: HMFN Study Report, p.65)

Discontinuations

Table 5: HMFN Overall Reasons for Discontinuation Treatment Phase II-IV

Reason for Discontinuation	Overall N=72 n (%)
Discontinued due to any reason	31 (43.1)
Parent/Caregiver Decision	10 (13.9)
Lost to follow-up	6 (8.3)
Adverse Event	4 (5.6)
Lack of Efficacy	3 (4.2)
Physician Decision	3 (4.2)
Protocol Violation	3 (4.2)
Subject Decision	2 (2.8)

(Source: HMFN Study Report, p. 66)

Table 6 provides further information about the specifics of *Caregiver Request* as a reason for discontinuation.

Table 6: HMFN Reason for Study Discontinuation: Caregiver Request

Patient	Visit	Last Dose	Reason for Discontinuation
710	16	120	Caregiver Request – Father withdrew consent due to internal family problems
400	4	30	Caregiver Request – Mother withdrew consent in order to start regular clinical visits outside of protocol for child
1200	6	60	Caregiver Request – Moving out of town
2704	9	60	Caregiver Request – Needs ADHD meds
103	16	90	Caregiver Request – Patient needed family therapy
3107	16	30	Caregiver request – Patient will spend summer out of town
3106	16	90	Caregiver request – Personal reasons
2703	10	90	Caregiver Request – Withdrew consent
800	4	30	Caregiver Request– Patient is moving out of state

(Source: HMFN Study Report, p. 69)

Compliance

Compliance by visit was > 85%. Overall compliance for Study Periods II/III was 52.8% and overall compliance for Study Period IV was 84.5%

PK Results

- The pharmacokinetics of duloxetine following QD oral administration were adequately characterized by a one-compartment pharmacokinetic model.
- Terminal half-lives were 7.1 h and 4.9 h for female and male patients, respectively.
- In 4 patients identified as CYP2D6 poor metabolizers, the steady state duloxetine concentrations were higher than in CYP2D6 extensive metabolizers.
- Pharmacokinetics of oral duloxetine in pediatric patients were linear in the dose range of 20 to 120 mg. Body weight, age, CYP2D6 genotype status, menarche status, ethnic origin, creatinine clearance, and dose did not have a statistically significant effect on duloxetine pharmacokinetic parameters. Therefore, differential dosing based on body weight or age is not necessary in the pediatric population.
- Gender was the only covariate with a statistically significant effect on oral clearance (CL/F) where the CL/F in a female patient is 31% lower than in a male patient, resulting in 45% higher steady state average concentration in females relative to males.[1] However, given the interpatient and intrapatient

[1] According to the sponsor, the effect of gender is likely related to the differences in cytochrome P450 1A2 (CYP1A2) activity due to higher CYP1A2 expression in males. Therefore, greater amounts of duloxetine may be metabolized, resulting in the higher clearance in males than in female patients.

variability, there was considerable overlap in duloxetine concentration-time profile in females and males. Therefore, differential dosing based on gender is not necessary.

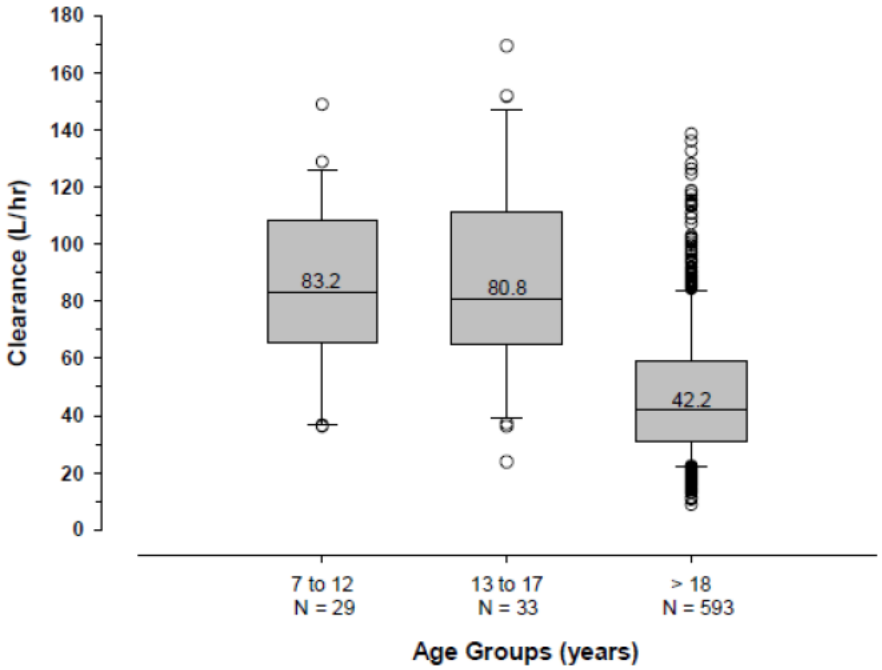
- Following duloxetine 20 – 120 mg QD dosing regimen, the observed steady-state duloxetine plasma concentration range in pediatric patients (median = 28.4 ng/mL, range: 0.5 to 203 ng/mL) are in the lower range of those observed in adults (median = 49.4 ng/mL, range: 0.5 to 445 ng/mL). The model predicted average steady-state duloxetine concentration in pediatric patients is typically 37% lower than in adults. Therefore, the sponsor concluded that investigation of lower doses (5 – 20 mg) in pediatric patients relative to the adult recommended dose (60 mg) may not be necessary.

Table 7: HMFN Population PK Parameters for Duloxetine in Children/Adolescent and Adults

Parameter Estimate from Final Population Model		
	Children & Adolescents	**Adults***
CL/F, female (L/h)	66.3	34.5
CL/F, male (L/h)	96.1	56.5
V/F (L)	682	814
$t_{1/2}$, female (h)	7.13	16.4
$t_{1/2}$, male (h)	4.92	9.98

CL/F=oral clearance; $t_{1/2}$=elimination half-life; V/F=oral volume of distribution
* In non-smokers following a 60-mg QD dose of duloxetine
(Source: HMFN, p.96)

Figure 2: HMFN Effect of Age on Duloxetine CL/F (L/h) in Children, Adolescents, and Adults



(Source: HMFN Study Report, p. 97)

Safety Results

Overall, safety findings from this study were consistent with the known safety and tolerability profiles for duloxetine.

Exposure

Table 8: HMFN Mean Duration of Exposure by Period

Parameter	Period II/III N=72	Period IV N=48
Mean Duration of Exposure	106.7 days	77.5 days

(Source: HMFN Study Report, p.103, 108)

Modal Duloxetine Dose

Table 9: HMFN Modal Duloxetine Dose by Period

Period	60, 90, or 120 mg daily	30 mg daily	20 mg daily
	n (%)	n	n
II/III	52 (72%)	17	3
IV	42 (88%)	5	0

(Source HMFN Synopsis, p.4 and Study Report, p. 104-111)

Deaths

There were no deaths reported during the study.

SAEs

A total of 5 patients reported 6 SAEs (depression, viral gastroenteritis, oppositional defiant disorder, suicidal ideation, and 2 self-injurious behaviors). All of the SAEs occurred during Study II/III Period. None of the SAEs were considered by the investigator to be related to study drug.

AEs Leading to Discontinuation

Table 10: HMFN Adverse Events Leading to Discontinuations by Study Period

Period	n	AE	Related to Study Drug
II/III	3	Nausea	Yes
		Rash	Yes
		ADHD	Yes
IV	1	Irritability	No

(Source: HMFN Study Report, p.126-127)

AEs Leading to Dose Reduction

AEs leading to dose reduction included headache, vomiting, nausea, insomnia, sedation, restlessness, increased agitation, feeling jittery, sweating, and dry mouth.

TEAEs

During Study Period II/III, nausea was the most common TEAE (18 patients, 25%). Other TEAEs reported by at least 5% of patients during Study Period II/III were headache, vomiting, nasopharyngitis, dizziness, sedation, somnolence, upper abdominal pain, fatigue, decreased appetite, dry mouth, viral gastroenteritis, and rhinorrhea. Similar types of TEAEs were reported during Study Period IV. However, no one TEAE was reported by more than 2 patients. In general, the pediatric subjects experienced the majority of TEAEs during the initiation of duloxetine treatment. Fewer TEAEs were reported during the longer-term treatment.

Table 11: HMFN TEAEs by Study Period

Period	n (%)
II/III	57 (79.2%)
IV	21 (43.8%)

(Source: HMFN Study Report, p.113)

Labs

- One subject experienced a potentially clinically significant (PCS) elevation of alanine aminotransferase (ALT). After approximately 14 weeks, the patient's ALT reached 5X upper limit of normal (ULN), but total bilirubin, AST, GGT, and CPK were all normal. A retest revealed that the ALT elevation had returned to normal within 3 days while the patient continued to take study drug, and the event appeared to be an isolated elevation.
- Greater than 5% of subjects experienced a PCS of low hematocrit (8, 13.3%), high creatine phosphokinase (6, 8.7%), and high inorganic phosphorus (16, 25.8%). According to the sponsor, transient elevations in creatine phosphokinase and inorganic phosphorus have also been observed in duloxetine-treated adults.

Vital Signs

- ~ 20% of patients experienced PCS high diastolic blood pressure
- ~ 10% of patients experienced PCS high systolic blood pressure
- 3% of patients experienced PCS high pulse at anytime.
- 5.6% (4/72) of patients experienced sustained elevation of blood pressure (1 diastolic and 3 systolic); maximum sustained elevation of diastolic BP was 87 mm Hg and maximum sustained elevation of systolic BP was 142 mm Hg

Table 12: HMFN Mean Change from Baseline to Endpoint in Vital Signs

Parameter (mean change)	**Study Period II/III**	**Study Period IV**
BP Diastolic (mm Hg)	4.53	5.24
BP Systolic (mm Hg)	1.49	4.62
Pulse (bpm)	-0.24	-1.36
Weight (kg)	0.14	0.86

(Source: HMFN Study Report, p. 142-143)

ECG

- 2 patients met the high QTc (Bazett) interval PCS criteria (470 msec and 454 msec). However, these patients did not meet PCS criteria for high QTc interval when the Fridericia correction was used.

Suicidality

- One nonfatal suicide attempt was reported in this study (Period II/III).
- One patient experienced worsening of suicidal ideation from baseline (Period II/III).
- One patient experienced worsening of suicidal ideation from baseline (Period IV).
- Out of 19 patients who reported suicidal ideation at baseline, 17 (89.5%) reported an improvement in suicidal ideation at last observation during Study Periods II and III. For patients who had suicidal ideation at baseline and continued in the study through Study Period IV (N=8), all 8 patients (100%) reported an improvement in suicidal ideation at last observation during Study Period IV.

Overall Conclusions

- Tolerability, pharmacokinetic, and efficacy results support 30 mg as the lowest starting dose for the efficacy trials in pediatric patients (7 – 17 years).
- No new safety findings in pediatric MDD patients relative to adult patients.
- Differential dosing based on body weight or age is not warranted for duloxetine in pediatric population.
- Given the magnitude of the effect of gender and the high interpatient variability in duloxetine pharmacokinetics, differential dosing based on gender is not necessary for pediatric patients.
- Median steady state duloxetine concentrations in pediatric patients are lower than in adults.
- Duloxetine 30 to 120 mg QD was well tolerated in children (7 through 11 years) and adolescents (12 through 17 years) with MDD.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study **HMFN** was a Phase 2, multicenter (22 US sites), open-label, single-arm study of the tolerability, safety, and pharmacokinetics of duloxetine (20-120 mg) in children and adolescents outpatients (aged 7 to 17 years) meeting criteria for MDD. See Section 4.4.3 for a review of Study HMFN.

Results from Study HMFN determined the doses of duloxetine to be administered in the pivotal studies **HMCK** and **HMCL**.

Table 13: Pivotal Pediatric Controlled Efficacy and Safety Studies

Study	Design	Treatment Groups (Period II)	Subjects (Period II) N n (% completed)	Efficacy Results (Period II) p-value
HMCK	Phase 3, multicenter, randomized, double-blind, placebo-controlled study of duloxetine versus placebo in the treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder (DSM-IV-TR and MINI-KID) **Flexible doses of duloxetine (60-120 mg QD)** and **fluoxetine (20-40 mg QD)** were administered during the 10-week acute phase of the study (Study Period II). Flexible doses of duloxetine (60 to 120 mg QD) and fluoxetine (20-40 mg QD) were administered during the 6-month double-blind extension period (Study Period III). The fluoxetine treatment arm was included to provide evidence of assay sensitivity. The **primary efficacy endpoint** was the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.	DLX60120* FLX2040** Placebo	N=117 87 (74.4%) N=117 91 (77%) N=103 87 (84.5%)	0.999 0.687
HMCL	Phase 3, multicenter, randomized, double-blind, placebo-controlled study of duloxetine versus placebo in the treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder (DSM-IV-TR and MINI-KID) **Fixed doses of duloxetine (30 and 60 mg QD)** and **fluoxetine (20 mg QD)** were administered during the 10-week acute phase of the study (Study Period II). Flexible doses of duloxetine (60 to 120 mg QD) and fluoxetine (20-40 mg QD) were administered during the 6-month double-blind extension period (Study Period III). The fluoxetine treatment arm was included to provide evidence of assay sensitivity. The **primary efficacy endpoint** was the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.	DLX60 DLX30 FLX20 Placebo	N=108 75 (69.4%) N=116 81 (69.8%) N=117 84 (71.8%) N=122 85 (69.7%)	0.193 0.093 0.588

*DLX60120=flexible doses of duloxetine 60 mg to 120 mg
**FLX2040=flexible doses of fluoxetine 20 mg to 40 mg

HMCK was conducted at 65 study sites in 4 world regions: United States (41.5%), Western Europe (5%), Eastern Europe (33.5%), and South Africa (19.9 %).

Table 14: HMCK Patient Allocation by Country

Country	N=337 N (%)
United States	140 (41.5)
Finland	5 (1.5)
France	8 (2.4)
Germany	4 (1.2)
Slovakia	6 (1.8)
Ukraine	66 (19.6)
Russia	40 (11.9)
Estonia	1 (0.3)
South Africa	67 (19.9)

(Source: HMCK Study Report, p. 470-474)

HMCL was conducted at 60 study sites in 4 countries: United States (78.6%), Canada (5.2 %), Mexico (16 %), and Argentina (0.2 %).

5.2 Review Strategy

The clinical study reports of HMFN, HMCK, and HMCL were reviewed in detail. The *Reports of Analyses of Cymbalta Data from More than One Study of Pediatric Major Depressive Disorder* was also reviewed in detail. Raw data sets were reviewed in JMP and compared to the data detailed in the clinical study reports.

5.3 Discussion of Individual Studies/Clinical Trials

HMCK and HMCL were similar in design. Both were multicenter, randomized, double-blind, placebo-controlled study of duloxetine versus placebo in the treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder (DSM-IV-TR and MINI-KID). Both had a fluoxetine treatment arm to provide evidence of assay sensitivity. Both had a 2-week screening period, a 10-week double-blind acute therapy period, a 6-month double-blind extension period, and a 2-week tapering period. The main difference between the two trials was that HMCK employed flexible doses of duloxetine and fluoxetine during the 10-week acute therapy period and HMCL employed fixed doses of duloxetine and fluoxetine during this period. The results of HMCK and HMCL are discussed in detail in Sections 6 and 7.

6 Review of Efficacy

HMCK Efficacy Summary

HMCK was an adequate and well controlled study. However, it is inconclusive because neither duloxetine nor the active control (fluoxetine) demonstrated a statistically significant separation from placebo on the primary efficacy analysis of mean change from baseline to Week 10 on the CDRS-R total score. The mean improvement in depression symptom severity (as measured by the CDRS-R and CGI-S) was observed for the duloxetine-, fluoxetine-, and placebo-treated groups. However, the difference in mean change was not statistically significant for duloxetine compared to placebo and for fluoxetine compared to placebo.

In general, the secondary analyses of mean change on the CDRS-R total score, CDRS-R subscales, and CGI-Severity demonstrated no statistically significant differences for duloxetine-treated patients compared with placebo-treated patients at endpoint or between the fluoxetine-treated patients compared to placebo-treated patients at endpoint.

6.1 Indication

Treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder (MDD)

6.1.1 Methods

Objectives

Primary Objective:

- To assess the efficacy of duloxetine compared with placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who met criteria for MDD (DSM-IV-TR). The primary objective was evaluated by assessing the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.

Secondary Objectives:

- To test assay sensitivity by comparing fluoxetine with placebo treatment in children and adolescents with MDD, during a 10-week, double-blind, acute treatment phase, as measured by the mean change from baseline to endpoint on CDRS-R total score.
- To evaluate the efficacy of treatment with duloxetine compared with placebo in the treatment of children and adolescents with MDD, during a 10-week, double-blind, acute treatment phase, as measured by: (1) Mean change from

baseline to endpoint on the CDRS-R subscales; (2) Remission rates at endpoint using the CDRS-R total score; (3) Mean change from baseline to endpoint on the Clinical Global Impression of Severity (CGI-S) scale

- To assess changes in depressive symptoms of children and adolescents with MDD treated with duloxetine during a 6-month, double-blind extension phase using the above measures.
- To evaluate the safety and tolerability of treatment with duloxetine compared with placebo
- To characterize the pharmacokinetics (PK) of duloxetine at steady-state in the treatment of children and adolescents with MDD.
- To compare the steady-state duloxetine PK in the treatment of children and adolescents with MDD with historical adult duloxetine PK
- To investigate the relationship between duloxetine exposure and efficacy endpoints during a 10-week, double-blind, acute treatment phase in children and adolescents with MDD using steady-state duloxetine plasma concentrations and CDRS-R total score

Subjects

Key Inclusion Criteria

The study population for this trial included children and adolescents aged 7 to 17 years who met the criteria for MDD without psychotic features, single or recurrent episode, as defined by the DSM-IV-TR and supported by the MINI-KID. The MDD was of moderate or greater severity as determined by CDRS-R total score ≥40 and a CGI-S rating of ≥4.

Key Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria at study entry:

- Had a current or previous diagnosis of bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, anorexia, bulimia, obsessive compulsive disorder, or pervasive development disorder
- Patients with an Axis II disorder (eg, borderline personality disorder) were excluded if, in the judgment of the investigator, the Axis II disorder would have interfered significantly with protocol compliance.
- Had a history of DSM-IV-TR-defined substance abuse or dependence within the past year prior to study entry
- Had a current primary DSM-IV-TR Axis I disorder other than MDD or a current secondary DSM-IV-TR Axis I disorder that required any pharmacologic treatment
- Had 1 or more first-degree relatives (parents or siblings) with diagnosed bipolar I disorder.
- Had a significant suicide attempt within 1 year or were at risk of suicide
- Had a weight less than 20 kg at any screening phase visit.

- Had a lack of response to 2 or more adequate treatment trials of antidepressants at a clinically appropriate dose for a minimum of 4 weeks for the same MDD episode.
- Had had a lack of response of their current depressive episode to a clinically appropriate dose of fluoxetine or duloxetine
- Had initiated, stopped, or changed the type or intensity of psychotherapy within 6 weeks prior to Visit 1. Patients who would require a change to psychotherapy (start, stop, or change in type, intensity, or frequency) during Study Period II were excluded.
- Had a history of any seizure disorder
- Had a history of electroconvulsive therapy within 1 year
- Had treatment with a monoamine oxidase inhibitor (MAOI) within 14 days, or fluoxetine within 30 days of Visit 3
- Had acute liver injury (eg, hepatitis) or severe cirrhosis (Child-Pugh Class C)
- Had a serious or unstable medical illness, psychological condition, or clinically significant laboratory or ECG
- Female patients who were either pregnant or nursing or had recently given birth.
- Need to use thioridazine during the study or within 5 weeks after discontinuation of study drug or needed to use pimozide during the study.

Design

HMCK was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of duloxetine versus placebo in the treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder (DSM-IV-TR and MINI-KID). Safety and efficacy of duloxetine was assessed across a flexible dose range of 60 to 120 mg QD. A fluoxetine treatment arm (20-40 mg QD) was included to provide evidence of assay sensitivity.

The study used stratified randomization by age: children (7 through 11 years) and adolescents (12 through 17 years).Enrollment was monitored to assure that at least 40% of the enrolled patients were children, aged 7 to 11 years old.

The study consisted of 4 periods:

Period I: 2-week screening period

Period II: 10-week double-blind acute therapy period

Subjects were randomized 1:1:1 to receive one of three treatments:

- Duloxetine flexible dosing (60, 90, or 120 mg), given orally once a day
- Placebo (comparator), given orally once a day
- Fluoxetine (active control) flexible dosing (20 mg or 40 mg), given orally once a day

Period III: 6-month double-blind extension period

- Duloxetine flexible dosing (60, 90, or 120 mg), given orally once a day
- Fluoxetine flexible dosing (20 mg or 40 mg), given orally once a day

Period IV: 2-week tapering period

Primary efficacy endpoint

The primary efficacy endpoint was the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.

Study Period I: Screening

At Visit 1 or Visit 2, patients were evaluated by a psychiatrist to determine if they met criteria for MDD based upon DSM-IV-TR. The Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) was administered at both Visits 1 and 2 by different evaluators (at least one of whom was a psychiatrist) to support the diagnosis of MDD. The CDRS-R and CGI-S scale were administered to assess MDD severity. The CGI-Severity scale was administered by a physician and the CDRS-R was administered by a qualified clinician. Patients underwent clinical laboratory tests, 3 separate ECGs, and a physical examination to ensure consistency with inclusion and exclusion criteria.

Study Period II: 10-Week Double-Blind Acute Treatment Period

Patients initially had weekly visits (Visits 4 and 5), then a visit every 2 weeks (Visit 6), and then every 3 weeks (Visits 7, and 8).

Patients randomly assigned to placebo remained on placebo throughout Study Period II.

Patients randomly assigned to the duloxetine treatment group initiated duloxetine at 30 mg QD for 2 weeks. At Visit 5 (Week 2), the dose was escalated to 60 mg QD. At Visit 6 (Week 4) and thereafter, patients could have their duloxetine dose adjusted in 30 mg increments across the range of 60 to 120 mg QD.

