EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Ariclaim/Cymbalta/Xeristar/Yentreve

(duloxetine hydrochloride)

Procedure No. EMEA/H/C/000552/P46/039, 039.1 (Ariclaim)
EMEA/H/C/000572/P46/044, 044.1 (Cymbalta)
EMEA/H/C/000573/P46/045, 045.1 (Xeristar)
EMEA/H/C/000545/P46/040, 040.1 (Yentreve)

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

I. INTRODUCTION

On 2 March 2012, the MAH submitted the final clinical study report for study F1J-MC-HMCL (HMCL), 'A Double-Blind, Efficacy and Safety Study of Duloxetine versus Placebo in the Treatment of Children and Adolescents with Major Depressive Disorder', in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. On 11 April 2012 a second study, F1J-MC-HMCK (HMCK), 'A Double-Blind, Efficacy and Safety Study of Duloxetine versus Placebo in the Treatment of Children and Adolescents with Major Depressive Disorder' was submitted accompanied by a clinical overview discussing the results of both studies and any considerations for the Product Information.

These studies are provided in line with the current 6 months reporting timeline.

The MAH stated that a brief summary of the now submitted paediatric studies results will be proposed for inclusion in the SmPC (Sections 4.2. and 5.1) within 2 months of the CHMP's assessment of this Article 46 filing, in order to provide appropriate SmPC wording taking into consideration the CHMP's review of the data.

II. SCIENTIFIC DISCUSSION

II.1 Information on the development program

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Duloxetine is authorised in EU in adults for the treatment of major depressive episodes; the treatment of diabetic peripheral neuropathic pain; the treatment of generalised anxiety disorder and for women for the treatment of moderate to severe stress urinary incontinence.

Studies HMCK and HMCL were conducted to comply with a US postmarketing requirement.

The Phase 2 paediatric study (F1J-MC-HMFN [HMFN1]) that preceded HMCK and HMCL was conducted as part of a paediatric plan committed with the FDA and submitted per Article 46 in April 2009 with CHMP outcome on 30 June 2009 (EMEA/412163/2009).

On 19 October 2009 the applicant submitted to the European Medicines Agency an application for a paediatric investigation plan including a deferral and a waiver for Duloxetine hydrochloride in diabetic neuropathic pain, chronic pain, major depressive disorder, generalized anxiety disorder and stress urinary incontinence. The European Medicines Agency adopted a decision granting a waiver for duloxetine hydrochloride for all subsets of the paediatric population from birth to less than 18 years of age; on the grounds that the specific medicinal product is likely to be unsafe. [EMA decision P/21/2010 of 02 March 2010 revised 17 November 2010 (P/268/2010)].

Rapporteur's comments:

At the time of submitting the application for the paediatric investigation plan, the phase II study HMFN was yet completed and the two phase III studies (HMCL and HMCK) were on-going.

The EMA Paediatric Working Party in their Assessment of the Paediatric Needs – Psychiatry (EMEA/288917/2007), considered duloxetine to be devoid of interest to be developed in paediatric psychiatric indications or below the authorised age group.

Two separate reports will be provided by the Company with pooled data from duloxetine paediatric studies:

- a report on population PK

- a report discussing observations regarding growth and development.

No additional on-going or planned studies for the indication are declared.

II.2 Information on the pharmaceutical formulation used in the study

Duloxetine is authorised as 30 mg, 40 mg and 60 mg, hard gastro-resistant capsules. Duloxetine is not indicated for use in children. No suitable paediatric formulation is available.

30-mg capsules of duloxetine hydrochloride (size 3 capsule) were dispensed in these two phase III studies.

Rapporteur's comments:

Patients involved in the studies now submitted were treated with the currently marketed formulation. The commercial formulation seems to be acceptable for older children.

20 and 30 mg capsules of duloxetine enteric-coated pellets were administered to patients participating in Phase II HMFN study, which included children and adolescents form 7 up to 18 years old. No further data on PK bioequivalence between both formulations are provided.

II.3 Non-clinical aspects

No information provided.

Rapporteur's comments:

The MAH should submit relevant data from completed juvenile studies in order to evaluate the inclusion of this information in the SPC.

II.4 Clinical aspects

1. Introduction

The MAH provides an overview of 2 completed Phase 3 randomised, double-blind, placebo controlled studies of duloxetine [F1J-MC-HMCK (HMCK)] and F1J-MC-HMCL (HMCL)] in paediatric patients with major depressive disorder (MDD).

The design of both studies are the same with the only difference that HMCK is a flexible dosing study (60 mg to 120mg once daily) whereas HMCL is a fixed-dose study during the acute treatment period (30 mg and 60 mg once daily). Both studies included a fluoxetine treatment arm to test assay sensitivity.

A number of plasma samples were collected in both studies in order to characterize the pharmacokinetics of duloxetine at steady-state.

- **Pharmacokinetic results**

The findings related to the descriptive summary statistics of duloxetine steady-state concentrations in Studies HMCL and HMCK have been summarized.

HMCL Study

A total of 1157 plasma samples (collected throughout the full 36-week study) were obtained from 268 patients for the measurement of duloxetine concentrations. 730 quantifiable plasma concentrations from 214 patients were included in the PK evaluation.

Of the 214 patients that contributed quantifiable plasma concentrations, 37% were children (aged 7 to 11 years) and 63% were adolescents (aged 12 to 18 years). The number of males and females were similar at 48% and 52%, respectively. The majority of the patients were nonsmokers (92%), extensive CYP2D6 metabolizers (84%) and White (59%). Seventy percent (70%) of female patients had attained menarche. Disposition of doses for the quantifiable plasma concentrations included in the PK assessment was 20%, 30-mg; 46%, 60-mg; 14%, 90-mg; and 20%, 120-mg duloxetine administered once daily. Summary statistics for duloxetine concentrations, age, and body weight by dose are presented in Table HMCL.11.25 below

Table HMCL.11.25. Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose[a]

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 (0.6 – 113.1)	44.1 ± 43.1 (0.5 – 244.2)	67.3 ± 52.9 (0.5 – 267.4)	77.1 ± 61.9 (0.5 – 304.9)
BQL[b]	N = 25 n = 36	N = 65 n = 104	N = 29 n = 37	N = 49 n = 98
Age (years)	13.1 ± 2.94 (7.1 – 18.0)	12.9 ± 2.88 (7.0 – 17.8)	12.7 ± 2.81 (7.1 – 18.0)	13.2 ± 2.79 (7.1 – 17.8)
Body Weight (kg)	57.5 ± 20.6 (20.0 – 117.6)	57.8 ± 24.7 (20.2 – 145.4)	57.8 ± 21.0 (21.5 – 135.8)	60.2 ± 23.7 (23.1 – 135.2)

Abbreviations: BQL = below the lower quantification limit of the assay; N = number of patients; n = number of duloxetine concentrations.

[a] Summary statistics reported as Mean ± Standard Deviation (Minimum – Maximum).

[b] Postdose concentration reported as below the quantification limit of the assay.

Typical duloxetine plasma concentrations increased in proportion to the increase in dose. This apparent dose proportionality was observed for 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. Because the PK of duloxetine are linear, dose-normalized plasma concentrations were utilized for subsequent evaluation of the effect of the various patient factors on duloxetine plasma concentrations.

HMCK Study

A total of 793 plasma samples were obtained from the patients for the measurement of duloxetine concentrations. 532 quantifiable plasma concentrations from 152 patients were included in the PK evaluation.

Of the 152 patients that contributed quantifiable plasma concentrations, 36% were children (7 to 11 years old) and 64% were adolescents (12 to 18 years old). The number of males and females were similar at 51% and 49%, respectively. The majority of the patients were nonsmokers (89%), extensive CYP2D6 metabolizers (93%) and Caucasian (84%). Sixty-four percent (64%) of female patients had attained menarche. Disposition of doses for the 532 quantifiable plasma concentrations included in the PK assessment was <1%, 30-mg; 48%, 60-mg; 13%, 90-mg; and 39%, 120-mg duloxetine administered once-daily. Summary statistics for duloxetine concentrations, age and body weight by dose are presented in Table HMCK.11.25 below.

Table HMCK.11.25. Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose [a]

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 (0.5 – 70.6)	41.4 ± 39.5 (0.5 – 199.8)	60.6 ± 50.4 (0.5 – 313.6)	89.6 ± 85.1 (0.5 – 528)
BQL [b]	N = 4 n = 4	N = 46 n = 73	N = 17 n = 26	N = 34 n = 77
Age (years)	16.3 ± 0.907 (15.3 – 17.1)	12.7 ± 2.81 (7.4 – 17.8)	13.1 ± 3.27 (7.3 – 17.9)	13.2 ± 3.13 (7.3 – 17.9)
Body Weight (kg)	75.7 ± 31.2 (52 – 111)	53.0 ± 17.8 (21 – 115.4)	53.8 ± 21.9 (24.1 – 105.9)	53.4 ± 19.3 (20.3 – 112.3)

Abbreviations: BQL = below the lower quantification limit of the assay ; N = number of patients; n = number of duloxetine concentrations.

[a] Summary statistics reported as Mean ± Standard Deviation (Minimum – Maximum).

[b] Post dose concentration reported as below the quantification limit of the assay.

Duloxetine plasma concentrations appeared to increase in a linear manner with increasing doses in the dose range of 60 to 120 mg as shown in Table HMCK.11.25. For a given dose, there were no discernible differences in median duloxetine concentration in children and adolescents; the distribution and range of concentration were similar in the 2 populations. The median dose-normalized concentration in females is similar to that in males along with the distribution range of duloxetine concentration. Similarly, dose-normalized steady state duloxetine concentrations were similar in subgroups defined by ethnicity, race, age and body weight. It should be noted that the number of patients is low for certain ethnicity (Hispanics) and race (Native American, Black, Multi-racial) relative to Caucasians.

Rapporteur's comments:

The results of the phase II study (HMFN) showed that duloxetine plasma concentrations increased in proportion to the increase of the dose, and that gender (and not age, body weight, creatinine clearance, CYP2D6 status, or dose) was the only characteristic that seemed to influence the pharmacokinetic of duloxetine. As it was observed in adults the inter- and intrapatient variability is very high, with an overlap in duloxetine concentration-time profile in females and males.

In Studies HMCL and HMCK now submitted subjects received 30 to 120 mg duloxetine doses regardless of they were children or adolescents (30 to 120 mg in HMCL; 60 to 120 mg in HMCK). The steady-state duloxetine plasma concentrations increased with increasing dose in both children and adolescents. No relevant differences in Cmax and AUC were observed between the two age groups. Patient characteristics such as CYP2D6 metabolizer status, ethnicity, sex, age, and body weight did not appear to have an effect on steady-state duloxetine plasma concentrations. No dose adjustment seems to be required in the adolescent population with respect to the younger group.

The MAH states that a comprehensive report on the population PK of duloxetine in children and adolescents using data collected from this study and others will be provided as a separate report. In that report, PK data from this study will be analysed using population modelling approaches along with data from Studies HMFN, HMCL and HMCK.

2. Clinical studies

	Study Description	Study Treatments	No. of Subjects	Primary Endopoint
F1J-MC-HMCK US Eastern Europe Western Europe South Africa	Phase 3, multicenter, randomized, double-blind, flexible dosing, placebo-controlled study to assess efficacy and safety of duloxetine (60 to 120 mg QD) in paediatric patients with MDD. A fluoxetine treatment arm is included for assay sensitivity.	Duloxetine 30 mg to 120 mg QD Fluoxetine 20-40 mg QD Placebo	N=337 (261 patients enter long-term exposure)	Change from baseline to last visit of the acute treatment period in the CDRS-R total score
F1J-MC-HMCL US Canada Mexico Argentina	Phase 3, multicenter, randomized, double-blind, fixed-dose during acute period/flexible dosing during long-term exposure, placebo-controlled study to assess efficacy and safety of duloxetine in paediatric patients with MDD. A fluoxetine treatment arm is included for assay sensitivity.	Duloxetine 30 mg to 120 mg QD Fluoxetine 20-40 mg QD Placebo	N=463 (322 patients enter long-term exposure)	Change from baseline to last visit of the acute treatment period in the CDRS-R total score

- **Methods**

  - **Study design**

The two studies had 4 periods and employed stratified randomization by age (children aged 7 to 11 years; adolescents aged 12 to 17 years) to allow a separate assessment of efficacy and safety in these 2 distinct subsets of the paediatric population. Enrolment was monitored to ensure at least 40% of the patient population was children.

- Study period I: screening phase of no more than 30 days.

- Study period II: 10-week acute treatment phase which included a 2-week titration period aimed to improving tolerability

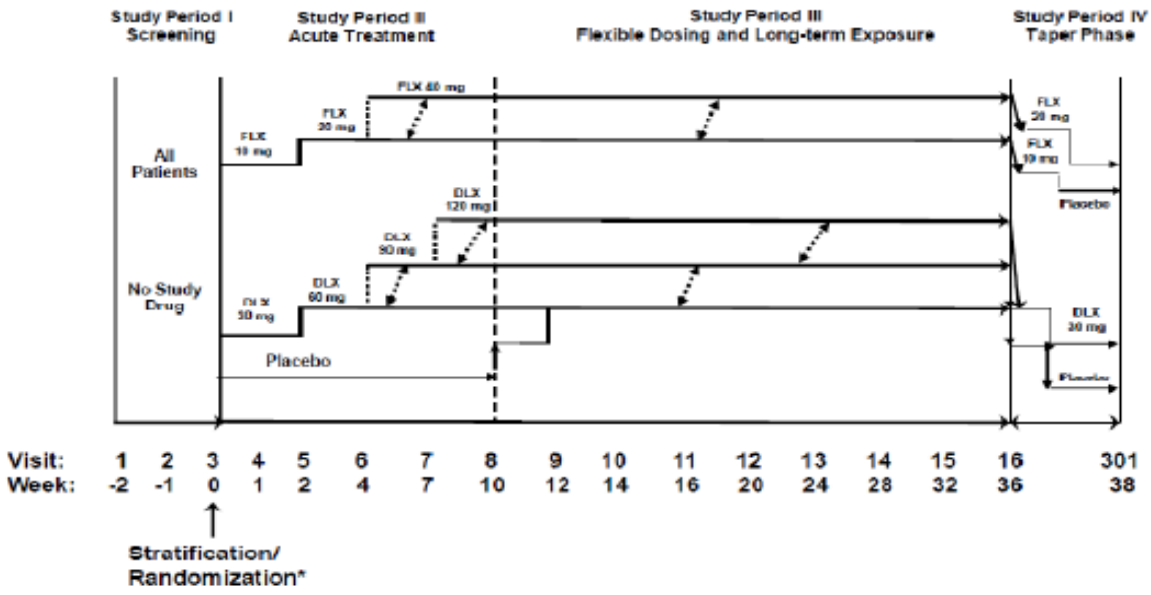
- Study period III: a 6-month double-blind extension period.

- Study period IV: a 2-week tapering phase to minimize discontinuation AEs.

Placebo assigned patients in study period II were assigned to duloxetine flexible doses for study period III. Patients discontinued the study if at any time they could not tolerate the study drug sufficiently to remain compliant based on the investigator's judgment. Additionally, patients discontinued the study if in their or in the investigator's opinion there was no adequate response or if patient safety may have been compromised.

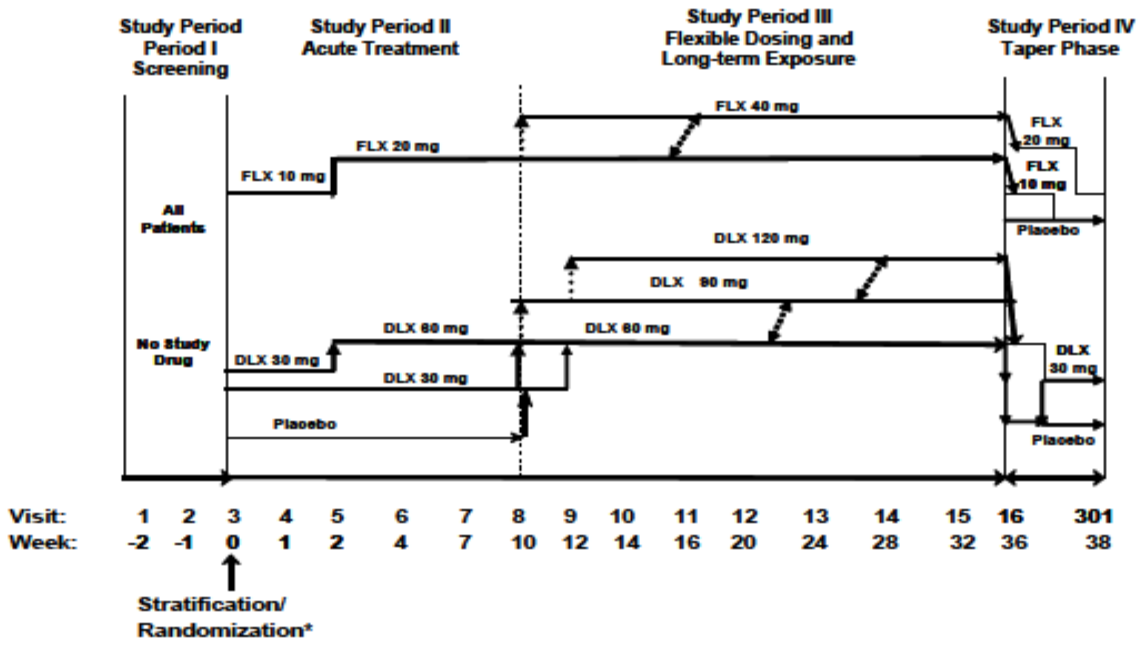
<u>Study HMCK</u> (Flexible-dose study).

