U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	21,427
Supplement #:	SUPPL-41
Drug Name:	Duloxetine
Indication(s):	Major Depressive Disorder (MDD)
Applicant:	Eli Lilly and Co.
Dates:	Submission date: 04/19/12
	PDUFA: 10/19/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Keywords:
NDA review, pediatric written request, mixed models.

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1 EXECUTIVE SUMMARY

To satisfy the pediatric Written Request (WR) issued by the Division, the sponsor submitted clinical study reports for two short-term efficacy studies F1J-MC-HMCK and F1J-MC-HMCL investigating treatment of MDD in pediatric population (children and adolescents).

Both studies were multicenter, randomized, double-blind, placebo-controlled clinical trials with fluoxetine treatment arms included to test assay sensitivity. Study F1J-MC-HMCK investigated treatment effect of a flexible dose of duloxetine (60 mg – 120 mg). Study F1J-MC-HMCL included two fixed dose duloxetine arms: 30 mg and 60 mg. In both studies, the efficacy of duloxetine was evaluated by assessing the mean change from baseline to endpoint visit (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine arms and placebo.

The primary results of both studies did not show a statistically significant difference between duloxetine and placebo in decreasing depression symptoms in children and adolescents who met criteria for MDD without psychotic features.

Although both studies failed, it appears that the sponsor conducted these studies in accordance with the statistical analysis plan agreed upon by the Agency. From the statistical perspective, there is no evidence against fulfilling the Pediatric Written Request.

2 INTRODUCTION

2.1 Overview

Duloxetine hydrochloride, hereafter referred to as duloxetine, is currently approved in the United States (US) for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), and fibromyalgia, for the management of diabetic peripheral neuropathic pain (DPNP), and chronic musculoskeletal pain in adults at least 18 years of age. It is approved in the European Union (EU) for the treatment of adults with MDD, GAD, DPNP, and moderate to severe stress urinary incontinence in women.

To satisfy the pediatric Written Request (WR) issued by the Division, the sponsor submitted clinical study reports for two short-term efficacy studies: F1J-MC-HMCK and F1J-MC-HMCL investigating treatment of MDD in pediatric population. The key information regarding the studies is summarized in Table 1.

Table 1. Studies F1J-MC-HMCK and F1J-MC-HMCL

	Phase & design	Treatment period	Follow-up period	# of subjects per arm	Study population
F1J-MC-HMCK	Phase 3	10 weeks	26 weeks of long-term exposure + 2 weeks of taper phase	DLX: 117 FLX: 117 Placebo: 103	Children & adolescents with MDD
F1J-MC-HMCL	Phase 3	10 weeks	26 weeks of long-term exposure + 2 weeks of taper phase	DLX 60mg: 108 DLX 30mg: 116 FLX 20mg: 117 Placebo: 122	Children & adolescents with MDD

Source: summarized by reviewers.

The studies F1J-MC-HMCK and F1J-MC-HMCL had 65 and 60 study centers respectively. Study F1J-MC-HMCK was conducted in 9 countries, grouped in 4 regions: America (USA), Western Europe (Finland, France, Germany), Eastern Europe (Slovakia, Ukraine, Russia, Estonia), and South Africa (South Africa). Study F1J-MC-HMCL was conducted in 4 countries: USA, Canada, Mexico, Argentina.

Reference is made to the Agency's original pediatric written request (PWR) letter dated June 23, 2006 and amendments dated September 22, 2009 and November 02, 2009.

2.2 Data Sources

The sponsor's submitted data and program listings are available in the following directories of the CDER' electronic document room (EDR):
\\Cdsesub1\evsprod\NDA021427\0139\m5\datasets\f1j-mc-hmck\analysis\datasets
\\Cdsesub1\evsprod\NDA021427\0139\m5\datasets\f1j-mc-hmcl\analysis\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

3.2 Evaluation of Efficacy

The *primary objective* of the study F1J-MC-HMCK was 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 without psychotic features, single or recurrent episode, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