For patients randomly assigned to the fluoxetine treatment group, the initial dose of fluoxetine was 10 mg QD for 2 weeks. Subsequent dose escalation to 20 mg QD occurred at Visit 5 (Week 2). Further escalation to a dose of 40 mg QD was allowed at Visit 6 (Week 4) and thereafter.

Dose adjustments (increases or decreases) for all patients occurred through the use of the Interactive Voice Response System (IVRS). At each visit, the patient's CGI-Severity score was entered into the IVRS. At Visit 6 and thereafter, the IVRS queried whether

the patient tolerated the current dose. If the patient tolerated the current dose and the CGI-Severity score was >2, then the dose was escalated within the allowed range as specified above. Dose increases could only occur at scheduled study visits. If necessary due to tolerability, dose decreases could occur at unscheduled visits. If at any time the patient could not tolerate the study drug well enough to remain compliant, the patient was discontinued. The patient was also discontinued from the study if at any time the investigator or patient felt that study drug therapy was not sufficiently helping the patient, or if the patient's safety was compromised.

Study Period III: 6-Month Double-Blind Extension

Study Period III was a 6-month extension phase designed to provide long-term exposure data and safety data. Patients were seen every 2 weeks for Visits 8 through 11, and then monthly for Visits 11 through 16. Investigators remained blinded to the patient's treatment.

For patients treated with fluoxetine during Study Period II, flexible dosing from 20 to 40 mg QD in 20-mg QD increments was allowed during Study Period III. For patients treated with duloxetine during Study Period II, flexible dosing and dose adjustments in 30-mg QD increments (across the range of 60 to 120 mg QD) were allowed during Study Period III.

Patients initially randomized to placebo in Study Period II received duloxetine 30 mg QD for the first 2 weeks of Study Period III. The duloxetine dose was then increased to 60 mg QD at Visit 9 (Week 12). After this visit, flexible dosing (with dose adjustments in 30-mg QD increments) was allowed across the range of 60 to 120 mg QD.

Duloxetine and fluoxetine dose escalation followed good clinical practices. The dose was increased based on the investigator's clinical judgment of treatment response and tolerability at the current dose. Dose adjustments (increases or decreases) for all patients occurred through the use of the IVRS. At each visit, the patient's CGI-S score was entered into the IVRS. At Visit 6 and thereafter, the IVRS queried whether the patient tolerated the current dose. If the patient tolerated the current dose and the CGI-S score was >2, then the dose was escalated. If the patient could tolerate the current dose and CGI-S score was ≤2, then the dose was maintained. If, in the opinion of the investigator, the patient could not tolerate the dose, then the dose was decreased. If a decrease in dose was requested through the IVRS and the patient was currently at the lowest dose (20 mg QD for fluoxetine or 60 mg QD for duloxetine), the IVRS dispensed study drug at the same dosage strength. If a dose decrease occurred due to tolerability, no further dose increases were permitted.

Dose increases could only occur at scheduled study visits. If necessary due to tolerability, dose decreases could occur at unscheduled visits. If at any time the patient could not tolerate the study drug well enough to remain compliant, the patient was

discontinued. The patient was also discontinued from the study if, at any time, the investigator or patient felt that study drug therapy was not sufficiently helping the patient, or if the patient's safety may have been compromised. In addition, investigators were instructed to discontinue patients who had not shown evidence of clinically relevant benefit (CGI-S score >3) by Visit 10 (Week 14). If the investigator determined that a patient with a CGI-S score >3 should continue in the study, the reason for continuing the patient was documented by the site.

Study Period IV: Tapering Phase

At discontinuation or at any point during the study after Visit 5, the study drug was tapered over a 2-week period to minimize the occurrence of discontinuation-emergent adverse events (AEs). Tapering was based on the investigator's determination of safety for the patient. If a patient had a TEAE believed to be study drug related, a taper may not have been advised.

6.1.2 Demographics

The study was conducted at 65 study centers in 9 countries in 4 world regions. Over 40% of subjects were from the United States.

Table 15: HMCK Baseline Demographic Characteristics--Region (Study Period II)

Region (%)	DLX60120 n=117	FLX2040 n=117	Placebo n=103	Total N=337
US	42.7	38.5	43. 7	**41.5 %**
Eastern Europe	35	35	30.1	33.5 %
South Africa	17.9	20.5	21.4	19.9 %
Western Europe	4.3	6	4.9	5 %

(Source: HMCK Study Report, p. 132)

The median age of the subjects was 13.5. The number of males was roughly equally to the number of females and most of the subjects were white.

Table 16: HMCK Baseline Demographic Characteristics--Study Period II (ITT)

Parameter	Result
Median Age	13.5 (40% children, 60% adolescents)
Sex	Males ≈ Females
Race	81.4% White; 12% African American

(Source: HMCK Study Report, p. 130-131)

There were no statistically significant differences between treatment groups for any of the baseline demographic characteristics.

Table 17: HMCK Baseline Demographic Characteristics by Treatment Group--Study Period II (ITT)

Parameter	DLX60120 n=117	FLX2040 n=117	Placebo n=103	Total N=337
Age (years)				
Mean	13.1	13.1	13.3	13.2
Median	13.7	13.34	13.4	13.5
Min-Max	7.1-17.9	7.1-17.8	7.3-17.9	7.1-17.9
Age Category				
7-11 years	40.2 %	42.7 %	36.9 %	40.1 %
12-17 years	59.8 %	57.3 %	63.1 %	59.9 %
Sex				
Male	45.3 %	47.9 %	50.5 %	47.8 %
Female	54.7 %	52.1 %	49.5 %	52.2 %
Achieved Mensus Prior to Study Entry	57.8 %	50.8 %	64.7 %	57.4 %
Race				
Black or African American	15.2 %	8.0 %	13.3 %	12.1 %
White	80.4 %	83 %	80.6 %	81.4 %
Mean BMI	21.7	21.7	21.2	21.5

(Source: HMCK Study Report, p. 130-132)

Baseline Psychiatric History

The mean age of first episode of MDD was 11.6. The mean number of previous episodes was 0.5 (median 0.0) and 71.5% of patients were experiencing a first episode of MDD. 49% had first-degree relative with depression.

Table 18: HMCK Family Psychiatric History in First-Degree Relative

Family Psychiatric History First-Degree Relative	DLX60120 n=117	FLX2040 n=117	Placebo n=103	Total N=337
Bipolar Disorder	2 (1.8)	0	2 (2.1)	4 (1.3)
Depression	53 (48.6)	50 (44.2)	54 (55.7)	**157 (49.2)**
Anxiety	16 (15)	15 (13.5)	13 (14.3)	44 (14.2)
Psychosis/Schizophrenia	0	2 (1.8)	1 (1.0)	3 (0.9)

(Source: HMCK Study Report, p 522)

There were no statistically significant differences for baseline severity of illness between treatment groups for any of the baseline CDRS-R total scores and CGI-S scores

Table 19: HMCK Baseline CDRS-R Total Score and CGI-S (Study Period II)

Scale	DLX60120 n=117	FLX2040 n=117	Placebo n=103
CDRS-R Total Score Mean	59.2	58.8	60.2
CGI-S Mean	4.5	4.5	4.6

(Source: HMCK Study Report, p. 137-138)

Previous therapies are those therapies for the treatment of any psychiatric condition that started and stopped prior to or on the date of visit 3. The most common previous therapies were "all other therapeutic products" (8.9%). All other therapeutic products included psychotherapy, counseling, and other nonpharmacological psychiatric or psychological therapy. Sertraline/sertraline hydrochloride (5.4%), amitriptyline (3.3%), escitalopram oxalate (3.0%), paracetamol (3.0%), ibuprofen (2.7%), fluoxetine/fluoxetine hydrochloride (2.1%), and obetrol (2.1%) were the most commonly used medications. There were no statistically significant differences between treatment groups in previous drug therapy for any psychiatric condition.

Concomitant Medications

For Study Period II, concomitant therapies with reported frequency ≥2% of patients were: paracetamol (13.1%), ibuprofen (9.2%), all other therapeutic products (5.0%), EMLA (3.6%), multivitamins (3.0%), amoxicillin (2.1%), and loratadine (2.1%). With the exceptions of amoxicillin and loratadine (both used by 3.9% of patients randomized to placebo and 0% of patients randomized to duloxetine (p=.047), there were no statistically significant differences between groups for reported concomitant therapies.

For Study Period III, concomitant therapies with reported frequency ≥2% of patients were: paracetamol (16.1%), ibuprofen (10.0%), all other therapeutic products (6.9%), amoxicillin (3.4%), diphenhydramine (3.1%), azithromycin (2.7%), and multivitamins (2.7%).

6.1.3 Subject Disposition

Table 20: HMCK Subject Disposition

Treatment	DLX60120	FLX2040	Placebo	Total
Randomized	117	117	103	337
Completed Period II (10-week double-blind acute therapy period)	87 (74.4%)	91 (77.8%)	87 (84.5%)	265 (78.6%)
Treatment	**DLX60120/DLX60120**	**FLX2040/FLX2040**	**PBO/DLX60120**	**Total**
Entered Period III	83	92	86	261
Completed Period III (6-month double-blind extension period)	56 (67.5%)	65 (70.7%)	69 (80.2%)	190 (72.8%)

(Source: HMCK Study Report, p. 107)
Note: A total of 91 fluoxetine-treated patients completed acute treatment and 92 fluoxetine-treated patients entered extension period, because one patient (Patient 706-7256) had discon inued from the acute period due to an AE and was accidentally dispensed drug. Based on intent-to-treat principle, this patient was included in the extension phase analyses; although, this pa ient did not contribute any data in the extension period.

The most common reasons for discontinuation from Study Period II were parent/caregiver decision (5.9%), patient decision (5.3%), and adverse event (3.9%). There were no statistically significant differences for treatment discontinuation between the treatment groups.

The most common reasons for discontinuation from Study Period III were also parent/caregiver decision (6.9%), patient decision (6.1%), and adverse event (5.4%).

Table 21: HMCK Periods II and III Reasons for Study Discontinuation (ITT)

Study Period II Reasons for Discontinuations	DLX60120 (N=117) n (%)	FLX2040 (N=117) n (%)	Placebo (N=103) n (%)	Total (N=337) n (%)
Overall n (%)	30 (25.6)	26 (22.2)	16 (15.5)	72 (21.4)
Adverse Event	9 (7.7)	1 (0.9)	3 (2.9)	13 (3.9)
Lost to Follow Up	2 (1.7)	4 (3.4)	1 (1.0)	7 (2.1)
Death	0	0	0	0
Protocol Violation	0	2 (1.7)	1 (1.0)	3 (0.9)
Subject Decision	4 (3.4)	10 (8.5)	4 (3.9)	18 (5.3)
Parent/Caregiver Decision	11 (9.4)	5 (4.3)	4 (3.9)	20 (5.9)
Physician Decision	1 (0.9)	1 (0.9)	1 (1.0)	3 (0.9)
Sponsor Decision	1 (0.9)	0	0	1 (0.3)
Lack of Efficacy	2 (1.7)	3 (2.6)	2 (1.9)	7 (2.1)

Study Period III Reasons for Discontinuations	DLX60120/DLX60120 (N=83) n (%)	FLX2040/FLX2040 (N=92) n (%)	PBO/DLX60120 (N=86) n (%)	Total (N=261) n (%)
Overall n (%)	27 (32.5)	26 (28.3)	17 (19.8)	70 (26.8)
Adverse Event	2 (2.4)	8 (8.7)	4 (4.7)	14 (5.4)
Lost to Follow Up	3 (3.6)	0	1 (1.2)	4 (1.5)
Death	0	0	0	0
Protocol Violation	2 (2.4)	2 (2.2)	4 (4.7)	8 (3.1)
Subject Decision	7 (8.4)	6 (6.5)	3 (3.5)	16 (6.1)
Parent/Caregiver Decision	10 (12.0)	4 (4.3)	4 (4.7)	18 (6.9)
Physician Decision	1 (1.2)	2 (2.2)	0	3 (1.1)
Sponsor Decision	0	0	0	0
Lack of Efficacy	2 (2.4)	4 (4.3)	1 (1.2)	7 (2.7)

(Source: HMCK Study Report, p. 96, 107)

Protocol Violations Study Period II

The most common protocol violations were *visit interval outside specified limits*, *noncompliance to study drug regimen*, and *use of prohibited concomitant medications*. Treatment noncompliance was defined as: <80% or >120% of study drug was taken for ≥2 visits (consecutive or nonconsecutive).

The sponsor notes that, in some cases, the listing of patients with Important Protocol Violations is conservative and identifies patients with protocol violations when a violation did not occur (e.g., a patient taking an excluded medication for the acute treatment of an SAE).

Table 22: HMCK Protocol Violations ITT Population Study Period II

Protocol Violations Study Period II	DLX60120 (N=117) n (%)	FLX2040 (N=117) n (%)	Placebo (N=103) n (%)	Total (N=337) n (%)
Non-compliance to Study Drug Regimen	9 (7.7)	1 (0.9)	3 (2.9)	13 (3.9)
Improper Administration of Informed Consent	0	0	0	0
Use of Prohibited Concomitant Medications	5 (4.3)	4 (3.4)	3 (2.9)	12 (3.6)
Violation of Inclusion and Exclusion Criteria	2 (1.7)	0	0	2 (0.6)
Key Measurements Not Collected	1 (0.9)	1 (0.9)	1 (1.0)	3 (0.9)
Visit Interval Outside Specified Limits	13 (11.1)	11 (9.4)	7 (6.8)	31 (9.2)
Other Protocol Violations	0	2 (1.7)	1 (1.0)	3 (0.9)
Patients with ≥ 1 Protocol Violation	27 (23.1)	18 (15.4)	13 (12.6)	58 (17.2)

(Source: HMCK Study Report, p. 114)

Reviewer Comment:

The sponsor also includes a table of *other important patient and site level protocol violations and extraordinary events* that were not captured in Table 22. It is unclear to this reviewer why these protocol violations were not included in the above table.

Table 23: HMCK Other Protocol Violations and Extraordinary Events (Study Period II)

Table HMCK.10.4. Other Protocol Violations and Extraordinary Events (Study Period II)

Category	DLX 60120	FLX 2040	PBO	Total
Unqualified Personnel Performing Study-Related Activity	10	5	6	21
Improper Administration of Informed Consent/Assent	6	5	4	15
Improper Administration of Efficacy Measure	3	4	1	8
Key Safety Measurement not Reviewed Prior to Randomization	3	6	0	9
Violation of Inclusion/Exclusion Criteria	0	3	3	6
Improper Collection of Safety Information	1	1	1	3
Key Safety Measures Not Collected	2	1	0	3
Improper Administration of Diagnostic Tool	1	1	0	2
Improper Administration of Investigational Product	0	0	1	1
Use of Prohibited/Restricted Medication	0	1	0	1

Note: There were site level deviations for site 310 and 801 related to documentation practices. See Other Protocol Violations and Extraordinary Events patient listings (Table HMCK.14.5) for more details.
Sources: Listing of protocol violations from monitoring report. Dosing: l_15_9_1_1_pdrug.sas.
(Source: HMCK Study Report, p. 115)

Unqualified personnel performed study-related activity included:

- CGI-S was performed by a non-physician
- Clinician administered scales prior to completing training

Improper administration of efficacy measure included:

- MINI-KID was performed by the same investigator at Visit 1 and 2
- Patient and parent were interviewed by different raters for CDRS-R scale
- Parent interviewed for CDRS-R scale over telephone
- Parent/Guardian not interviewed for CDRS-R scale

Reviewer's Comment:
These types of protocol violations described above could have impacted the integrity of the study but the numbers appear to be relatively low and evenly distributed among the treatment groups.

There were also site level deviations:

Table 24: HMCK Site Level Protocol Deviations Study Period II

Listing of Other Protocol Violations and Extraordinary Events

Inv Number	Patient Number	Treatment	Visit	Protocol Violation/ Extraordinary Event Category	Description
310	NA	Site Level Deviation	NA	Site Documentation Practices	Inappropriate source documentation at site.
801	NA	Site level Deviation	NA	Site Documentation Practices	Site had general source to eCRF discrepancies. The majority of scales completed in pencil. Temperature log inappropriately completed.

Sources: Listing of protocol violations from monitoring report. Dosing. l_15_9_1_1_pdrug.sas.
(Source: HMCK Study Report, p. 518)

Reviewer Comment:
Site 310 was in Germany and enrolled 2 subjects and Site 801 was in Slovakia and enrolled 1 subject. Therefore, it is unlikely that these site level protocol deviations significantly affected the results of this study.

Protocol Violations Study Period III
The most common protocol violations were *visit interval outside specified limits* and *noncompliance to study drug regimen.*

Table 25: HMCK Protocol Violations Study Period III

Protocol Violations Study Period III	DLX60120/DLX60120 (N=83) n (%)	FLX2040/FLX2040 (N=92) n (%)	PBO/DLX60120 (N=86) n (%)	Total (N=261) n (%)
Non-compliance to Study Drug Regimen	7 (8.4)	9 (9.8)	9 (10.5)	25 (9.6)
Improper Administration of Informed Consent	0	0	0	0
Use of Prohibited Concomitant Medications	3 (3.6)	5 (5.4)	4 (4.7)	12 (4.6)
Violation of Inclusion and Exclusion Criteria	0	0	0	0 (0.6)
Key Measurements Not Collected	1 (1.2)	0	1 (1.2)	2(0.8)

Visit Interval Outside Specified Limits	17 (20.5)	9 (9.8)	9 (10.5)	35 (13.4)
Other Protocol Violations	2 (2.4)	0	1 (1.2)	3 (1.1)
Patients with ≥ 1 Protocol Violation	25 (30.1)	21 (22.8)	21 (24.4)	67 (25.7)

(Source: HMCK Study Report, p. 120)

Table 26: HMCK Other Protocol Violations and Extraordinary Events (Study Period III)

Table HMCK.10.7. Other Protocol Violations and Extraordinary Events (Study Period III)

Category	DLX60120/ DLX60120	FLX2040/ FLX2040	PBO/ DLX60120	Total
Improper Administration of Informed Consent/Assent	0	5	6	11
Improper Administration of Efficacy Measure	1	1	5	7
Unqualified Personnel Performing Study-Related Activity	0	2	1	3
Key Safety Measurement Not Collected	1	1	0	2
Use of Prohibited/Restricted Concomitant Medications	0	0	1	1

Sources: Listing of protocol violations from monitoring report. Dosing: l_15_9_1_1_pdrug.sas.

(Source: HMCK Study Report, p. 121)

Compliance

A patient was defined to be compliant at a visit if he/she had taken at least 80% and not more than 120% of the study drug capsules prescribed for that interval. A patient was defined to be compliant overall if the patient was compliant at all visits during the Study Period. For Study Period II, total compliance at each visit was at least 94%. Overall compliance was 79% for Study Period II. There were no statistically significant differences between treatment groups for overall compliance.

Table 27 : HMCK Overall Study Drug Compliance--Study Period II

Overall Compliance %	DLX60120 N=117	FLX2040 N=117	Placebo N=103	Total N=337
Yes	76.7	79.3	81.6	79.1
No	23.3	20.7	18.4	20.9

(Source: HMCK Study Report, p. 142)

For Study Period III, total compliance at each visit was at least 91% and overall compliance was 69.5%. The DLX60120/DLX60120 group appeared to have a lower overall compliance than the other treatment groups.

Table 28: HMCK Overall Study Drug Compliance--Study Period III

Overall Compliance %	DLX60120/DLX60120 N=83	FLX2040/FLX2040 N=92	PBO/DLX60120 N=86	Total N=261
Yes	62.2	71.4	74.4	69.5
No	37.8	28.6	25.6	30.5

(Source: HMCK Study Report, p. 628)

6.1.4 Analysis of Primary Endpoint(s)

Sponsor's Primary Analysis

The primary efficacy analysis was the difference between duloxetine QD (DLX60120) and placebo at the last visit in Study Period II (Visit 8, Week 10) based on an MMRM analysis on mean change from baseline in the CDRS-R total. The ITT population was used to perform this analysis.

Duloxetine was not significantly different from placebo in the treatment of children and adolescents with MDD as measured by the mean change from baseline to endpoint (10 weeks) CDRS-R total score. In addition, the active control (fluoxetine), with known efficacy in children and adolescents with MDD, was not statistically significantly different from placebo on the primary outcome measure in this study.

Table 29: HMCK CDRS-R Total Score: MMRM Mean Change from Baseline to Week 10 (Study Period II)

Therapy	N	LS Mean	LS Mean Change	LS Mean Change Difference	p-value
DLX (60-120 mg)	88	35.0	-24.3		
FLX (20- 40 mg)	95	35.6	-23.7		
Placebo	89	35.0	-24.3		
DLX (60-120 mg) versus Placebo				0	0.999
FLX (20-40 mg) versus Placebo				0.6	0.687
DLX (60-120 mg versus FLX (20-40 mg)				-0.6	0.686

(Source: HMCK Study Report, p. 150)

FDA's Primary Analysis

Dr. Andrejus Parfionaovas and Dr. George Kordzakhia of the Division of Biometrics I reviewed Study HMCK. They concluded that the study was conducted in accordance with the statistical analysis plan agreed upon by the Agency. They found the quality and integrity of the submitted data to be acceptable. They were able to reproduce the primary analysis dataset from the raw data and trace how the primary endpoint was derived. The reviewers confirmed the sponsor's analysis results for the primary efficacy endpoint. No statistically significant treatment effect was observed for either the investigational drug or the active control as demonstrated in Table 8 of the FDA Biometrics Review.

Table 8. Primary Efficacy Analysis for CDRS-TS at Visit 8 for F1J-MC-HMCK Study (Analysis Set).