During the acute and extension phases, the duloxetine dose could be adjusted within the study range (60 mg to 120 mg) based on the investigator's clinical judgment of treatment response and tolerability at the current dose. If a dose decrease occurred, no further dose increases were permitted.



<u>Study HMCL</u> (Fixed-dose study)

Three fixed-dose arms were included: duloxetine 30 mg, duloxetine 60 mg, and fluoxetine 20 mg.



- **Objectives**

Primary Objective

To assess the efficacy of duloxetine (60 mg once daily for Study HMCL; 60 mg to 120 mg for Study HMCK) compared with placebo, as measured by CDRS-R total score, in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through17 years) with major depressive disorder without psychotic features, single or recurrent episode.

Secondary Objectives

• To test assay sensitivity by comparing fluoxetine with placebo during the acute treatment.

• To evaluate the efficacy of treatment of duloxetine (30 and 60 mg or 60-120 mg QD) compared with placebo during acute treatment phase as measured by CDRS-R total score, CDRS-R subscales, Remission rates, Clinical Global Impression of Severity (CGI-S) scale.

• To assess changes in depressive symptoms 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 during acute treatment phase

• To assess safety [illegible] 6-month, double-blind extension phase.

• To characterize the pharmacokinetics (PK) of duloxetine at steady-state.

• To compare the steady-state duloxetine PK with historical adult duloxetine PK using duloxetine steady-state concentration data and PK parameters.

• To investigate the relationship between duloxetine exposure and efficacy endpoints during acute treatment using steady-state duloxetine plasma concentrations and CDRS-R total score.

- **Study population / Sample size**

Inclusion Criteria

Male and female outpatients 7 to17 years of age who met DSM-IVTR criteria for MDD, with a severity defined by CDRS-R Total Score of >40 and a Clinical Global Impression of Severity (CGI-S) of >4 at each screening and randomization visit.

The Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) was also administered to support the diagnosis of MDD.

Exclusion Criteria

•Any lifetime psychotic disorders, bipolar disorder (or those with 1 or more first degree relatives [parents or siblings] with diagnosed Bipolar I disorder), OCD, eating disorders, or pervasive development disorder.

•Suicide attempt within 1 year of Visit 1 or, in the opinion of the investigator, were currently at risk of suicide.

•Any changes in psychotherapy within 6 weeks of Visit 1. Patients requiring changes to psychotherapy during Study Period II may have been discontinued from the study if such changes could confound assessment of efficacy. Changes to psychotherapy were allowed during Study Period III.

Sample size

A sample size of 100 patients in each group was calculated to have adequate power (approximately 80% power) to detect an effect size of 0.40 (duloxetine efficacy relative to placebo on CDRS-R total score) using a 2-group t-test with a 0.05 2-sided significance level. Allowing for 10% of patients to have missing post-baseline data, at least 112 patients were randomized to each treatment arm.

- **Treatments**

Enrolled patients were assigned to duloxetine once daily (30 mg or 60 mg for Study HMCL; 60 mg to 120 mg for Study HMCK), fluoxetine once daily (20 mg for Study HMCL; 20 mg to 40 mg for Study HMCK) or placebo. Duloxetine 30 mg and Fluoxetine 10 mg were administrated for titration and tapering.

Concomitant medications with primarily central nervous system (CNS) activity were not allowed. Cough and cold medications containing pseudoephedrine and antihistamines (eg, diphenhydramine) were allowed for ≤3 consecutive days or 15 cumulative days during Study Period II or 10 cumulative days per month in Study Period III.

- **Outcomes/endpoints**

The primary efficacy endpoint was the contrast between duloxetine and placebo at the last visit in Study Period II (Visit 8, Week 10), based on a mixed model repeated measures (MMRM) analysis on change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R) total score.

Secondary efficacy endpoints:

- Change from baseline to endpoint for CDRS-R total score, CDRS-R Item 13 (suicidal ideation), and CGI-S

- Change from baseline at each postbaseline visit for CDRS-R total score (Study Periods II/III and III), CDRS-R Total Score (excluding age and age*visit covariates), CDRS-R Subscale (mood, somatic, subjective, behavior) and Item 13 scores, CGI-S

- Categorical variable for Remission Rate (CDRS-R) at endpoint, CDRS-R Remission Rate at last 2 nonmissing visits, 30% Response Rate (CDRS-R total score), 50% Response Rate (CDRS-R total score), Continuous Responder Analysis (CDRS-R total score), and CGI-S Response Rate

- Categorical Variable at each postbaseline Visit Visitwise for Remission Rate, 30% Response Rate (CDRS-R total score), 50% Response Rate (CDRS-R total score), and CGI-S Response Rate

- Time to event for time to first remission (defined by the first visit that CDRS-R total score of ⩽ 28), and time to first - 50% Response on CDRS total score

Safety endpoints:

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

- Mean change in laboratory analytes, 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

- Columbia Suicide Severity Rating Scale (C-SSRS) serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), vital signs and weight, discontinuation due to adverse

events, laboratory measurements and ECGs. Suicide risk and suicide-related events (behaviour and/or ideation) were assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS).

Efficacy Measures

- Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al. 1983, 1984, 1985) 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 (Hamilton 1960) and includes questions about school. The scale consists of 17 items scored on a 1-to-5- 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.

- Clinical Global Impressions of Severity (CGI-S) Scale (Guy 1976): Evaluation of the severity of illness at the time of assessment. The score ranged from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-S had to be administered by a study physician in the presence of the patient or after having been in the presence of the patient.

- Remission rate (CDRS-R): CDRS-R total score of $\leq$ 28 at endpoint

- 30% Response Rate (CDRS-R total score): $\geqslant$30% reduction from baseline to LOCF endpoint

- 50% Response Rate (CDRS-R total score) 050% reduction from baseline to LOCF endpoin

- **Statistical Methods**

Efficacy and safety analysis were conducted on an intent-to-treat (ITT) basis unless otherwise specified. All tests of hypotheses were to be based on the significance level of 0.05. No adjustments for multiple comparisons were made.

The primary analysis method was a repeated measures analysis; that is, a restricted maximum likelihood (REML)-based, mixed-effects repeated measures (MMRM) analysis using all the longitudinal observations at each post-baseline visit. Significance tests between duloxetine (60 mg for HMCL, 60 mg to 120 mg for HMCK) and placebo were based on least-squares means (LSMean) using a 2-sided α=0.05.

LSMean was used for the statistical comparison using ANOVA or ANCOVA. The last observation carried forward (LOCF) method was used for these analyses.

Categorical comparisons between treatment groups were performed using Cochran-Mantel-Haenszel (CMH), controlling for pooled investigative site, and Fisher's exact tests, where appropriate, or Pearson's chisquared test

The secondary efficacy analyses was performed on the secondary variables mentioned above. Descriptive statistics were used to summarize these variables by treatment (fluoxetine and duloxetine) group during Study Period III. The treatment-by-investigator interaction was tested using a full ANCOVA model. When the interaction was statistically significant, the nature of the interaction was investigated and the appropriate statistical approaches were adapted based on the findings from the investigation.

Rapporteur's comments:

These two efficacy studies included children and adolescents diagnosed of Major Depressive Disorder according to standard criteria. Patients were required to have a minimum severity degree to be enrolled. No specific requirement regarding the concomitant or previous use of psychotherapy was made.

The main proof of efficacy relies on the relief of the depression symptoms after 10 weeks of treatment. In addition to the comparison with placebo an active arm (fluoxetine) was included in order to provide assay sensitivity to the trial. Fluoxetine is authorized in EU countries by Mutual Recognition Procedure with the indication in children and adolescents aged 8 years and above (Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions). It can be accepted as an adequate control treatment. After the acute phase, patients entered in an extension phase where only active treatments (duloxetine and fluoxetine) were administered.

Standards methods of measurement were employed. Relief of MDD symptoms were measured through the CDRS-R total score as primary endpoint and a global assessment (CGI-I) was included among the secondary endpoints. Additionally the relevance of the changes was estimated as remission and responder rates, which is agreeable.

According to the Guideline on clinical investigation of medicinal products in the treatment of depression (CPMP/EWP/518/97) and also to the current draft revision (Rev.1) differentiation should be made between children and adolescents either in separate studies or stratifying for age group in the case of an only trial. In these studies stratification has been employed although no sample size calculation for demonstration of efficacy in each group independently has performed.

- **Results**

  - **Recruitment/ Number analysed**

A total of 1073 patients were screened and 800 patients were enrolled in the acute treatment phases of Studies HMCK and HMCL combined. A total of 590 (74%) patients completed the acute treatment phase.

A total of 376 patients completed the extension phase of these studies. For Study HMCK, completion rates across the treatment arms were 67.5% for duloxetine patients, 70.6% for fluoxetine patients and 80.2% for placebo/duloxetine patients. For Study HMCL, completion rates across the treatment arms

were 58.9% DLX60/DLX60120, 61.7% DLX30/DLX60120, 58,3% for fluoxetine patients and 53.7% PBO/DLX60120.

	HMCL				HMCK		
	DLX60	DLX30	FLX20	PBO	DLX60-120	FLX20-40	PBO
Planned	112	112	112	112	112	112	112
Randomized	108	116	117	122	117	117	103
Treated in 8 wk Period II	108	116	117	122	117	117	103
Completed Period II	75	81	84	85	87	91	87
	DLX 60/ DLX60-120	DLX 30/ DLX60-120	FLX20/FLX20-40	PBO/DLX60-120	DLX 60/ DLX60-120	FLX20-40/ FLX20-40	PBO/DLX 60-120
Entered 26 wk period III	73	81	84	82	83	92	86
Completed 26 wk period III	43	50	49	44	56	65	69

- **Baseline data**

Table 5.1 show the key baseline characteristics of enrolled patients.

Table 5.1. **Summary of Key Baseline Characteristics and Illness**
All enrolled patients
Studies HMCK and HMCL

	HMCK			HMCL			
	DLX (N=117)	PBO (N=103)	p-value[a] (DLX vs. PBO)	DLX30 (N=116)	DLX60 (N=108)	PBO (N=122)	p-value[a] (DLX30 vs. PBO), (DLX60 vs. PBO)
Gender (%)							
Male	45	51	.499	59	44	43	.014, .895
Female	55	49		41	56	57	
Age							
Mean (SD)	13.1(3.04)	13.3 (3.06)	.733	12.9 (2.90)	12.9 (2.93)	13.1 (2.895)	.692, .661
7-11 y (%)	40	37	.678	42	41	40	.793, 1.0
12-17 y (%)	60	63		58	59	60	
Region (%)							
Mexico/Argentina	-	-	.853	22	15	14	.130, .853
Europe, Western	4.3	4.9		-	-	-	
Europe, Eastern	35	30		-	-	-	
South Africa	18	21		-	-	-	
US/Canada[b]	43	44		78	85	86	
CDRS-R Total Score: Mean (SD)	59.2 (10.5)	60.2 (11.7)	.457	59.8 (11.0)	59.3 (10.9)	58.2 (9.35)	.216, .279
CGI-S: Mean (SD)	4.5 (0.62)	4.6 (0.65)	.810	4.6 (0.65)	4.6 (0.65)	4.5 (0.63)	.867, .723

Abbreviations: DLX = duloxetine; N = number of patients with at least one non-missing post-baseline measure; PBO = placebo.

[a] For continuous variable: analysis of variance (ANOVA) adjusted for treatment and pooled investigative site; categorical variable: Fisher's exact test.

[b] Canada included in US/Canada number only in Study HMCL

Source: t_14_1_5_1_t_demog; t_14_1_12_1_t_bassev; for HMCL - t_14_1_5_1_t_demog, t_14_1_12_1_t_bassev

Rapporteur's comments

Patients with moderate levels of depression were preferably recruited. Patients had a mean CDR-S total score around 60 and a CGI-Severity score around 4.5 at baseline. Diagnosis was confirmed by the Mini International Neuro psychiatric Interview for paediatric population. No relevant baseline differences between groups with respect to demographic characteristics (age, gender, baseline severity) are observed. However, no data regarding the use of non-pharmacological treatment (psychotherapy) have been provided.

Patients were mainly recruited from non-EU regions (mainly USA). Only 130 patients (17 from Western Europe – Finland, France and Germany -; and 113 from Eastern Europe – Slovakia, Ukraine, Estonia and Russia) out of the total 800 randomised patients represent the European population included in both trials. The extrapolation of the results may be object of concern.

Study designs were very similar except for the different regimen of drug administration (fixed dose in HMCL and flexible dose in HMCK). No formal dose finding study has been performed in

children/adolescents. Doses of duloxetine and fluoxetine were those already administered to the adult population. Posology was determined by pK results. It was suggested that drug exposure was not influenced by factors such as the age, the gender or weight. No dose adjustment was subsequently implemented.

- **Efficacy results**

F1J-MC-HMCL Study

10-week acute treatment phase

Mean improvement in depression symptom severity was observed for the duloxetine 60 mg-treated group compared with the placebo-treated group at Week 10; however, the difference in the mean change (baseline to Visit 8) between the duloxetine 60 mg treatment group and placebo was not statistically significant.

Similarly, mean improvement in depression symptom severity was observed for the duloxetine 30 mg-treated group compared with the placebo-treated group at Visit 8; however, the difference in the mean change (baseline to Week 10) between the duloxetine 30 mg treatment group and placebo was not statistically significant.

Mean improvement in depression symptom severity was observed for the fluoxetine 20 mg-treated group compared with the placebo-treated group at Visit 8; however, the difference in the mean change (baseline to Visit 8) between the fluoxetine 20 mg treatment group and placebo was not statistically significant.

CDRS-R Total Score
Repeated Measures Analysis: Mean Change from Baseline
ITT Population
F1J-MC-HMCL
Study Period II

			MMRM Analysis Results					
Therapy	Visit (Week)	N	LS Mean	LS Mean Change(SE)	Within Group p-value	LS Mean Change Difference (SE)	95% CI for Difference	p-value
DLX60	8 (10)	83	35.0	-23.9 (1.30)	<0.001			
DLX30		84	34.4	-24.6 (1.29)	<0.001			
FLX20		84	36.4	-22.6 (1.27)	<0.001			
Placebo		88	37.4	-21.6 (1.27)	<0.001			
DLX60 vs Placebo						-2.3 (1.78)	(-5.8, 1.2)	0.193
DLX30 vs Placebo						-3.0 (1.77)	(-6.5, 0.5)	0.093
FLX20 vs Placebo						-1.0 (1.76)	(-4.4, 2.5)	0.588
DLX60 vs DLX30						0.7 (1.79)	(-2.9, 4.2)	0.715
DLX60 vs FLX20						-1.4 (1.79)	(-4.9, 2.2)	0.445
DLX30 vs FLX20						-2.0 (1.78)	(-5.5, 1.5)	0.256

Note: Baseline is defined as the last nonmissing value at 1<=Visit<=3.
Note: Table presents patients with both a baseline and at least one post-baseline CDRS-R total score.
Note: Mean Change=Treatment, pooled investigative site, visit, treatment*visit, age category, age category*visit, baseline, baseline*visit; Covariance Structure=unstructured; Denominator degrees of freedom were estimated using the Kenwood-Rogers method.

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.

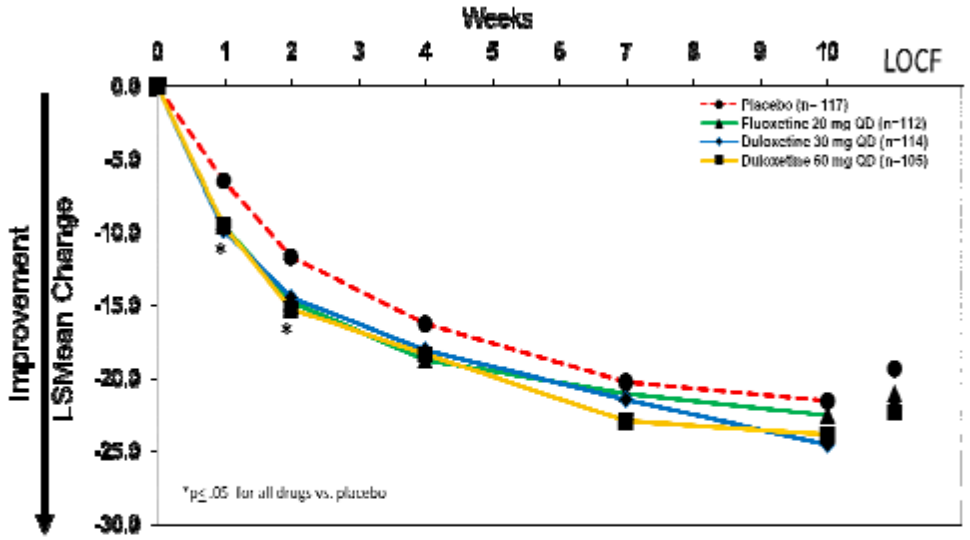


Figure 5.2. **Mean change in the CDRS-R Total Score at each visit (MMRM) and at LOCF acute phase endpoint for Study HMCL.**

Secondary efficacy analyses of the 10-week acute treatment period generally showed no statistically significant differences between the active drugs (duloxetine and fluoxetine) or between the active drugs and placebo; except for a few exceptions.

a) both the duloxetine 60 mg and 30 mg treatment arms demonstrated a statistically significant difference from placebo in the overall main effect of treatment analysis,

b) in the subgroup analysis of mean change in the CDRS-R total score by gender, statistically significant improvement was observed for duloxetine 60 mg- and for duloxetine 30 mg-treated females compared with placebo-treated females.

c) in a cumulative responder analysis, there was a statistically significant difference for the distribution of responders between duloxetine 60 mgtreated patients and placebo-treated patients

d) there was a statistically significantly greater remission rate at endpoint for the duloxetine 30 mg-treated group compared to the placebo treated group.

e) a statistically significantly greater proportion of duloxetine 60 mg-treated patients compared with placebo-treated patients met remission criteria at the last 2 nonmissing visits.