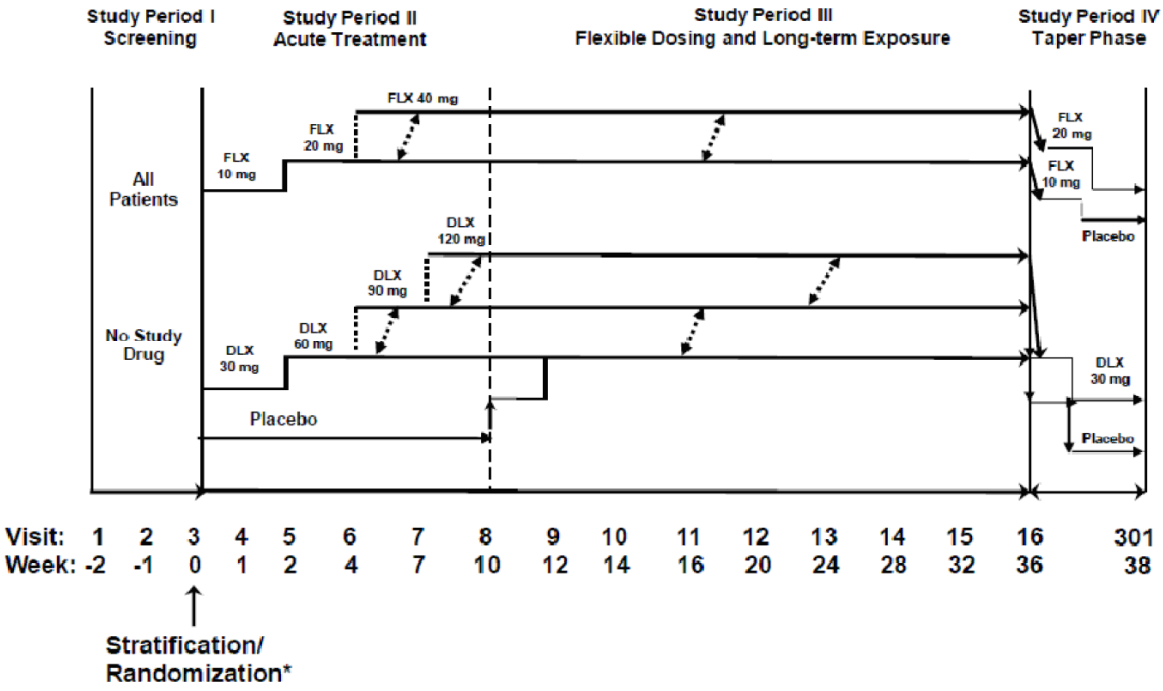
The *primary objective* of the study F1J-MC-HMCL was to assess the *efficacy of duloxetine 60 mg* QD compared with placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who met criteria for MDD without psychotic features, single or recurrent episode, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

3.2.1 Study Design and Endpoints

3.2.1.1 Study F1J-MC-HMCK

Study F1J-MC-HMCK was a Phase 3, multicenter, randomized, double-blind, clinical trial of duloxetine (flexible dose of 60 mg – 120 mg) versus placebo in children and adolescents meeting DSM-IV-TR criteria for MDD. To test assay sensitivity, a fluoxetine treatment arm was included in this study. This study used stratified randomization by age: children (7 through 11 years) and adolescents (12 through 17 years). The study consisted of 4 periods: a screening period, a 10-week acute treatment period, a 6-month extension period, and a 2-week tapering period. The overall study design is presented in Figure 1.

Figure 1. Study design for F1J-MC-HMCK.



Source: Figure HMCK.9.1 from F1J-MC-HMCK Clinical Study Report.

The primary objective of the study F1J-MC-HMCK was evaluated by assessing the mean change from baseline to endpoint visit (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine and placebo. The CDRS-R total score was calculated by summing the 17 individual scores. If three or fewer CDRS-R items were missing, the average of the non-missing values was substituted for the missing items. If more than three assessment items were missing, the total assessment score was set to missing.

3.2.1.2 Study F1J-MC-HMCL

Study F1J-MC-HMCL was a Phase 3, multicenter, randomized, double-blind, clinical trial of two fixed doses of duloxetine (30 mg and 60 mg) versus placebo in children and adolescents meeting DSM-IV-TR criteria for MDD. The duloxetine 30 mg arm was initially included by the sponsor for exploratory purpose, with sample size equal to 50% of the sample size for 60 mg arm. Per the amended ,Written Request, the sponsor amended the HMCL protocol to increase the sample size of the 30mg arm. The assessment of the efficacy of duloxetine 30 mg compared with placebo was included as a secondary objective.

To test assay sensitivity, a fluoxetine treatment arm was included in this study. This study used stratified randomization by age: children (7 through 11 years) and adolescents (12 through 17 years). The study consisted of 4 periods: a screening phase; a 10-week acute treatment phase; a 6-month extension phase; and a 2-week tapering phase. The overall study design is presented in Figure 2.

Figure 2. Study design for F1J-MC-HMCL.