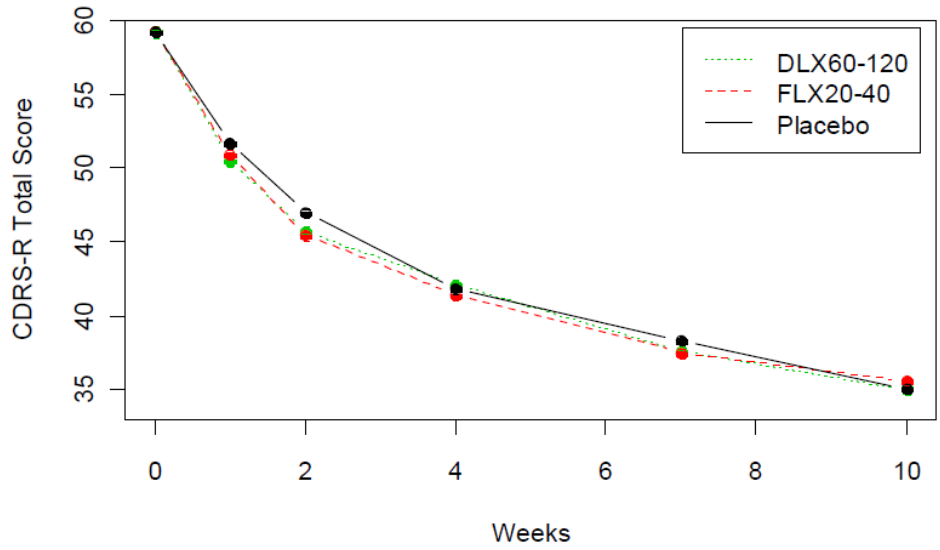
	N	LS mean	LS mean Change (SE)	LS Mean Change Difference (SE)	95% CI for Difference	p-value*
DLX (60-120 mg)	88	35.0	-24.3 (1.09)			
FLX (20-40 mg)	95	35.6	-23.7 (1.06)			
Placebo	89	35.0	-24.3 (1.11)			
DLX vs. Placebo				0.0 (1.53)	(-3.0, 3.0)	0.999
FLX vs. Placebo				0.6 (1.51)	(-2.4, 3.6)	0.687
DLX vs. FLX				-0.6 (1.50)	(-3.6, 2.4)	0.686

Source: F1J-MC-HMCK Clinical Study Report Table HMCK.11.5, pg. 150.

(Source: FDA Biometrics Review, p. 14)

The LS Mean CDRS-R total scores of the MMRM Analysis are depicted for each treatment group in Figure 3 of the FDA Biometrics Review. The trends for all treatment subgroups were very similar without clear separation from placebo throughout the visits (except Visit 2).

Figure 3. CDRS-R Total Score by visit in patients of F1J-MC-HMCK Study (ITT Population).



Source: computed by the reviewers.

(Source: FDA Biometrics Review, p. 15)

6.1.5 Analysis of Secondary Endpoints(s)

In general, the secondary analyses of mean change on the CDRS-R total score, CDRS-R subscales, and CGI-Severity showed no statistically significant differences for duloxetine-treated patients compared with placebo-treated patients at endpoint or between the fluoxetine-treated patients compared to placebo-treated patients at endpoint.

For example, one of the secondary endpoints was the CGI-S mean change from baseline to Week 10 (MMRM). No statistically significant differences were observed for the duloxetine- or fluoxetine-treated groups compared to the placebo-treated group at endpoint.

Table 30: HMCK CGI-S: MMRM Mean Change from Baseline to Week 10 (Study Period II)

Therapy	N	LS Mean	LS Mean Change	LS Mean Change Difference	p-value
DLX (60-120 mg)	88	2.7	-1.9		
FLX (20-40 mg)	95	2.7	-1.8		
Placebo	89	2.6	-1.9		
DLX (60-120 mg) versus Placebo				0	0.943
FLX (20-40 mg) versus Placebo				-0.1	0.583
DLX (60-120 mg) versus FLX (20-40 mg)				0	0.627

(Source: HMCK Study Report, p. 175)

6.1.7 Subpopulations

In subgroup analyses of mean change in the CDRS-R total score by age (children vs. adolescent), gender, race, ethnicity, and region, differences between the active drug compared to placebo were not statistically significant in any subgroup.

There were no statistically significant differences in LS mean change from baseline to endpoint in CDRS-R total score between the duloxetine-treated children compared with the placebo-treated children (ages 7 to 11 years) or between the duloxetine-treated adolescents compared with the placebo-treated adolescents (ages 12 to 17 years).

Table 31: HMCK ANCOVA Change from Baseline CDRS-R Total Score to Endpoint by Age Group (Study Period II)

Treatment	Age (7-11)	Age (12-17)	Age (7-11)		Age (12-17)	
	LS mean change	LS mean change	LS Mean Diff	p-value	LS Mean Diff	p-value
DLX(60-120 mg)	-23.1	-21.6				
FLX (20-40 mg)	-22.3	-22.4				
Placebo	-22.4	-23.2				
DLX (60-120 mg) versus Placebo			-0.6	0.815	1.6	0.472
FLX (20-40 mg) versus Placebo			0.1	0.966	0.8	0.728
DLX (60-120 mg) versus FLX (20-40 mg)			-0.7	0.773	0.8	0.715

(Source: HMCK Study Report, p. 639)

There were also no statistically significant differences in LS mean change from baseline to endpoint in CDRS-R total score between the duloxetine-treated females compared with the placebo-treated females or between the duloxetine-treated males compared with the placebo-treated males. The treatment-by-pooled investigator interaction and treatment-by-region interaction were also not statistically significant for duloxetine-treated patients compared with the placebo group.

The treatment-by-race interaction was statistically significant (p=.011). The placebo group had greater improvement than either the duloxetine or fluoxetine group in Black subjects.

Table 32: HMCK Change from Baseline to Endpoint in CDRS-R Total Score by Race (Study Period II)

Treatment	Black	White
	Mean Change	Mean Change
DLX (60-120 mg)	-17.6	-21.9
FLX (20-40 mg)	-16.4	-23.7
Placebo	-27.4	-22.0

(Source: HMCK Study Report, p. 644)

However, there were no statistically significant differences in LS mean change from baseline to endpoint CDRS-R total score between duloxetine-treated subjects and placebo-treated subjects.

Table 33: HMCK LS Mean Change from Baseline to Endpoint in CDRS-R Total Score by Race (Study Period II)

Treatment	Black	White	Black		White	
	LS mean change	LS mean change	LS Mean Diff	p-value	LS Mean Diff	p-value
DLX60120	-17.6	-22.2				
FLX2040	-14.5	-23.5				
Placebo	-20.3	-21.4				
DLX60120 versus Placebo			2.7	0.593	-0.8	0.645
FLX2040 versus Placebo			5.7	0.337	-2.0	0.225
DLX60120 versus FLX2040			-3.0	0.617	1.3	0.436

(Source: HMCK Study Report, p. 645, 644)

No statistically significant differences in LS mean change from baseline to endpoint in CDRS-R total score were observed for fluoxetine-treated patients compared to placebo-treated patients for age, gender, race, ethnicity, or regional subgroups

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

During Study Period II, most subjects had a modal dose of duloxetine 90 mg. For completers of Study Period III, most subjects had a modal dose of duloxetine 120 mg. Fluoxetine 40 mg was the most common modal dose in Study Periods II and III.

Table 34: HMCK Modal Dose and Last Prescribed Dose (Study Period II)

Dose	Modal Dose for n (%)	Last Prescribed Dose at LOCF Endpoint for n (%)
DLX 30 mg	17 (14.5)	13 (11.1)
DLX 60	29 (24.8)	20 (17.1)
DLX 90	38 (32.5)	32 (27.4)
DLX 120	32 (27.4)	51 (43.6)
FLX 10	9 (7.7)	9 (7.7)
FLX 20	28 (23.9)	22 (18.8)
FLX 40	80 (68.4)	86 (73.5)

(Source: HMCK Study Report, p. 216)

Table 35: HMCK Modal Dose for Completers (Study Period III)

Dose	Modal Dose for n (%)
DLX 30 mg	0 (0)
DLX 60	48 (38.1)
DLX 90	15 (11.9)
DLX 120	63 (50.0)
FLX 20	10 (15.2)
FLX 40	56 (84.8)

(Source: HMCK Study Report, p. 222)

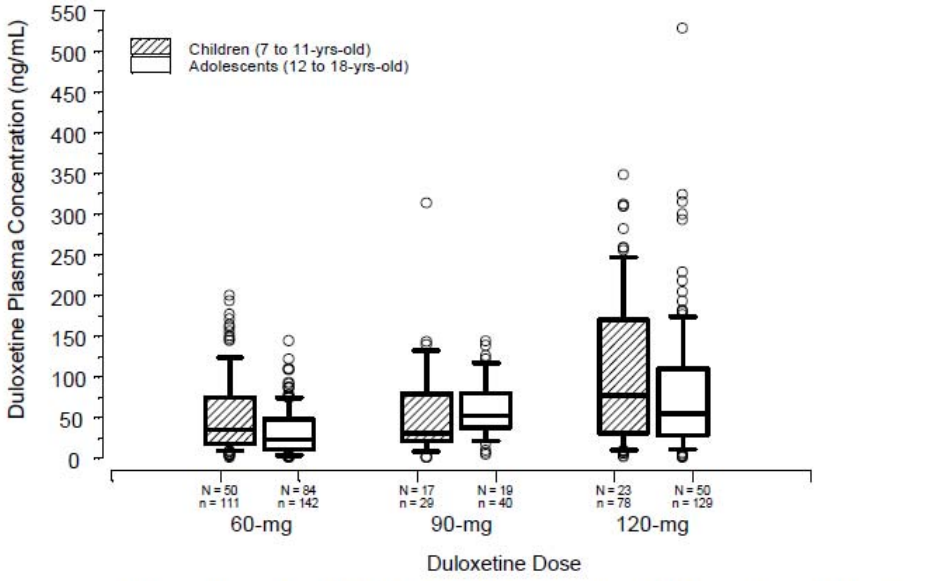
Duloxetine plasma concentrations appeared to increase in a linear manner with increasing doses in the dose range of 60 to 120 mg. There were no discernible differences in median duloxetine concentration in children and adolescents.

Table 36: HMCK Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose

Dose (mg)	**30** (N=3) (n=3)	**60** (N=134) (n=253)	**90** (N=36) (n=69)	**120** (N=73) (n=207)
Concentration (ng/mL)	35.3± 35.1	41.4± 39.5	60.6± 50.4	89.6± 85.1

(Source: HMCK Study Report, p. 200)

Figure 3: HMCK Observed Duloxetine Plasma Concentrations at Steady-State in Pediatric Patients



Abbreviations: N = number of patients; n = number of duloxetine concentrations

(Source: HMCK Study Report, p. 203)

Dose-normalized steady state duloxetine concentrations were also similar in subgroups defined by sex, ethnicity, race, age, and body weight.

HMCL Efficacy Summary

HMCL was an adequate and well controlled study. However, the study is inconclusive because neither duloxetine nor the active control (fluoxetine) demonstrated a statistically significant separation from placebo on the primary efficacy analysis of mean change from baseline to Week 10 on the CDRS-R total score. Mean improvement in depression symptom severity (as measured by the CDRS-R and CGI-S) was observed for the duloxetine-, fluoxetine-, and placebo-treated groups. However, the difference in mean change among these groups was not statistically significant.

In general, the secondary analyses of mean change on the CDRS-R total score, CDRS-R subscales, and CGI-Severity showed no statistically significant differences for duloxetine-treated patients compared with placebo-treated patients at endpoint or between the fluoxetine-treated patients compared to placebo-treated patients at endpoint.

6.2 Indication

Treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder

6.2.1 Methods

Objectives

Primary Objective:

- To assess the efficacy of duloxetine 60 mg QD compared with placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who met criteria for MDD (DSM-IV-TR). The primary objective was evaluated by assessing the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.

Secondary Objective:

- To test assay sensitivity by comparing fluoxetine with placebo treatment in children and adolescents with MDD, during a 10-week, double-blind, acute treatment phase, as measured by the mean change from baseline to endpoint on CDRS-R total score.
- To evaluate the efficacy of treatment with duloxetine 30 and 60 mg QD compared with placebo in the treatment of children and adolescents with MDD, during a 10-week, double-blind, acute treatment phase, as measured by: (1) Mean change from baseline to endpoint on the CDRS-R subscales; (2) Remission rates at endpoint using the CDRS-R total score; (3) Mean change from baseline to endpoint on the Clinical Global Impression of Severity (CGI-S)

scale; (4) Mean change from baseline to endpoint on the CDRS-R total score for duloxetine 30 mg QD

- To assess changes in depressive symptoms of children and adolescents with MDD treated with duloxetine during a 6-month, double-blind extension phase using the above measures.
- To evaluate the safety and tolerability of treatment with duloxetine 30 and 60 mg QD compared with placebo
- To characterize the pharmacokinetics (PK) of duloxetine at steady-state in the treatment of children and adolescents with MDD.
- To compare the steady-state duloxetine PK in the treatment of children and adolescents with MDD with historical adult duloxetine PK
- To investigate the relationship between duloxetine exposure and efficacy endpoints during a 10-week, double-blind, acute treatment phase in children and adolescents with MDD using steady-state duloxetine plasma concentrations and CDRS-R total score

Subjects

Key Inclusion Criteria
The study population for this trial included children and adolescents aged 7 to 17 years who met the criteria for MDD without psychotic features, single or recurrent episode, as defined by the DSM-IV-TR and supported by the MINI-KID. The MDD was of moderate or greater severity as determined by CDRS-R total score ≥40 and a CGI-S rating of ≥4.

Key Exclusion Criteria
Same as exclusion criteria for HMCK

Design

HMCL was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of duloxetine versus placebo in the treatment of children and adolescents (7-17 years of age) with Major Depressive Disorder (DSM-IV-TR and MINI-KID). Safety and efficacy of fixed doses of duloxetine (30 and 60 mg QD) were assessed. A fluoxetine treatment arm (20 mg QD) was included to provide evidence of assay sensitivity.

The study consisted of 4 periods:

Period I: 2-week screening period

Period II: 10-week double-blind acute therapy period

- Duloxetine dose (30 and 60 mg), given orally once a day
- Placebo (comparator), given orally once a day
- Fluoxetine (active control) dose (20 mg), given orally once a day

Period III: 6-month double-blind extension period

- Duloxetine flexible dosing (60, 90, or 120 mg), given orally once a day
- Fluoxetine flexible dosing (20 or 40 mg), given orally once a day

Period IV: 2-week tapering period

Primary efficacy endpoint

The primary efficacy endpoint was the mean change from baseline to endpoint (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo.

Study Period I: Screening

At Visit 1 or Visit 2, patients were evaluated by a psychiatrist to determine if they met criteria for MDD based upon DSM-IV-TR. The Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) was administered at both Visits 1 and 2 by different evaluators (at least one of whom was a psychiatrist) to support the diagnosis of MDD. The CDRS-R and CGI-S scale were administered to assess MDD severity. The CGI-Severity scale was administered by a physician and the CDRS-R was administered by a qualified clinician. Patients underwent clinical laboratory tests, 3 separate ECGs, and a physical examination to ensure consistency with inclusion and exclusion criteria.

Study Period II: 10-Week Double-Blind Acute Treatment Period

Patients initially had weekly visits (Visits 4 and 5), then a visit every 2 weeks (Visit 6), and then every 3 weeks (Visits 7, and 8).

Patients randomly assigned to placebo remained on placebo throughout Study Period II.

For patients randomly assigned to the fluoxetine treatment group, the initial dose of fluoxetine was 10 mg QD for 2 weeks. Subsequent dose escalation to 20 mg QD occurred at Visit 5 (Week 2).

Patients randomly assigned to the duloxetine 30 mg QD treatment group initiated duloxetine at 30 mg QD and maintained that dose throughout Study Period II.

For patients randomly assigned to the duloxetine 60 mg QD treatment group, the initial dose of duloxetine was 30 mg QD for 2 weeks followed by escalation to 60 mg QD at Visit 5 (Week 2). Patients remained at 60 mg QD for the duration of Study Period II.

If, at any time, the patient could not tolerate the study drug well enough to remain compliant, the patient was discontinued. The patient was also discontinued from the

study if, at any time, the investigator or patient felt that study drug therapy was not sufficiently helping the patient, or if the patient's safety was compromised.

Study Period III: 6-Month Double-Blind Extension

Study Period III was a 6-month extension phase designed to provide long-term exposure data and safety data. Patients were seen every 2 weeks for Visits 8 through 11, and then monthly for Visits 11 through 16. Investigators remained blinded to the patient's treatment.

Patients in the duloxetine and fluoxetine treatment groups entered Study Period III on their medication and dose at the end of the Study Period II. For patients treated with fluoxetine during Study Period II, flexible dosing from 20 to 40 mg QD in 20-mg QD increments was allowed during Study Period III. For patients treated with duloxetine during Study Period II, flexible dosing and dose adjustments in 30-mg QD increments (across the range of 60 to 120 mg QD) were allowed during Study Period III.

Patients initially randomized to placebo in Study Period II received duloxetine 30 mg QD for the first 2 weeks of Study Period III. The duloxetine dose was then increased to 60 mg QD at Visit 9 (Week 12). After this visit, flexible dosing (with dose adjustments in 30-mg QD increments) was allowed across the range of 60 to 120 mg QD.

Duloxetine and fluoxetine dose escalation followed good clinical practices. The dose was increased based on the investigator's clinical judgment of treatment response and tolerability at the current dose. Dose adjustments (increases or decreases) for all patients occurred through the use of the IVRS. At each visit, the patient's CGI-S score was entered into the IVRS. At Visit 8 and thereafter, the IVRS queried whether the patient tolerated the current dose. If the patient tolerated the current dose and the CGI-S score was >2, then the dose was escalated. If the patient could tolerate the current dose and CGI-S score was ≤2, then the dose was maintained. If, in the opinion of the investigator, the patient could not tolerate the dose, then the dose was decreased. If a decrease in dose was requested through the IVRS and the patient was currently at the lowest dose (20 mg QD for fluoxetine or 60 mg QD for duloxetine), the IVRS dispensed study drug at the same dosage strength. If a dose decrease occurred due to tolerability, no further dose increases were permitted.

Dose increases could only occur at scheduled study visits. If necessary due to tolerability, dose decreases could occur at unscheduled visits. If at any time the patient could not tolerate the study drug well enough to remain compliant, the patient was discontinued. The patient was also discontinued from the study if, at any time, the investigator or patient felt that study drug therapy was not sufficiently helping the patient, or if the patient's safety may have been compromised. In addition, investigators were instructed to discontinue patients who had not shown evidence of clinically relevant benefit (CGI-S score >3) by Visit 10 (Week 14). If the investigator determined

that a patient with a CGI-S score >3 should continue in the study, the reason for continuing the patient was documented by the site.

Study Period IV: Tapering Phase

At discontinuation or at any point during the study after Visit 5, the study drug was tapered over a 2-week period to minimize the occurrence of discontinuation-emergent adverse events (AEs). Tapering was based on the investigator's determination of safety for the patient. If a patient had a TEAE believed to be study drug related, a taper may not have been advised.

6.2.2 Demographics

The study was conducted at 60 study centers in 4 countries.

Table 37: HMCL Baseline Demographic Characteristics Study Period II--Region

Country	% Subjects
US	78.6 %
Canada	5.2 %
Mexico	16.0 %
Argentina	0.2 %

(Source: HMCL Study Report, p.88)

Table 38: HMCL Baseline Demographic Characteristics by Treatment Group--Region

Region (%)	DLX60 N=108	DLX30 N=116	FLX20 N=117	Placebo N=122	Total N=463
US/Canada	85.2	78.4	85.5	86.1	**83.8**
Mexico/Argentina	14.8	21.6	14.5	13.9	16.2

(Source: HMCL Study Report, p. 125)

The median age of the subjects was 13. Overall, the number of males was roughly equally to the number of females and the majority of the subjects were white. The proportion of males to females in the duloxetine 30 mg-treated group was significantly higher than the proportion of males to females in the duloxetine 60 mg treated group (p=.032) and in the placebo-treated group (p=.014). There were no statistically significant differences between treatment groups for any other patient demographic.

Table 39: HMCL Baseline Demographic Characteristics--Study Period II (ITT)

Parameter	Result
Mean Age	13 (42% children, 58% adolescents)
Sex	Males ≈ Females
Race	54.5% White

(Source: HMCL Study Report, p. 123-124)

Table 40: HMCL Baseline Demographic Characteristics by Treatment Group--Study Period II (ITT)

Parameter	DLX60 N=108	DLX30 N=116	FLX20 N=117	Placebo N=122	Total N=463
Age (years)					
Mean	12.9	12.9	13.0	13.1	12.98
Median	13.2	13.1	13.3	13.2	13.2
Min-Max	7.1-17.9	7.1-18	7.1-18	7.0-17.9	7.0-18.0
Age Category					
7-11 years	40.7 %	42.2%	42.7 %	40.2 %	41.5 %
12-17 years	59.3 %	57.8%	57.3 %	59.8 %	58.5 %
Sex					
Male	44.4 %	59.5%	47.9 %	43.4 %	48.8 %
Female	55.6 %	40.5%	52.1 %	56.6 %	51.2 %
Achieved Mensus Prior to Study Entry	71.7 %	68.1%	55.7 %	62.3 %	64.1 %
Race					
Black or African American	26.5 %	18.6%	18.4 %	20.2 %	20.8 %
White	52.9 %	54.0%	58.8 %	52.1 %	54.5 %
American Indian/Alaska Native	14.7 %	20.4%	14.0 %	16.0 %	16.3 %
Mean BMI	23.7	22.5	23.2	23.98	23.3

(Source: HMCL Study Report, p. 123-125)

Baseline Psychiatric History

The mean age of first episode of MDD was 10.18 years. The mean number of previous episodes was 1.6 and 42% of patients were experiencing a first episode of MDD. 59% had first-degree relative with depression.

Table 41: HMCL Family Psychiatric History

Family Psychiatric History First-Degree Relative	DLX60 N=108	DLX30 N=116	FLX20 N=117	Placebo N=122	Total N=463
Bipolar Disorder	1 (0.9)	1 (0.9)	0	1 (0.8)	3 (0.7)
Depression	56 (53.8)	65 (56.5)	77 (67.5)	70 (58.3)	**268 (59.2)**
Anxiety	20 (18.9)	19 (16.4)	22 (19.6)	17 (14.4)	78 (17.3)
Psychosis/Schizophrenia	0	3 (2.6)	2 (1.8)	3 (2.5)	8 (1.8)

(Source: HMCL Study Report, p. 130-131)

Table 42: HMCL Mean Baseline CDRS-R Total Score and CGI-S (Study Period II)

Scale	DLX60 N=108	DLX30 N=116	FLX20 N=117	Placebo N=122
CDRS-R Total Score	59.3	59.8	57.9	58.2
CGI-S	4.6	4.6	4.6	4.5

(Source: HMCL Study Report, p. 130-131)

Previous therapies are those therapies for the treatment of any psychiatric condition that started and stopped prior to or on the date of visit 3. The most common previous therapies were "all other therapeutic products" (9.7%). All other therapeutic products included psychotherapy, counseling, and other nonpharmacological psychiatric or psychological therapy. Methylphenidate hydrochloride (5.4%), fluoxetine/fluoxetine hydrochloride (5.2%), sertraline (4.3%), escitalopram oxalate (4.3%), obetrol (3.7%), ibuprofen (3.2%), and atomoxetine hydrochloride (2.2%) were the most commonly used medications. There were no statistically significant differences between treatment groups in previous drug therapy for any psychiatric condition.