Two sensitivity analyses on the primary efficacy analysis were performed:

1. A repeated measures analysis to address the impact of missing data (Missing at Random (MAR) versus Missing Not at Random (MNAR))

2. A repeated measures analysis of the CDRS-R total score mean change from baseline, excluding age as a covariate.

The results of these sensitivity analyses on the primary measure are consistent with the results of the primary analysis. The secondary analysis of mean change from baseline to acute period endpoint on the CDRS-R using LOCF methodology also did not result in a statistically significant separation between duloxetine and placebo.

In the subgroup analyses based of mean change in the CDRS-R total score during acute period (ANCOVA), the treatment-by-age, race, ethnicity, pooled investigator, and region interaction, was not statistically significant. The treatment-by-gender interaction was not statistically significant, but a statistically significant difference in LS mean change from baseline to endpoint (LOCF) in CDRS-R total score was observed for duloxetine 60 mg-treated females compared with placebo-treated females (p=.039) and for duloxetine 30 mg-treated females compared with placebo-treated females (p=.017).

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 (mood, somatic, subjective, behavior) and item 13 score (suicidal ideation), 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).

Response rates: there was not a statistically significant difference in the probability of meeting 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 the last visit of acute period (Week 10) /endpoint (LOCF).

There were no statistically significant differences on remission rate (CDRS-R total score of ⩽28 at LOCF endpoint) between the duloxetine 60 mg-treated group and the placebo-treated group (34% versus 24%, respectively; p=.071) or between the fluoxetine 20 mg-treated group and the placebo-treated group (28% versus 24%, respectively; p=.606). There was a statistically significant difference on remission rate at endpoint between the duloxetine 30 mg-treated group and the placebo-treated group (36% versus 24%, respectively; p=.041).

There were no statistically significant differences observed for the duloxetine60 mg-, duloxetine 30 mg-, or fluoxetine 20 mg-treated groups compared with the placebo-treated group on the CGI-S mean change from baseline to Week 10 (MMRM).

· ***Extension phase***

For patients initially randomized to duloxetine 60 mg QD or fluoxetine 20 mg QD for the 10-week acute treatment period and continued on flexibly-dosed duloxetine (60 to 120 mg QD) or fluoxetine (20 to 40 mg QD) during the 6-month extension period, improvement in MDD symptoms was observed for both treatment groups based on the mean improvement on the CDRS-R total score and CGI-S score; however, there was no statistically significant difference between the DLX60120-treated group compared with the FLX2040-treated group at any time point during the 36-week study. Similarly, for both treatment groups (DLX60120 and FLX2040), there were no statistically significant differences at any timepoint in the probability of achieving remission during the 36-week study.

Rapporteur's comments:

After 10 weeks of treatment neither duloxetine nor fluoxetine did separate from placebo. No relevant differences were observed when the investigator made the global assessment of the response. The secondary endpoints results were consistent with the results of the primary analysis. In addition, no dose-response relationship could be identified when duloxetine 30 mg and 60 mg were administered.

When doses were increased during the extension phase, both groups experienced an improvement in symptoms. The lack of a placebo arm and the flexible regimen of dosing administered hamper drawing sound conclusions.

F1J-MC-HMCK Study

· *10-week acute treatment phase*

Mean improvement in depression symptom severity was observed for the duloxetine-treated group over the 10-week course of acute treatment; however, the difference in the mean change from baseline between the duloxetine treatment group and placebo was not statistically significant at endpoint (Week 10), or at any timepoint during Study Period II.

Mean improvement in depression symptom severity was observed for the fluoxetine-treated group over the 10-week course of acute treatment; however, the difference in the mean change from baseline

between the fluoxetine treatment group and placebo was not statistically significant at endpoint (Week 10), or at any timepoint during Study Period II

CDRS-R Total Score
Repeated Measures Analysis: Mean Change from Baseline
ITT Population
F1J-MC-HMCK
Study Period II

Therapy	Visit (Week)	N	MMRM Analysis Results: LS Mean	LS Mean Change (SE)	Within Group p-value	LS Mean Change Difference (SE)	95% CI for Difference	p-value
DLX60120	8 (10)	88	35.0	-24.3 (1.09)	<0.001			
FLX2040		95	35.6	-23.7 (1.06)	<0.001			
Placebo		89	35.0	-24.3 (1.11)	<0.001			
DLX60120 vs Placebo						0.0 (1.53)	(-3.0, 3.0)	0.999
FLX2040 vs Placebo						0.6 (1.51)	(-2.4, 3.6)	0.687
DLX60120 vs FLX2040						-0.6 (1.50)	(-3.6, 2.4)	0.686
DLX60120	Overall	113	42.2	-17.1 (0.80)	<0.001			
FLX2040		113	42.2	-17.1 (0.79)	<0.001			
Placebo		103	42.8	-16.5 (0.83)	<0.001			
DLX60120 vs Placebo						-0.6 (1.13)	(-2.8, 1.6)	0.604
FLX2040 vs Placebo						-0.6 (1.13)	(-2.8, 1.6)	0.606
DLX60120 vs FLX2040						-0.0 (1.11)	(-2.2, 2.2)	0.998

Note: Baseline is defined as the last nonmissing value at 1<=Visit<=3.
Note: Table presents patients with both a baseline and at least one post-baseline CDRS-R total score.
Note: Mean Change=Treatment, pooled investigative site, visit, treatment*visit, age category, age category*visit, baseline, baseline*visit; Covariance Structure=unstructured; Denominator degrees of freedom were estimated using the Kenwood-Rogers method.
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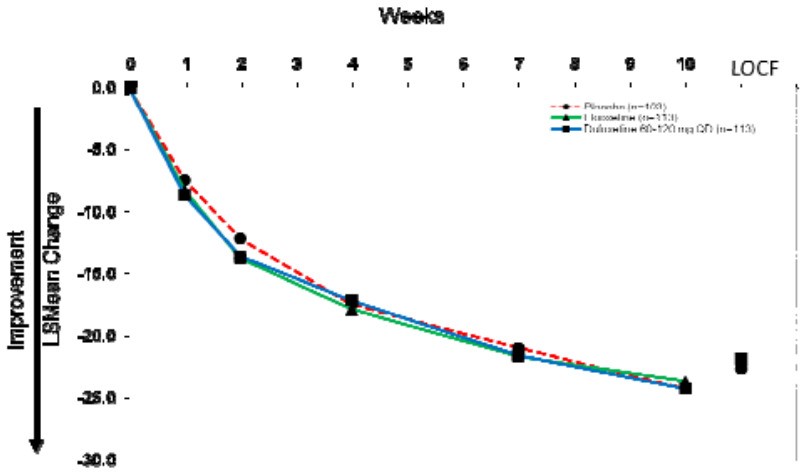


Figure 5.1. Mean change in the CDRS-R Total Score at each visit (MMRM) and at LOCF acute phase endpoint for Study HMCK

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.

Secondary efficacy analyses of the 10-week acute treatment period generally showed no statistically significant differences between the active drugs (duloxetine and fluoxetine) or between the active drugs and placebo; however, there was 1 exception. In the subgroup analysis of mean change in the CDRS-R total score by race, the treatment by race interaction was statistically significant (p=.011) due

to different responses to drug vs. placebo within each race subgroup. In Black or African American patients, the placebo group had greater improvement than either active drug group. In White patients, both drug groups had greater improvement than the placebo group. In the pooled race (including

Two sensitivity analyses on the primary measure were performed:

1. A repeated analysis to address the impact of missing data (Missing at Random (MAR) versus Missing Not at Random (MNAR))

2. A repeated measures analysis of the CDRS-R total score mean change from baseline, excluding age as a covariate.

The results of these sensitivity analyses on the primary measure are consistent with the results of the primary analysis. The secondary analysis of mean change from baseline to acute period endpoint on the CDRS-R using LOCF methodology also did not result in a statistically significant separation between duloxetine and placebo.

In the subgroup analyses based of mean change in the CDRS-R total score during acute period (ANCOVA), the treatment-by-age, gender, ethnicity, pooled investigator, and region interaction, was not statistically significant. The treatment-by-race interaction was statistically significant (p=.011). In Black or African American patients, the placebo group had greater improvement than either active drug group. In White patients, both drug groups had greater improvement than the placebo group. In the pooled race group, duloxetine had greater improvement compared with placebo, and placebo had greater improvement compared with fluoxetine.

No statistically significant differences were observed at Week 10 for the duloxetine-treated group compared with the placebo-treated group, on all CDRS-R subscales (mood, somatic, subjective, behavior) and item 13 score (suicidal ideation). No statistically significant differences in mean changes from baseline (MMRM) in the CDRS-R subscale scores at Week 10 were observed for the fluoxetine -treated group compared to the placebo-treated group. A statistically significant mean improvement from baseline (MMRM) in the CDRS-R Item 13 (suicidal ideation) score was observed for the placebo-treated group (0.4 point improvement) compared with the fluoxetine-treated group (0.2 point improvement) at Week 10 (p=.007). No statistically significant differences were observed at endpoint (LOCF) for the duloxetine-treated group compared with the placebo-treated group on all CDRS-R subscales (mood, somatic, subjective, behavior) and Item 13 score (suicidal ideation). A statistically significant mean improvement at endpoint was observed for the placebo-treated group compared with the fluoxetine-treated group for the CDRS-R Item 13 score (suicidal ideation [p=.045]).

No statistically significant difference was observed in the probability of meeting 30% or 50% response on the CDRS-R for duloxetine-treated patients or fluoxetine-treated patients compared with placebo-treated patients at the last visit of the acute period (Week 10) / endpoint (LOCF).

There were no statistically significant differences on remission rate between the duloxetine -treated group and the placebo-treated group (35% versus 36%, respectively; p=.990) or between the fluoxetine -treated group and the placebo group (30% versus 36%, respectively; p=.817).

At Week 10, no statistically significant differences on the CGI-S mean change from baseline to Week 10 were observed for the duloxetine- or the fluoxetine-treated groups compared with the placebo-treated group.

· ***Extension phase***

For patients initially randomized to flexible dose duloxetine or fluoxetine for the 10-week acute treatment period and continued on flexibly dosed duloxetine or fluoxetine during the 6 month extension period, improvement in MDD symptoms was observed for both treatment groups based on the mean improvement on the CDRS-R total score and CGI-S score; however, there was no statistically significant difference between the DLX60120-treated group compared with the FLX2040-treated group at any time point during the 36-week study on the CDRS-R total score. There was a statistically significantly greater improvement observed for fluoxetine compared with duloxetine at 36-Weeks (study endpoint) on the CGI-Severity. There were no statistically significant differences between the duloxetine and fluoxetine treatment groups at any timepoint in the probability of achieving remission during the 36-week study. The probability of achieving remission at 36 weeks was 72% for duloxetine and 83% for fluoxetine.

Rapporteur's comments:

Similarly, in this study both active treatments (duloxetine and fluoxetine) did not behave differently from placebo after10 weeks of treatment. Almost 44% of patients titrated up to 120 mg, the remaining receiving 30 mg (11.1%); 60 mg (17.1%) or 90 mg (27.4%).The magnitude of the effect is similar to that observed in Study HMCL. The response measured by the secondary endpoints as well as the sensitivity analyses conducted by the MAH also mirror the primary effect.

When patients were treated for further 6 months with duloxetine or fluoxetine showed an improvement in symptoms although of similar magnitude for both drugs.

Overall conclusions on clinical efficacy and pharmacokinetic

The paediatric clinical development for duloxetine in the treatment of Major Depressive Disorder consists of two randomised, double-blind, parallel trials. These studies featured a 10 week- placebo and active (fluoxetine) controlled acute phase following a 6 month period of active controlled extension treatment. Study designs were very similar except for the different regimen of drug administration: fixed dose in HMCL (duloxetine 30 mg, duloxetine 60 mg, fluoxetine 20 mg and placebo; and flexible dose in HMCK (duloxetine 60 mg to 120 mg, fluoxetine 20 mg to 40 mg and placebo). Posology was determined according pK results, in which drug exposure appears not to be influenced by factors such as age, gender or weight.

Children and adolescents (7 to 17 years) included had a MDD of moderate severity. Although accepted, the concomitant or previous use of psychotherapy was not standardised. The studies were stratified by age although no sample size calculation for demonstration of efficacy in children and adolescents groups independently was performed.

After 10 weeks of treatment neither duloxetine nor fluoxetine did separate from placebo in none of the studies. No relevant differences were observed when the investigator made the global assessment of

the response. The secondary endpoints results were consistent with the results of the primary analysis. In addition, no dose-response relationship could be identified when duloxetine 30 mg and 60 mg were administered. When doses were increased during the extension phases, both groups experienced an improvement in symptoms. The lack of a placebo arm and the flexible regimen of dosing administered hamper drawing sound conclusions. Subgroup analysis by age does not suggest benefit in a particular stratum. The antidepressant effect of duloxetine in children and adolescents has not been demonstrated.

According to the MAH the extension of the therapeutic indication cannot be granted. However, it is considered that the inclusion of a brief description of the studies (including the inconclusive results) in the product information could be of help for prescribers.

- **Safety results**

The safety data from Study HMCK and Study HMCL was pooled into an integrated paediatric safety database. Subgroup analyses by paediatric subset (ie. 7 to 11 years; 12 to 17 years) were also performed for TEAEs of individual studies in the HMCK and HMCL CSRs.

Exposure

In Study HMCK, flexible dosing of duloxetine from 60 to 120 mg QD was allowed during acute and extension treatment, and most patients were escalated to higher doses (90 mg to 120 mg). The duloxetine dose was initiated at 30 mg QD for 2 weeks. During acute treatment, the mean duloxetine total dispensed dose was 66.1 mg and the last prescribed dose for duloxetine patients was a 30 mg-titration dose (11.1%), 60 mg (17.1%), 90 mg (27.4%) and 120 mg (43.6%), while 74% of fluoxetine-treated patients had a final dose of 40 mg QD. During extension treatment, the mean duloxetine total dispensed dose was 88.8 mg. The last prescribed dose of duloxetine for patients in the DLX60120/DLX60120 group was 60 mg (14.5%), 90 mg (16.9%) and 120 mg (68.7%). The last prescribed dose of duloxetine for patients in the PBO/DLX60120 group was a 30-mg titration dose (3.5%), 60 mg (49.4%), 90 mg (16.5%) and 120 mg (30.6%). A total of 105 duloxetine- and 56 fluoxetine-treated patients had $\geqslant$ 6 months of exposure to the drug.

In Study HMCL, the acute treatment phase included 2 duloxetine fixed dose arms (30 mg and 60 mg QD). During the extension phase of Study HMCL, flexible dosing of duloxetine from 60 to 120 mg QD was allowed, and most patients were escalated to the higher doses (90 mg to 120 mg). During extension treatment, the mean duloxetine total dispensed dose was 84.3 mg. The last prescribed dose of duloxetine was 60 mg, 90 mg and 120 mg for 30.8%, 20.9% and 46.2% of patients, respectively. 70% of fluoxetine-treated patients had a final dose of 40 mg QD. A total of 125 duloxetine- and 45 fluoxetine-treated patients had $\geqslant$ 6 months of exposure to the drug.

Rapporteur's *comment*

In order to assess the safety profile of duloxetine in the paediatric population the global number of subjects (and by age subgroups) exposed to study medication should be provided. Information on the

study drug exposure by total daily dose (acute and extended administration), and a summary of the demographic characteristics of the involved population is also expected.

Adverse Events

Acute treatment phase

No deaths due to completed suicides or other causes were reported during either study.

No statistically significant difference in the frequency of patients reporting at least 1 SAE was observed between duloxetine and placebo during the acute treatment phase of either study. The frequency of SAEs for the pooled acute phases was 2.6% duloxetine vs. 1.3% placebo.

As it would be expected based on previous duloxetine studies, more patients in the duloxetine group discontinued due to an AE compared with those in the placebo group (8.2% duloxetine vs. 3.1% placebo, p=.013 for pooled acute data)

Table 5.2. Summary of Serious Adverse Events and Discontinuation due to an Adverse Event Studies HMCK and HMCL, Acute and Extension Phases

	HMCK				HMCL				
Acute Treatment Phase (II)									
Patients Reporting At Least 1:	DLX60-120 N=117 n (%)	PBO N=103 n (%)	FXT20-40 N=117 n (%)	p-value[a] (DLX vs PBO)	DLX30 N=116 n (%)	DLX60 N=108 n (%)	PBO N=122 n (%)	FXT20 N=117 n (%)	p-value[a] (DLX30 vs PBO); (DLX60 vs PBO)
SAE	3 (2.6)	1(1.0)	2 (1.7)	.625	2 (1.7)	3 (2.8)	2 (1.6)	6 (5.1)	1.0 ; .423
Discontinuation due to an AE	9 (7.7)	3 (2.9)	1 (0.9)	.145	7 (6.0)	12 (11.1)	4 (3.3)	6 (5.1)	.366; **.035**
TEAE	70 (59.8)	68 (66.0)	73 (62.4)	.402	67 (57.8)	79 (73.1)	71 (58.2)	72 (61.5)	1.0; **.019**
Extension Treatmen Phase (III)									
Patients Reporting At Least 1:	DLX/DLX60-120 N=83 n (%)	PBO/DLX60-120 N=86 n (%)	FXT20-40 N=92 n (%)		DLX30/DLX60-120 N=81 n (%)	DLX60/DLX60-120 N=73 n (%)	PBO/DLX60-120 N=82 n (%)	FXT20/FXT20-40 N=84 n (%)	
SAE	1 (1.2)	3 (3.5)	4 (4.3)		2 (2.5)	3 (4.1)	4 (4.9)	0 (0)	
Discontinuation due to an AE	2 (2.4)	4 (4.7)	8 (8.7)		6 (7.4)	4 (5.5)	7 (8.5)	3 (3.6)	
TEAE	53 (63.9)	62 (72.1)	57 (62.0)		46 (56.8)	50 (68.5)	55 (67.1)	45 (53.6)	

Abbreviations: AE = adverse event; DLX = duloxetine; n=number of patients with an event; N = number of randomized patients; PBO = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Fisher's exact test.
Source: Individual Study Reports

Rapporteur's comments

Depressed children and adolescents treated with duloxetine were more prone to withdraw for safety reasons than patients treated with placebo. Duloxetine showed a higher incidence of adverse events, of SAEs and discontinuations with higher doses. The corresponding figures for fluoxetine should be provided in a global analysis of the studies.