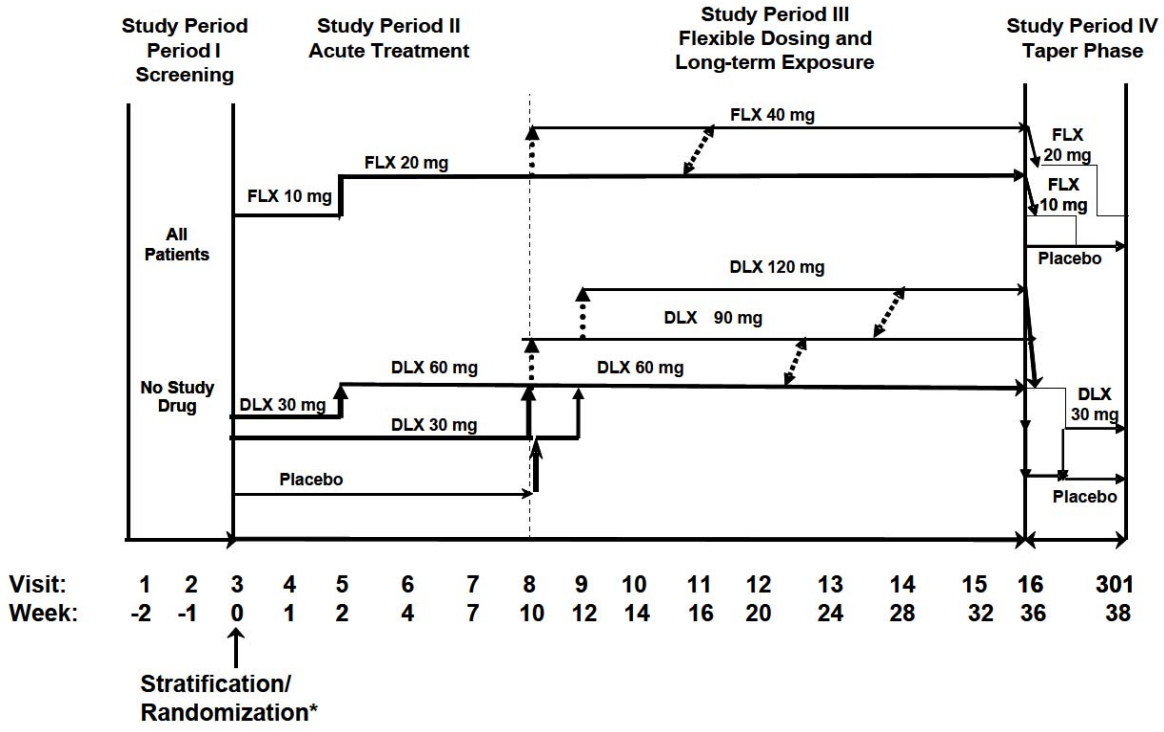


Figure HMCL.9.1 from F1J-MC-HMCL Clinical Study Report.

The primary objective was evaluated by assessing the mean change from baseline to endpoint visit (10 weeks) on the Children's Depression Rating Scale Revised (CDRS-R) total score between duloxetine 60 mg QD and placebo. The CDRS-R total score was calculated by summing the 17 individual scores. If 3 or fewer CDRS-R items were missing, the average of the non-missing values was substituted for the missing items. If more than 3 assessment items were missing, the total assessment score was set to missing.

3.2.2 Statistical Methodologies

3.2.2.1 Study F1J-MC-HMCK

The sponsor estimated that a sample size of 100 in each group provides approximately 80% power to detect an effect size of 0.40 (duloxetine efficacy relative to placebo on CDRS-R total score) using a two group t-test with a 0.05 two-sided significance level.

The **primary efficacy analysis** was the contrast between duloxetine and placebo at the last visit in Study Period II (visit 8, week 10) from a MMRM analysis on mean change from baseline in the CDRS-R total score. The model for this analyses included the fixed, categorical effects of treatment, investigator, visit, treatment-by-visit interaction, age category (pediatrics 7-11, adolescents 12-17), and age category-by-visit interaction, as well as the continuous, fixed

covariates of baseline CDRS-R total score and baseline CDRS-R total score-by-visit interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Statistical analyses were conducted on an intent-to-treat (ITT) basis, meaning that data were analyzed by the treatment groups to which patients were randomized, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol. Thus, the sponsor refers to 337 randomized patients enrolled in Study Period II as *ITT population*. However, only 336 patients (116 duloxetine, 117 fluoxetine, and 103 placebo) were summarized for study drug exposure, because one duloxetine-treated patient (subject ID: 504-5151) did not have any study drug records past randomization (Visit 3). All efficacy and safety analyses of continuous measures included randomized patients with both a baseline and at least 1 post-baseline value from Visit 3 trough 8, which corresponds to 329 patients (*Analysis Set*).

3.2.2.2 Study F1J-MC-HMCL

The sponsor estimated that a sample size of 100 in each group provides approximately 80% power to detect an effect size of 0.40 on the CDRS-R total score using a 2 group t-test with a 0.05 two-sided significance level.