Concomitant Medications

For Study Period II, concomitant therapies with reported frequency >2% of patients were: ibuprofen (16.4%), paracetamol (12.5%), salbutamol (5.0%), multivitamins (4.1%), all other therapeutic products (4.1%), amoxicillin (3.7%), naproxen sodium (3.2%), cetirizine hydrochloride (3.2%), loratadine (2.6%), and fluticasone propionate (2.2%). There were no statistically significant differences between groups for reported concomitant therapies, with the exception that a statistically significantly lower incidence of fluoxetine-treated patients were on cetirizine hydrochloride compared with both duloxetine 30mg- and placebo-treated patients (p=.014).

For Study Period III, concomitant therapies with reported frequency >2% of patients were: ibuprofen (18.4%), paracetamol (16.3%), loratadine (5.3%), salbutamol (5.0%), azithromycin (4.7%), multivitamins (4.4%), all other therapeutic products (4.1%), cetirizine hydrochloride (3.8%), bismuth subsalicylate (3.8%), amoxicillin (3.4%); diphenhydramine hydrochloride (3.4%), naproxen sodium (2.8%), Bactrim (2.5%), and medroxyprogesterone acetate (2.2%).

6.2.3 Subject Disposition

Table 43: HMCL Subject Disposition

Treatment	DLX60	DLX30	FLX20	Placebo	Total
Randomized	108	116	117	122	463
Completed Period II (10-week double-blind acute herapy period)	75 (69.4%)	81 (69.8)	84 (71.8%)	85 (69.7%)	325(70.2%)
Treatment	**DLX60/DLX60120**	**DLX30/DLX60120**	**FLX20/FLX2040**	**PBO/DLX60120**	**Total**
Entered Period III	73	81	84	82	320
Completed Period III (6-month double-blind extension period)	43 (58.9%)	50 (61.7%)	49 (58.3%)	44 (53.7%)	186(58.1%)

(Source: HMCL Study Report, p. 90, 101)

The most common reasons for discontinuation from Study Period II were lost to follow-up (7.1%), adverse event (6.3%), and parent/caregiver decision (5.8%), subject decision (4.5%), and protocol violation (3.0%). Significantly (p=.035) more duloxetine 60 mg-treated patients discontinued treatment due to AEs compared with placebo-treated patients.

Table 44: HMCL Reasons for Discontinuation Study Period II (ITT)

Reason for Discontinuation	DLX60 (N=108) n (%)	DLX30 (N=116) n (%)	FLX20 (N=117) n (%)	Placebo (N=122) n (%)
Adverse Event	12 (11.1)	7 (6.0)	6 (5.1)	4 (3.3)
Lost to Follow-up	5 (4.6)	8 (6.9)	11 (9.4)	9 (7.4)
Protocol Violation	1 (0.9)	5 (4.3)	2 (1.7)	6 (4.9)
Subject Decision	5 (4.6)	5 (4.3)	3 (2.6)	8 (6.6)
Parent/Caretaker Decision	7 (6.5)	6 (5.2)	7 (6.0)	7 (5.7)
Physician Decision	2 (1.9)	1 (0.9)	2 (1.7)	1 (0.8)
Sponsor Decision	0	0	1 (0.9)	0
Lack of Efficacy	1 (0.9)	3 (2.6)	1 (0.9)	2 (1.6)

(Source: HMCL Study Report, p. 90)

The most common reasons for discontinuation from Study Period III were subject decision (12.5%), parent/caregiver decision (8.8%), lost to follow-up (7.5%), adverse event (6.3%), protocol violation (2.5%), and lack of efficacy (2.2%).

Table 45: HMCL Reasons for Discontinuation Study Period III (ITT)

Reason for Discontinuation	DLX60/DLX60120 (N=73) n (%)	DLX30//DLX60120 (N=81) n (%)	FLX20/FLX2040 (N=84) n (%)	Placebo/DLX60120 (N=82) n (%)
Adverse Event	4 (5.5)	6 (7.4)	3 (3.6)	7 (8.5)
Lost to Follow-up	7 (9.6)	5 (6.2)	6 (7.1)	6 (7.3)
Protocol Violation	0	3 (3.7)	2 (2.4)	3 (3.7)
Subject Decision	6 (8.2)	9 (11.1)	10 (11.9)	15 (18.3)
Parent/Caretaker Decision	9 (12.3)	4 (4.9)	10 (11.9)	5 (6.1)
Physician Decision	1 (1.4)	1 (1.2)	2 (2.4)	0
Sponsor Decision	1 (1.4)	0	0	1 (1.2)
Lack of Efficacy	2 (2.7)	2 (2.5)	2 (2.4)	1 (1.2)

(Source: HMCL Study Report, p. 101)

Protocol Violations Study Period II

The most common protocol violations were *visit interval outside specified limits* and *noncompliance to study drug regimen.* Treatment noncompliance was defined as: <80% or >120% of study drug was taken for ≥2 visits (consecutive or nonconsecutive).

The sponsor notes that, in some cases, the listing of patients with Important Protocol Violations is conservative and identifies patients with protocol violations when a violation did not occur (e.g., a patient taking an excluded medication for the acute treatment of an SAE or a patient who was lost to follow-up and therefore had no measures collected at the final visit).

For the most common protocol violation, *visit interval outside specified limits,* there appears to be no significant difference between treatment groups.

Table 46: HMCL Protocol Violations Study Period II (ITT)

Protocol Violation	DLX60 (N=108) n (%)	DLX30 (N=116) n (%)	FLX20 (N=117) n (%)	Placebo (N=122) n (%)
Patients with ≥ 1 Protocol Violation	30 (27.8)	26 (22.4)	37 (31.6)	34 (27.9)
Non-compliance to Study Drug Regimen	10 (9.3)	5 (4.3)	5 (4.3)	8 (6.6)
Improper Administration of Informed Consent	0	0	0	0
Use of Prohibited Concomitant Medications	2 (1.9)	1 (0.9)	5 (4.3)	3 (2.5)
Violation of Inclusion and Exclusion Criteria	2 (1.9)	3 (2.6)	4 (3.4)	0
Key Measurements Not Collected	1(0.9)	1 (0.9)	4 (3.4)	5 (4.1)
Visit Interval Outside Specified Limits	18 (16.7)	20 (17.2)	21 (17.9)	21 (17.2)
Other Protocol Violations	1 (0.9)	3 (2.6)	1 (0.9)	1 (0.8)

(Source: HMCL Study Report, p. 108)

Reviewer Comment:

The sponsor also includes a table of *Other Protocol Violations and Extraordinary Events* that were not captured in Table 46. It is unclear to this reviewer why these protocol violations were not included in the above table. These types of protocol violations described in the table below could have impacted the integrity of the study but the numbers appear to be fairly evenly distributed among the treatment groups.

Table 47: HMCL Other Protocol Violations and Extraordinary Events Study Period II

Table HMCL.10.4. Other Protocol Violations and Extraordinary Events[a] (Study Period II)

	DLX 60	DLX 30	FLX 20	PBO	Total
Improper Administration of Informed Consent/ Assent	7	9	7	10	33
Improper Administration of Diagnostic Tool	2	1	4	3	10
Improper Administration of Efficacy Measure	5	3	9	6	23
Unqualified Personnel Performing Study-Related Activity	5	1	6	5	17
Violation of Inclusion/Exclusion Criteria	0	3	0	0	3
Key Safety Measurement not Reviewed Prior to Randomization	0	1	0	0	1
Improper Reporting of Serious Adverse Event	0	0	1	0	1
Improper Administration of Investigational Product	1	0	0	0	1

[a] For one site, multiple out-of-allowed-range temperature excursions were noted in the investigational product storage room (potential impact for all patients for this site 760).

Sources: Listing of protocol violations from monitoring report; dosing: l_15_9_1_1_pdrug.sas

(Source: HMCL Study Report, p. 109)

Protocol Violations Study Period III

The most common protocol violations were *visit interval outside specified limits* and *noncompliance to study drug regimen.*

Table 48: HMCL Protocol Violations Study Period III (ITT)

Reason for Discontinuation	DLX60/DLX60120 (N=73) n (%)	DLX30//DLX60120 (N=81) n (%)	FLX20/FLX2040 (N=84) n (%)	Placebo/DLX60120 (N=82) n (%)
Patients with ≥ 1 Protocol Violation	19 (26.0)	23 (28.4)	27 (32.1)	27 (32.9)
Non-compliance to Study Drug Regimen	5 (6.8)	4 (4.9)	5 (6.0)	5 (6.1)
Improper Administration of Informed Consent	0	0	0	0
Use of Prohibited Concomitant Medications	1 (1.4)	2 (2.5)	2 (2.4)	2 (2.4)
Violation of Inclusion and Exclusion Criteria	0	0	0	0
Key Measurements Not Collected	2 (2.7)	2 (2.5)	0	3 (3.7)
Visit Interval Outside Specified Limits	15 (20.5)	18 (22.2)	21 (25.0)	19 (23.2)
Other Protocol Violations	0	1 (1.2)	2 (2.4)	1 (1.2)

(Source: HMCL Study Report, p. 113)

Table 49: HMCL Other Protocol Violations and Extraordinary Events Study Period III

Table HMCL.10.7. Other Protocol Violations and Extraordinary Events (Study Period III)

	DLX 60/ DLX60120	DLX 30/ DLX60120	FLX 20/ FLX2040	PBO/ DLX60120	Total
Key Measurements Not Collected	1	0	0	0	1
Improper Administration of Informed Consent/Assent	2	1	5[a]	1	9
Improper Administration of Efficacy Measure	0	2[a]	1	0	3
Unqualified Personnel Performing Study-Related Activity	1	3	0	0	4

Abbreviations: DLX = duloxetine; FLX = fluoxetine; PBO = placebo.
[a] One of these events occurred during the Taper Phase (Study Period IV)
Sources: Listing of protocol violations from monitoring report. Dosing: l_15_9_1_1_pdrug.sas.

(Source: HMCL Study Report, p. 114)

Compliance

A patient was defined to be compliant at a visit if he/she had taken at least 80% and not more than 120% of the study drug capsules prescribed for that interval. Total compliance at each visit during Study Period II was at least 91%. Total overall compliance was 69% for Study Period II. A patient was defined to be compliant overall if the patient was compliant at all visits during the Study Period. There were no statistically significant differences between treatment groups for overall compliance.

Table 50: HMCL Overall Study Drug Compliance--Study Period II

Overall Compliance %	DLX60 n=106	DLX30 n=115	FLX20 n=116	Placebo n=118	Total n=455
Yes	69.8	72.2	65.5	69.5	69.2
No	30.2	27.8	34.5	30.5	30.8

(Source: HMCL Study Report, p. 135)

Total compliance at each visit during Study Period III was ≥90%. Total overall compliance was ~61%.

Table 51: HMCL Overall Study Drug Compliance--Study Period III

Overall Compliance %	DLX60/DLX60120 n=71	DLX30/DLX60120 n=78	FLX20/FLX2040 n=81	PBO/DLX60120 n=79	Total n=309
Yes	64.8	65.4	59.3	54.4	60.8
No	35.2	34.6	40.7	45.6	39.2

(Source: HMCL Study Report, p. 632)

6.2.4 Analysis of Primary Endpoint(s)

Sponsor's Primary Analysis

The primary objective of this study was to assess the efficacy of duloxetine 60 mg QD compared with placebo in the acute treatment of children and adolescents who met criteria for MDD based on the mean change from baseline to endpoint on the CDRS-R total score. The primary efficacy analysis was the contrast between duloxetine 60 mg QD (DLX60) and placebo at the last visit in Study Period II (Visit 8, Week 10) based on an MMRM analysis on mean change from baseline in the CDRS-R total score. The ITT population was used to perform this analysis.

Duloxetine 30 mg and duloxetine 60 mg were not significantly different from placebo in the treatment of children and adolescents with MDD as measured by the mean change from baseline to endpoint (10 weeks) CDRS-R total score. In addition, the active control (fluoxetine), with known efficacy in children and adolescents with MDD, was not statistically significantly different from placebo on the primary outcome measure in this study.

The study is considered to be inconclusive as neither the investigational drug (duloxetine) nor the active control (fluoxetine) demonstrated a statistically significant separation from placebo on the primary efficacy analysis of mean change from baseline to Week 10 on the CDRS-R total score.

Table 52: HMCL CDRS-R Total Score: Mean Change from Baseline to Week 10 of Study Period II (ITT)

Therapy	N	LS Mean	LS Mean Change	LS Mean Change Difference	p-value
DLX60	83	35	-23.9		
DLX30	84	34	-24.6		
FLX20	84	36.4	-22.6		
Placebo	88	37.4	-21.6		
DLX60 versus Placebo				-2.3	0.193
DLX30 versus Placebo				-3.0	0.093
FLX20 versus Placebo				-1.0	0.588

(Source: HMCL Study Report, p. 145)

There were statistically significant improvements for the duloxetine 60 mg-treated group, the duloxetine 30 mg-treated group, and the fluoxetine 20 mg-treated compared with the placebo-treated group at Week 1 and Week 2. In addition, both the duloxetine 60- and 30-mg treatment arms demonstrated a statistically significant difference from placebo in the overall main effect of treatment analysis.

Table 53: HMCL CDRS-R Total Score: MMRM Mean Change from Baseline-Overall (Study Period II)

Therapy	N	LS Mean Change	LS Mean Change Difference	p-value
DLX60	105	-18.0		
DLX30	114	-17.7		
FLX20	112	-17.4		
Placebo	117	-15.3		
DLX60 versus Placebo			-2.7	**0.018**
DLX30 versus Placebo			-2.4	**0.032**
FLX20 versus Placebo			-2.1	0.065

(Source: HMCL Study Report, p. 146)

FDA's Primary Analysis

Dr. Andrejus Parfionaovas and Dr. George Kordzakhia of the Division of Biometrics I reviewed Study HMCL. They concluded that the study was conducted in accordance with the statistical analysis plan agreed upon by the Agency. They found the quality and integrity of the submitted data to be acceptable. They were able to reproduce the primary analysis dataset from the raw data and trace how the primary endpoint was derived. The reviewers confirmed the sponsor's analysis results for the primary efficacy endpoint. No statistically significant treatment effect was observed between the duloxetine arms and placebo. Also, no statistically significant difference was observed between the active comparator (fluoxetine) and placebo. These results are displayed in Table 9 of the FDA Biometrics Review:

Table 9. Primary Efficacy Analysis for CDRS-TS at Visit 8 for F1J-MC-HMCL Study (Analysis Set).

	N	LS mean	LS mean Change (SE)	LS Mean Change Difference (SE)	95% CI for Difference	p-value*
DLX 60 mg	83	35.0	-23.9 (1.30)			
DLX 30 mg	84	34.4	-24.6 (1.29)			
FLX 20 mg	84	36.4	-22.6 (1.27)			
Placebo	88	37.4	-21.6 (1.27)			
DLX 60 mg vs. Placebo				-2.3 (1.78)	(-5.8, 1.2)	0.193
DLX 30 mg vs. Placebo				-3.0 (1.77)	(-6.5, 0.5)	0.093
FLX 20 mg vs. Placebo				-1.0 (1.76)	(-4.4, 2.5)	0.588
DLX 60 mg vs. DLX30				0.7(1.79)	(-2.9, 4.2)	0.715
DLX 60 mg vs. FLX 20 mg				-1.4 (1.79)	(-4.9, 2.2)	0.445
DLX 30 mg vs. FLX 20 mg				-2.0 (1.78)	(-5.5, 1.5)	0.256

Source: F1J-MC-HMCL Clinical Study Report Table HMCL.11.5, pg. 145.

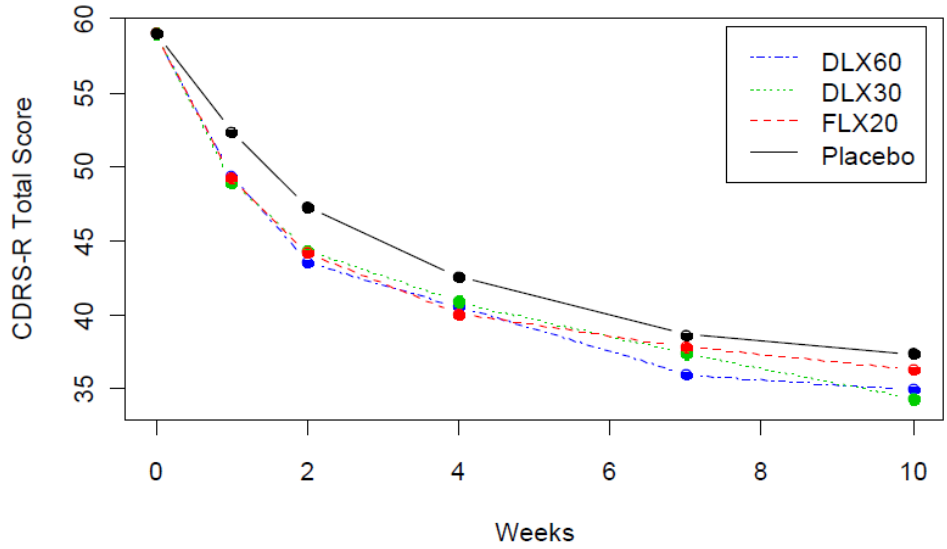
* The listed p-values are not adjusted for multiplicity.

(Source: FDA Biometrics Review, p. 14)

The LS Mean CDRS-R total scores of the MMRM Analysis are depicted for each treatment group in Figure 4 of the FDA Biometrics Review. The trends for all treatment groups were decreasing in a similar way. The LS Mean values of the Placebo arm were

slightly higher compared to the LS mean values of the fluoxetine and both duloxetine arms.

Figure 4. CDRS-R Total Score by visit in patients of F1J-MC-HMCL Study (ITT Population).



Source: computed by the reviewers.

(Source: FDA Biometrics Review, p. 16)

6.2.5 Analysis of Secondary Endpoints(s)

In most secondary analyses of mean change on the CDRS-R total score, CDRS-R subscales, and CGI-S, no statistically significant differences were observed for duloxetine 60 mg- and duloxetine 30 mg-treated patients compared with placebo-treated patients at endpoint or between the fluoxetine-treated patients compared to placebo-treated patients at endpoint.

No statistically significant differences at Week 10 were observed for the duloxetine 60 mg- or the duloxetine 30 mg-treated groups compared with the placebo-treated group for any of the CDRS-R subscales and Item-13 (suicidal ideation) score, with the exception of the CDRS-R somatic subscale where a statistically significant difference was observed at Week 10 for the duloxetine 30 mg-treated group compared with the placebo-treated group (p=.023).

There was not a statistically significant difference in the probability of meeting a 30% or 50% response on the CDRS-R for the duloxetine 60 mg-, duloxetine 30 mg-, or fluoxetine 20 mg-treated groups compared with the placebo-treated group at visit of Week 10.

Remission is defined as a CDRS-R total score of ≤28 at LOCF endpoint. There were no statistically significant differences on remission rate at endpoint between the duloxetine 60 mg-treated group and the placebo-treated group or between the fluoxetine 20 mg-treated group and the placebo-treated group. There was a statistically significant difference on remission rate at endpoint between the duloxetine 30 mg-treated group and the placebo-treated group (p=.04).

A Kaplan-Meier analysis of time to first remission for patients with a CDRS-R ≤28 was performed. There were no statistically significant differences between the duloxetine 60 mg-, duloxetine 30 mg-, or fluoxetine 20 mg-treated groups compared with the placebo-treated group. Median time (days) to first remission was approximately 70-75 days for all treatment groups.

At Week 10, there were no statistically significant differences observed for the duloxetine 60 mg-, duloxetine 30 mg-, or fluoxetine 20 mg-treated groups compared with the placebo-treated group in CGI-S mean change from baseline to Week 10 (MMRM).

Table 54: HMCL CGI-S: MMRM Mean Change from Baseline to Week 10 (Study Period II)

Therapy	N	LS Mean	LS Mean Change	LS Mean Change Difference	p-value
DLX60	83	3.1	-1.5		
DLX30	84	3.1	-1.5		
FLX20	84	3.1	-1.5		
Placebo	88	3.1	-1.5		
DLX60 versus Placebo				0	0.815
DLX30 versus Placebo				-0.1	0.658
FLX20 versus Placebo				0	0.973

(Source: HMCL Study Report, p. 176)

6.2.7 Subpopulations

In subgroup analyses of mean change in the CDRS-R total score (by age, race, ethnicity, and region), differences between the active drug treatment arms compared to placebo were not statistically significant in any subgroup. In the subgroup analysis of mean change in the CDRS-R total score by gender (LOCF), statistically significant improvement was observed for duloxetine 60 mg-treated females compared with placebo-treated females and for duloxetine 30 mg-treated females compared with placebo-treated females.

Analyses of CDRS-R total score (ANCOVA) change from baseline to endpoint by subgroup were performed. For Study Period II, the treatment-by-age, -gender, -race, -

ethnicity, -pooled investigators, and -region interactions were not statistically significant for duloxetine.