The TEAEs reported at least twice as a reason for discontinuation in Study HMCK or HMCL for duloxetine-treated patients were (HMCK; HMCL): nausea (2; 4), intentional overdose (0; 2), and depression (1; 2).

A similar frequency of TEAEs was observed between duloxetine (63%) and placebo (62%) based on pooled acute phase data from both studies. The nature of the reported TEAEs was consistent with the know safety profile of duloxetine and/or the patient population, primarily involving the system organ classes of gastrointestinal disorders, psychiatric disorders and nervous system disorders. For the analysis of pooled data from both studies, individual TEAEs of nausea, diarrhoea, and abnormal dreams were reported statistically significantly more frequently with duloxetine (17%, 5.3%, and 1.8%, respectively) than placebo (9.8%, 1.8%, and 0%, p-value<.05%).

Treatment Emergent Adverse Events by Decreasing Frequency

MedDRA Preferred Term. All Randomized Patients. Primary Placebo-Controlled Analyses Set

HMCK and HMCL Acute Phase

Event	PLACEBO (N=225) n(%)	DULOXETINE (N=341) n(%)	FLUOXETINE (N=234) n(%)	DULOXETINE vs PLACEBO		FLUOXETINE vs PLACEBO	
				CMH p-value	Criteria	CMH p-value	Criteria
PATIENTS WITH >=1 TEAE	139(61.778%)	216(63.343%)	145(61.966%)	.705	C	.999	C
Nausea	22(9.778%)	59(17.302%)	26(11.111%)	.012	AC	.669	C
Headache	25(11.111%)	58(17.009%)	40(17.094%)	.066	C	.059	C
*Abdominal pain	22(9.778%)	42(12.317%)	19(8.120%)	.413	C	.522	
*Somnolence	13(5.778%)	33(9.677%)	13(5.556%)	.101		.870	
Dizziness	11(4.889%)	29(8.504%)	9(3.846%)	.120		.619	
*Decreased appetite	11(4.889%)	26(7.625%)	16(6.838%)	.162		.412	
*Fatigue	10(4.444%)	21(6.158%)	7(2.991%)	.293		.400	
Diarrhoea	4(1.778%)	19(5.572%)	5(2.137%)	.027	AB	.775	
Vomiting	6(2.667%)	19(5.572%)	8(3.419%)	.095	B	.677	
*Insomnia	7(3.111%)	18(5.279%)	12(5.128%)	.212		.269	
Influenza	8(3.556%)	11(3.226%)	4(1.709%)	.923		.186	
Upper respiratory tract infection	7(3.111%)	11(3.226%)	6(2.564%)	.970		.764	
Nasopharyngitis	8(3.556%)	9(2.639%)	11(4.701%)	.545		.537	
Dry mouth	2(0.889%)	8(2.346%)	3(1.282%)	.218	B	.674	
Oropharyngeal pain	4(1.778%)	8(2.346%)	10(4.274%)	.677		.111	B
*Abnormal dreams	0(0.000%)	6(1.760%)	5(2.137%)	.047	A	.029	A

N = Number of randomized patients, n = Number of patients with treatment-emergent adverse event
MEDDRA VERSION: 14.0
Criterion A: Adverse event rate higher in Duloxetine/Fluoxetine group than in Placebo group and CMH P-value < 0.05.
Criterion B: Adverse event rate in Duloxetine/Fluoxetine group is twice that of Placebo group and rate in Placebo group greater than zero.
Criterion C: Adverse event rate in Duloxetine/Fluoxetine group is greater than or equal to 10 percent.

Extension treatment phase

No deaths due to completed suicides or other causes were reported during either study.

A similar frequency of SAEs (1to 5% across duloxetine treatment arms) was observed between treatment groups in the individual studies.

The frequency of discontinuation due to an AE during extension treatment was consistent with the known profile of duloxetine.

A similar frequency of TEAEs was observed between treatment groups and across both studies. Consistent with the known safety profile of duloxetine, the nature of the reported TEAEs were similar to that observed during acute treatment though with a greater frequency of events in the infections and investigations system organ classes during the extension than the acute treatment phase. The frequency of infections and infestations was similar in all treatment groups and was not considered clinically meaningful.

Rapporteur's comments:

Nature of adverse events reported, involving primarily gastrointestinal, psychiatric and nervous system disorders, is consistent with that of adult studies as stated in the SmPC. Nausea, headache, abdominal pain, somnolence, dizziness, decreased appetite, fatigue, diarrhoea, vomiting and insomnia were the most frequent reported AEs (>5%). All but headache and insomnia were also more frequently reported in duloxetine treated patients than those reported with fluoxetine.

Suicide-Related Events

With regard to suicidal ideation, behaviour, and non-suicidal self-injurious behaviour, the results of the C-SSRS provide the most complete information on which to base conclusions for Studies HMCK and HMCL, and differences between the AE database and the C-SSRS results do not change the interpretation of the study results with regard to suicide related events (ideation and behaviour) or non-suicidal self-injurious behaviour.

C-SSRS Results (Acute – 10 weeks, placebo-controlled):

Suicide-related events (ideation or behaviour) as well as non-suicidal self-injurious behaviour were analyzed compared to lead-in baseline to determine whether the events were treatment emergent. That is, events during treatment that were new or more severe compared to baseline (study screening period also referred to as lead-in) were considered to be treatment-emergent. In addition, suicidal ideation was analyzed to determine if there was treatment-emergent improvement for patients who had suicidal ideation during the study screening period. The frequency of treatment-emergent suicide-related events (ideation or behaviour) as well as nonsuicidal self-injurious behaviour reported during acute treatment are presented in Table 5.3.

There were no statistically significant differences between the duloxetine and placebo groups with regard to treatment-emergent suicide-related events (ideation or behaviour) as well as nonsuicidal self-injurious behaviour reported during acute treatment.

Table 5.3. Treatment-Emergent Suicide-Related Events and Non-suicidal Self-Injurious Behaviour
Columbia Suicide Severity Rating Scale
Pooled Acute Analyses Set

	DLX		PBO		p-value[a]
	N	n (%)	N	n (%)	
Lead-in Baseline[b]					
TE Suicidal ideation (categories 1-5) [c]	333	22 (6.6)	220	18 (8.2)	.464
Improvement in suicidal ideation (categories 1-5) [d]	52	44 (84.6)	34	32 (94.1)	.193
TE Suicidal behaviour (categories 6-10)	333	0 (0.0)	220	1 (0.5)	.168
TE Non-suicidal self injurious behaviour [e]	328	10 (3.0)	216	6 (2.8)	.920

Abbreviations: C-SSRS (Columbia Suicide Severity Rating Scale); DLX = duloxetine; n = number of patients; N = number of enrolled patients with baseline and at least 1 post-baseline C-SSRS suicidal ideation or behaviour score; PBO = placebo; TE = treatment-emergent.

[a] Cochran-Mantel Haenszel test controlling for study.

[b] Lead-in baseline includes Visits 2-3.

[c] N= Number of enrolled patients with at least 1 post-baseline suicidal ideation score and whose maximum C-SSRS suicidal ideation score during the lead-in baseline period is non-missing and <5.

[d] N= Number of enrolled patients whose suicidal ideation score is non-missing and >0 during lead in baseline.

[e] N= Number of enrolled patients without non-suicidal self injurious behaviour at any baseline visits and with non-missing post baseline.

Source: integrations/pedss_peds/programs_stat/tfl_output/fqsuip11

C-SSRS Results (Extension – 26 weeks, double-blind):

During the extension phase for Studies HMCK and HMCL, all patients received duloxetine or fluoxetine. Patients initially randomized to placebo were transitioned to duloxetine in the extension phase (referred to as the PBO/DLX group). Statistical comparisons between treatment groups were not conducted for the extension phase analyses because of selection bias. In other words, only patients who completed the acute phase of the study were included in the extension phase analyses, therefore patient characteristics at the beginning of the extension phase were expected to be different between treatment groups due to lack of randomization. Suicide-related events (ideation or behaviour) as well as non-suicidal self-injurious behaviour were analyzed compared to lead-in baseline to determine whether the events were treatment emergent during the extension phase. For analyses of the extension phase, “lead-in” baseline refers to Visits 7 to 8 (that is the end of the acute treatment phase). The frequency of treatment emergent suicide-related events (ideation or behaviour) as well as non-suicidal self-injurious behaviour reported during extension treatment are presented in Table 5.4.

Table 5.4. Treatment-Emergent Suicide-Related Events During Extension Treatment
Columbia Suicide Severity Rating Scale
Pooled Studies HMCK and HMCL

	DLX/DLX		PBO/DLX		Total	
	N	n (%)	N	n (%)	N	n(%)
Lead-in Baseline[a]						
TE Suicidal ideation (categories 1-5)[b]	230	22 (9.6)	164	14 (8.5)	394	36 (9.1)
Improvement in suicidal ideation (categories 1-5)[c]	15	10 (66.7)	7	5 (71.4)	22	15 (68.2)
TE Suicidal behaviour (categories 6-10)	230	6 (2.6)	164	1 (0.6)	394	7 (1.8)
TE Non-suicidal self injurious behaviour[d]	225	9 (4.0)	162	3 (1.9)	387	12 (3.1)

Abbreviations: C-SSRS (Columbia Suicide Severity Rating Scale); DLX = duloxetine; n = number of patients; N = number of enrolled patients with baseline and at least 1 post-baseline C-SSRS suicidal ideation or behaviour score; PBO = placebo; TE = treatment-emergent.

[a] Lead-in baseline includes Visits 7-8.

[b] N= Number of enrolled patients with at least 1 post-baseline suicidal ideation score and whose maximum C-SSRS suicidal ideation score during the lead-in baseline period is non-missing and <5.

[c] N= Number of enrolled patients whose suicidal ideation score is non-missing and >0 during lead in baseline.

[d] N= Number of enrolled patients without Non suicidal self injurious behaviour at any baseline visits and with non-missing post baseline.

Source: integrations/pedss_peds/programs_stat/tfl_output/fqsuil61

The frequency of treatment emergent suicide-related events (ideation or behaviour) as well as non-suicidal self-injurious behaviour reported during acute and extension treatment for the two separate studies are presented below:

Treatment-Emergent Suicide-related events and non-suicidal self-injurious behaviour
Columbia Suicide Severity Rating Scale

	HMCK			HMCL			
Acute Treatment Phase (II)							
	DLX60-120 N=113 n (%)	FXT20-40 N=113 n (%)	PBO N=103 n (%)	DLX60 N=105 n (%)	DLX30 N=115 n (%)	FXT20 N=112 n (%)	PBO N=117 n (%)
Suicidal Ideation	16 (14.2)	16 (14.2)	15 (14.6)	16 (15.2)	11 (9.6)	13 (11.6)	15 (12.8)
Suicidal behaviour	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)
Non-suicidal self injurious behaviour	4 (3.5)	6 (5.3)	2 (1.9)	3 (2.9)	6 (5.2)	2 (1.8)	5 (4.3)
Extension Treatmen Phase (III)							
	DLX60-120/DLX60-120 N=81 n (%)	FXT20-40 N=91 n (%)	PBO/DLX60-120 N=85 n (%)	DLX60/DLX60-120 N=71 n (%)	DLX30/DLX60-120 N=78 n (%)	FXT20/FXT20-40 N=80 n (%)	PBO/DLX60-120 N=79 n (%)
Suicidal Ideation	13 (16)	13 (14.3)	8 (9.4)	6 (8.5)	12 (15.4)	8 (10.0)	8 (10.1)
Suicidal behaviour	1 (1.2)	1 (1.1)	0 (0.0)	2 (2.8)	3 (3.8)	0 (0.0)	1 (1.3)
Non-suicidal self injurious behaviour	4 (4.9)	2 (2.2)	2 (2.4)	4 (5.6)	3 (3.8)	1 (1.3)	1 (1.3)

Rapporteur's comments:

Results from Columbia Suicide Severity Rating Scale reveal 0 (duloxetine), 2 (fluoxetine) and 1 (placebo) suicidal behaviour events during the acute phase and 7 (duloxetine), 1 (fluoxetine) events

during the extension phase. Given these apparent differences between both products, a global comparison of duloxetine versus fluoxetine is of interest and deserves further discussion by the MAH.

Cardiovascular-Related Events

Acute Results (10 Weeks)

- *Blood Pressure and Pulse*

Results from the analyses of pooled categorical data did not reveal any statistically significant differences in potential clinical significant increases of blood pressure or pulse between duloxetine and placebo during acute treatment (Table 5.5). For HMCK, there was a statistically significant increase of pulse in duloxetine 60/120 group compared with placebo group. The mean increase in blood pressure observed with paediatric patients is also noted as a risk in the SmPC for adult patients.

Table 5.5. Least-Squared Mean Change at LOCF Endpoint and Potentially Clinically Significant Values at Any Time for Blood Pressure and Pulse Pooled HMCK and HMCL Data from Acute Treatment (10 Weeks)

LSMean Change at Endpoint				PCS High at Any Time[c]				Sustained Elevation (PCS at 3 consecutive visits)			
	DLX (N=332)	PBO (N=220)	p-value[a] (DLX vs. PBO)		DLX	PBO	p-value[b] (DLX vs. PBO)		DLX	PBO	p-value[b] (DLX vs. PBO)
Systolic BP (mm Hg)	0.88	0.11	.364	N n[c] (%)	283 27 (9.5)	188 16 (8.5)	.600	N n[d] (%)	283 1 (0.4)	188 2 (1.1)	.412
Diastolic BP (mm Hg)	1.17	0.49	.378	N n[c] (%)	295 27 (9.2)	203 21 (10.3)	.969	N n[d] (%)	295 1 (0.3)	203 2 (1.0)	.412
Sitting Pulse (bpm)	1.0	-0.45	.129	N n[c] (%)	332 0 (0.0)	220 1 (0.5)	.295	no pooled analyses			
QTcF	N=257 -2.9	N=176 1.0	.008	no pooled analyses				no pooled analyses			

Abbreviations: BP = sitting blood pressure; DLX = duloxetine; mm Hg = millimeters of mercury; N = Number of patients with baseline and non-missing post-baseline measure.; PBO = placebo; PCS = potentially clinically significant.

[a] Type III Sums of Squares from an analysis of variance (ANOVA) on the raw data: Change=Study, treatment.

[b] Cochran-Mantel-Haenszel test for general association controlling for study.

[c] N = Number of patients with normal or low blood pressure or pulse at baseline; n = number of patients with a PCS postbaseline measurement.

[d] N = Number of patients with normal or low blood pressure or pulse at baseline; n = number of patients with sustained elevation.

Source: integrations/pedss_peds/programs_stat/tfl_output/loecgp11, lovitp11, fqvitp11, fqvitp31

One potential cardiovascular-related SAE of syncope was reported in a duloxetine-treated female patient who had previous episodes of syncope prior to entering the study. The etiology of the syncopal episodes is unknown. Syncope is included as an undesirable effect in the duloxetine SmPC. No other serious cardiovascular events were reported during Studies HMCK and HMCL.

- *Electrocardiogram*

In acute pooled data, a statistically significant (p=.002) mean increase in heart rate of 2.4 bpm was observed for the duloxetine group, compared with a mean decrease in heart rate of 1.1 bpm in the placebo group. Abnormal high heart rate was reported in 1 (0.4%) duloxetine-treated patient and 1

(0.6%) placebo-treated patient during acute treatment. Abnormal low heart rate was reported in 2 (0.8%) duloxetine-treated patients and 5 (2.9%) placebo-treated patients during acute treatment. In the pooled mean change analysis of QTcF, patients in the duloxetine group had a mean decrease in QTcF, which is not considered clinically relevant.

With respect to categorical analyses of QTcF, 1 male patient (0.6%) in the duloxetine group experienced an abnormal QTcF interval increase of >40 msec from baseline to a value 408 msec during acute treatment, which did not meet the gender-specific abnormal threshold of >450 msec. This was the only duloxetine-treated patient with a QTcF observation that met abnormal criteria (increase or gender-specific) at anytime during the 10-week acute-treatment period of the studies. No duloxetine-treated patients had a potentially clinically significant QTcF observation (>500 msec) at anytime during the 10-week acute treatment period of the studies.

Combined Acute and Extension Results (up to 36 Weeks)

- *Blood Pressure*

During the 36 weeks of treatment, the frequency of either potential clinical significant high systolic or diastolic blood pressure at any time was 15.9% and 18.3%, respectively, in the duloxetine group. The majority of these events resolved during the study, as evidenced by the lower frequency of events noted at endpoint (4.2% high systolic and 3.4% high diastolic). For patients in the duloxetine group, less than 2% of patients (N=4 systolic, N=5 diastolic) with normal systolic or diastolic blood pressure at baseline met criteria for sustained elevation of systolic or diastolic blood pressure, which is less than the rate of sustained elevation of blood pressure reported in duloxetine-treated adult MDD patients (Hudson et al. 2005). Of these patients, the majority met the sustained criteria at endpoint. The SmPC already includes language that duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients.