The **primary efficacy analysis** was the contrast between duloxetine 60 mg and placebo at the last visit in Study Period II (Visit 8, Week 10) from a MMRM analysis on mean change from baseline in the CDRS-R total score. The model for this analysis included the fixed, categorical effects of treatment, investigator, visit, treatment-by-visit interaction, age category (children 7 through 11, adolescents 12 through 17), age category-by-visit interaction, as well as the continuous, fixed covariates of baseline CDRS-R total score and baseline CDRS-R total score-by-visit interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. No adjustments were made for multiple comparisons.

Unless otherwise specified, analyses were conducted on an intent-to-treat (ITT) basis, meaning that data were analyzed by the treatment groups to which patients were randomly assigned, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol. Thus, the sponsor refers to 463 randomized patients enrolled in Study Period II as *ITT population*. The dataset used for all the efficacy and safety analyses of included the randomized patients with both a baseline and at least 1 post-baseline value from Visit 3 trough 8, which corresponds to 448 patients (*Analysis Set*).

The assessment of the efficacy of duloxetine 30 mg versus placebo at the last visit in Study Period II was considered as a secondary efficacy objective. The contrast was to be evaluated by the MMRM model used for the primary efficacy analysis.

In the response to IND 38,838 SN 442 (05/27/2009) the Agency suggested to use a fixed-sequence approach to deal with the multiplicity issue by first comparing the 60 mg dose with

placebo and then testing duloxetine 30 mg versus placebo if duloxetine 60 mg is shown to be superior.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study F1J-MC-HMCK

The demographic and baseline characteristics for the ITT population are summarized in Table 2.

Table 2. Baseline Demographic Characteristics of the F1J-MC-HMCK Study (ITT population).

	DLX (60-120 mg) N = 117	**FLX (20-40 mg)** N = 117	**Placebo** N = 103	**Total** N = 337
Age *years*				
Mean (SD)	13.14 (3.043)	13.08 (3.272)	13.28 (3.055)	13.16 (3.120)
Min – Max	7.1 – 17.9	7.1 – 17.8	7.3 – 17.9	7.1 – 17.9
Age category *n (%)*				
7 – 11 years	47 (40.2)	50 (42.7)	38 (36.9)	135 (40.1)
12 – 17 years	70 (59.8)	67 (57.3)	65 (63.1)	202 (59.9)
Gender *n (%)*				
Male	53 (45.3)	56 (47.9)	52 (50.5)	161 (47.8)
Female	64 (54.7)	61 (52.1)	51 (49.5)	176 (52.2)
Ethnicity *n (%)*				
Hispanic or Latino	8 (7.4)	3 (3.0)	6 (6.5)	17 (5.6)
Not Hispanic or Latino	100 (92.6)	98 (97.0)	87 (93.5)	285 (94.4)
Not answered	9	16	10	35
Race *n (%)*				
Asian	0 (0.0)	2 (1.8)	0 (0.0)	2 (0.9)
Black/African American	17 (15.2)	9 (8.0)	13 (13.3)	39 (12.1)
White	90 (80.4)	93 (83.0)	79 (80.6)	262 (81.4)
Multiracial	4 (3.6)	7 (6.3)	5 (5.1)	16 (5.0)
Other	1 (0.9)	1 (0.9)	1 (1.0)	3 (0.9)
Not provided	5	5	5	15
Weight				
Mean (SD)	54.32 (21.582)	52.37 (20.529)	52.07 (17.368)	52.95 (19.972)
Min – Max	20.6 – 116.4	20.5 – 129.8	21.8 – 110.0	20 – 129.8
Height				
Mean (SD)	155.14 (16.585)	152.95 (17.144)	154.90 (15.719)	154.31 (16.505)
Min – Max	118.5 – 186.0	100.5 – 191.0	117.0 – 187.0	100.5 – 191.0
BMI				
Mean (SD)	21.66 (5.726)	21.68 (5.640)	21.16 (4.851)	31.51 (5.431)
Min – Max	12.3 – 38.0	13.7 – 42.7	12.7 – 39.0	12.3 – 42.7
Region *n (%)*				
United States	50 (42.7)	45 (38.5)	45 (43.7)	140 (41.5)
Western Europe	5 (4.3)	7 (6.0)	5 (4.9)	17 (5.0)
Eastern Europe	41 (35.0)	41 (35.0)	31 (30.1)	113 (33.5)
South Africa	21 (17.9)	24 (20.5)	22 (21.4)	67 (19.9)

Source: F1J-MC-HMCK Clinical Study Report Table HMCK.11.1, pg. 130.

The disposition of ITT patients, including the reasons for discontinuation during Study Period II are summarized in Table 3. The discontinuation by visit is presented in Table 4.