Table 55: HMCL ANCOVA Change from Baseline CDRS-R Total Score to Endpoint by Age Group (Study Period II)

Treatment	Age (7-11)	Age (12-17)	Age (7-11)		Age (12-17)	
	LS Mean Change	LS Mean Change	LS Mean Diff	p-value	LS Mean Diff	p-value
DLX60	-23.0	-22.2				
DLX30	-19.0	-24.2				
FLX20	-20.1	-21.5				
Placebo	-18.5	-19.8				
DLX60 versus Placebo			-4.5	0.093	-2.3	0.318
DLX30 versus Placebo			-0.5	0.854	-4.3	0.063
FLX20 versus Placebo			-4.0	0.129	2.0	0.397
DLX60 versus FLX20			-2.9	0.282	-0.6	0.793

(Source HMCL Study Report, p.646-647)

For Study Period II, no statistically significant differences in LS mean change from baseline to endpoint in CDRS-R total score were observed for fluoxetine-treated patients compared to placebo-treated patients for age, gender, ethnicity, or regional subgroups.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

For completers of Study Period III, most subjects had a modal dose of duloxetine 120 mg or fluoxetine 40 mg.

Table 56: HMCL Modal Dose for Completers Study Period III

Dose	**Modal Dose for n (%)**
DLX 30 mg	0 (0)
DLX 60	61 (42.1)
DLX 90	21 (14.5)
DLX 120	63 (43.4)
FLX 20	14 (25.5)
FLX 40	41 (74.5)

(Source: HMCL Study Report, p.222)

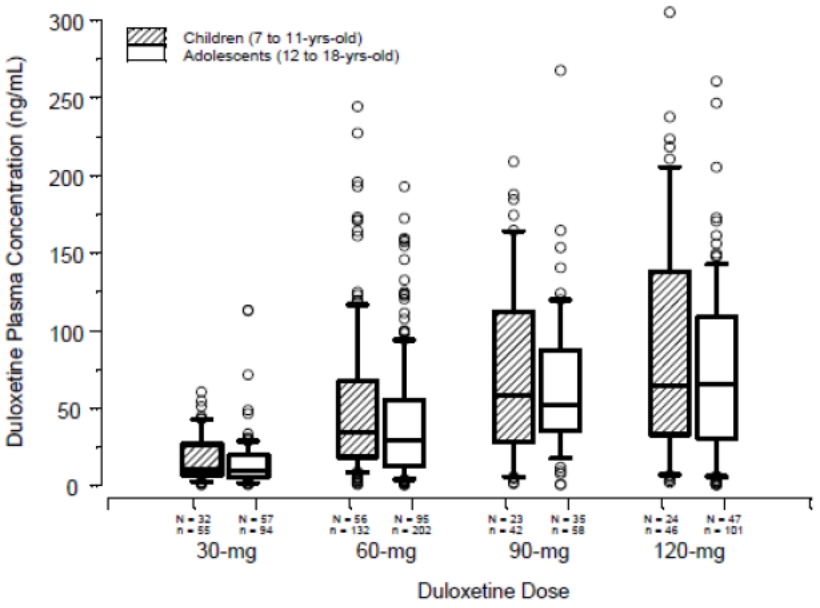
Typical duloxetine plasma concentrations increased in proportion to the increase in dose in both children and adolescents. For a given dose, the median duloxetine concentrations as well as the range of concentration were similar in children and adolescents.

Table 57: HMCL Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose

Dose (mg)	**30** (N=89) (n=149)	**60** (N=151) (n=334)	**90** (N=58) (n=100)	**120** (N=71) (n=147)
Concentration (ng/mL)	16.5 ± 17.5	44.1 ± 43.1	67.3 ± 52.9	77.1 ± 61.9

(Source: HMCL Study Report, p. 205)

Figure 4: HMCL Effect of Dose on Observed Duloxetine Steady-State Concentrations in Pediatric Patients Following Once Daily Oral Duloxetine Dosing Regimen



Note: The middle line in each box plot represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers extend to the 90th and 10th percentiles; data points outside the whiskers represent the points beyond the percentiles.

Abbreviations: N = number of patients; n = number of duloxetine concentrations.

(Source: HMCL Study Report, p. 207)

Dose-normalized steady state duloxetine concentrations were similar in subgroups defined by sex, ethnicity, race, age, and body weight.

7 Review of Safety

Safety Summary

In general, there were no new or unexpected findings with respect to safety. The safety findings were consistent with the known safety and tolerability profile for Cymbalta. There were no deaths in Study HMCK or Study HMCL. The numbers of SAEs in the duloxetine group in the acute phase (Period II) of HMCK and HMCL were not statistically different from the number of SAEs in the placebo groups. The majority of SAEs were psychiatric-related events. There were no statistically significant differences on suicidal ideation, suicidal behavior, or non-suicidal self-injurious behavior between duloxetine and fluoxetine during the 36 weeks of treatment. As in the adult trials, adverse reactions such as nausea, decreased appetite, somnolence, and fatigue were common.

7.1 Methods

7.1.1 Studies Used to Evaluate Safety

Safety findings from HMCK and HMCL are discussed in this section. Both trials had 10-week double-blind, placebo-controlled periods (Study Period II) and 6-month double-blind extension phases (Study Period III), allowing evaluation of both short and longer term safety data.

Safety findings from HMFN, the open-label PK study, were previously discussed in Section 4.4.3.

7.1.2 Categorization of Adverse Events

The sponsor's categorization of adverse events was assessed and found to be adequate. Verbatim terms compared well with the preferred terms. MedDRA 14.0 Version was used. Safety signals did not appear to be diminished through splitting.

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

The sponsor submitted an Integrated Data Report, *Reports of Analyses of Cymbalta Data from More than One Study of Pediatric Major Depressive Disorder*. In this Integrated Data Report, the sponsor analyzed the data from the acute analyses set (Study Period II for HMCK and HMCL) and the long-term analyses set (36 weeks). The long-term analyses set (Period II/III) pooled the data from the combined acute (Study Period II) and extension phases (Study Period III) of HMCK and HMCL. Only data from subjects taking duloxetine during both study periods (II and III) were included in the

extension phase and long-term analyses sets in this Integrated Data Report. Data from subjects who took placebo during Study Period II and duloxetine during Study Period III were not assessed in these extension and long-term analyses.

Topics covered in this Integrated Data Report include *Submission Specific Safety Concerns* such as growth (weight and height), suicidality, hepatic-related laboratory values, extrapyramidal symptoms and changes in vital signs. These topics are covered in Sections 7.4.3 and 7.4.4.

The remaining safety data for HMCK and HMCL are not pooled. Key data are analyzed by trial and by study period.

7.2 Adequacy of Safety Assessments

All tests reasonably applicable were conducted to assess the safety of duloxetine in children and adolescents. The number of patients in each age group and the duration of exposure were adequate. The doses explored were appropriate.

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

The overall exposure at appropriate doses and durations was adequate. The total placebo plus uncontrolled duloxetine (60-120 mg) exposure in HMCK and HMCL was 98.9 patient-years.

Table 58: HMCK and HMCL Duloxetine Exposure in Patient-Years

Parameter	HMCK	HMCL	Total
Total placebo-controlled duloxetine (60-120 mg) exposure in patient-years	19.1	17.6	36.7
Total uncontrolled duloxetine (60-120 mg) exposure in patient-years	32.9	29.3	62.2
Total placebo plus uncontrolled duloxetine (60-120 mg) exposure in patient-years	52	46.9	**98.9**

Duration of Study Exposure by Study and Period

Study Period II:10-week placebo-controlled phase
For Study HMCK, the total mean duration of study drug exposure for all treatment groups was 63.4 days. The mean duration of study drug exposure was statistically significantly (p=.007) longer in the placebo-treated patients (66.8 days) compared with duloxetine-treated patients (60.2 days).

Table 59: HMCK Study Drug Exposure-Study Period II (ITT)

HMCK Study Period II	DLX60120 (N=117)	FLX2040 (N=117)	Placebo (N=103)
Duration of Study Exposure (Days)			
n	116	117	103
Mean	60.2	63.5	66.8
Median	69.0	70.0	70.0
Min-Max	1-77	2-91	17-83
Duration of Study Exposure (Day Intervals)	n (%)	n (%)	n (%)
≥ 70 days	57 (48.7)	61 (52.1)	64 (62.1)
Total Patient-Years Exposure	19.1	20.3	18.8

(Source: HMCK Study Report, p. 214)

For Study HMCL, the total mean duration of study drug exposure for all treatment groups was 59.3 days and there was no statistically significantly difference between the treatment groups.

Table 60 : HMCL Study Drug Exposure-Study Period II (ITT)

HMCL Study Period II	DLX60 (N=108)	DLX30 (N=116)	FLX20 (N=117)	Placebo (N=122)
Duration of Study Exposure (Days)				
n	108	116	117	122
Mean	59.3	59.8	60.0	58.3
Median	69.0	70.0	69.0	69.0
Min-Max	1-84	1-97	3-97	3-83
Duration of Study Exposure (Day Intervals)	n (%)	n (%)	n (%)	n (%)
≥ 70 days	45 (41.7)	63 (54.3)	56 (47.9)	54 (44.3)
Total Patient-Years Exposure	17.5	19.0	19.2	19.5

(Source: HMCL Study Report, p. 217)

Study Period III: 6-month, double-blind, uncontrolled phase

For HMCK Study Period III, the total mean duration of study drug exposure for all treatment groups was 151.5 days. A total of 61.9% of patients were exposed to study drug for at least 6 months.

Table 61: HMCK Study Drug Exposure-Study Period III (ITT)

HMCK Study Period III	DLX60120/DLX60120	FLX2040/FLX2040	Placebo/ DLX60120
Duration of Study Exposure (Days) n Mean Median	 82 144.8 182.0	 91 151.7 182.0	 86 157.6 181.0
Patients with 6 months (180 days) exposure	n (%) 50 (60.2)	n (%) 56 (61.5)	n (%) 55 (64.0)
Total Patient-Years Exposure	32.9	37.8	37.1

(Source: HMCK Study Report, p 219)

For HMCL Study Period III, the total mean duration of study drug exposure for all treatment groups was 142.3 days. A total of 53.5% of patients were exposed to study drug for at least 6 months.

Table 62: HMCL Study Drug Exposure--Study Period III (ITT)

HMCL Study Period III	DLX60/DLX60120 (N=73)	DLX30/ DLX60120 (N=81)	FLX20/FLX2040 (N=84)	Placebo/ DLX60120 (N=82)
Duration of Study Exposure (Days) n Mean Median	 73 146.6 180.0	 79 143.7 181.0	 84 144.0 180.5	 82 135.4 180.0
Patients with 6 months (180 days) exposure	n (%) 38 (52.1)	n (%) 45 (57.0)	n (%) 45 (53.6)	n (%) 42 (51.2)
Total Patient-Years Exposure	29.3	31.1	33.1	30.4

(Source: HMCL Study Report, p. 220)

HMCK and HMCL Study Period II/III

Table 63 details the number of subjects who were exposed to duloxetine for 6 months during Study Periods II/III for HMCK and HMCL. There were a total of 113 subjects exposed to duloxetine for 6 months.

Table 63: HMCK/HMCL Study Drug Exposure--Study Period II/III

Study Period II/III	**HMCK DLX60120 (N=117)**	**HMCL DLX60120 (N=108)**
Duration of Study Exposure (Days) n Mean Median	 116 163.7 224	 108 158.6 173.5
Patients with 6 months (180 days) exposure	n (%) **62** (53.4)	n (%) **51** (42.7)
Total Patient-Years Exposure	52.0	46.9

(Source: HMCK Study Report, p. 224 and HMCL Study Report, p. 230)

Reviewer Comment:
The overall exposure is adequate.

Modal Dose

HMCK
During HMCK Study Period II, most subjects had a modal dose of duloxetine 90 mg. For completers of HMCK Study Period III, most subjects had a modal dose of duloxetine 120 mg. Fluoxetine 40 mg was the most common modal dose in HMCK Study Periods II and III.

Table 64: HMCK Modal Dose and Last Prescribed Dose (Study Period II)

Dose	**Modal Dose for n (%)**	**Last Prescribed Dose at LOCF Endpoint for n (%)**
DLX 30 mg	17 (14.5)	13 (11.1)
DLX 60	29 (24.8)	20 (17.1)
DLX 90	**38 (32.5)**	32 (27.4)
DLX 120	32 (27.4)	**51 (43.6)**
FLX 10	9 (7.7)	9 (7.7)
FLX 20	28 (23.9)	22 (18.8)
FLX 40	**80 (68.4)**	**86 (73.5)**

(Source: HMCK Study Report, p. 216)

Table 65: HMCK Modal Dose for Completers (Study Period III)

Dose	Modal Dose for n (%)
DLX 30 mg	0 (0)
DLX 60	48 (38.1)
DLX 90	15 (11.9)
DLX 120	**63 (50.0)**
FLX 20	10 (15.2)
FLX 40	**56 (84.8)**

(Source: HMCK Study Report, p. 222)

HMCL
For completers of HMCL Study Period III, most subjects had a modal dose of duloxetine 120 mg or fluoxetine 40 mg.

Table 66: HMCL Modal Dose for Completers (Study Period III)

Dose	Modal Dose for n (%)
DLX 30 mg	0 (0)
DLX 60	61 (42.1)
DLX 90	21 (14.5)
DLX 120	**63 (43.4)**
FLX 20	14 (25.5)
FLX 40	**41 (74.5)**

(Source: HMCL Study Report, p. 222)

Reviewer Comment:
The doses explored were appropriate. The majority of duloxetine-treated patients had dose escalations to 90 and 120 mg QD to attempt to optimize efficacy in both HMCK and HMCL.

7.2.2 Explorations for Dose Response

Only Study Period II of HMCL was a fixed-dose trial. In this period, subjects treated with duloxetine 60 mg had a significantly greater percentage of TEAEs (73%) than subjects treated with duloxetine 30 mg (57.8%). This is consistent with current labeling which states that some adverse reactions were observed to be dose-dependent in the adult trials. However, duloxetine 60 mg was not more efficacious than duloxetine 30 mg. As noted previously, neither dose was significantly different from placebo with respect to efficacy in HMCL.

Although a significant difference from placebo was not demonstrated in either HMCK or HMCL, the majority of duloxetine-treated patients in both trials needed dose escalations to 90 and 120 mg QD to attempt to optimize efficacy. Similarly, the majority of patients (76%) in the open-label PK study (HMFN) required escalation of the duloxetine dose to 60, 90, or 120 mg QD in order to optimize efficacy.

7.2.4 Routine Clinical Testing

The routine clinical testing of the subjects appeared to be adequate. For Study Period II, patients initially had weekly visits (Visits 4 and 5), then a visit every 2 weeks (Visit 6), and then every 3 weeks (Visits 7, and 8). For Study Period III, patients were seen every 2 weeks for Visits 8 through 11, and then monthly for Visits 11 through 16. Weight and vital signs were obtained at each visit. ECGs were obtained at baseline, Week 10, Week 24, and Week 36. Laboratory assessments were obtained at baseline, Week 4, Week 10, Week 14, Week 20, Week 24, and Week 36.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information was submitted for this supplement.

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

The sponsor adequately attempted to assess all potential adverse events that might be associated with this drug class.

7.3 Major Safety Results

The safety findings were consistent with the known safety and tolerability profile for Cymbalta.

7.3.1 Deaths

There were no deaths in Study HMCK or Study HMCL.

7.3.2 Nonfatal Serious Adverse Events

The number of SAEs in the duloxetine groups in the acute phase (Period II) of HMCK and HMCL was not statistically different from the number of SAEs in the placebo groups. There were no new or unexpected findings in these trials.

Table 67: Serious Adverse Events Studies HMCK and HMCL (Periods II and III)

Study Period	HMCK		HMCL		
Period II	DLX60120 N=117 n (%)	PBO N=103 n (%)	DLX30 N=116 n (%)	DLX60 N=108 n (%)	PBO N=122 n (%)
	3 (2.6)	1 (1.0)	2 (1.7)	4 (3.7)	2 (1.6)
Study Period	**HMCK**		**HMCL**		
Period III	DLX60120/DLX60120 N=83 n (%)	PBO/DLX60120 N=86 n (%)	DLX30/DLX60120 N=81 n (%)	DLX60/DLX60120 N=73 n (%)	PBO/DLX60120 N=82 n (%)
	1 (1.2)	4 (4.7)	2 (2.5)	3 (4.1)	4 (4.9)

(Source: Integrated Data Report, p.17)

HMCK

There were 3 patients in the duloxetine-treated group that experienced 4 SAEs during the Study HMCK Study Period II.

Table 68: HMCK SAEs Study Period II (ITT)

SAE Preferred Term	DLX60120 (N=117) n (%)	FLX2040 (N=117) n (%)	Placebo (N=103) n (%)
Subjects with ≥ 1 SAE	3 (2.6)	2 (1.7)	1 (1.00
Drug Abuse	1	0	0
Panic Attack	1	0	0
Social Phobia	1	0	0
Syncope	1	0	0
Gastritis	0	1	0
Lymphadenitis	0	1	0
Major Depression	0	0	1
Ulna Fracture	0	1	0

(Source: HMCK Study Report, p. 239)

Only the SAE of syncope was considered possibly related to duloxetine:

Patient 706-7254, a 17 year-old female who had prior episodes of syncope, experienced the SAE of syncope 40 days after starting duloxetine. The patient was taking duloxetine 90 mg QD at the time of the event. The patient had several episodes of losing consciousness for approximately 1 to 2 minutes. The patient was hospitalized and experienced subsequent syncopal episodes while hospitalized. Electrocardiogram, electroencephalogram (EEG), and neuroimaging were all normal. The patient recovered. The investigator stated that the syncope was possibly related to study drug

as the etiology was unknown. The patient was discontinued from the study due to syncope.

Reviewer Comment:
Given the patient's history of prior episodes of syncope, a causal relationship to duloxetine treatment seems less likely. However, Cymbalta's current label has a warning for orthostatic hypotension and syncope.

For HMCK Study Period III, 5 subjects receiving duloxetine experienced 6 SAEs.

Table 69: HMCK SAEs Study Period III (ITT)

SAE Preferred Term	**DLX60120/DLX60120 N=83 n (%)**	**FLX2040/FLX2040 N=92 n (%)**	**PBO/DLX60120 N=86 n (%)**
Subjects with ≥ 1 SAE	1 (1.2)	4 (4.3)	4 (4.7)
Pneumonia	1	0	0
Adjustment Disorder with Disturbance of Conduct	0	1	0
Conversion Disorder	0	0	1
Convulsion	0	1	0
Epilepsy	0	1	0
Hypomania	0	1	0
Intentional Overdose	0	1	0
Major Depression	0	0	1
Pilonidal Cyst	0	0	1
Restlessness	0	0	1
Suicidal Ideation	0	0	1
Suicide Attempt	0	1	0

(Source: HMCK Study Report, p. 243)

One subject in the PBO/DLX60120 group experienced the SAE of suicidal ideation which, in the opinion of the investigator, was not related to the study drug:

Patient 708-7358, a 17 year-old female, experienced the SAE of suicidal ideation and restlessness (elopement), approximately 3 months after entering Study Period III on duloxetine. She had been originally randomized to placebo during Study Period II and had transitioned to duloxetine for Study Period III. The prescribed duloxetine dose at the time of the event was 120 mg QD; however, the patient had not been compliant with taking study drug for approximately 3 weeks prior to the event. The patient ran away and threatened to kill herself. She returned home 2 days later and was hospitalized. She had homicidal thoughts toward her brother and had auditory hallucinations telling her to shoot herself. The patient was discharged from the hospital on fluoxetine. The patient recovered and was discontinued from the study due to protocol violation (non-compliance with study drug). In the opinion of the investigator, the event was not related

to study drug since patient had not been taking study drug for approximately 3 weeks prior to the event.

HMCL

For Study HMCL Study Period II, there were no statistically significant differences observed between treatment groups for rate of SAEs. The majority of SAEs were psychiatric-related events. Suicidal thoughts and self-injurious behaviors were experienced by 4 duloxetine-treated subjects, 3 fluoxetine-treated subjects, and 2 placebo-treated subjects.

Table 70: HMCL SAEs Study Period II (ITT)

SAE Preferred Term	**DLX60 (N=108) n (%)**	**DLX30 (N=116) n (%)**	**FLX20 (N=117) n (%)**	**Placebo (N=122) n (%)**
Subjects with ≥ 1 SAE	4 (3.7)	2 (1.7)	6 (5.1)	2 (1.6)
Intentional Overdose	2	0	1	0
Irritable Bowel Syndrome	1	0	0	0
Suicidal Ideation	1	0	2	0
Abnormal Behaviour	0	0	1	0
Aggression	0	0	2	0
Depression	0	1	0	0
Hallucination	0	1	0	0
Homicidal Ideation	0	0	0	1
Self-Injurious Behaviour	0	1	0	1
Somnolence	0	0	1	0
Suicide Attempt	0	0	0	1
Tuberculosis of Peripheral Lymph Nodes	0	0	1	0

(Source: HMCL Study Report, p. 240)

The narratives for the 4 duloxetine-treated subjects with suicidal thoughts and/or self-injurious behavior include the following:

Patient 122-3203, a 16-year-old female with a history of self-injurious behavior, a previous suicide attempt at age 9, frequent mood swings and hallucinations, experienced the SAE of intentional overdose 53 days after randomization to duloxetine 60 mg QD. The patient ingested 42 capsules of investigational product and stated that the reason she took the overdose was because she had not been taking the medicine as instructed; therefore, she took it all the day before her next site visit because she thought she would not get the money for the study. The patient denied any suicidal intent. The patient was discharged on bupropion and hydroxyzine hydrochloride. The investigator did not consider the event related to the investigational product. The patient was discontinued from the study due to the event.

Patient 720-7204, a 12-year-old female with no previous history of suicidal behavior, experienced the SAE of intentional overdose 63 days after randomization to duloxetine 60 mg QD. The patient ingested 78 capsules of investigational product and 27 tablets of naproxen and immediately told her parent. She was taken to the hospital and a gastric lavage was performed. The patient stated she took the medicine because she wanted to sleep without the idea of dying. The patient was treated with omeprazole and was discharged 1 week later. The investigator considered the event related to investigational product but did not consider the event a suicide attempt since the patient stated she took the medicine without the idea of dying. The patient was discontinued from the study due to the event.

Patient 111-2105, a 12-year-old male, who had a history of self-injurious behavior and auditory hallucinations, experienced the SAE of suicidal ideation 4 days after starting duloxetine titration dose of 30 mg (randomized to 60 mg QD). The patient made a suicidal threat and was admitted to an inpatient psychiatric hospital for 3 days and was treated with risperidone. The patient stated he was having auditory hallucinations, hearing 3 different voices. He was discharged and readmitted the same day with suicidal ideation after a disagreement with his father and was treated with olanzapine and fluoxetine. The investigator did not consider the event related to investigational product and noted the patient had no intent to die. The patient was discontinued from the study due to the event.