- *Pulse*

With respect to pulse, 1 patient in the duloxetine group met potential clinical significant high criteria during long-term treatment. Patient HMCL 149-5901, who was on duloxetine 120 mg with a baseline pulse of 94 beats per minute (bpm), experienced a potential clinical significant increase at Week 32 to 126 bpm that decreased to a non-potential clinical significant value of 108 bpm at the 36-week endpoint.

- *Electrocardiogram*

In pooled data across 36 weeks, a mean increase in heart rate of 2.9 bpm was observed for the duloxetine group. In addition to the 2 duloxetine-treated patients who experienced abnormal low heart rate during the 10-week acute treatment period, abnormal low heart rate was reported in 3 more duloxetine-treated patients during extension treatment. No duloxetine-treated patients experienced abnormal high heart rate after the 10-week time point. One duloxetine-treated patient met criteria for abnormal increase in QTcF (>40 msec) to 408 msec during the acute treatment period. This was the only duloxetine treated patient with a QTcF observation that met criteria for abnormal increase (>40 msec from baseline) or gender-specific abnormal value ($\geqslant$470 msec for females or $\geqslant$450 msec for males) at anytime during the 36-week studies. No duloxetine-treated patients had a potentially clinically significant QTcF observation (>500 msec) at anytime during the 36-week studies.

Conclusion

The above data are consistent with the cardiovascular safety profile of duloxetine in adult patients; the increase in blood pressure is an identified risk and is included in the SmPC.

Rapporteur's comments:

The effect of duloxetine on blood pressure, cardiac frequency and ECG data (including QT interval) has been assessed in this paediatric population. The variations observed in cardiovascular parameters were apparently minimal and did not derive in major clinical events.

Growth-Related Events

Duloxetine has been known to lead to acute mean weight loss in adult patients followed by recovery to baseline values. As the impact of this known weight loss risk could be greater for paediatric patients compared with adult patients, due to active physiological growth, analyses of pooled data from HMCK and HMCL were performed to assess mean and individual weight changes over time (Table 5.6). Weight loss was not reported as an SAE during either study and no patient discontinued from the study due to weight loss.

It is important to evaluate growth relative to the general population using standardized height and weight scores. A z-score (or the standard deviation score) is one such analysis; that is, a z-score analysis normalizes a patient's weight to their age and sex-matched peers (specifically, the US population for the analyses below, since reference data from other countries were not available). A z-score of zero, therefore, would be equivalent to the median weight of the reference population; a z-score of -0.67 and 0.67 are approximately equivalent to the 25th percentile and the 75th percentile, respectively, of the reference population. This analysis was performed for the mean change of weight, height, and body-mass index (Tables 5.7 and 5.8)

Table 5.6. Mean Change and PCS Weight Decrease
All Randomized Patients
HMCK and HMCL Acute and Extension Period

	Acute				Extension[c]		Acute+Extension	
	DLX N=332	FLX N=226	PBO N=220	p-val[a] (DLX vs. PBO)	DLX N=230	FLX N=172	DLX N=332	FLX N=226
Mean Change to Endpoint (kg)[b]	-0.20	0.11	0.64	<.001	1.98	2.32	-	-
PCS Decrease at Any Time n (%)	38 (11.4)	26 (11.5)	12 (5.5)	.015	14 (6.1)	6 (3.5)	66 (19.9)	37 (16.4)
PCS Decrease at Endpoint n (%)	-	-	-	-	-	-	28 (8.4)	18 (8.0)

Abbreviations: DLX = duloxetine; FLX = fluoxetine; kg = kilogram; N = number of patients with baseline and at least 1 postbaseline measure; n = number of patients meeting criteria; PBO = placebo; PCS = potentially clinically significant; p-val = p-value.

[a] Duloxetine compared with placebo; for continuous variable calculated using Type III Sums of Squares from an analysis of variance (ANOVA) on the raw data: Change=Study, treatment; for categorical variable, calculated using Cochran-Mantel-Haenszel controlling for study.

[b] Mean baseline values (kg): for acute, 56.1 DLX, 54.7 FLX, 56.0 PBO; for extension: 55.9 DLX, 54.4 FLX.

[c] For extension phase analysis, baseline is end of acute phase for mean change analysis, lowest of study baseline and acute phase for PCS decrease analysis.

Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/lovitp11, lovitlb1, fqvitp11, fqvitl11, fqvitl21, fqvitl61

Table 5.7. Height, Weight, BMI Z-score Change During Acute Phase (10 Weeks)

Measures	Treatment	N	Baseline Mean	LSmean Change to Endpoint	p-value for DLX vs. PBO	p-value for FLX vs. PBO
Height	DLX	331	0.20	-0.02	.802	
	FLX	226	-0.06	-0.02		.726
	PBO	220	0.15	-0.02		
Weight	DLX	331	0.76	-0.09	<.001	
	FLX	226	0.60	-0.07		<.001
	PBO	220	0.68	-0.01		
BMI	DLX	331	0.76	-0.10	<.001	
	FLX	226	0.70	-0.09		.003
	PBO	220	0.71	-0.01		

Abbreviations: BMI = body mass index; DLX = duloxetine; FLX = fluoxetine; LS = least squares; N = number of patients with baseline and at least 1 postbaseline measure; PBO = placebo.

Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/lovitp61

Table 5.8. Height, Weight, BMI Z-score Change During the 36 Weeks of Study Treatment

Measures	Treatment	N	Baseline Mean	LSmean Change to Endpoint	Within Group p-value
Height	DLX	331	0.20	-0.004	.774
	FLX	226	-0.06	-0.056	<.001
Weight	DLX	331	0.76	-0.031	.057
	FLX	226	0.60	0.032	.092
BMI	DLX	331	0.76	-0.042	.042
	FLX	226	0.70	0.061	.011

Abbreviations: BMI = body mass index; DLX = duloxetine; FLX = fluoxetine; LS = least squares; N = number of patients with baseline and at least 1 postbaseline measure; PBO = placebo.

Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/lovitl61

On an individual patient level, when plotting the weight z-scores over time for all duloxetine patients meeting PCS weight loss criteria (⩾3.5% decrease at any time during 36 weeks of acute and extension treatment), their weight z-score decrease did not persist. Even though some patients, such as those meeting PCS criteria at endpoint (8.4%), had not yet recovered to their baseline weight value, most patients trended towards recovery to their baseline weight z-scores by their study endpoint.

Rapporteur's comments:

In principle there appear to be no signal of safety concerns on potential growth effect in paediatric patients treated with duloxetin. The MAH is committed to provide a report discussing observations regarding growth and development from pooled data obtained in paediatric studies.

Overall conclusions on safety

A total of 341 patients were randomized to duloxetine in these to studies. Mean duloxetine total dispensed dose during extension treatment was 88.8 mg in study HMCK and 84.3 mg in study HMCL. The MAH should provide the global number of subjects (and by age subgroups) exposed to study medication. Information on the study drug exposure by total daily dose (acute and extended administration), and a summary of the demographic characteristics of the involved population is also expected.

In principle there appear to be no new signal of safety concerns in children and adolescents related to duloxetine treatment. The nature of the adverse events reported, involving primarily gastrointestinal, psychiatric and nervous system disorders, is consistent with that of adult studies as stated in the SmPC. Nausea, headache, abdominal pain, somnolence, dizziness, decreased appetite, fatigue, diarrhoea, vomiting and insomnia were the most frequent reported AEs (>5%). Qualitatively, duloxetine and fluoxetine appear to be similar; however, duloxetine safety profile seems to be more adverse than that reported for fluoxetine. Duloxetine showed a higher incidence of most of adverse events; children and adolescents treated with duloxetine were more prone to withdraw for safety reasons than patients treated with fluoxetine.

The clinical differences in safety profile across the age subgroups, if any, should also be provided.

According to the findings identified during the continuous safety assessment of duloxetine in its different indications in adults a number of key events are closely monitored. Among them:

a) Suicidality: Results from Columbia Suicide Severity Rating Scale reveal 0 (duloxetine), 2 (fluoxetine) and 1 (placebo) suicidal behaviour events during the acute phase and 7 (duloxetine), 1 (fluoxetine) events during the extension phase. Given these apparent differences between both products, a global comparison of duloxetine versus fluoxetine is of interest and deserves further discussion by the MAH.

b) Hepatic risk: Neither the effect of duloxetine on laboratory parameters nor the changes in liver enzymes/hepatic adverse events have been described.

c) Cardiovascular events: The effect of duloxetine on blood pressure, cardiac frequency and ECG data (including QT interval) has been assessed in the paediatric population. The data on the cardiovascular safety profile are consistent with that of duloxetine in adult patients; the increase in blood pressure is an identified risk and is included in the SmPC.

c) Severe cutaneous reactions: No data have been provided.

d) Growth effect: In principle there appear to be no signal of safety concerns on potential growth effect in paediatric patients treated with duloxetine.

3. Discussion on clinical aspects

Duloxetine is authorised in EU in adults for the treatment of major depressive episodes; the treatment of diabetic peripheral neuropathic pain; the treatment of generalised anxiety disorder and for women for the treatment of moderate to severe stress urinary incontinence. It is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

The MAH has submitted the results of two phase III randomized, double-blind, placebo controlled studies of duloxetine in paediatric patients with major depressive disorder (F1J-MC-HMCL and F1J-MC-HMCK). A fluoxetine control arm was included for assay sensitivity.

After 10 weeks of treatment neither duloxetine nor fluoxetine did separate from placebo in none of the studies. No relevant differences were observed when the investigator made the global assessment of the response. The secondary endpoints results were consistent with the results of the primary analysis. In addition, no dose-response relationship could be identified when duloxetine 30 mg and 60 mg were administered. When doses were increased during the extension phases, both groups experienced an improvement in symptoms. The lack of a placebo arm and the flexible regimen of dosing administered hamper drawing sound conclusions. Subgroup analysis by age does not suggest benefit in a particular stratum. The antidepressant effect of duloxetine in children and adolescents has not been demonstrated.

Respecting pharmacokinetics, the steady-state duloxetine plasma concentrations increased with increasing dose in both children and adolescents. No relevant differences in Cmax and AUC were observed between the two age groups. Patient characteristics such as CYP2D6 metabolizer status, ethnicity, sex, age, and body weight did not appear to have an effect on steady-state duloxetine plasma concentrations. No dose adjustment seems to be required in the adolescent population with respect to the younger group. For enrichment of these data, an additional analysis population PK modelling on the integrated dataset from HMFN, HMCK and HMCL studies comprised by the company is expected.

In principle there appear to be no new signal of safety concerns in children and adolescents related to duloxetine treatment. With regard to the comparison with fluoxetine, both medications products appear to be qualitatively similar; however, duloxetine safety profile seems to be more adverse than that reported for fluoxetine. This information is deemed useful for prescribers and therefore it should be translated to the SmPC. Additional data for clarification is requested.

4. Product Information

Currently, the SmPC of duloxetine reflects that it is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (4.2) / should not be used in the treatment of children and adolescents under the age of 18 years (4.4). The MAH proposes to reflect the clinical relevant data obtained in these two studies in the SmPC (sections 4.2 and 5.1).

According to the MAH the extension of the therapeutic indication cannot be granted. However, it is considered that the inclusion of a brief description of the studies (including the inconclusive results) in the product information could be of help for prescribers. The Rapporteur also considers that submission of the two pending additional PK and safety analysis before completting the ongoing procedure, in case the timeline is not very delayed, will contribute to finally present a more complete information in the SmPC.

III. Rapporteur's Overall Conclusion and Recommendation

- **Overall conclusion**

Given the results of these two phase III efficacy and safety trials in which neither the investigational drug nor the active control separated significantly from placebo, the studies are considered inconclusive. A positive benefit of duloxetine in the treatment of paediatric patients with major depressive disorder has not been demonstrated. There appear to be no new signal of safety concerns in children and adolescents related to duloxetine treatment.

- **Recommendation**

As a positive benefit for paediatric population has not been demonstrated with these two studies, no recommendation about the use of duloxetine in paediatric population can be made. For reflecting the clinical relevant data obtained in the product SmPC, sections 4.2, 4.4, 4.8, 5.1 and 5.2 should be updated.

In this sense, the MAH should commit to submit the responses to the questions below together with a type II variation to include the comments no the SPC proposed. This information should be received in September 2012.

FUM not fulfilled

IV. ADDITIONAL CLARIFICATIONS REQUESTED

List of questions adopted

Non-clinical

1. The MAH should submit relevant data from completed juvenile studies in order to evaluate the inclusion of this information in the SPC.

Clinical

2. The MAH is encourged to submit within this procedure, the two additional planned analysis claimed:

    - A population PK modelling on the integrated dataset from HMFN, HMCK and HMCL

    - A report discussing growth and development using pooled data form several studies.

Safety

3. The MAH should provide the global number of subjects (and by age subgroups) exposed to study medication. Information on the study drug exposure by total daily dose (acute and extended administration), and a summary of the demographic characteristics of the involved population is also expected.

4. The clinical differences in safety profile across the age subgroups, if any, should also be provided.

5. Further discussion on the global comparison of duloxetine versus fluoxetine is expected, including the disposition of the patients and the AEs reported. A specific duscussion for suicide-related events is expected.

6. The MAH should provide the data regarding monitoring of some key events that has not been discussed in this report:

    - Hepatic risk: effect of duloxetine on laboratory parameters and changes in liver enzymes/hepatic adverse events.

    - Severe cutaneous reactions.

SmPC changes

- **4.2 Posology and method of adminsitration**

  Paediatric population

  The safety and efficacy of duloxetine in children and adolescents under the age of 18 years have not been established. Currently available data are described in sections 4.4, 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

- **4.4 Special warnings and precautions for use**

  Paediatric population

  Information regarding use in children and adolescents under 18 years of age should be replaced with the data from these two now submitted studies.

- **4.8 Undesirable effects**

  Paediatric population

  Information about undesirable effects from the submitted studies should be included.

- **5.1. Pharmacodynamic properties**

  Paediatric population

  A brief summary of the submitted paediatric study results, including comparative safety data with fluoxetine should be included.

- **5.2 Pharmacokinetic properties**

  Paediatric population

  Information from paediatric clinical studies and adittional analyses when available should be reflected.

V. ASSESSMENT OF THE RESPONSES PROVIDED

On June 21, 2012 the MAH submitted the Response to CHMP's Assessment Report for Paediatric Duloxetine Studies F1J-MC-HMCK and F1J-MC-HMCL.

Nonclinical Request 1

The MAH should submit relevant data from completed juvenile studies in order to evaluate the inclusion of this information in the SPC.

MAH Response

Four nonclinical studies of duloxetine in juvenile rats were conducted to support the paediatric development as shown in Table 4.1 below.

Table 4.1. Nonclinical Studies of Duloxetine in Juvenile Rats

Type of Study	Test System	Method of Administration	Study Number
Pharmacokinetic study in adult and juvenile rats	Rats	Oral	014RO6PK
Pilot study in juvenile rats [a]	Rats	Oral	901347
General toxicity in rats (Postnatal days 21 through 70)	Rats	Oral	901198
Neurobehavioral and reproductive toxicity study in juvenile rats (Postnatal days 21 through 90)	Rats	Oral	901221

[a] This exploratory pilot study was conducted in support of the definitive juvenile rat toxicology studies, 901198 and 901221.

The results of these studies demonstrate that:

- The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats.
- The main effects occurred at 45 mg/kg/day and included: significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation.
- There was no effect on male or female fertility.
- Minor, transient effects on neurobehaviour at 45 mg/kg/day, consisted of an increased number of errors in the Path B configuration of the Cincinnati water maze test performed during the treatment period, suggesting that these animals had difficulty with "elective-choice" sequential learning. The number of errors and the time taken to complete the maze (both Path A and Path B) were comparable to controls at all dose levels during the posttreatment period. Motor activity and auditory startle habituation were unaffected.

Based on these changes, the no-adverse effect level was determined to be 20 mg/kg/day.

In conclusion, the toxicology studies in juvenile rats demonstrated that the general toxicity profile of duloxetine in juvenile rats was similar to that in adults. There was no effect on fertility in the juvenile rat studies. Minor effects on neurobehaviour at 45 mg/kg/day in a water maze test were transient and did not persist. Therefore, these findings have no clinically meaningful impact and do not indicate any safety concerns relevant to a paediatric population. We propose to add the important clinical safety information from the paediatric studies in the SmPC as per CHMP's request. For duloxetine, the MAH consider the paediatric clinical data to be the most relevant information for the prescriber, as opposed to the nonclinical juvenile data which did not reveal any safety concerns or clinically relevant findings. Additionally, since the duloxetine paediatric data do not support an indication in this population, it is our view that the inclusion of the juvenile toxicity data, even if it were for completeness' sake, is not warranted. Thus, results from the nonclinical juvenile rat studies are not proposed for inclusion in the SmPC.

Rapporteur's comment

The MAH's response is mainly endorsed, nonetheless data on the juvenile studies should be adequately mentioned and updated in section 5.3 of the SmPC.

Clinical Request 2

The MAH is encouraged to submit within this procedure, the two additional planned analysis claimed:

- A population PK modelling on the integrated dataset from HMFN, HMCK and HMCL.

- A report discussing growth and development using pooled data from several studies.