Table 3. Discontinuation Reasons for Patients of the F1J-MC-HMCK Study (ITT Population).

	DLX (60-120) N = 117	FLX (20-40) N = 117	Placebo N = 103	Total N = 337
Number of Completers	87 (74.4)	91 (77.8)	87 (84.5)	265 (78.6)
Number of Dropouts	30 (25.6)	26 (22.2)	16 (15.5)	72 (21.4)
Reasons:				
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)
Protocol Violation	0 (0.0)	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 (0.0)	0 (0.0)	1 (0.3)
Lack of Efficacy	2 (1.7)	3 (2.6)	2 (1.9)	7 (2.1)

Source: F1J-MC-HMCK Clinical Study Report Table HMCK.10.1, pg. 96.

Table 4. Discontinuation of patients by visit during the Study F1J-MC-HMCK (ITT Population).

	DLX (60-120mg) N = 117	FLX (20-40 mg) N = 117	Placebo N = 103	Total N = 337
Discontinued at				
Visit 4	7 (6.0)	7 (6.0)	1 (1.0)	15 (4.5)
Visit 5	3 (2.6)	2 (1.7)	1 (1.0)	6 (1.8)
Visit 6	5 (4.3)	3 (2.6)	4 (3.9)	12 (3.6)
Visit 7	11 (9.4)	6 (5.1)	6 (5.8)	23 (6.8)
Visit 8	3 (2.6)	8 (6.8)	4 (3.9)	15 (4.5)
Totally	29 (24.8)	26 (22.2)	16 (15.5)	71 (21.1)

Source: F1J-MC-HMCK Clinical Study Report Table HMCK.10.1, pp. 98–104.

3.2.3.2 Study F1J-MC-HMCL

The demographic and baseline characteristics for all the randomized patients (ITT) of Study F1J-MC-HMCL are summarized in Table 5.

Table 5. Baseline Demographic Characteristics of the F1J-MC-HMCL Study (ITT population).

	DLX 60 mg N = 108	DLX 30 mg N = 116	FLX 20 mg N = 117	Placebo N = 122	Total N = 463
Age *years*					
Mean (SD)	12.92 (2.9)	12.86 (2.9)	13.04 (3.2)	13.09 (2.9)	12.98 (3.0)
Min – Max	7.1 - 17.9	7.1 - 18.0	7.1 - 18.0	7.0 - 17.9	7.0 - 18.0
Age category *n (%)*					
7 – 11 years	44 (40.7)	49 (42.2)	50 (42.7)	49 (40.2)	192 (41.5)
12 – 17 years	64 (59.3)	67 (57.8)	67 (57.3)	73 (59.8)	271 (58.5)
Gender *n (%)*					
Male	48 (44.4)	69 (59.5)	56 (47.9)	53 (43.4)	226 (48.8)
Female	60 (55.6)	47 (40.5)	61 (52.1)	69 (56.6)	237 (51.2)
Ethnicity *n (%)*					
Hispanic or Latino	34 (31.8)	38 (33.6)	39 (33.6)	46 (38.0)	157 (34.4)
Not Hispanic or Latino	73 (68.2)	75 (66.4)	77 (66.4)	75 (62.0)	300 (65.6)
Not answered	1	3	1	1	6

Race *n (%)*					
Asian	0 (0.0)	1 (0.9)	1 (0.9)	1 (0.8)	3 (0.7)
Black/African American	27 (26.5)	21 (18.6)	21 (18.4)	24 (20.2)	93 (20.8)
White	54 (52.9)	61 (54.0)	67 (58.8)	62 (52.1)	244 (54.5)
Multiracial	6 (5.9)	6 (5.3)	9 (7.9)	13 (10.9)	34 (7.6)
Other	15 (14.7)	24 (20.7)	16 (14.0)	19 (16.0)	74 (16.0)
Not provided	6	3	3	3	15
Weight					
Mean (SD)	57.91 (22.9)	55.98 (19.7)	56.53 (23.4)	59.54 (23.9)	57.51 (22.5)
Min – Max	23.4 - 142.5	20.4 - 116.6	20.2 - 127.1	23.0 - 142.4	20.0 - 142.5
Height					
Mean (SD)	153.94 (13.4)	155.12 (15.2)	153.01 (16.7)	154.84 (14.8)	154.23 (15.1)
Min – Max	120.0 - 185.0	117.0 - 188.0	119.2 - 191.0	120.0 - 185.4	117.0 - 191.0
BMI					
Mean (SD)	23.72 (7.2)	22.49 (5.2)	23.18 (6.7)	23.98 (6.8)	23.34 (6.5)
Min – Max	13.7 - 50.9	14.2 - 37.7	13.4 - 45.0	14.3 - 48.6	13.4 - 50.9
Region *n (%)*					
Canada and US	92 (85.2)	91 (78.4)	100 (8.5)	105 (86.1)	388 (83.8)
Argentina and Mexico	16 (14.8)	25 (21.6)	17 (14.5)	17 (13.9)	75 (16.2)

Source: F1J-MC-HMCL Clinical Study Report Table HMCL.11.1, pg. 123.