Patient 114-2417, a 13-year-old male with a history of self-injurious behavior, experienced the SAEs of worsening of self-injurious behavior and hallucinations 9 days after starting duloxetine 30 mg QD. The patient was admitted to the hospital for cutting his stomach and running away from school. The patient was treated with aripiprazole. He also reported hearing voices which prolonged the hospitalization. The patient stated he was tired and did not want to live anymore. The investigator did not consider the self-injurious behavior or hallucinations related to investigational product. The patient was discontinued from the study due to the events.

Reviewer Comment:
Suicidality: Monitor for worsening and suicide risk is a labeled warning for Cymbalta.

For HMCL Study Period III, over half of the SAEs were due to psychiatric disorders. Five duloxetine-treated subjects experienced a suicide attempt or an intentional overdose.

Table 71: HMCL SAEs Study Period III (ITT)

SAE Preferred Term	DLX60/DLX60120 (N=73) n (%)	DLX30/ DLX60120 (N=81) n (%)	FLX20/FLX2040 (N=84) n (%)	Placebo/ DLX60120 (N=82) n (%)
Subjects with ≥ 1 SAE	3 (4.1)	2 (2.5)	1 (1.2)	4 (4.9)
Irritable Bowel Syndrome	1	0	0	0
Stevens-Johnson Syndrome	1	0	0	0
Suicide Attempt	1	2	0	1
Wound	1	0	0	0
Depression	0	1	0	0
Epilepsy	0	0	0	1
Intentional Overdose	0	0	0	1
Road Traffic Accident	0	0	0	1
Somnolence	0	0	1	0

(Source: HMCL Study Report, p. 244)

The narratives for the 5 duloxetine-treated subjects who experienced a suicide attempt or an intentional overdose include the following:

Patient 4903 (DLX60/DLX60120), a 15-year-old male, attempted suicide by puncturing his abdomen with a knife after an argument with his family, approximately 3 months after starting duloxetine. The investigator stated the patient had definite intent to die. The event was classified as a nonfatal suicide attempt on the C-SSRS. The patient was discontinued from the study due to lack of efficacy. The investigator did not consider the event relate to investigational product.

Patient 3103 (DLX30/DLX60120), a 10-year-old male, experienced the SAEs of suicide attempt and depression 179 days after starting duloxetine. The patient tied an object around his neck at school and was hospitalized. The event was classified as a non-fatal suicide attempt on the C-SSRS. The patient was discontinued due to worsening of depression. The patient's uncle had completed suicide approximately 1 month prior to the event. The investigator did not consider the event relate to investigational product

Patient 2202 (DLX30/DLX60120), an 8 year-old male, experienced the SAE of suicide attempt 112 days after starting duloxetine. The patient admitted to trying to kill himself by choking himself. The patient's father later discovered him standing on the end of an open second story window threatening to jump, at which time the father physically restrained him. The event was classified as interrupted suicide attempt on the C-SSRS. The patient was hospitalized and then discontinued from the study due to the AE. The investigator considered the event possibly related to investigational product.

Patient 4507 (PBO/DLX60120), a 14-year-old female, experienced the SAE of suicide attempt 1 day after the last dose of study drug. The patient had been in trouble at school, argued with her mother, and had a grandfather die. The patient took at least 20 anti-inflammatory medications of her mother's and was hospitalized. The event was classified as a nonfatal suicide attempt on the C-SSRS. The patient was discontinued due to the suicide attempt. The investigator did not consider the event related to investigational product.

Patient 3903 (PBO/DLX60120), a 15-year-old female, took an overdose of Benadryl® approximately 2 months after starting duloxetine in Study Period III. The investigator reported that the overdose was an SAE and was not an act of self-harm. The patient took the overdose of Benadryl to help her insomnia. The patient denied any suicidal ideation and stated that she took the medication because she liked the way it made her feel. The patient completed the study. The investigator considered the event related to investigational product.

The narrative for the SAE of Stevens - Johnson syndrome is as follows:

Patient 106-1602, a 15-year-old White male, was hospitalized for the SAE of suspected Stevens - Johnson syndrome, 137 days after starting duloxetine. The patient was randomized to duloxetine 60 mg QD during Study Period II and had taken duloxetine 120 mg QD for approximately 6 weeks during Study Period III at the time the event was reported. The patient was experiencing symptoms of sinus infection, temperature, fatigue, and headache for approximately 2-3 months prior to the hospitalization. The patient also developed blisters in the mouth, cough, and conjunctivitis. No rash or other signs of allergic reaction were reported. Duloxetine was discontinued on the day of hospitalization and the patient was discontinued from the study. The patient recovered from the event. The investigator judged the event to be possibly related to drug. The patient recovered from the event.

Reviewer Comment:
The lack of a rash makes the diagnosis of Stevens-Johnson syndrome less likely. A viral infection could also have presented in this manner. However, the investigator (University of Cincinnati) "confirmed the diagnosis of Stevens-Johnson syndrome despite the absence of rash." A warning for serious skin reactions including Stevens-Johnson syndrome is in the current Cymbalta label.

7.3.3 Dropouts and/or Discontinuations

Table 72: Discontinuations Due to an Adverse Event Studies HMCK and HMCL (Periods II and III)

Study Period	HMCK		HMCL		
Period II	DLX60120 N=117 n (%)	PBO N=103 n (%)	DLX30 N=116 n (%)	DLX60 N=108 n (%)	PBO N=122 n (%)
	9 (7.7)	3 (2.9)	7 (6.0)	12 (11.1)	4 (3.3)
Study Period	**HMCK**		**HMCL**		
Period III	DLX60120/DLX60120 N=83 n (%)	PBO/DLX60120 N=86 n (%)	DLX30/DLX60120 N=81 n (%)	DLX60/DLX60120 N=73 n (%)	PBO/DLX60120 N=82 n (%)
	2 (2.4)	4 (4.7)	6 (7.4)	4 (5.5)	7 (8.5)

(Source: Integrated Data Report, p.17)

HMCK

Nausea was the most common reason for duloxetine discontinuation and for dose reduction during HMCK Study Period II. Nausea was also a common adverse reaction in the adult trials.

Table 73: HMCK AEs Reported as Reason for Discontinuation Study Period II (ITT)

Adverse Event by Preferred Term	DLX60120 (N=117) n (%)	FLX2040 (N=117) n (%)	Placebo (N=103) n (%)
Subjects with ≥ 1 AE	9 (7.7)	1 (0.9)	3 (2.9)
Nausea	2	0	0
Abdominal Pain Upper	1	0	1
Decreased Activity	1	0	0
Depression	1	0	0
Influenza	1	0	0
Muscular Weakness	1	0	0
Panic Attack	1	0	0
Syncope	1	0	0
Allergic Sinusitis	0	0	1
Intentional Overdose	0	0	1
Suicidal Ideation	0	1	0

(Source: HMCK Study Report, p. 248)

Table 74: HMCK AEs Reported as Reason for Dose Decrease Study Period II

Site	Patient	Age/Gender	Visit	Treatment/Dose at time of request	Adverse Event Reported for Reason for Dose Decrease
729	9401	8/M	7	FLX 20[a]	Activation Syndrome
606	6355	8/F	7/8	DLX 90/DLX60[a]	Nausea
733	9605	10/F	7	DLX 90	Abdominal Discomfort
402	4106	12/M	7	FLX 40	Tremor
510	5451	10/F	7	FLX 40	Decreased Appetite
702	7054	10/F	7	FLX 40	Vomiting
302	3051	14/F	7	PBO	Nausea
404	4202	14/F	7, 8	PBO	Asthenia
101	1000	14/M	8	DLX 120	Nausea
402	4101	16/M	8	DLX 120	Nausea

Abbreviations: DLX = duloxetine; F=female; FLX=fluoxetine; M=male; PBO=placebo

[a] Dose decrease requested but could not be implemented, because patient was at the lowest allowed dose. Patient continued in the study at the same dose or had dose increased at subsequent visits.

(Source: HMCK Study Report, p. 251)

For HMCK Study Period III, no individual AE led to discontinuation in more than 1 patient in any treatment group.

Table 75: HMCK AEs Reported as Reason for Discontinuation Study Period III (ITT)

Adverse Event by Preferred Term	DLX60120/DLX60120 N=83 n (%)	FLX2040/FLX2040 N=92 n (%)	PBO/DLX60120 N=86 n (%)
Subjects with ≥ 1 AE	2 (2.4)	8 (8.7)	4 (4.7)
ECG Abnormal	1	0	0
Emotional Distress	1	0	0
Activation Syndrome	0	1	0
Aggression	0	1	0
BP Diastolic Decreased	0	1	0
Chest Pain	0	1	0
Conversion Disorder	0	0	1
Convulsion	0	1	0
Depression	0	0	1
Gastritis	0	0	1
Hypomania	0	1	0
Intentional Overdose	0	1	0
Migraine	0	0	1
Tremor	0	1	0

(Source: HMCK Study Report, p. 254)

The following are the narratives for the subjects with *ECG Abnormal* and *Conversion Disorder*:

Patient 508-5356, a 10 year-old female who was randomized to duloxetine, discontinued due to the non-serious adverse event of ECG abnormal. The patient's baseline rhythm was normal sinus rhythm with heart rate of 88 bpm. After 70 days on duloxetine (120 mg at time of event), the patient's ECG was abnormal (sinus tachycardia) with a heart rate of 113 bpm. The patient's heart rate returned to baseline values prior to discontinuation of study drug. The investigator considered the event possibly related to study drug.

Reviewer Comment:
Small increases in heart rate have been seen with the use of SNRIs including Cymbalta. The current label states that duloxetine treatment, for up to 26 weeks in placebo-controlled trials, caused a small increase in heart rate of up to 1.36 beats per minute. For the pooled HMCK/HMCL acute analyses (Study Period II), there was no significant difference between placebo and duloxetine in pulse. For the pooled HMCK/HMCL long-term analyses (Study Period II/III), the least-squared mean increase in pulse was 2.9 bpm. Further discussion about changes in vital signs for HMCK and HMCL, including potentially clinically significant (PCS) categorical analyses for pulse, are detailed in Section 7.4.3.

Patient 510-5455, a 9 year-old female, was hospitalized due to the SAE of conversion disorder (pseudoseizures), 1 day after starting duloxetine 30 mg QD in Study Period III. The patient was originally randomized to placebo in Study Period II and transitioned to duloxetine for Study Period III. The patient experienced 2 pseudoseizures that were attributed to stress related to father. An EEG was normal. The patient recovered and was discharged and discontinued from the study due to the SAE of conversion disorder. The investigator did not consider the event related to study drug or protocol procedures.

HMCL
Twenty-nine patients discontinued the study due to an AE (11.1% in the duloxetine 60 mg group, 6.0% in the duloxetine 30 mg group, 5.1% in the fluoxetine 20 mg group, and 3.3% in the placebo group). Statistically significantly more duloxetine 60 mg-treated subjects discontinued due to an AE compared to placebo-treated patients (p=.035). There was no single AE leading to discontinuation that occurred statistically significantly more frequently between treatment groups. Most of the AEs that led to discontinuation were psychiatric-related events. The most common AEs that led to discontinuation were: nausea, intentional overdose, suicidal ideation/self-injurious behavior, and aggression.

Table 76: HMCL AEs Reported as Reason for Discontinuation Study Period II (ITT)

Adverse Event by Preferred Term	DLX60 (N=108) n (%)	DLX30 (N=116) n (%)	FLX20 (N=117) n (%)	Placebo (N=122) n (%)
Subjects with ≥ 1 AE	12 (11.1)	7 (6.0)	6 (5.1)	4 (3.3)
Nausea	3	1	0	0
Intentional Overdose	2	0	1	0
Aggression	1	0	2	0
Confusional State	1	0	0	0
Emotional Disorder	1	0	0	0
Fatigue	1	0	0	0
Hallucinations, mixed	1	0	0	0
Somnolence	1	0	0	0
Suicidal Ideation	1	0	0	1
Abdominal Pain Upper	0	1	0	1
Depression	0	2	0	0
Frequent Bowel Movements	0	0	1	0
Initial Insomnia	0	0	1	0
Self-Injurious Behaviour	0	1	0	1
Somnambulism	0	0	0	1
Tuberculosis	0	0	1	0
Upper Respiratory Tract Infection	0	1	0	0
Vomiting	0	1	0	0

(Source: HMCL Study Report, p. 248)

During HMCL Study Period III, 20 subjects discontinued due to an AE (5.5% in the DLX60/DLX60120-treated group, 7.4% subjects in the DLX30/DLX60120-treated group, 3.6% subjects in the FLX20/FLX2040-treated group, and 8.5% patients in the PBO/DLX60120-treated group).The most common AEs that led to discontinuation were irritability, suicidal ideation, suicide attempt, depression, and nausea.

Table 77: HMCL Discontinuation Due to Adverse Event by Patient (Study Period III)

Table HMCL.12.13. Discontinuation Due to Adverse Event by Patient (Study Period III)[§]

Site	Patient	Age	Gender	Visit	Treatment at Time of Discontinuation	Adverse Event as Reason for Discontinuation
130	4015[a]	12	M	9	DLX 60*	Irritability
124	3406[b]	15	F	10	DLX 60	Nausea
102	1204	15	F	10	FLX 40	Hallucination Auditory
113	2307	12	F	11	DLX 120	Rash Maculo-papular
117	2705	14	F	11	DLX 120	Fatigue
150	2202	8	M	11	DLX 60	SAE: Suicide Attempt
106	1604	15	M	11	FLX 20*	Suicidal Ideation
106	1602	15	M	12	DLX 120	SAE: Stevens-Johnson Syndrome
130	4013	12	F	12	DLX 120	Nausea
720	7201	10	M	12	DLX 60	Somnolence
610	6110	10	M	12	DLX 60*	Suicidal Ideation
117	2724	12	M	12	DLX 90	Irritability
620	6204	13	M	12	DLX 90	Irritability
102	1205	13	F	13	DLX 60	Depression
135	4507	14	F	13	DLX 90	SAE: Suicide Attempt
620	6208	7	M	13	DLX 90*	Irritability
620	6213	9	F	13	FLX 20	Irritability
121	3103	9	M	14	DLX 120	SAE: Depression
610	6105	7	F	14	DLX 60*	Irritability
123	3303	17	M	16	DLX 120	Suicidal Ideation

(Source: HMCL Study Report, p. 255)

7.3.4 Adverse Events

Table 78: Treatment Emergent Adverse Events Studies HMCK and HMCL (Periods II and III)

Study Period	HMCK		HMCL		
Period II	DLX60120 N=117 n (%)	PBO N=103 n (%)	DLX30 N=116 n (%)	DLX60 N=108 n (%)	PBO N=122 n (%)
	70 (59.8)	68 (66.0)	67 (57.8)	79 (73.1)	71 (58.2)
Study Period	**HMCK**		**HMCL**		
Period III	DLX60120/DLX60120 N=83 n (%)	PBO/DLX60120 N=86 n (%)	DLX30/DLX60120 N=81 n (%)	DLX60/DLX60120 N=73 n (%)	PBO/DLX60120 N=82 n (%)
	53 (63.9)	62 (72.1)	46 (56.8)	50 (68.5)	55 (67.1)

(Source: Integrated Data Report p.17)

HMCK

For HMCK Study Period II, There was no statistically significant difference in the percentage of patients who reported ≥1 TEAE between the duloxetine-treated group (59.8%) compared with the placebo-treated group (66.0%). The most common TEAEs for the duloxetine treatment group were nausea, headache, decreased appetite, dizziness, and fatigue. There were no statistically significant differences in the incidence of any individual TEAE between active drugs and placebo. There were no statistically significant treatment-by-age/gender interactions for any of the TEAEs.

Table 79: HMCK Common TEAEs Study Period II

Preferred Term	DLX60120 N=117 %	Placebo N=103 %
Patients with ≥ 1 TEAE	59.8%	66%
Nausea	17.1	10.7
Headache	16.2	8.7
Decreased appetite	8.5	6.8
Dizziness	8.5	2.9
Fatigue	6.8	4.9
Influenza	6.0	5.8
Somnolence	6.0	5.8
Vomiting	6.0	2.9
Diarrhea	5.1	1.9
Insomnia	5.1	1.9
Abdominal Pain Upper	3.4	6.8

Upper respiratory tract infection	3.4	1.0
Abdominal discomfort	2.6	1.0
Constipation	2.6	1.9
Dry mouth	2.6	0.0
Oropharyngeal pain	2.6	1.0
Anxiety	1.7	0.0

(Source: HMCK Study Report, p. 831)

Reviewer Comment:
Nausea, somnolence, fatigue, and decreased appetite were also some of the most common adverse reactions in the adult trials.

For HMCK Study Period III, TEAEs reported with incidence ≥5% in the DLX60/DLX60120-treated group were headache, nasopharyngitis, influenza, and upper respiratory tract infection. TEAEs reported with incidence ≥5% in the PBO/DLX60120-treated group were nausea, headache, nasopharyngitis, vomiting, upper abdominal pain, and dizziness. The patients in the PBO/DLX60120 group had a greater incidence of TEAEs in Study Period III compared to the DLX60/DLX60120 group and the FLX20/FLX2040 group.

Table 80: HMCK Common TEAEs Duloxetine Treatment Groups Study Period III

Preferred Term	**DLX60120/DLX60120 N=83 %**	**PBO/DLX60120 N=86 %**
Patients with ≥ 1 TEAE	63.9%	72.1%
Headache	10.8	11.6
Nasopharyngitis	10.8	10.5
Influenza	6.0	4.7
Upper respiratory tract infection	6.0	3.5
Gastroenteritis	4.8	3.5
Incorrect dose administered	4.8	0
Sinusitis	4.8	1.2
Vomiting	4.8	9.3
Abdominal discomfort	3.6	3.5
Diarrhea	3.6	2.3
Dizziness	3.6	7.0
Irritability	3.6	0
Nausea	3.6	7.6
Abdominal pain upper	1.2	8.1
Fatigue	1.2	4.7

(Source: HMCK Study Report, p. 1519, 1521-1522)

There were 3 non-serious adverse events of syncope or presycnope. The narratives for the 3 cases are as follows:

Patient 701-7014, a 12 year-old female who was randomized to duloxetine, experienced the non-serious adverse event of pre-syncope. The patient first reported dizziness 98 days after starting duloxetine. After 155 days on duloxetine, the patient reported near syncopal episodes that lasted for 8 days. The subject was on duloxetine 120 mg QD at time of event. Follow-up received from the site revealed that the patient felt the lightheadedness during menstruation but did not lose consciousness. The range of blood pressures during the study 98-118/60-78 mm Hg and heart rate ranged from 63 to 103 bpm. The investigator did not consider the event related to study drug.

Patient 708-7358, a 17 year-old female who was originally randomized to placebo in Study Period II, experienced the non-serious adverse event of pre-syncope 17 days after transitioning to duloxetine in Study Period III. The duloxetine dose was increased from 30 to 60 mg QD at the time of the event. The pre-syncope lasted for 8 days. Follow-up from the site revealed that the patient had experienced mild dizziness, fever and flu-like virus at the time of the event. The range of blood pressures during Study Period III was 112-129/78-95 mm Hg and heart rate ranged from 72 to 93 bpm. The investigator considered the event possibly related to study drug.

Patient 202-2052, a 13 year-old female who was originally randomized to placebo in Study Period II, experienced the non-serious adverse event of syncope (actual term: faint) 106 days after transitioning to duloxetine in Study Period III. The duloxetine dose was 60 mg QD at time of event. The syncope lasted for 1 day. The range of blood pressures during Study Period III was 88-119/47-85 mm Hg and heart rate ranged from 59 to 93 bpm. The investigator considered the event possibly related to study drug.
Reviewer Comment:
Cymbalta is labeled for orthostatic hypotension and syncope (5.3 Warnings and Precautions).

HMCL
In HMCL Period II, subjects treated with duloxetine 60 mg (73%) had a significantly greater percentage of TEAEs than subjects treated with duloxetine 30 mg (57.8%), fluoxetine 20 mg (61.5%), or placebo (58.2%). Treatment-emergent adverse events reported with incidence >5% in the duloxetine 60 mg-treated group were headache, nausea, abdominal pain upper, somnolence, dizziness, and decreased appetite. Treatment-emergent adverse events reported with incidence >5% in the duloxetine 30 mg-treated group were nausea, headache, abdominal pain upper, dizziness, decreased appetite, diarrhea, vomiting, and fatigue. In general, the most common TEAEs in the duloxetine groups occurred with a higher incidence compared with the placebo group. However, only sedation and diarrhea had a statistically significantly difference in incidence between duloxetine and placebo. There were no statistically significant treatment-by-age/gender interactions for any of the TEAEs.

Table 81: HMCL Common TEAEs Study Period II

Preferred Term	DLX60 N=108 %	DLX30 N=116 %	Placebo N=122 %
Patients with ≥ 1 TEAE	73.1%	57.8%	58.2%
Headache	17.6	16.4	13.9
Nausea	16.7	17.2	9.0
Abdominal Pain Upper	12.0	8.6	7.4
Somnolence	10.2	2.6	4.9
Dizziness	8.3	8.6	6.6
Decreased appetite	5.6	8.6	3.3
Fatigue	4.6	5.2	3.3
Sedation	4.6	1.7	0
Vomiting	4.6	6.0	2.5
Diarrhea	3.7	7.8	1.6
Abdominal pain	2.8	0.9	0
Dry mouth	2.8	1.7	1.6
Dyspepsia	2.8	0	0
Gastroenteritis	2.8	0	0
Insomnia	2.8	2.6	3.3
Irritability	2.8	1.7	1.6

(Source: HMCL Study Report, p. 862-863)

For HMCL Study Period II, the incidence of TEAEs in children (aged 7 to 11 years) was statistically significantly greater for the duloxetine 60 mg-treated group compared with the duloxetine 30 mg-treated group (68.2% versus 44.9%). The incidence of TEAEs in adolescents (aged 12 to 17 years) was statistically significantly greater in the duloxetine 60 mg-treated group compared with the placebo-treated group (76.6% versus 57.5%).