MAH Response

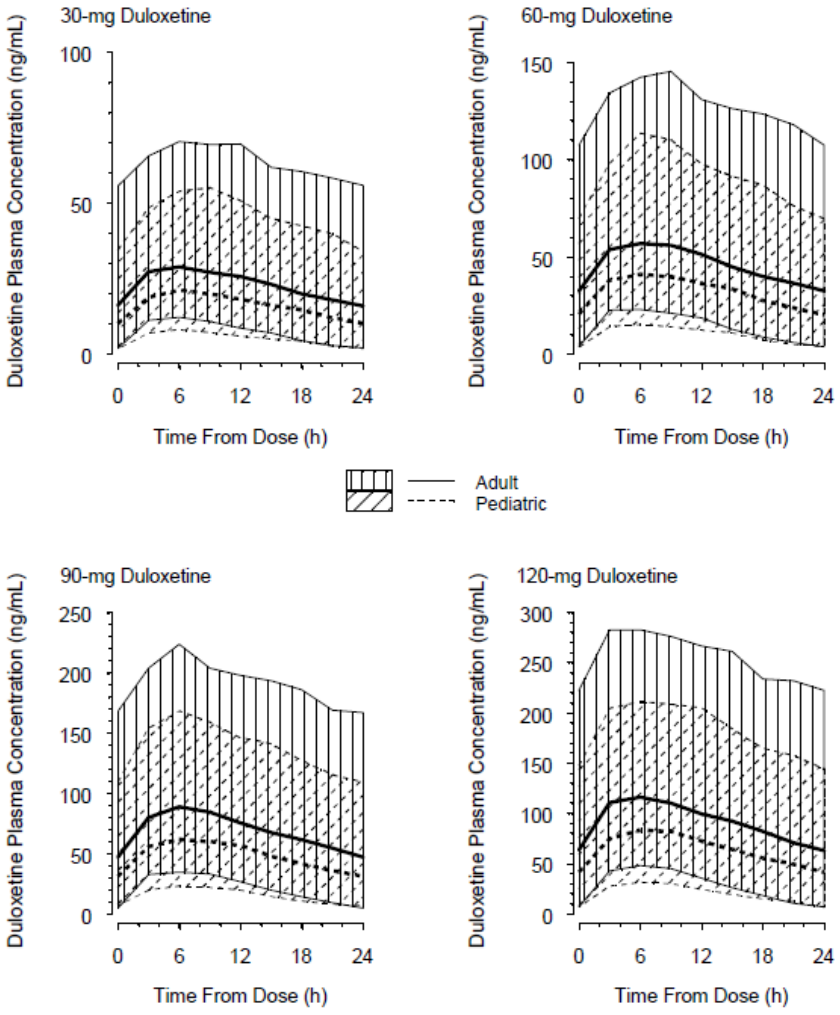
1.- Population PK Report

- The PK of duloxetine were well characterised by a 1 compartment model parameterised with first-order absorption, clearance (CL/F) and volume of distribution (V/F). Unexplained interpatient variability remained high for CL/F (68%), V/F (87%), and the residual error (57%).

- Body weight, age, sex, CYP2D6 predicted phenotype, race and ethnicity did not appear to have a clinically meaningful effect on duloxetine exposure. Dose, body surface area (BSA) and race were the only factors found to have a statistically significant effect on duloxetine PK parameters; however, these did not appear to have a clinically meaningful effect on duloxetine exposure.

- The model-predicted duloxetine concentration-time profile at steady state concentrations in paediatric patients appear to be slightly lower than those in adults and are mostly within the concentration range observed in adult patients.

- No conclusions related to dosing recommendations can be made because of the inconclusive efficacy results of Studies HMCK and HMCL.



Note: Lines represent the 5th, 50th, and 95th percentiles of 5000 simulated concentrations incorporating inter-subject variability as estimated from the final base models for studies HMAQ, HMAU, HMAV, HMEF and SAAW (adults) and studies HMCK, HMCL and HMFN (paediatrics).

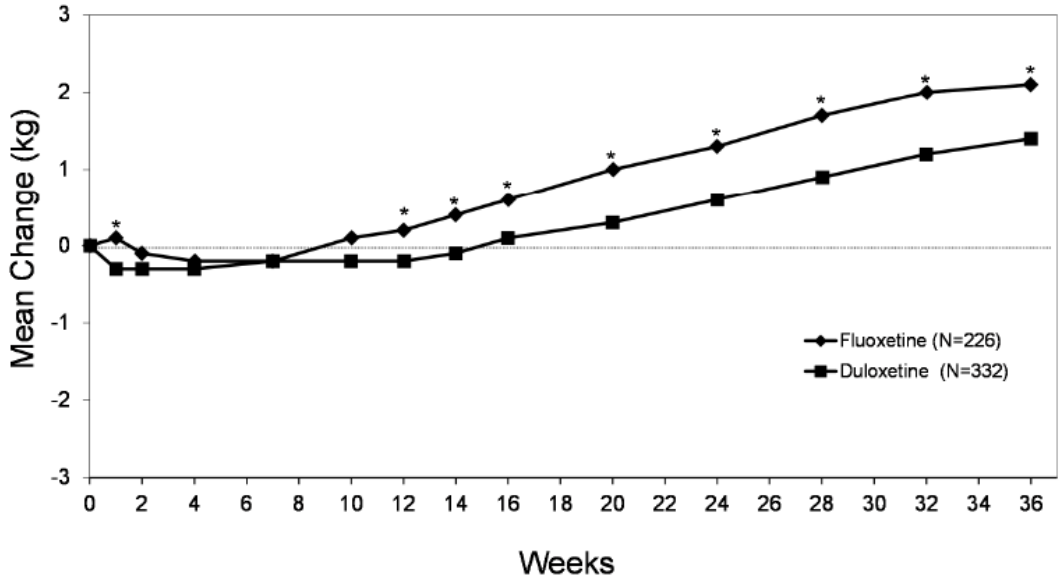
Figure 5.1. **Predicted duloxetine plasma concentration-time profile during the steady-state dosing interval of 24 hours following once-daily oral administration of duloxetine.**

Rapporteur's comments:

The steady-state duloxetine plasma concentrations increased with increasing dose in both children and adolescents being concentration-time profile lower than in adults although mostly within the concentration range observed in them. Interpatient variability was seen for clearance and volume of distribution. None patient-related characteristics appear to have an effect on duloxetine exposure that could result in a clinical relevant effect. Although no dose recommendation is proposed, these pharmacokinetic data should be reflected in the SmPC.

2.- Growth Report

Patients in the duloxetine group (initially randomised to duloxetine and continuing on duloxetine during extension treatment) experience a mean decrease in weight upon initiating treatment followed by weight recovery. These data further support the observations from the previously provided analyses. Similar results were observed for fluoxetine. The mean change (MMRM) by the end of the study was 1.4 kg (standard error [SE] 0.18) for duloxetine and 2.1 kg (SE 0.18) for fluoxetine.



Abbreviation: MMRM = mixed-model repeated measure
* p-value <.05
Source: SDD – integrations/pedss_peds/programs_stat/tfl_output/rmvitl11

Figure 5.2. **Mean change in weight over the 36 weeks of treatment (MMRM) in the long-term analyses set**

The quartile analysis of mean change in z-score by weight quartiles also indicated a trend towards baseline weight z-score upon continued duloxetine treatment in the long-term analyses set. Patients in the upper 3 duloxetine quartiles (of weight) experienced a smaller mean decrease in weight z-scores (see table below) by the end of longterm treatment compared with the mean weight z-score at end of acute treatment. For patients in which a decrease in weight would be of most concern, those in the first quartile ($\leqslant 25^{th}$ percentile), the weight z-score actually increased by study endpoint.

Table 4. **Weight Z-scores Change from Baseline to Endpoint By Baseline Weight Percentiles Long-Term Analyses Set**

1

Weight Z-scores
Change from Baseline to LOCF Endpoint By Baseline Weight Percentiles
Long term Analysis set
HMCK and HMCL Acute Phase and Extension Phase

Subgroup by Treatment interaction p-value(b)	Subgroup p-value(b)	Baseline Weight Percentile	Therapy	N	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	LSMean Change to Endpoint LSMean Change	LSMean Change to Endpoint SE	Within Group P-Value(a)	P-Value(a) Vs 2)
.628	.866	<=25th	1)DLX/DLX	26	-0.81	0.70	0.04	0.32	0.060	0.06	.322	.696
			2)FLX/FLX	30	-0.99	0.49	0.01	0.31	0.027	0.06	.664	
		>25th to 50th	1)DLX/DLX	61	-0.36	0.54	-0.03	0.27	-0.018	0.04	.641	.290
			2)FLX/FLX	30	-0.38	0.58	0.05	0.33	0.052	0.06	.348	
		>50th to 75th	1)DLX/DLX	69	0.25	0.49	-0.03	0.29	-0.031	0.04	.405	.158
			2)FLX/FLX	50	0.15	0.52	0.04	0.31	0.047	0.04	.266	
		>75th	1)DLX/DLX	175	1.59	0.75	-0.05	0.28	-0.037	0.02	.085	.036
			2)FLX/FLX	116	1.46	0.88	0.03	0.24	0.031	0.02	.208	

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
baseline: VISSTD 1-99, postbaseline: VISSTD 100-299
Zscores are calculated based on CDC reference data.

(a) Type III Sums of Squares from an analysis of covariance (ACNOVA) on the Zscores:
Model = Study, Treatment, Baseline zscore, Age category
(b) Type II Sums of Squares from an analysis of covariance (ANCOVA) on the Zscores:
Model = Study, Treatment, Age category, Subgroup, Subgroup*Treatment

Report: home/lillyce/prd/ly248686/integrations/pedss_peds/programs_stat/tfl_output/lovitl81
Program: home/lillyce/prd/ly248686/integrations/pedss_peds/programs_stat/lovitl8
Data: home/lillyce/prd/ly248686/integrations/q112sidb_peds/data/ads

There is little to no impact of duloxetine on mean change in height during the study.

Table 5.1. **Mean Change in Height from Baseline to Endpoint Study HMCK and HMCL Acute and Extension Phases**

	Acute				Extension[b]		
	DLX N=294	FLX N=201	PBO N=197	p-val[a] (DLX vs PBO)	DLX/DLX N=214	FLX/FLX N=156	PBO/DLX N=155
Baseline (cm)	154.7	152.9	155.3	.184	155.9	154.3	156.6
Mean Change (kg) (SE)	0.70	0.56	0.65	.658	1.1	0.7	0.7

Abbreviations: DLX = duloxetine; FLX = fluoxetine; N = number of patients with baseline and at least 1 non-missing postbaseline measure; PBO = placebo; SE = standard error.

a Duloxetine compared with placebo; calculated using Type III Sums of Squares from an analysis of variance (ANOVA) on the raw data: Model=Study and Treatment.

b For extension phase analysis, baseline is end of acute phase.

Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/lovitph1, lovitlc1, fqdmge11

Analyses of mean change in height indicated a similar height increase between the duloxetine and placebo groups during acute treatment, with continued increase during extension treatment. While notable differences between patients in the duloxetine and placebo groups were observed, the majority of patients who lost weight during acute treatment experienced recovery or a trend towards recovery

by the end of the study, whether assessed by mean change over time or by z-score as a way to normalise results to age- and sex-matched peers. Additionally, no serious adverse events (SAEs) or discontinuations due to weight-related events were reported during either study.

Rapporteur's comment:

Mean decrease in weight gain was observed mainly during short term treatment with duloxetine. It is not known whether weight recovery in the long-term is completed. Also the effect of duloxetine on weight gain during treatment periods longer than the studied is unknown. Height was not affected by duloxetine treatment during the study period. No data are available respecting sexual maturation (pubertal development). Adverse effects of duloxetine on growth should be reflected in section 4.8 as well as in section 5.1 of the SmPC.

Clinical Request 3

The MAH should provide the global number of subjects (and by age subgroups) exposed to study medication. Information on the study drug exposure by total daily dose (acute and extended administration), and a summary of the demographic characteristics of the involved population is also expected.

MAH Response

The mean days of duloxetine exposure were comparable between children and adolescents. Children had fewer patient years of exposure, driven by the smaller proportion of children than adolescents within the overall patient population. Approximately half of both children and adolescents patients remained on drug for at least 6 months.

Table 6.1. Duloxetine Exposure in the Total Duloxetine Group (DLX plus PLA/DLX) Studies HMCK and HMCL

	All Patients	Children (7-11 yrs)	Adolescents (12-17 yrs)
N (% Overall)	509	200 (40)	309 (60)
Duration			
mean days (patient years)	156 (217)	153 (83)	157 (133)
≥6 months	52%	50%	54%

Abbreviations: N = number of randomised patients.
Note that for the PLA/DLX group only the exposures for duloxetine is included.
Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/fqexpe11

With regards to duloxetine dosing during the studies (acute and extension phases), the mean dose for adolescents was higher at endpoint than the mean dose for children in both the DLX and PLA/DLX groups. This result was driven by adolescents being on a 120-mg dose for longer than children, as evidenced by a greater proportion of adolescents than children having a modal dose of 120 mg.

Table 6.2. Duloxetine Dose in Pooled Studies HMCK and HMCL

	DLX			PLA/DLX		
	Overall N=341	Children N=140	Adolescents N=201	Overall N=168	Children N=60	Adolescents N=108
Mean Dose (mg)	68	64	71	72	67	75
Modal Dose (%)						
60 mg	30	33	27	50	58	45
90 mg	11	11	11	13	12	13
120 mg	35	28	39	29	20	34

Abbreviations: DLX = duloxetine; PLA = placebo; N = number of randomised patients.
Note that for the PLA/DLX group only the exposures for duloxetine is included.
Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/fqexpe31

No statistically significant differences in patient demographics or baseline characteristics were observed between duloxetine or placebo in the complete patient population or within the age subgroups. Within the adolescent subgroup, the observed statistically significant differences between duloxetine and fluoxetine was mean age (greater mean age for fluoxetine, p=.043) and race distribution (larger proportion of white patients for fluoxetine, p=.040). These differences, however, were likely to have little to no impact on the interpretation of safety-related results. Overall, therefore, this study population was representative of the general child and adolescent population with MDD. No clinically meaningful differences were observed between treatment groups.

Table 6.3. Summary of Key Baseline Characteristics and Illness
All enrolled patients
Studies HMCK and HMCL

	Children				Adolescents			
	DLX (N=140)	FLX (N=100)	PLA (N=87)	p-value[a] (DLX v. PBO), (DLX v. FLX)	DLX (N=201)	FLX (N=134)	PLA (N=138)	p-value[a] (DLX v. PBO), (DLX v. FLX)
Age (yrs), Mean	9.9	9.8	10	.529, .478	15.1	15.5	15.2	.876, .043
Gender (%)								
Male	56	52	54	.727, .639	45	45	42	.577, .948
Female	44	48	46		55	55	58	
Race (%): White	58	69	61	.823, .706	66	72	68	.506, .040
Height, mean (cm)	141	138	141	.546, .065	165	164	164	.258, .740
Region (%)								
United States	62	55	64	.506, .903	68	62	63	.990, .884
Europe	11	17	9.2		15	23	20	
Other	27	28	26		17	15	17	
CDRS Total Score: Mean (SD)	58 (10)	58 (11)	58 (10)	.874, .823	61 (11)	59 (10)	60 (11)	.461, .205
CGI-S: Mean (SD)	4.5 (0.63)	4.6 (0.62)	4.5 (0.64)	.577, .222	4.6 (0.64)	4.5 (0.56)	4.6 (0.64)	.573, .089

Abbreviations: CDRS= Children's Depression Rating Scale; CGI-S= Clinical Global Impressions of severity; DLX = duloxetine; FLX = fluoxetine; N = number of patients with at least one non-missing post-baseline measure; PLA = placebo; SD = standard deviation; v = versus.

[a] For continuous variable: analysis of variance (ANOVA) adjusted for treatment and study; categorical variable: Cochrane Mantle-Haenszel.

Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/fqdmge11 and fqdmge31

Rapporteur's comments:

The mean duration of the patients in the studies was about 5 months being similar in children and adolescents. Approximately half of both children and adolescents remained on drug for at least 6 months. Mean daily dose was between 64-75 mg with higher doses in adolescents than in children at endpoint. There were not meaningful demographic differences between treatment groups or between age groups that could affect the trials outcome.

Clinical Request 4

The clinical differences in safety profile across the age subgroups, if any, should also be provided.

MAH Response

The analyses provided in this response are subject to increased Type I error due to the fact that we have conducted multiple analyses and there was no multiplicity adjustment. In addition, conclusions are limited due to small numbers within the subgroups. Because the primary focus of this section is to assess whether the safety profile is similar between the children and adolescent subgroups, the results discussed here include treatment by-subgroup interactions and within-subgroup treatment (duloxetine versus placebo) comparisons.

Overall, during the acute- or extension-treatment phases, few statistically significant treatment-by-subgroup interaction were observed in the analyses of SAEs, DC due to AE, TEAEs, standard laboratory and vital signs, indicating that the safety profile of duloxetine was similar between age subgroups.

Table 7.1. Summary of Serious Adverse Events and Discontinuation due to an Adverse Event
Studies HMCK and HMCL, Acute and Extension Phases

	Children (≥7<12 years)			Adolescents (≥12<18 years)			
	Acute Treatment Phase (II)						
Patients Reporting At Least 1:	DLX N=140 n (%)	PBO N=87 n (%)	p-val[a] (DLX vs PBO)	DLX N=201 n (%)	PBO N=138 n (%)	p-val[a] (DLX vs PBO)	Trt-by-sub Interaction
SAE	2 (1.4)	1 (1.1)	.966	7 (3.5)	2 (1.4)	.237	.274
DC due to AE	9 (6.4)	4 (4.6)	.558	19 (9.5)	3 (2.2)	.009	.399
TEAE	83 (59)	56 (64)	.549	133 (66)	83 (60)	.333	.432
	Extension Treatment Phase (III) [b]						
Patients Reporting At Least 1:	DLX/DLX N=93 n (%)	PBO/DLX N=60 n (%)		DLX/DLX N=144 n (%)	PBO/DLX N=108 n (%)		
SAE	4 (4.3)	2 (3.3)		2 (1.4)	6 (5.6)		-
DC due to AE	6 (6.5)	5 (8.3)		6 (4.2)	6 (5.6)		-
TEAE	60 (65)	43 (72)		89 (62)	74 (69)		-

Abbreviations: AE = adverse event; DC=discontinuation; DLX = duloxetine; n=number of patients with an event; N = number of randomised patients; PBO = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event; Trt=treatment.