The patients disposition by reasons for discontinuation during Period II is summarized in Table 6.

Table 6. Discontinuation Reasons for Patients of the F1J-MC-HMCL Study (ITT Population).

	DLX 60 mg N = 108	**DLX 30 mg** N = 116	**FLX 20 mg** N = 117	**Placebo** N = 122	**Total** N = 463
Number of Completers	75 (69.4)	81 (69.8)	84 (71.8)	85 (69.7)	325 (70.2)
Number of Dropouts	33 (30.6)	35 (30.2)	33 (28.2)	37 (30.3)	138 (29.8)
Reasons:					
Adverse Event	12 (11.1)	7 (6.0)	6 (5.1)	4 (3.3)	29 (6.3)
Lost to Follow Up	5 (4.6)	8 (6.9)	11 (9.4)	9 (7.4)	33 (7.1)
Protocol Violation	1 (0.9)	5 (4.3)	2 (1.7)	6 (4.9)	14 (3.0)
Subject Decision	5 (4.6)	5 (4.3)	3 (2.6)	8 (6.6)	21 (4.5)
Parent/Caregiver Decision	7 (6.5)	6 (5.2)	7 (6.0)	7 (5.7)	27 (5.8)
Physician Decision	2 (1.9)	1 (0.9)	2 (1.7)	1 (0.8)	6 (1.3)
Sponsor Decision	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Lack of Efficacy	1 (0.9)	3 (2.6)	1 (0.9)	2 (1.6)	7 (1.5)

Source: F1J-MC-HMCL Clinical Study Report Table HMCL.10.1, pg. 90.

The discontinuation of ITT patients by visit is presented in Table 7.

Table 7. Discontinuation of patients by visit during the Study F1J-MC-HMCL (ITT Population).

	DLX 60 mg N = 108	**DLX 30 mg** N = 116	**FLX 20 mg** N = 117	**Placebo** N = 122	**Total** N = 463
Discontinued at					
Visit 4	8 (7.4)	5 (4.3)	6 (5.1)	6 (4.9)	25 (5.4)
Visit 5	1 (0.9)	2 (1.7)	3 (2.6)	8 (6.6)	14 (3.0)
Visit 6	10 (9.3)	8 (6.9)	8 (6.8)	8 (6.6)	34 (7.3)
Visit 7	4 (3.7)	14 (12.1)	12 (10.3)	10 (8.2)	40 (8.6)
Visit 8	10 (9.3)	6 (5.2)	4 (3.4)	5 (4.1)	25 (5.4)
Totally	33 (30.6)	35 (30.2)	33 (28.2)	37 (30.3)	138 (29.8)

Source: F1J-MC-HMCL Clinical Study Report Table HMCL.10.1, pp. 92–98.

3.2.4 Sponsor's Efficacy Results and Conclusions

3.2.4.1 Study F1J-MC-HMCK

The results of the primary efficacy analysis (MMRM analysis using contrast between duloxetine and placebo on mean change from baseline in the CDRS-R total score at the Visit 8 in Study Period II) are presented in Table 8. The difference in the mean change from baseline between the duloxetine treatment group and placebo was not statistically significant (p-value > 0.05).

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) FLX (20-40 mg) Placebo	88 95 89	35.0 35.6 35.0	-24.3 (1.09) -23.7 (1.06) -24.3 (1.11)			
DLX vs. Placebo FLX vs. Placebo DLX vs. FLX				0.0 (1.53) 0.6 (1.51) -0.6 (1.50)	(-3.0, 3.0) (-2.4, 3.6) (-3.6, 2.4)	0.999 0.687 0.686

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

The sponsor considers the study 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.

3.2.4.2 Study F1J-MC-HMCL

The results of the primary efficacy analysis (MMRM analysis using contrast between duloxetine and placebo on mean change from baseline in the CDRS-R total score at the Visit 8 in Study Period in Study Period II) are presented in Table 9.

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

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

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

The difference in the mean change from baseline between the duloxetine treatment group and placebo was not statistically significant (p-value > 0.05). The sponsor considers the study 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.