For HMCL Study Period III, the patients in the DLX60/60120 group had the highest incidence of TEAEs. Headache, abdominal pain, and nausea were some of the most common TEAEs in the duloxetine treatment groups.

Table 82: HMCL Common TEAEs Duloxetine Treatment Groups Study Period III

Preferred Term	DLX60/DLX60120 N=73 %	DLX30/DLX60120 N=81 %	PBO/DLX60120 N=82 %
Patients with ≥ 1 TEAE	68.5%	56.8%	67.1%
Abdominal pain upper	8.2	7.4	4.9
Headache	8.2	4.9	13.4
Nausea	8.2	16.0	9.8
Incorrect Dose Administered	6.8	3.7	1.2
Upper respiratory tract infection	6.8	4.9	2.4
Abdominal pain	5.5	1.2	0
Vomiting	5.5	12.3	9.8
Dizziness	2.7	7.4	8.5
Diarrhea	1.4	6.2	2.4

(Source: HMCL Study Report, p. 1605)

7.3.5 Submission Specific Primary Safety Concerns

Growth

Because duloxetine has been associated with weight loss in some adult patients, analyses of pooled data from HMCK and HMCL were performed to assess mean and individual weight changes over time. Pooled weight and height data were also assessed against normative values, calculated as z-scores.

Weight

Patients treated with duloxetine in these studies experienced a 0.2 kg mean decrease in weight at the end of acute treatment (10 weeks), with some experiencing a potentially clinically significant (≥3.5%) decrease in weight. Subsequently, over the 6-month extension period, most patients trended toward recovery to their baseline weight z-score based on population data from age- and gender-matched peers. No SAEs or discontinuations due to weight-related events were reported during either study.

Table 83: Integrated Data Report--Weight Mean Change from Baseline to Endpoint (LOCF) Acute Analyses Set

Treatment Group	Mean Baseline	LS Mean Change	p-value
Duloxetine	56.14 kg	-0.20	<.001
Placebo	56.02 kg	0.64	

(Source: Integrated Data Report, p. 147)

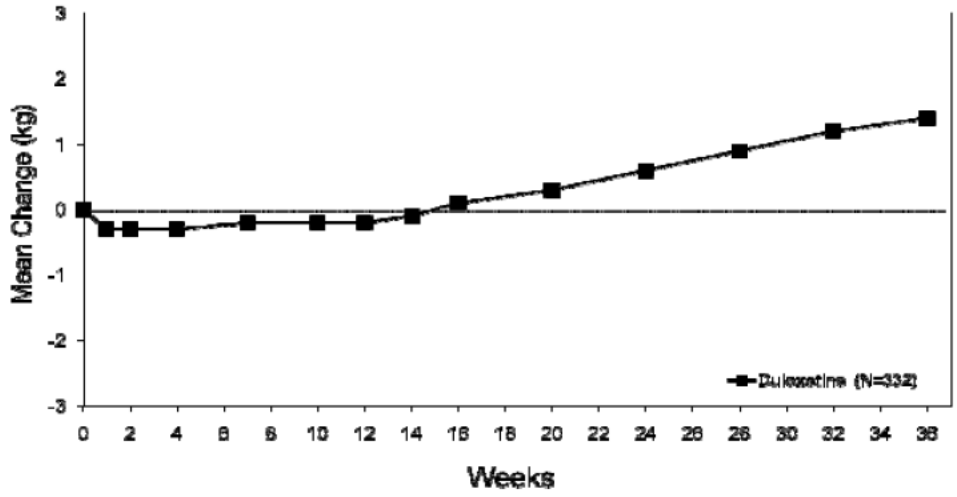
Table 84: Treatment-Emergent PCS Weight Loss (Acute Analyses Set)

Parameter	DLX N=332 n (%)	Placebo N=220 n (%)	p-value
Weight PCS Loss (≥ 3.5%)	38 (11.4%)	12 (5.5%)	.015

(Source: Integrated Data Report, p. 156)

Subjects in the DLX/DLX group experienced a group mean increase of 2 kg by study endpoint in the extension analyses set (Study Period III).

Figure 5: Integrated Data Report--Mean Change in Weight Over the 36 Weeks of Treatment (MMRM) in the Long-Term Analyses Set



(Source: Integrated Data Report, p. 45)

Height
Analyses of mean change in height indicated a similar height increase between duloxetine-treated and placebo-treated patients in the acute analyses set.

Suicidality

The Columbia Suicide Severity Rating Scale was used prospectively to capture the occurrence, severity, and frequency of suicide-related thoughts and behaviors in Studies HMCK and HMCL.

There were no statistically significant differences between the duloxetine and placebo groups in the frequency of patients reporting suicide-related events (ideation, behavior) or non-suicidal self-injurious behavior at baseline. Patients with significant suicidal risk were excluded from the studies.

There were no statistically significant differences between the duloxetine and placebo groups with regard to suicide-related events (ideation or behavior) or non-suicidal self-injurious behavior reported during Study Period II.

Table 85: Integrated Data Report--Suicide-Related Events and Non-Suicidal Self-Injurious Behavior Study Period II (C-SSRS)

	Duloxetine		Placebo		p-value[b]
	N	n (%)	N	n (%)	
Suicidal ideation (Categories 1-5) [a]	333	44 (13.2)	220	30 (13.6)	.941
Suicidal behavior (Categories 6-10) [a]	333	0 (0.0)	220	1 (0.5)	.168
Non-suicidal self-injurious behavior [a]	333	13 (3.9)	219 [c]	7 (3.2)	.743

(Source: Integrated Data Report, p. 21)

Four subjects spontaneously reported intentional overdose on the AE CRF. In 3 out of the 4 cases, the investigator determined that the intentional overdose was not done with intent to die or with intent for self-injury. Therefore, these cases were not reported on the C-SSRS. For example, one HMCL subject with an SAE of intentional overdose had the following narrative:

The patient ingested 42 capsules of investigational product and stated that the reason she took the overdose was because she had not been taking the medicine as instructed; therefore, she took it all the day before her next site visit because she thought she would not get the money for the study. The patient denied any suicidal intent. The patient was discharged on bupropion and hydroxyzine hydrochloride. The investigator did not consider the event related to the investigational product (IP). The patient was discontinued from the study due to the event.

Suicidal behavior was reported for 7 duloxetine-treated patients during extension treatment (Study Period III). There were 4 non-fatal suicide attempts, 2 interrupted suicide attempts, and 1 aborted suicide attempt. The duloxetine dose was 120 mg QD

for 4 patients, 90 mg QD for 1 patient, and 60 mg QD for 2 patients at the time of the suicidal behavior.

Table 86: Integrated Data Report--Suicide-Related Events Study Period III (C-SSRS)

	DLX/DLX		PBO/DLX		Total	
	N	n (%)	N	n (%)	N	n (%)
Suicidal ideation[a] (Categories 1-5)	230	31 (13.5)	164	16 (9.8)	394	47 (11.9)
Suicidal behavior[a] (Categories 6-10)	230	6 (2.6)	164	1 (0.6)	394	7 (1.8)
Non-suicidal self-injurious behaviour[a]	230	11 (4.8)	164	3 (1.8)	394	14 (3.6)

(Source: Integrated Data Report, p. 24)

There were no statistically significant differences on suicidal ideation, suicidal behavior, or non-suicidal self-injurious behavior between duloxetine and fluoxetine during the 36 weeks of treatment.

Hepatic-Related Laboratory Values

No patient had an SAE related to laboratory results, and no patient discontinued due to abnormal laboratory values For chemistry analytes related to hepatology, the difference between duloxetine (-1.2) and placebo (-0.32) in change from baseline to endpoint (Study Period II) was statistically significant only for GGT. However, this finding was not considered clinically meaningful since a decrease is not indicative of liver injury.

Treatment-emergent ALT ≥3 times ULN was reported in the extension analyses set for 1 patient in the HMCK duloxetine group. The patient was initially randomized to placebo for Study Period II and then transitioned to duloxetine for Study Period III. The patient had an abnormal ALT value at baseline and experienced a treatment-emergent ALT increase to ≥3 times ULN at the last study visit while taking duloxetine (Week 36). The patient completed the study by entering the taper phase, during which time the patient's ALT levels decreased towards normal values by the end of the taper phase.

Extrapyramidal Symptoms including Dyskinesia

There was no statistically significant difference in the frequency of extrapyramidal-related symptoms observed between the duloxetine and placebo groups. In addition, there were fewer extrapyramidal-related symptoms reported in the extension analyses set than the acute analysis set.

Table 87: Integrated Data Report--Treatment Emergent Extrapyramidal-related Symptoms Including Dyskinesia, Acute and Extension Analyses Sets

	Acute Analyses Set			Extension Analyses Set	
MedDRA Preferred Term	DLX N=341 n (%)	PBO N=225 n (%)	p-value[a]	PBO/DLX N=168 n (%)	DLX/DLX N=237 n (%)
Patients with ≥1 event	8 (2.3)	4 (1.8)	.677	3 (1.8)	1 (0.4)
Muscle spasms	4 (1.2)	0 (0.0)	.114	0 (0.0)	0 (0.0)
Musculoskeletal stiffness	1 (0.3)	0 (0.0)	.461	1 (0.6)	0 (0.0)
Oesophageal spasm	1 (0.3)	0 (0.0)	.348	-	-
Psychomotor hyperactivity	1 (0.3)	1 (0.4)	.795	1 (0.6)	0 (0.0)
Tic	1 (0.3)	0 (0.0)	.461	-	-
Akathisia	0 (0.0)	0 (0.0)	-	-	-
Blepharospasm	0 (0.0)	1 (0.4)	.175	-	-
Muscle twitching	0 (0.0)	1 (0.4)	.287	-	-
Restlessness	0 (0.0)	1 (0.4)	.175	1 (0.6)	1 (0.4)

(Source: Integrated Data Report, p. 51)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

HMCK

During Study Period II, treatment-emergent adverse events reported with an incidence >5% in the duloxetine treatment group were nausea, headache, decreased appetite, dizziness, fatigue, influenza, somnolence, vomiting, diarrhea and insomnia.

Treatment-emergent adverse events reported with an incidence >5% in the fluoxetine treatment group were headache, nausea, decreased appetite, somnolence, vomiting, and insomnia.

Treatment-emergent adverse events reported with incidence >5% in the placebo treatment group were nausea, headache, decreased appetite, abdominal pain upper, influenza and somnolence.

There were no statistically significant differences in the incidence of any individual TEAE between active drugs and placebo. There were no statistically significant treatment-by-age/gender interactions for any of the TEAEs. The incidence of TEAEs in children and adolescents was not statistically significantly different for the duloxetine-treated group compared with the placebo-treated group.

During Study Period III, TEAEs reported with an incidence ≥5% in the DLX60/DLX60120-treated group were headache, nasopharyngitis, influenza, and upper respiratory tract infection. Treatment-emergent adverse events reported with an incidence ≥5% in the FLX20/FLX2040-treated group were headache, nasopharyngitis, nausea, upper respiratory tract infection, and vomiting. Treatment-emergent adverse events reported with an incidence ≥5% in the PBO/DLX60120-treated group were nausea, headache, nasopharyngitis, vomiting, upper abdominal pain, and dizziness.

HMCL
During HMCL Study Period II, TEAEs with an incidence >5% in the duloxetine 60 mg-treated group were: headache, nausea, abdominal pain upper, somnolence, dizziness, and decreased appetite. TEAEs with an incidence >5% in the duloxetine 30 mg-treated group were: nausea, headache, upper abdominal pain, dizziness, and decreased appetite, diarrhea, vomiting, and fatigue.

Most TEAEs occurred more commonly in the duloxetine groups than the placebo group. However, only 2 adverse events were statistically significantly more common in the duloxetine group than the placebo group: sedation in the 60 mg duloxetine group and diarrhea in the 30 mg duloxetine group.

During HMCL Study Period III, TEAEs with an incidence >5% in the DLX60/DLX60120-treated group were: headache, nausea, upper abdominal pain, incorrect dose administered, upper respiratory tract infection, abdominal pain, and vomiting. TEAEs reported with an incidence >5% in the DLX30/DLX60120-treated group were: nausea, vomiting, upper abdominal pain, nasopharyngitis, dizziness, and diarrhea. Treatment-emergent adverse events reported with an incidence >5% in the PBO/DLX60120-treated group were: headache, nausea, vomiting, pyrexia, dizziness, and fatigue.

7.4.2 Laboratory Findings

HMCK
No subject had an SAE related to abnormal laboratory values or discontinued Study Period II due to abnormal laboratory values. Small, statistically significant within-group baseline to endpoint changes were observed in the 3 treatment groups. For Study Period II, statistically significant differences between the duloxetine treatment group compared to the placebo treatment group were seen for the following analytes:

Chloride: small mean decrease in chloride was observed in the duloxetine-treated group compared to no change in the placebo-treated group; a statistically significant difference was observed between the 2 treatment groups (p=.015).

Bicarbonate: small mean increase in bicarbonate was observed in the duloxetine-treated group compared with a small mean decrease in the placebo-treated group; a

statistically significant difference was observed between the 2 treatment groups (p=.020).

Uric acid: mean decrease in uric acid was observed in the duloxetine-treated group compared with a small mean increase in the placebo-treated group; a statistically significant difference was observed between the 2 treatment groups (p<.001).

Basophils: very small mean change in basophils (mean change = 0) were observed in the duloxetine-treated group and the placebo-treated group; a statistically significant difference was observed between the 2 treatment groups (p=.035).

Alkaline phosphatase: statistically significantly more duloxetine-treated patients experienced a treatment emergent high alkaline phosphatase value at endpoint compared to placebo-treated patients (p=.038). Duloxetine has been associated with small mean increases in alkaline phosphatase in the adult population.

No subject had an SAE related to abnormal laboratory values or discontinued Study Period III due to abnormal laboratory values. Statistically significant within-group baseline to endpoint changes were observed in the 3 treatment groups for some laboratory analytes. These changes were considered small relative to baseline.

HMCL
No subject had an SAE related to abnormal laboratory values or discontinued Study Period II due to abnormal laboratory values. Statistically significant within-group baseline to endpoint changes were observed in the 4 treatment groups for some laboratory analytes; however, these changes were considered small relative to baseline. Statistically significant differences between the duloxetine treatment groups compared to the placebo treatment group were seen for the following analytes:

y-glutamyltransferase: small mean decreases were observed in the duloxetine 60 mg- and duloxetine 30 mg- groups; a statistically significant difference was observed for the duloxetine groups compared with the placebo group.

Uric acid: small mean decreases were observed in the duloxetine 60 mg- and duloxetine 30 mg- groups; a statistically significant difference was observed for the duloxetine 30 mg group compared with the placebo group.

Platelet count: mean decreases were observed in the duloxetine 60 mg- and duloxetine 30 mg- groups; a statistically significant difference was observed for the duloxetine 30 mg group compared with the placebo group.

Lymphocyte and mean cell hemoglobin: mean decreases were observed in the duloxetine 60 mg- and duloxetine 30 mg- groups; a statistically significant difference was observed for the duloxetine 30 mg group compared with the placebo group.

No subject had an SAE related to abnormal laboratory values or discontinued Study Period III due to abnormal laboratory values.

7.4.3 Vital Signs

In the Integrated Data Report, the sponsor analyzed the data from the acute analyses set (Study Period II for HMCK and HMCL) and the long-term analyses set (36 weeks). The long-term analyses set pooled the data from the combined acute (Study Period II) and extension phases (Study Period III) of Studies HMCK and HMCL. Only data from subjects taking duloxetine during both study periods were presented in these analyses. Data from subjects who took placebo during Study Period II and duloxetine during Study Period III were not assessed in these analyses.

Mean Change Analyses for Blood Pressure and Pulse

For Study Period II, there were no statistically significant differences between duloxetine and placebo for mean change from baseline to endpoint in systolic blood pressure, diastolic blood pressure or sitting pulse.

Table 88: Integrated Data Report--Least-Squared Mean Change in Blood Pressure and Pulse at Endpoint Study Period II (MMRM)

Parameter	MMRM Endpoint		
	Duloxetine N=332	Placebo N=220	p-value
Systolic BP (mm Hg)	0.8	-0.2	.213
Diastolic BP (mm Hg)	1.5	0.3	.084
Sitting Pulse (bpm)	1.0	0.1	.290

(Source Integrated Data Report, p. 30)

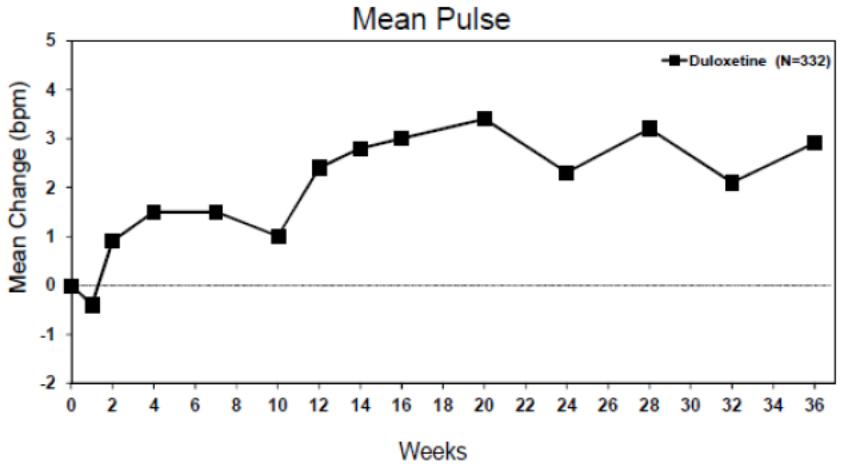
For the long-term analyses (Study Period II/III), the mean increase in systolic and diastolic BP was similar to Study Period II. The mean increase in pulse was higher in the long-term analyses.

Table 89: Integrated Data Report--Least-Squared Mean Change in BP and Pulse at Endpoint, Acute versus Long-Term Analyses (MMRM)

Parameter	Acute Analyses (Study Period II)	Long-Term Analyses (Study Period II/III)
	DLX N=332	DLX/DLX N=332
Systolic BP (mm Hg)	0.8	1.3
Diastolic BP (mm Hg)	1.5	1.7
Sitting Pulse (bpm)	1.0	2.9

(Source: Integrated Data Report, p. 35)

Figure 6: Integrated Data Report--Change in Mean Pulse Over Time for DLX/DLX Treatment Group



(Source: Integrated Data Report, p.36)

Potentially Clinically Significant (PCS) Categorical Analyses for BP and Pulse

PCS parameters included:

- For systolic and diastolic blood pressure: >95th percentile by age, gender, height and an increase from baseline high of ≥5 mm Hg.
- For high pulse: >140 bpm and increase from baseline high ≥15 bpm for children; >120 bpm and increase from baseline high ≥15 bpm for adolescent.
- For low pulse: <60 and decrease from baseline ≥25 for children; <50 and decrease from baseline ≥15 for adolescent.

For Study Period II, there were no statistically significant differences between duloxetine and placebo in the incidence of PCS blood pressure or pulse.

Table 90: Integrated Data Report--Incidence of PCS Increase in BP or Pulse Study Period II (LOCF)

Parameter	Duloxetine		Placebo		p-value
	N	n (%)	N	n (%)	
Systolic BP (mm Hg)	283	27 (9.5)	188	16 (8.5)	.600
Diastolic BP (mm Hg)	295	27 (9.2)	203	21 (10.3)	.969
Pulse (bpm)	332	0	220	1 (0.5)	.295

(Source: Integrated Data Report, p. 31)

For the long-term analyses set, the frequency of either PCS high systolic or diastolic blood pressure at any time during 36 weeks of treatment was 15.9% and 18.3%, respectively, in the duloxetine group. The majority of these events resolved during the study. One subject had a PCS high criterion for pulse that resolved (94 bpm at baseline, PCS pulse of 126 at Week 32, and non-PCS pulse of 108 at 36-week endpoint).

Sustained Elevation of Blood Pressure

Sustained elevation of systolic or diastolic blood pressure was defined as blood pressure >95th percentile (by age, gender, height) and an increase from baseline high of ≥5 mm Hg at 3 consecutive postbaseline visits.

For Study Period II, there were no statistically significant differences between duloxetine and placebo with respect to sustained elevation of blood pressure.

Table 91: Integrated Data Report--Incidence of Sustained Elevation of BP Study Period II

Parameter	Duloxetine		Placebo		p-value
	N	n (%)	N	n (%)	
Systolic BP (mm Hg)	283	1 (.4)	188	2 (1.1)	.412
Diastolic BP (mm Hg)	295	1 (.3)	203	2 (1.0)	.412

(Source: Integrated Data Report, p. 31)

For the long-term analyses set, subjects with normal blood pressure at baseline had a 1.4% incidence of sustained elevation of systolic blood pressure and 1.7% incidence of sustained elevation of diastolic blood pressure. The majority met the sustained criteria at endpoint.

Shifts in Blood Pressure Categories

The blood pressure categories were defined as follows:

- **Normal**: <90th percentile systolic or diastolic blood pressure at baseline
- **Prehypertension**: ≥90th to <95th percentile or systolic BP >120 (diastolic BP >80).
- **Stage 1 hypertension**: ≥95th to ≤99th percentile, with a 5-mm Hg increase from baseline.
- **Stage 2 hypertension**: >99th percentile, with a 5-mm Hg increase from baseline.

Shifts in Blood Pressure Categories for Subjects with Normal Baseline Blood Pressure

For Period II, the majority of duloxetine-treated subjects (74%) and placebo-treated subjects (73%) remained in the normal range throughout the acute treatment period.

Table 92: Integrated Data Report--Categorical Shifts in Blood Pressure for Subjects with Normal Baseline Study Period II

	At Any Time				At Endpoint			
	Normal n (%)	Pre-HTN n (%)	Stage 1 HTN n (%)	Stage 2 HTN n (%)	Normal n (%)	Pre-HTN n (%)	Stage 1 HTN n (%)	Stage 2 HTN n (%)
Systolic BP (mm Hg)								
Duloxetine N=275	204 (74.2)	45 (16.4)	18 (6.5)	8 (2.9)	243 (88.4)	22 (8.0)	7 (2.5)	3 (1.1)
Placebo N=187	136 (72.7)	31 (16.6)	16 (8.6)	4 (2.1)	166 (88.8)	15 (8.0)	4 (2.1)	2 (1.1)
Diastolic BP (mm Hg)								
Duloxetine N=304	217 (71.4)	52 (17.1)	31 (10.2)	4 (1.3)	266 (87.5)	23 (7.6)	14 (4.6)	1 (0.3)
Placebo N=201	150 (74.6)	29 (14.4)	18 (9.0)	4 (2.0)	177 (88.1)	14 (7.0)	8 (4.0)	2 (1.0)

(Source: Integrated Data Report, p.32)

For the long-term analyses set, the majority (65%) of subjects in the duloxetine group with normal mean baseline blood pressure remained in the normal range throughout the 36 weeks of treatment. Most shifts occurred during acute treatment for those subjects who did experience a shift to a higher category.