[a] Cochran Mantel-Haenszel test controlling for study.

[b] For extension phase analysis, baseline is end of acute phase.

Source: SDD – acute: integrations/pedss_peds/programs_stat/tfl_output/fqsaep21, fqrdcp21, fqaesp81; extension: integrations/pedss_peds/programs_stat/tfl_output/fqsael21, fqrdcl21, fqaesl81.

The reported SAEs during the acute treatment phase in the adolescent duloxetine group were drug abuse, hallucination, intentional overdose (2 reports), panic attack, self-injurious behaviour, social phobia, suicidal ideation, and syncope. In the children duloxetine group, the 2 reported SAEs were depressive symptoms and irritable bowel syndrome (IBS). Of note, the SAE of IBS is captured in both Study Period II and Study Period III because the patient had the preexisting event of irritable bowel at

study entry but the event did not become serious until hospitalization during Study Period III. In summary, no new safety signals were identified. The only statistically significant finding was more discontinuations due to adverse events in the adolescent duloxetine group (9.5%) than the adolescent placebo group (2.2%, p=.009) during acute treatment. This rate of DC due to an AE is consistent with, and lower than, that observed in adult clinical studies of duloxetine. The only event reported by more than 2 patients in one subgroup was nausea, which was more frequent in the duloxetine-treated adolescent (4 events) than child (2 events) subgroup, with no discontinuations due to nausea in either placebo group. When compared with the adult patient population, the rate of discontinuation was lower in paediatric patients. The frequency of TEAEs was similar between treatment groups and across subpopulations and no statistically significant treatment-by-subgroup interaction was observed. Headache was the most frequently reported TEAE in duloxetine-treated adolescents (n, %: 41, 20% duloxetine; 11, 8.0% placebo), followed closely by nausea (n,%: 38, 19% duloxetine; 15, 11% placebo). Nausea was the most frequently reported TEAE in duloxetine-treated children (n,%: 21, 15% duloxetine; 7, 8% placebo), followed by headache (n,%: 17, 12% duloxetine; 14, 16% placebo). The other TEAEs reported in duloxetine-treated patients also were consistent with the know safety profile of duloxetine. Thus, no notable differences in the nature or frequency of TEAEs were observed between subgroups.

During extension treatment phase two children and 2 adolescents reported a suicide attempt. One male adolescent patient was hospitalized for the SAE of suspected Stevens-Johnson Syndrome. The other reported SAEs are either not unexpected in a psychiatric population or most likely not related to study drug. The frequency of DC due to an AE and TEAEs was similar between treatment groups and between subgroups. No single event was reported more frequently as the reason for discontinuation in either treatment group or subpopulation. These DC due to an AE rates are comparable to those observed in longer-term adult clinical studies of duloxetine. The most commonly reported (⩾5%) TEAEs in the duloxetine-treated adolescent subgroup were nausea, headache, vomiting, abdominal pain upper, nasopharyngitis, and dizziness. The first 4 of these TEAEs were also commonly reported in the duloxetine-treated children subgroup. Additionally, children commonly reported pyrexia and influenza. Overall, however, the reported TEAEs did not form an obvious differential pattern between children and adolescents. As noted above, these events are consistent with the safety profile of duloxetine within the adult population.

Analyses of Laboratory Data

Abnormal laboratory values were defined as outside of the Covance reference range of normal. Overall, no clinically meaningful differences were observed between duloxetine and placebo (acute) or DLX and PLA/DLX (extension) groups with regards to abnormally high or low laboratory values. Similarly, while statistically significant treatment-by-subgroup interactions were observed for some analytes, the differences were not considered clinically meaningful either due to the direction of the abnormal change or the apparent resolution of abnormal values at endpoint. Further, no SAEs or discontinuations related to abnormal laboratory values were reported.

During the acute treatment phase one statistically significant interaction was noted for low total bilirubin. This finding was driven by a greater duloxetine/placebo difference in children compared with duloxetine/placebo difference in adolescents. However, low total bilirubin was not considered a clinically relevant finding. The frequency of patients meeting abnormal criteria on any laboratory value at endpoint was lower, in general, than that observed at any time. Abnormally high platelet count and abnormal red blood cell morphology was observed statistically significantly more frequently at endpoint

within the adolescent duloxetine group compared with the adolescent placebo group; however, these were not considered a clinically relevant finding.

For extension-phase analyses, the baseline is the end of the acute phase. In general, the frequency of patients meeting abnormal criteria at any time and at endpoint was lower during extension treatment than acute treatment. The following abnormal criteria at any time occurred more frequently in children than adolescents and were reported by at least 5% of patients in the total duloxetine group (DLX/DLX plus PLA/DLX arms): high alanine aminotransferase, low bilirubin total, high calcium, high cholesterol, high creatinine, high eosinophils, high platelet count, and high hematocrit. Conversely, the following abnormal criteria were met at any time by at least 5% of patients in the total duloxetine group and by adolescents more frequently than children: high albumin, high alkaline phosphatase, high creatine phosphokinase, low glucose, high uric acid, low erythrocyte count, low mean cell hemoglobin (concentration), urinalysis (UA) occult blood, UA protein. Overall, when considering results from the acute and extension treatment, while the frequency of patients meeting some abnormal laboratory analyte criteria was higher in one subgroup over another, no clinically meaningful pattern was observed. Therefore, no clinically meaningful differences in the safety profile were observed between the children and adolescent subgroups.

Analyses of Vital Signs and Electrocardiogram Results

Analyses of categorical data were performed in addition to mean change from baseline to identify the frequency of patients meeting Potentially Clinically Significant (PCS) increases for the specified parameters. Overall, the results did not reveal a clinically meaningful differences between adolescents or children with respect to vital signs or ECGs. Nevertheless, these data should be interpreted with caution due to the limited number of patients meeting abnormal categorical criteria.

No statistically significant differences in mean change in systolic blood pressure, diastolic blood pressure, pulse were observed between duloxetine and placebo in either the children or adolescent subgroups. Both duloxetine-treated children and duloxetine-treated adolescents experienced mean decrease in weight that was statistically significant when compared with placebo-treated children and adolescent patients, respectively. A statistically significant within-subgroup difference in low systolic blood pressure was observed in children, but the frequency was higher in placebo (3, 3.6%) than duloxetine (0, 0%). No other within-subgroup differences in blood pressure or pulse were observed during the acute-treatment period. Few patients in any treatment group met criteria for sustained elevation (that is, meeting PCS criteria for at least 3 consecutive visits) during the acute-treatment period. For sustained elevation in diastolic blood pressure, a total of 2 adolescents, both in the placebo group, and 1 child in the duloxetine group met sustained diastolic blood pressure criteria. No discontinuations due to sustained elevation in blood pressure were reported. For sustained elevation in systolic blood pressure, 1 adolescent in the duloxetine group and 2 adolescents in the placebo group met sustained criteria. No children met sustained elevation in systolic blood pressure criteria during acute treatment. Treatment-by-subgroup interaction test could not be performed due to no events in some subgroups. Overall, however, few patients experienced sustained elevation in blood pressure, suggesting that elevations in blood pressure during acute treatment were sporadic.

For electrocardiogram results, few treatment-by-subgroup interactions were calculated due to lack of events in at least 1 treatment arm.

Table 7.2. Summary of Electrocardiogram Results by Age Subgroup Acute Phase of Pooled Studies HMCK and HMCL

	Children				Adolescents			
	DLX N=103 n (%)	PLA N=65 n (%)	p-value[a] (DLX v PLA)	Trt-by-sub Interaction	DLX N=154 n (%)	PLA N=111 n (%)	p-value[a] (DLX v PLA)	Trt-by-sub Interaction
High Heart Rate	0 (0.0)	0 (0.0)	-	-	1 (0.6)	1(0.9)	.871	-
Low Heart Rate	2 (2%)	4 (6%)	.123	-	0 (0.0)	1 (0.9)	.334	-
Abnormal increase in QTcF[b]	0 (0.0)	0 (0.0)	-	-	1 (0.7*)	0 (0.0)	.304	-
Gender-specific High QTcF[c]	0 (0.0)	0 (0.0)	-	-	0 (0.0)	0 (0.0)	-	-
PCS QTcF (>500 msec)	0 (0.0)	0 (0.0)	-	-	0 (0.0)	0 (0.0)	-	-

Abbreviations: DLX = duloxetine; N = number of patients with at least one non-missing post-baseline measure; PLA = placebo; v = versus.

* One patient in the duloxetine group had a missing post-baseline measure for this analysis; thus, percentage was calculated using N=153.

[a] For continuous variable: analysis of variance (ANOVA) adjusted for treatment and study; categorical variable: Cochrane Mantle-Haenszel.

[b] >40 msec increase from baseline

[c] ≥470 msec for Female or ≥450 msec Male

Source: SDD - integrations/pedss_peds/programs_stat/tfl_output/ fqecge11

For patients randomised to duloxetine and remaining on duloxetine during extension treatment, children generally experienced a greater mean increase in blood pressure and pulse when compared with adolescents. However, the differences in the mean changes were small (⩽2 mm Hg) and not likely clinically significant. These results observed during extension treatment are consistent with those observed during acute treatment. Conversely, for patients initially randomised to placebo and switched to duloxetine during the extension treatment, the mean increase in blood pressure and pulse was generally greater in adolescents than children. These observations are not likely clinically significant because the adolescents transitioning from placebo to duloxetine had vital-sign changes similar to those seen by the adolescents treated with duloxetine in the acute phase._A greater frequency of children (13%) met PCS high diastolic blood pressure at any time when compared with adolescents (9%) in the duloxetine group. A similar result was observed for PCS high systolic blood pressure at any time, where children (12%) met the criteria more frequently than adolescents (9%) in the duloxetine group. Few duloxetine-treated patients met criteria for PCS high pulse, with a total of 2 (0.8%) adolescents meeting criteria at any time during extension treatment. These observations do not support a differential tolerability regarding blood pressure between the child and adolescent duloxetine-treated subgroups. No duloxetine-treated children or adolescents met criteria for sustained elevation in diastolic blood pressure during extension treatment. One adolescent in the duloxetine group met criteria for sustained elevation in systolic blood pressure during extension treatment. As with the acute-treatment phase, few patients met criteria, limiting the ability to draw conclusions and suggesting that any noted abnormal elevations in blood pressure were sporadic._A total of 2 (0.9%) duloxetine-treated adolescents and 4 children (3%) in the duloxetine group met low heart rate criteria. For QTcF results, no duloxetine-treated children or adolescents met high or abnormal increase criteria.

Rapporteur's comments:

Adverse events, laboratory data, vital signs and electrocardiogram were analyzed. Overall, the safety profile of duloxetine was similar between age subgroups. Statistical significant interactions were founded although they were not considered clinically relevant. Adverse events were consistent with those in the adult population. There was more discontinuation due to adverse events in the adolescent duloxetine group than in the adolescent placebo group (statistically significant). Children and adolescent treated with duloxetine experienced a statistically significant mean decrease in weight compared with placebo. Suicide-related events (by subgroup) are not discussed in this section. Safety profile of fluoxetine by age-subgroups is not presented.

Clinical Request 5

Further discussion on the global comparison of duloxetine versus fluoxetine is expected, including the disposition of the patients and the AEs reported. A specific discussion for suicide-related events is expected.

MAH response

For the acute-treatment phase, completion rates were comparable across treatment groups in Study HMCL (approximately 70%) and Study HMCK (75% and 78% for duloxetine and fluoxetine respectively). The most frequently reported reason for discontinuation was an AE, with patients in the duloxetine group DC due to AE more frequently than patients in the fluoxetine group, primarily due to the event of nausea. For the extension period, completion rates were approximately 60% across treatment groups in Study HMCL and approximately 80% in Study HMCK. The most frequently reported reason for discontinuation in the duloxetine and fluoxetine groups was patient or caregiver decision.

Because the comparison of interest is between duloxetine and fluoxetine, characterization of the safety profiles over long-term treatment requires analysis of only those patients initially randomised to duloxetine or to fluoxetine. This avoids selection bias by not including patients initially randomised to placebo who are then switched to duloxetine during extension treatment.

The frequency of DC due to an AE in the acute treatment phase was statistically significantly higher with duloxetine than with fluoxetine. This difference was primarily driven by discontinuations due to nausea: 6 (1.8%) reports with duloxetine and 0 reports with fluoxetine. The frequency of TEAEs was also similar across the treatment groups. The individual TEAEs of nausea (17%, 11%) and dizziness (8.5%, 3.8%) were reported statistically significantly more frequently with duloxetine compared with fluoxetine. Discontinuation due to an AE remained higher in the duloxetine group than the fluoxetine group at study endpoint; as noted above, this was primarily driven by the greater frequency of discontinuations due to nausea with duloxetine (7, 2.2%) than fluoxetine (0, 0%, p=.032). The median time to discontinuation due to nausea was 41 days. Of note, 6 of the 7 nausea events reported as a reason for discontinuation from duloxetine occurred during the acute-treatment period. This is consistent with the known profile of duloxetine, where nausea, a commonly reported AE upon duloxetine initiation, tends to resolve with continued duloxetine treatment. The only other AEs reported by more than 2 patients in a treatment group as a reason for discontinuation was depression for duloxetine (4, 1.2%, versus 0, 0% with fluoxetine) and aggression for fluoxetine (3, 1.3% versus 1, 0.3% with duloxetine).

Table 8.1. Summary of Serious Adverse Events, Discontinuation Due to an Adverse Event and Treatment Emergent Adverse Events Studies HMCK and HMCL, Acute and Extension Phases

Acute Treatment (Phase II)			
Patients Reporting At Least 1:	DLX N=341 n (%)	FLX N=234 n (%)	p-value[a] (DLX vs FLX)
SAE	9 (2.6)	8 (3.4)	.481
Discontinuation due to an AE	28 (8.2)	7 (3.0)	.017
TEAE	216 (63)	145 (62)	.792
Acute plus Extension Treatment (Phase II-III)			
Patients Reporting At Least 1 of:	DLX/DLX N=341 n (%)	FLX/FLX N=234 n (%)	p-value[a]
SAE	14 (4.1)	12 (5.1)	.532
Discontinuation due to an AE	40 (12)	18 (7.7)	.150
TEAE	256 (75)	169 (72)	.386

Abbreviations: AE = adverse event; DLX = duloxetine; n=number of patients with an event; N = number of randomised patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Cochrane Mantel-Haenzel for general association controlling for study.

Source: SDD – integrations/peds_peds/ programs_stat/tfl_output/ fqsaep11, fqrdcp11, fqaesp11, fqsael1, fqrdcl1, fqaesl11

Analyses of mean change in laboratory analytes during acute treatment revealed few significant differences between duloxetine and fluoxetine. Due to the direction or magnitude of change, these were not considered clinically meaningful. Analyses of treatment-emergent abnormal laboratory analytes did not reveal any statistically significant differences between duloxetine and fluoxetine during acute treatment. During extension treatment, low levels of lymphocytes and neutrophils were observed at least 2 times more frequently with fluoxetine than duloxetine (that is, the DLX/DLX group). Low levels of mean cell hemoglobin and neutrophils, as well as high neutrophil and abnormal protein levels occurred at least 2 times more frequently with duloxetine than fluoxetine. These differences were not considered clinically meaningful, however.

With respect to mean change from baseline (blood pressure and pulse), PCS abnormalities (blood

pressure and pulse) and sustained elevations of blood pressure, no statistically significant differences were observed between duloxetine and fluoxetine. A statistically significant difference for mean change in QTcF was observed between duloxetine and fluoxetine, with patients in the duloxetine group experiencing a mean decrease and those in the fluoxetine group experiencing a mean increase. Overall mean changes were small (increase or decrease of less than 4 msec), however, and not considered clinically relevant for either drug. Categorical analyses of QTcF identified 1 male patient (0.4%) in the duloxetine group who experienced an abnormal increase in QTcF interval (that is, an increase of greater than 40 msec from baseline). One male patient (0.6%) in the fluoxetine group met the gender-specific high QTcF criteria (⩾450 msec). Neither patient met PCS criteria for QTcF (an absolute interval >500 msec). Abnormal high heart rate was reported in 1 (0.4%) duloxetine-treated patient and no fluoxetine-treated patient during acute treatment. There were no SAEs or TEAEs related to QTc

prolongation reported for patients in the duloxetine or fluoxetine groups in the acute analyses set. Overall, therefore, no new signal regarding QTcF data was identified.

Table 8.2. Mean Change at LOCF Endpoint and Potentially Clinically Significant Values at Any Time for Blood Pressure and Pulse Acute Analyses Set (10 Weeks)

	LSMean Change at Endpoint			PCS High at Any Time[c]			Sustained Elevation (PCS at 3 consecutive visits)		
	DLX N=332	FLX N=226	p-value[a] (DLX vs FLX)	DLX N n[c] (%)	FLX N n[c] (%)	p-value[b] (DLX vs FLX)	DLX N n[d] (%)	FLX N n[d] (%)	p-value[b] (DLX vs FLX)
Systolic BP (mm Hg)	0.88	0.05	.323	283 27 (9.5)	199 18 (9.0)	.649	283 1 (0.4)	199 1 (0.5)	.817
Diastolic BP (mm Hg)	1.17	0.89	.714	295 27 (9.2)	205 18 (8.8)	.823	295 1 (0.3)	205 1 (0.5)	.629
Sitting Pulse (bpm)	1.0	-0.83	.055	332 0 (0.0)	226 0 (0.0)	-	-		
ECG	N=257	N=172		N=259	N=176				
QTcF (msec)	-2.9	3.6	<.001	0 (0.0)	0 (0.0)	-	-		
Heart Rate (bpm)	2.4	-2.9	<.001	1 (0.4)	0 (0.0)				

Abbreviations: BP = sitting blood pressure; DLX = duloxetine; mm Hg = millimeters of mercury; N = Number of patients with baseline and non-missing post-baseline measure; PCS = potentially clinically significant.