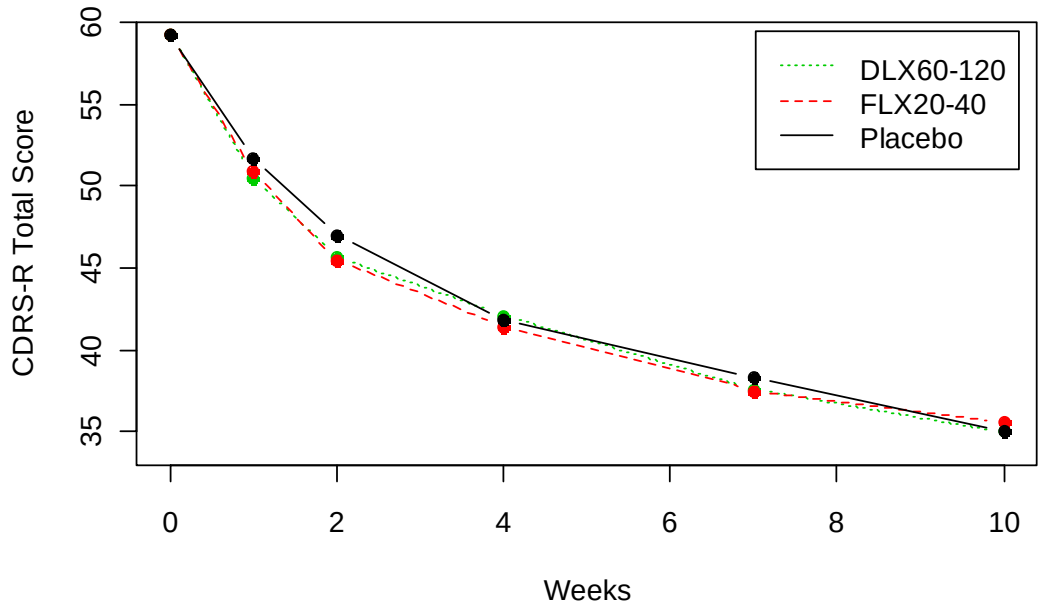
3.2.5 Reviewer's Results and Conclusions

3.2.5.1 Study F1J-MC-HMCK

The reviewers confirm 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.

The LS Mean CDRS-R total scores of the MMRM Analysis are depicted for each treatment group in Figure 3. 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).



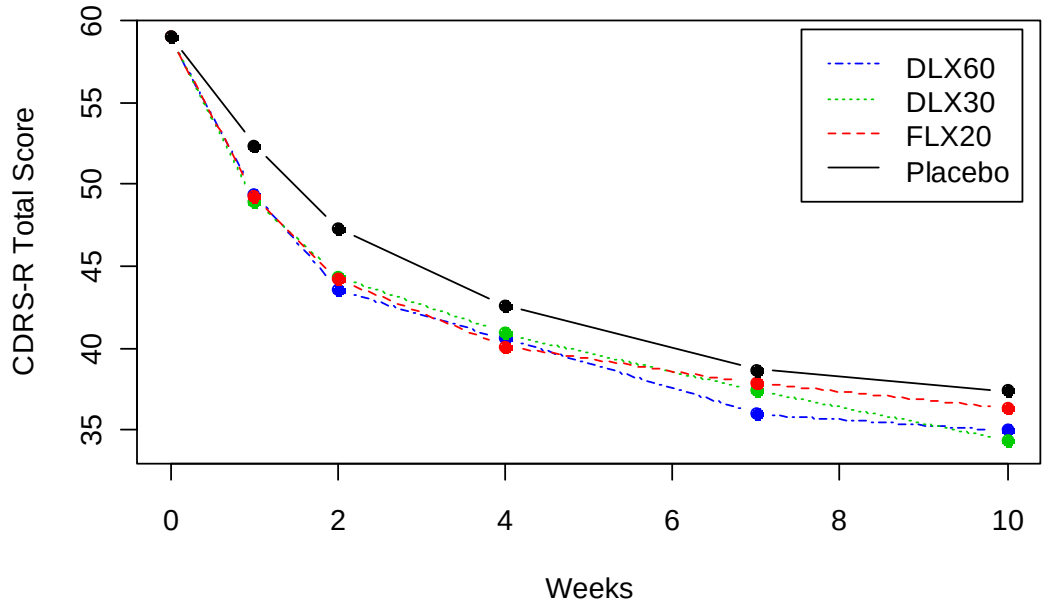
Source: computed by the reviewers.

3.2.5.2 Study F1J-MC-HMCL

The reviewers confirmed the sponsor's analysis results for the primary efficacy endpoint. No statistically significant difference was observed between the duloxetine arms and placebo. Also,

no statistically significant difference was observed between the active comparator (fluoxetine) and placebo either.
The LS Mean CDRS-R total scores of the MMRM Analysis are depicted for each treatment group in Figure 4. 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.