Shifts in Blood Pressure Categories for Subjects with Abnormal Baseline Blood Pressure

For Study Period II, subjects in the duloxetine group were more likely than subjects in the placebo group to experience a postbaseline maximum shift into a higher category for systolic BP. For diastolic BP, the frequency of shifts to a higher category was similar for patients in the placebo group compared with the duloxetine group.

Table 93: Integrated Data Report--Categorical Shifts in Systolic Blood Pressure for Subjects with Abnormal Baseline Values

	At Any Time				At Endpoint			
Baseline Category	Normal n (%)	Pre-HTN n (%)	Stage 1 HTN n (%)	Stage 2 HTN n (%)	Normal n (%)	Pre-HTN n (%)	Stage 1 HTN n (%)	Stage 2 HTN n (%)
Systolic BP (mm Hg)								
Pre-HTN								
DLX (N=46)	7 (15.2)	15 (32.6)	13 (28.3)	7 (15.2)	19 (41.3)	19 (41.3)	4 (8.7)	3 (6.5)
PBO (N=24)	6 (25.0)	12 (50.0)	2 (8.3)	2 (8.3)	17 (70.8)	7 (29.2)	0 (0.0)	0 (0.0)
Stage 1 HTN								
DLX (N=7)	0 (0.0)	1 (14.3)	1 (14.3)	4 (57.1)	2 (28.6)	2 (28.6)	0 (0.0)	1 (14.3)
PBO (N=6)	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)
Stage 2 HTN								
DLX (N=2)	0 (0.0)	0 (0.0)	0 (0.0)	2(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PBO (N=3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)

(Source: Integrated Data Report, p. 33)

For the long-term analyses set, the majority of subjects with abnormal systolic BP at baseline shifted into a higher category at some time during the 36 weeks of treatment. Most of the shifts occurred during the acute treatment phase. The data from both the acute and long-term analyses sets are limited by the small sample size.

Table 94: Integrated Data Report--Categorical Shifts in BP for Subjects with Abnormal Baseline Values Long-Term Analyses Set

	At Any Time				At Endpoint			
Baseline Category	Normal n (%)	Pre-HTN n (%)	Stage 1 HTN n (%)	Stage 2 HTN n (%)	Normal n (%)	Pre-HTN n (%)	Stage 1 HTN n (%)	Stage 2 HTN n (%)
Systolic BP (mm Hg)								
Pre-HTN								
DLX (N=46)	4 (8.7)	16 (34.8)	14 (30.4)	9 (19.6)	25 (54.3)	13 (28.3)	4 (8.7)	2 (4.3)
Stage 1 HTN								
DLX (N=7)	0 (0.0)	1 (14.3)	1 (14.3)	5 (71.4)	2 (28.6)	2 (28.6)	0 (0.0)	2 (28.6)
Stage 2 HTN								
DLX (N=2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diastolic BP (mm Hg)								
Pre-HTN								
DLX (N=19)	4 (21.1)	4 (21.1)	6 (31.6)	3 (15.8)	13 (68.4)	3 (15.8)	2 (10.5)	1 (5.3)
Stage 1 HTN								
DLX (N=7)	0 (0.0)	2 (28.6)	1 (14.3)	1 (14.3)	2 (28.6)	3 (42.9)	1 (14.3)	0 (0.0)
Stage 2 HTN								
DLX (N=0)	-	-	-	-	-	-	-	-

(Source: Integrated Data Report, p. 39)

7.4.4 Electrocardiograms (ECGs)

In the acute analyses set, there was a statistically significant difference in the mean change in heart rate observed between duloxetine (+2.4 bpm) and placebo (-1.1 bpm). In the long-term analyses set, the duloxetine group had a mean increase of 2.8 bpm.

In both the acute and long-term analyses sets, patients in the duloxetine group had a decrease in QTcF, which was not considered clinically relevant.

In general, the analyses of ECG data did not reveal any new safety findings in pediatric patients.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only Study Period II of HMCL was a fixed-dose trial. In this period, subjects treated with duloxetine 60 mg had a significantly greater percentage of TEAEs (73%) than subjects treated with duloxetine 30 mg (57.8%). However, only *somnolence* was statistically significantly more common in subjects treated with duloxetine 60 mg compared to subjects treated with duloxetine 30 mg. The data from this trial is consistent with current labeling which states that some adverse reactions were observed to be dose-dependent in the adult trials.

7.5.2 Time Dependency for Adverse Events

Shifts in Blood Pressure Categories
Most shifts occurred during acute treatment (Study Period II) for those subjects who did experience a shift to a higher category.

7.5.3 Drug-Demographic Interactions

In general, there were no significant drug-demographic interactions.

7.5.4 Drug-Disease Interactions

No new information on drug-disease interactions was submitted to this sNDA.

7.5.5 Drug-Drug Interactions

No new information on drug-drug interactions was submitted to this sNDA.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information on human carcinogenicity was submitted to this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

No new information on human reproduction and pregnancy was submitted to this sNDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

See section 7.3.5

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information on drug abuse potential, withdrawal and rebound was submitted to this sNDA.

Two patients in HMCL Study Period II had intentional overdoses of significant amounts of duloxetine with minimal sequelae as noted in the following narratives:

Patient HMCL-122-3203 *experienced an overdose of the study drug. She was 16 year old white female randomized to Duloxetine 60 mg QD. She began the trial on 29-MAY-2009. On* (b) (6)*, the patient took 42 capsules of the investigative product (IP) and was taken to the emergency room (ER) for the overdose with the investigational product by her mother after her mother observed the patient's unusual behavior. The subject started to have visual hallucinations, was dizzy and had blurred vision. The investigator considered the visual hallucinations (adverse event) moderate in intensity on* (b) (6) *and dizziness (adverse event) mild in intensity on* (b) (6) *When the patient was confronted she told her mother that she took the entire investigational product that she had missed. She reportedly was not taking the study medication the previous two to three weeks. She was scared that she was not going to get money from the study. The subject was taken to the emergency room. The patient presented with visual symptoms for the event of overdose with investigational product. The patient denied any suicidal intentions. Abdominal pain was also reported that was mild in intensity on* (b) (6)*. On exam, the subject was sleepy but was awake, alert and oriented with clear speech. A gastric lavage was performed and charcoal was given. 1000 ml of sodium chloride was given intravenously. An electrocardiogram (EKG) showed normal sinus rhythm at 72 beats per minute (BPM) with sinus arrhythmia. A urine toxicology screen was negative. Vital signs included a temperature of 98.4; heart rate of 86; respiratory rate of 18; oxygen saturation of 99% and blood pressure of 138/92. On* (b) (6) *a white blood cell*

count was 12.1 k/uL, a blood glucose level of 119 mg/dL and blood alkaline phosphatase of 52 IU/L. A urine toxicology screen was negative. The patient was considered stable and recovering and was transferred to a children's hospital for admission on (b) (6). *Vitals signs included a temperature of 98.4; pulse 70; respiratory rate 18 and blood pressure of 107/59. An EKG on* (b) (6) *was normal sinus rhythm with a rate of 58 BPM. On 23-JUL-2009 the subject was given 600 mg of ibuprofen for a headache. The subject was recovered from the overdose with IP on* (b) (6). *The investigator confirmed that the subject was discharged from the hospital on* (b) (6) *The subject was discharged on bupropion hydrochloride and hydroxyzine hydrochloride.*

Patient HMCL-720-7204 *experienced an overdose of the study drug. She was 12 year old Hispanic female randomized to Duloxetine 60 mg QD. The patient received the study drug beginning on 06-MAY-2010. The patient's last dose of study drug prior the event of overdose was on 06-Jul-2010. The study drug was discontinued on 07-Jul-2010. On* (b) (6) *after the first dose of study drug, the patient took seventy-eight study drug capsules and twenty tablets of naproxen (250 milligrams each). The patient was admitted to the hospital on the same day,* (b) (6), *for the intentional overdose and a gastric lavage was done. The chemistry, hematology, and urinalysis were all within normal limits on* (b) (6). *The patient went to general therapeutic and nursing care on* (b) (6) *with a good mood. The patient noted that she took the medications without the idea of dying but because she "wanted to sleep". The diagnosis given for this event per the hospital was "attempting suicide, is stable without problems." In the Investigator's opinion, this event of intentional overdose is not a suicide attempt because it was a conscious decision that the patient wanted to sleep and "the diagnosis is based on the opinion of a pediatrician and not a qualified investigator." Additionally in the Investigator's opinion, "the (intentional overdose) was severe but taking these steps (was) not done with the intention of dying and it does not qualify as an attempted suicide because there was not a thought of dying or suicide planning." Additional treatment that the patient received was omeprazole 60mg intravenously every 12 hours until 09-Jul-2010 then 20 milligram orally every eight hours until 13-Jul-2010. The omeprazole 20 milligrams was continued every 24 hours from 14-Jul-2010 until 30-Aug-2010. On* (b) (6) *the patient had additional lab testing and electrocardiogram that were within normal limits. Upon physical examination, the patient was noted to be in good physical condition. She was discharged from the hospital on* (b) (6) *The patient was considered recovered from the event of intentional overdose on* (b) (6). *In the Investigator's opinion, this event of intentional overdose is related to the study drug as antidepressants increase the impulse.*

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

The sponsor did not submit any new information on the postmarket experience with this sNDA.

9 Appendices

9.1 Literature Review/References

No literature review was submitted for this sNDA.

9.2 Labeling Recommendations

The sponsor has proposed the following changes to **Section 8.4 Pediatric Use** of the label:

(b) (4)

[redacted]

Reviewer Comment:
An e-mail was sent to Lilly on 06 August 2012 stating that the proposed changes to labeling were acceptable with the following additions:

8.4 Pediatric Use

(b) (4)

[redacted]

Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Pediatric patients treated with Cymbalta in MDD clinical trials experienced a 0.2 kg mean decrease in weight at 10-weeks, compared with a mean weight gain of approximately 0.6 kg in placebo-treated patients. (b) (4)

(b) (4). Subsequently, over the six-month extension period, most patients trended toward recovery to their baseline weight percentile expected based on population data from age- and gender-matched peers. (b) (4)

In the 2 pediatric MDD studies, the safety findings were consistent with the known safety and tolerability profile for Cymbalta.

On 13 August 2012, Lilly sent an e-mail to the Division stating that they accepted all the labeling changes proposed by the FDA. The Division then met with the Pediatric Review Committee (PeRC) on September 12, 2012. The committee recommended further modifications to section 8.4 Pediatric Use of the label. The amended label was submitted to the sponsor. The following are the proposed changes to section 8.4 Pediatric Use:

(b) (4)

Changes were also made to the boxed warning to reflect the Division's current standard language. The statement (b) (4)

On 27 September 2012, the sponsor agreed to proposed changes to section 8.4

(b) (4)

The sponsor also requested that the statement *Cymbalta is not approved for use in pediatric patients* remain in the boxed warning. The Division has agreed to these requests.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned.

9.4 HMCK and HMCL Schedules of Assessments and Illustrations of Study Design

Table HMCK.9.3. Study Schedule

Study Period	I		II						III								IV	ET
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	301	
Week	-2	-1	0	1	2	4	7	10	12	14	16	20	24	28	32	36		
Days from Visit 3	-30 to -12	-9 to -5	n/a	5 to 9	12 to 16	26 to 30	47 to 51	68 to 72	82 to 86	96 to 100	110 to 114	138 to 142	166 to 170	194 to 198	222 to 226	250 to 254	n/a	n/a
Description																		
Informed consent/assent	X																	
Psychiatric, medical, drug, and family history	X																	
Demographics	X																	
Habits	X															X		X
Physical exam		X																
Height		X						X					X				X	X
Weight & Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Date of first menses		X														X		X
Electrocardiogram		Xa						X					X			X		X
Pregnancy test[b]		X																
TSH		X																
Chemistry		X				X		X		X		X	X			X		X
Hematology		X				X		X		X		X	X			X		X
Cotinine & UDS[b]	X																	
Urinalysis		X						X								X		X
CYP2D6 genotyping		X																
Hemoglobin A1c		X						X					X			X		X
Pharmacokinetics[c]					X *	X	X*	X		X		X	X			X		X
Preexisting conditions and AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(continued)

Study Schedule, Protocol F1J-MC-HMCK

Study Period	I		II						III								IV	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	301	ET
Week	-2	-1	0	1	2	4	7	10	12	14	16	20	24	28	32	36		
Days from Visit 3	-30 to -12	-9 to -5	n/a	5 to 9	12 to 16	26 to 30	47 to 51	68 to 72	82 to 86	96 to 100	110 to 114	138 to 142	166 to 170	194 to 198	222 to 226	250 to 254	n/a	n/a
Description																		
MINI-KID	X	Xd																
CDRS-R	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS/Self-Harm Supplement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-Up Forme																		
CGI-Severity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug			X	X	X	X	X	X	X	X	X	X	X	X	X	Xf		Xf
Drug return/accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Date/time first dose				X														
Date/time last 3 dosesc					X	X	X	X		X		X	X			X		X
Date of last dose																X	X	X

C-SSRS = Columbia-Suicide Severity Rating Scale; ECGs = electrocardiograms; ET = Early Termination; IVRS = Interactive Voice Response System; MINI-KID = Mini International Neuropsychiatric Interview for children and adolescents; n/a = not applicable; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; UDS = urine drug screen.

* The PK samples at Visits 5 and 7 are optional.

a Three (3) ECGs will be collected approximately 1 minute apart during this visit.

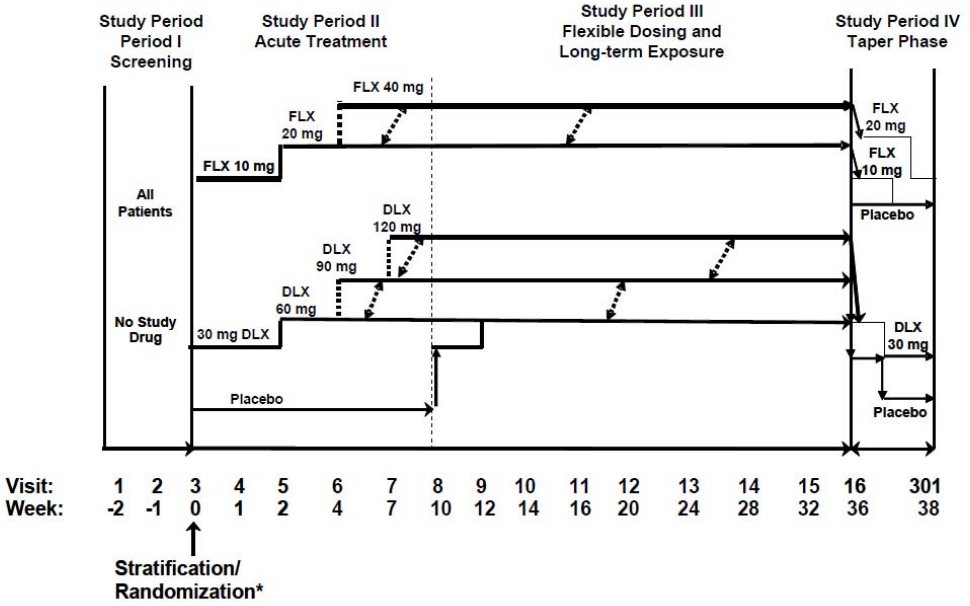
b May be repeated at investigator's discretion throughout the trial.

c A minimum of 2 PK samples must be collected during Study Period II. If PK samples were not collected at the scheduled visits, they can be collected at the subsequent visit.

d Second evaluator administers the Mini-KID at Visit 2.

e The Self-Harm Follow-Up Form will be completed at any visit when a suicidal or non-suicidal self-injurious behavior is identified.

f Study drug dispensed only if patient entering Tapering Phase.



Abbreviations: FLX = fluoxetine, DLX = duloxetine

*Patients will be stratified by age (children aged 7-11 years or adolescents aged 12-17 years) before randomization into the three treatment arms. Enrollment will be monitored to achieve no less than 40% total complement of children.

Figure HMCK.1. Illustration of study design for Clinical Protocol F1J-MC-HMCK.

Table HMCL.9.3. Study Schedule

Study Period	I		II						III								IV	ET
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	301	
Week	-2	-1	0	1	2	4	7	10	12	14	16	20	24	28	32	36		
Days from Visit 3	-30 to -12	-9 to -5	n/a	5 to 9	12 to 16	26 to 30	47 to 51	68 to 72	82 to 86	96 to 100	110 to 114	138 to 142	166 to 170	194 to 198	222 to 226	250 to 254	n/a	n/a
Description																		
Informed consent/assent	X																	
Psychiatric, medical, drug, and family history	X																	
Demographics	X																	
Habits	X															X		X
Physical exam		X																
Height		X						X					X				X	X
Weight & Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Date of first menses		X														X		X
Electrocardiogram		X[a]						X					X			X		X
Pregnancy test[b]		X																
TSH		X																
Chemistry		X				X		X		X		X	X			X		X
Hematology		X				X		X		X		X	X			X		X
Cotinine & UDS[b]	X																	
Urinalysis		X						X								X		X
CYP2D6 genotyping		X																
Hemoglobin A1c		X						X					X			X		X
Pharmacokinetics[c]					X *	X	X*	X		X		X	X			X		X
Preexisting conditions and AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Schedule, Protocol F1J-MC-HMCL

Study Period	I		II						III								IV	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	301	ET
Week	-2	-1	0	1	2	4	7	10	12	14	16	20	24	28	32	36		
Days from Visit 3	-30 to -12	-9 to -5	n/a	5 to 9	12 to 16	26 to 30	47 to 51	68 to 72	82 to 86	96 to 100	110 to 114	138 to 142	166 to 170	194 to 198	222 to 226	250 to 254	n/a	n/a
Description																		
MINI-Kid	X	X[d]																
CDRS-R	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS/Self-Harm Supplement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-Up Form[e]																		
CGI-Severity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug			X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]		X[f]
Drug return/accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Date/time first dose				X														
Date/time last three doses[c]					X	X	X	X		X		X	X			X		X
Date of last dose																X	X	X

C-SSRS = Columbia-Suicide Severity Rating Scale; ECGs = electrocardiograms; ET = Early Termination; IVRS = Interactive Voice Response System; MINI-KID = Mini International Neuropsychiatric Interview for children and adolescents; n/a = not applicable; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; UDS = urine drug screen.

* The PK samples at Visits 5 and 7 are optional.

[a] Three (3) ECGs will be collected approximately 1 minute apart during this visit.

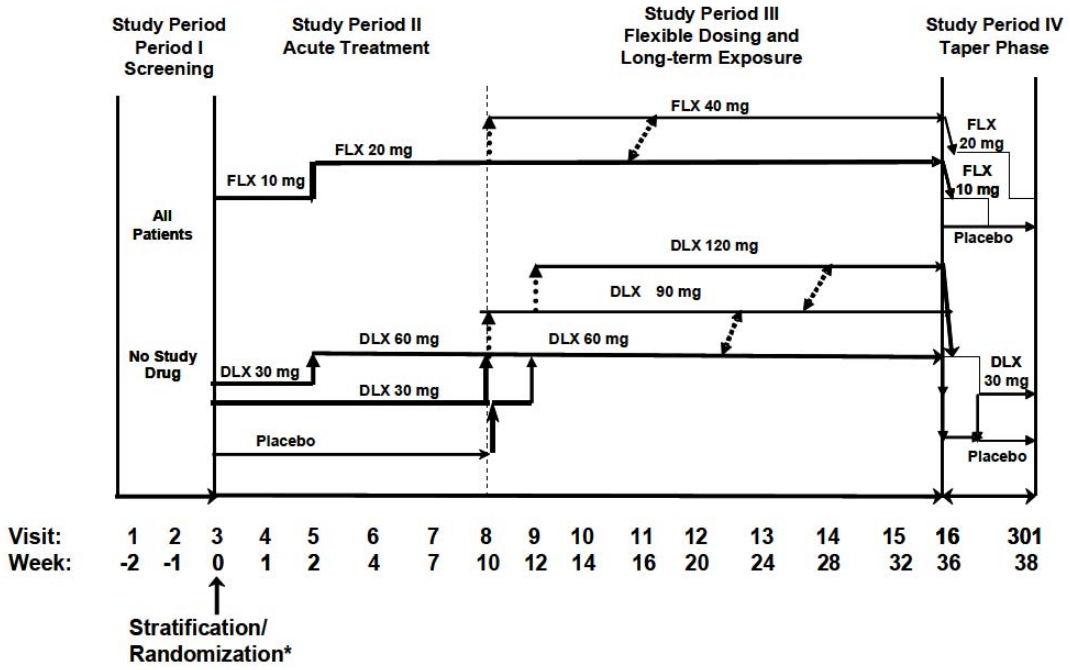
[b] May be repeated at investigator's discretion throughout the trial.

[c] A minimum of 2 PK samples must be collected during Study Period II. If PK samples were not collected at the scheduled visits, they can be collected at the subsequent visit.

[d] Second evaluator administers the Mini-Kid at Visit 2.

[e] The Self-Harm Follow-Up Form will be completed at any visit when a suicidal or non-suicidal self-injurious behavior is identified.

[f] Study drug dispensed only if patient entering Tapering Phase.



* Patients will be stratified by age (children ages 7-11 years or adolescents ages 12-17 years) before randomization into the four treatment arms. Enrollment will be monitored to achieve no less than 40% total complement of children.

Figure HMCL.1. Illustration of study design for Protocol F1J-MC-HMCL.

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

/s/

CHRISTINA P BURKHART
10/02/2012

ROBERT L LEVIN
10/02/2012
I agree with Dr. Burkhart's conclusions and recommendations. See memo to follow.