3.3 Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This section contains the reviewer's results of the exploratory subgroup analysis for Studies F1J-MC-HMCK (Table 10) and F1J_MC-HMCL (Table 11).The data were grouped by gender, race, ethnicity, age category, and region.

Table 10. Primary efficacy endpoint analysis by subgroup for study F1J-MC-HMCK.

	DLX 60-120 mg vs. Placebo at Visit 8	
	LS Difference Estimate (SE)	**95 % CI**
Full Analysis Set (n=329)	0.00 (1.53)	(-3.02, 3.02)

Gender		
Male (n=155)	0.32 (2.09)	(-3.82, 4.47)
Female (n=174)	-0.23 (2.37)	(-4.93, 4.47)
Age category		
7-11 years (n=130)	-2.20 (2.15)	
12-17 years (n=199)	1.55 (2.16)	
Race/Ethnicity		
White (n=256)	-1.62 (1.60)	(-4.78, 1.53)
Black/African American (n=37)	6.59 (5.65)	(-5.30, 18.47)
Region		
United States (n=136)	0.95 (2.71)	(-4.43, 6.32)
Western Europe (n=17)	6.87 (7.30)	(-11.49, 25.23)
Eastern Europe (n=112)	-2.11 (2.49)	(-7.05, 2.84)
South Africa (n=64)	-0.50 (2.85)	(-6.30, 5.31)

Source: computed by the reviewers.

Table 11. Primary efficacy endpoint analysis by subgroup for study F1J-MC-HMCL.

	DLX 60 mg vs. Placebo at Visit 8	
	LS Difference Estimate (SE)	**95 % CI**
Full Analysis Set (n=448)	-2.33 (1.78)	(-5.84, 1.18)
Gender		
Male (n=218)	1.50 (2.57)	(-3.57, 6.57)
Female (n=230)	-5.73 (2.47)	(-10.62, -0.84)
Age category		
7-11 years (n=183)	-2.73 (2.82)	(-8.30, 2.84)
12-17 years (n=265)	-2.43 (2.35)	(-7.06, 2.21)
Race/Ethnicity		
White (n=239)	0.94 (2.41)	(-3.83, 5.70)
Black/African American (n=89)	-8.59 (3.43)	(-15.45, -1.72)
Region		
Canada and US (n=378)	-1.64 (1.95)	(-5.48, 2.21)
Argentina and Mexico (n=70)	-5.29 (4.41)	(-14.11, 3.53)

Source: computed by the reviewers.

The subgroup analysis performed by the reviewer did not reveal consistent efficacy patterns for most of the subgroups. For instance, the numerical estimates of the treatment effect in Black/ African American population vary from 6.6 points in favor of the drug (Study F1J-MC-HMCK) to 8.6 points in favor of placebo (Study F1J-MC-HMCL). Similarly, the effect in US population varied from 0.9 points in favor of the drug (Study F1J-MC-HMCK) to 1.6 points in favor of placebo (Study F1J-MC-HMCL).

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

For both studies all treatment arms (including placebo) demonstrated substantial numerical improvement in primary efficacy variable CDRS-R total score: LS Mean score decreased by more than 20 points.

In both studies the primary analysis (MMRM) of CDRS-R total score did not demonstrate statistically significant difference between the duloxetine treatment group and the placebo arm. In the Study F1J-MC-HMCK , the observed LS mean treatment effect of flexible dose of duloxetine (relative to placebo) was 0.002 points (p-value 0.999). In the Study F1J-MC-HMCL, the primary comparison of duloxetine 60mg and placebo produced observed treatment effect of -2.3289 points (p-value of 0.192). The active comparator arm (fluoxetine) also failed to demonstrate superiority to placebo in both studies (p-values of 0.687 and 0.594 respectively).

5.2 Collective Evidence

The primary results of both studies did not show a statistically significant difference between duloxetine and placebo in decreasing depression symptoms in children and adolescents who met criteria for MDD without psychotic features. Assay sensitivity test also failed to show a statistically significant difference between fluoxetine (previously approved by the FDA for use in treating depression in children ages 8 and older) and placebo. The lack of statistical significance in both studies may be, in particular, attributed to high placebo response.

5.3 Conclusions and Recommendations

Although both studies failed, it appears that the sponsor conducted these studies in accordance with the statistical analysis plan agreed upon by the Agency. From the statistical perspective, there is no evidence against fulfilling the Pediatric Written Request.

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/s/

ANDREJUS PARFIONOVAS
09/25/2012

GEORGE KORDZAKHIA
09/25/2012

PEILING YANG
09/25/2012
I concur with the joint review by Drs. Parfionovas and Kordzakhia.

KOOROS MAHJOOB
09/25/2012
I concur with the review.