[a] Type III Sums of Squares from an analysis of variance (ANOVA) on the raw data: Change=Study, treatment.

[b] Cochran-Mantel-Haenszel test for general association controlling for study.

[c] N=Number of patients with normal or low blood pressure or pulse at baseline; n = number of patients with a PCS postbaseline measurement, where PCS definitions are as follows: for high blood pressure, >95th percentile by age, gender, height and an increase from baseline high of ≥5 mm Hg; for high pulse, >140 bpm (for children) or >120 bpm (for adolescence) along with an increase of ≥15 bpm from the maximum baseline value; for high QTcF, >500 msec for both male and female.

[d] N = Number of patients with normal or low blood pressure or pulse at baseline; n = number of patients with sustained elevation, where sustained elevation systolic or diastolic blood pressure was defined as >95th percentile by age, gender, height and an increase from baseline high of ≥5 mm Hg at 3 consecutive post-baseline visits.

Source: integrations/pedss_peds/programs_stat/tfl_output/loecgp11, lovitp11, fqvitp11, fqvitp31

Longer-term data are important for assessing cardiovascular risk. To this end, data from the combined acute and extension phase treatment periods (36 weeks) were pooled from both studies to ascertain the frequency and duration of PCS vital signs and sustained elevation in blood pressure. In this pooled analyses, only patients randomised to duloxetine or fluoxetine at the beginning of the studies were analysed. In other words, patients randomised to placebo were excluded since these patients were only exposed to duloxetine for 26 weeks and not the complete study duration. Categorical analyses of blood pressure at endpoint compared with at any time suggest that the majority of PCS events at any time occurring in the duloxetine and fluoxetine groups tended to resolve during the studies, as evidenced by the lower frequency of events at endpoint (Table 8.3). With respect to sustained elevation of blood pressure, less than 2% of patients in the duloxetine and fluoxetine groups met criteria for sustained elevation of systolic or diastolic blood pressure. Overall, therefore, no new signal with respect to pulse and blood pressure was identified.

Table 8.3. Categorical Analyses for Blood Pressure and Pulse All Randomised Patients with Normal Blood Pressure at Baseline Long-term Analyses Set (36 Weeks)

	DLX/DLX n (%)	FLX/FLX n (%)	p-value[a] (DLX vs FLX)
High PCS Systolic BP[b] (mm Hg)			
Any Time	45 (15.9)	33 (16.6)	.632
Endpoint	12 (4.2)	9 (4.5)	.756
High PCS Diastolic BP[b] (mm Hg)			
Any Time	54 (18.3)	44 (21.5)	.431
Endpoint	10 (3.4)	9 (4.4)	.785
High PCS Pulse[b] (bpm)			
Any Time	1 (0.3)	0 (0)	.475
Endpoint	0 (0)	0 (0)	-
Sustained Elevation Systolic BP[c]	4 (1.4)	3 (1.5)	.913
Sustained Elevation Diastolic BP[c]	5 (1.7)	2 (1.0)	.426

Abbreviations: BP = sitting blood pressure; DLX = duloxetine; mm Hg = millimeters of mercury; n = number of patients with normal or low blood pressure or pulse at baseline and with a postbaseline measurement meeting event criteria; PCS = potentially clinically significant.

[a] Cochran-Mantel-Haenszel test for general association controlling for study.

[b] PCS definitions are as follows: for high blood pressure, >95th percentile by age, gender, height and an increase from baseline high of ≥5 mm Hg; for high pulse, >140 bpm (for children) or >120 bpm (for adolescence) along with an increase of ≥15 bpm from the maximum baseline value.

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

Source: integrations/pedss_peds/programs_stat/tfl_output/ fqvitl11, fqvitl21, fqvitl31

With respect to ECG results, a mean increase in heart rate of 2.8 bpm was observed for the duloxetine group, while a mean decrease (-2.3 bpm) was observed in the fluoxetine group over the 36 weeks of the study. Patients in the duloxetine group experienced a mean decrease in QTcF (-1.9 msec) while those in the fluoxetine group experienced a mean increase (2.3 msec). The difference between treatment groups for both heart rate and QTcF were both statistically significant (<.001 and .005, respectively). Over the entire study, 1 duloxetine-treated patient experienced abnormal high heart rate and 1 duloxetine-treated patient experienced abnormal increase in QTcF interval, and both events occurred during acute treatment. There were 3 patients in the fluoxetine group who experienced gender-specific high QTcF (⩾470 msec for females and ⩾450 msec for males), with 1 event occurring during acute treatment. There were 3 patients in the fluoxetine group with abnormal increase in QTcF interval (>40 msec increase) from study baseline.

In order to provide more robust comparisons for suicide-related events between duloxetine and fluoxetine accounting for differences in number of patients assigned to each treatment group and duration of exposure, an exposure adjusted analysis was conducted for the overall population, and also for each age subgroup (children and adolescent). Exposure adjusted incidence rate (EAIR), that is, number of patients with events divided by the total patient years, was calculated separately for acute phase, extension phase, as well as acute and extension phase combined. EAIR was compared between treatment groups for acute phase or acute and extension phase combined using Miettinen and Nurminen (MN) method (Miettinen and Nurminen 1985; Chan and Wang 2009). There were no completed suicides in Studies HMCK and HMCL. The frequency of treatment emergent suicidal ideation and non-suicidal self-injurious behaviour as collected via CSSR-S was similar across all treatment groups during acute treatment. Suicidal ideation occurred in a similar proportion of patients in all

treatment groups and occurred in both children and adolescents, with the frequency being greater in adolescents. Suicidal behaviour as collected via CSSR-S occurred in <1% of patients within any treatment group during acute treatment. Three cases of suicidal behaviour were reported during acute treatment with 2 cases for fluoxetine, 1 case for placebo, and 0 cases for duloxetine. Regarding exposure adjusted analyses for the acute-treatment phase, there were no statistically significant differences between duloxetine and fluoxetine for EAIR for overall population or for the adolescent subgroups.

Table 8.4. Treatment-Emergent Suicide-Related Events and Non-Suicidal Self-Injurious Behaviour Using Columbia Suicide Severity Rating Scale and Exposure Adjusted Analysis Acute Analyses Set

	Duloxetine		Fluoxetine		Placebo		p-value[b]
Rates from CSSR-S	N	n (%)	N	n (%)	N	n (%)	(DLX vs FLX)
TE Suicidal ideation (Categories 1-5)[a]							
Overall	333	22 (6.6)	225	18 (8.0)	220	18 (8.2)	.556
Children	135	8 (5.9)	94	5 (5.3)	84	4 (4.8)	nc
Adolescents	198	14 (7.1)	131	13 (9.9)	136	14 (10.3)	nc
TE Suicidal behaviour (Categories 6-10)[a]							
Overall	333	0 (0)	225	2 (0.9)	220	1(0.5)	0.091
Children	135	0 (0)	94	0 (0)	84	1(1.2)	nc
Adolescents	198	0 (0)	131	2 (1.5)	136	0(0)	nc
Non-suicidal self-injurious behaviour[a, c]	328	10 (3.0)	224	8 (3.6)	216	6 (2.8)	.895
Exposure Adjusted Analysis	**PY**	**Events per PY**	**PY**	**Events per PY**	**PY**	**Events per PY**	**p-value[d] (DLX vs FLX)**
Exposure Adjusted TE suicidal ideation							
Overall	57.6	0.38	40.0	0.45	38.8	0.46	.636
Children	23.5	0.34	16.9	0.29	14.7	0.27	.740
Adolescents	34.1	0.41	23.1	0.56	24.1	0.58	.405
Exposure Adjusted TE suicidal behaviour							
Overall	59.1	0.00	41.0	0.05	40.2	0.03	.096
Children	24.0	0.00	17.3	0.00	15.0	0.06	-
Adolescents	35.1	0.00	23.8	0.08	25.1	0.00	.091

Abbreviations: CSSR-S = Columbia Suicide Severity Rating Scale; DLX = duloxetine; n = number of patients with an event; N = number of enrolled patients with baseline and at least 1 post-baseline C-SSRS suicidal ideation or behaviour score; nc = not calculated; PBO = placebo; PY = patient years; TE = treatment-emergent.

[a] Compared with lead-in baseline.

[b] p-value compares duloxetine with fluoxetine; Cochran-Mantel-Haenszel test controlling for study.

[c] N= Number of patients with baseline and non-missing post-baseline Non-suicidal self-injurious behaviour.

[d] p-value is from Stratified Miettinen and Nurminen method with Cochran-Mantel-Haenszel weights.

Source: SDD –integrations/pedss_peds/programs_stat/tfl_output/fqsuip11, fqsuie11

The frequency of treatment emergent suicidal ideation as collected via C-SSRS was similar across all treatment groups during the extension-treatment period. Suicidal ideation occurred in a similar proportion of patients in all treatment groups and occurred in both children and adolescents, with the frequency generally being greater in adolescents. Suicidal behaviour as collected via C-SSRS occurred in <1% of patients within the PBO/DLX and FLX/FLX treatment groups and in 2.6% of patients in the DLX/DLX treatment group during extension treatment. A total of 8 cases of suicidal behaviour were

reported during extension treatment with 7 cases for duloxetine- and 1 case for fluoxetine-treated patients.

Regarding exposure adjusted analyses for the extension-treatment phase, the number of events (ideation or behaviour) per patient years was similar for duloxetine and fluoxetine. More specifically, even though the actual number of suicide behaviours was greater for duloxetine compared with fluoxetine, the difference between duloxetine and fluoxetine treatment groups in the exposure adjusted incidence rate was smaller due to greater number of patients exposed to duloxetine.

Table 8.5. Treatment-Emergent Suicide-Related Events and Non-Suicidal Self-Injurious Behaviour Using Columbia Suicide Severity Rating Scale and Exposure Adjusted Analysis
Extension Analyses Set

	DLX/DLX		PBO/DLX [c]		FLX/FLX	
	N	n (%)	N	n (%)	N	n (%)
TE Suicidal ideation [a] (Categories 1-5)						
Overall	230	22 (9.6)	164	14 (8.5)	171	20 (11.7)
Children	91	9 (9.9)	59	3 (5.1)	72	6 (8.3)
Adolescents	139	13 (9.4)	105	11 (10.5)	99	14 (14.1)
TE Suicidal behaviour [a] (Categories 6-10)						
Overall	230	6 (2.6)	164	1 (0.6)	171	1 (0.6)
Children	91	5 (5.5)	72	0 (0)	59	0 (0)
Adolescents	139	1(0.7)	105	1 (1.0)	99	1 (1.0)
Non-suicidal self-injurious behaviour [a, b] Overall	225	9 (4.0)	162	3 (1.9)	169	2 (1.2)
Exposure Adjusted Analysis	**PY**	**Events per PY**	**PY**	**Events per PY**	**PY**	**Events per PY**
Exposure Adjusted TE suicidal ideation						
Overall	136.0	0.16	98.7	0.14	101.3	0.20
Children	53.0	0.17	35.8	0.08	44.5	0.14
Adolescents	83.0	0.16	63.0	0.18	56.8	0.25
Exposure Adjusted TE suicidal behaviour						
Overall	140.4	0.04	101.4	0.01	105.6	0.01
Children	54.6	0.01	36.3	0.00	45.9	0.00
Adolescents	85.8	0.01	65.1	0.02	59.7	0.02

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale; DLX = duloxetine; n = number of patients with an event; N = number of enrolled patients with baseline and at least 1 post-baseline C-SSRS suicidal ideation or behaviour score; PY = patient years; TE = treatment-emergent.

[a] Compared with lead-in baseline.

[b] N= of enrolled patients **without** non-suicidal self-injurious behavior at any baseline visits and with a nonmissing postbaseline.

[c] All patients initially randomised to placebo at the beginning of acute phase and also entered the extension phase taking duloxetine

Source: SDD – integrations/pedss_peds/programs_stat/tfl_output/fqsuil61, fqsuie21

An additional exposure adjusted analysis using data from C-SSRS over the 36-week study for patients initially randomised to duloxetine or fluoxetine shows no statistically significant difference in the EAIR between duloxetine and fluoxetine in the overall patient population or within the child or adolescent subgroup. As noted in the discussion of the extension dataset above, even though the actual number of suicide behaviours was greater for duloxetine compared with fluoxetine, the difference between

duloxetine and fluoxetine treatment groups in the exposure adjusted incidence rate was smaller due to greater number of patients exposed to duloxetine.

Table 8.6. Exposure Adjusted Analyses using Data from the Columbia Suicide Severity Rating Scale Acute and Extension Analyses Set

	Duloxetine		Fluoxetine		p-value [a] (DLX vs FLX)
	PY	Events per PY	PY	Events per PY	
Exposure Adjusted TE suicidal ideation					
Overall	148	0.25	107	0.32	.381
Children	57.7	0.26	47.4	0.19	.417
Adolescents	90.2	0.24	59.2	0.42	.080
Exposure Adjusted TE suicidal behaviour					
Overall	156	0.04	114	0.03	.646
Children	61.1	0.08	49.3	0.00	.062
Adolescents	94.7	0.01	64.5	0.05	.176

Abbreviations: DLX = duloxetine; FLX= fluoxetine; PY = patient years; TE = treatment-emergent.
[a] p-value is from Stratified Miettinen and Nurminen method with Cochran-Mantel-Haenszel weights.
Source: SDD – integrations/pedss_peds/programs_stat/tfl_output/fqsuie31.

No new signals were identified with regard to suicide-related events or non-suicidal self-injurious behaviour. Results with regard to the frequency of suicidality (ideation or behaviour) for Studies HMCK and HMCL are fairly consistent with previously published studies of antidepressants in the treatment of children and adolescents with MDD. The SmPC currently contains a class labelling warning for both duloxetine and fluoxetine regarding use in paediatric patients and suicide-related events (ideation, behaviour) (SmPC section 4.4). The recommendation for carefully monitoring of paediatric patients with MDD for the appearance of suicidal symptoms remains a suitably cautious clinical approach.

Overall, no clinically important differences in safety and tolerability findings were noted between duloxetine and fluoxetine except for a higher rate of DC due to an AE with duloxetine, which was driven by nausea. Results of laboratory analyses of mean change and treatment-emergent abnormal values reveal similar mean changes and frequencies of abnormal laboratory values between duloxetine and fluoxetine, but these differences were not considered clinically meaningful. Similarly, with the possible exception of modest mean increase of QTcF interval with fluoxetine, no meaningful differences between duloxetine and fluoxetine were observed from analyses of vital signs and ECG parameters during acute treatment or over the entire study. No new safety signals were identified with regard to suicide-related events (ideation, behaviour) or non-suicidal self-injurious behaviour during acute treatment or extension treatment. Even though the actual number of suicide behaviours was greater for duloxetine compared with fluoxetine, the difference between duloxetine and fluoxetine treatment groups in the exposure adjusted incidence rate was smaller due to greater number of patients exposed to duloxetine.

Rapporteur's comments:

More patients in the duloxetine than the fluoxetine group discontinued due to an adverse events in the acute treatment, principally due to nausea. Discontinuation rates due to an AE remained higher in the

duloxetine group at study endpoint. A higher frequency of nausea and dizziness were reported with duloxetine compared with fluoxetine. These results are consistent with the known profile of duloxetine. Differences between duloxetine and fluoxetine observed in laboratory-related data were not considered clinically meaningful. Differences in results from analyses of vital signs (blood pressure, pulse) and ECGs were small for both duloxetine and fluoxetine in these studies, generally not considered clinically meaningful, and concordant with known safety profile of both compounds. A mean increase in heart rate and a mean decrease in QTcF were observed for the duloxetine group over the 36 weeks of the study (statistically significant compared with fluoxetine).

An exposure adjusted analysis was conducted for suicide-related events including those patients initially randomized to placebo and switched to duloxetine in the extension phase. Suicidal ideation occurred in a similar proportion of patients in all treatment groups and occurred in both children and adolescents, with the frequency being greater in adolescent. In the acute phase the number of events (suicidal ideation or behaviour) per patient years was similar for duloxetine and fluoxetine. During extension treatment the number of suicidal behaviours was greater for duloxetine (2.6%) compared with fluoxetine (0.6%) and placebo/fluoxetine (0.6%).

When the incidence rate was adjusted by exposure, these differences between treatment for the extension-treatment phase were smaller (duloxetine: 0.04 Events per PY; fluoxetine: 0.01 Events per PY; placebo/duloxetine: 0.01 Events per PY). It must be due to greater number of patients exposed to duloxetine. When looking at the exposure adjusted analysis over the 36-week study, no statistically significant differences in the exposure-adjusted incidence rates for suicidal behaviour were observed between duloxetine and fluoxetine in the overall patient population or within the child or adolescent subgroup (duloxetine: 0.04 Events per PY; fluoxetine: 0.03 Events per PY; p=.646). There were not remarkable differences respecting non-suicidal self-injurious behaviour.

The higher numbers of suicidal behaviour in patients treated with duloxetine compared with those receiving fluoxetine can be considered as a safety signal that, although it is not possible to objectively assign to duloxetin, could represent a matter of concern.

In view of all of these uncertainties this information is considered sufficiently relevant for physicians to be included in the SmPC.

Clinical Request 6

The MAH should provide the data regarding monitoring of some key events that has not been discussed in this report:

- Hepatic risk: effect of duloxetine on laboratory parameters and changes in liver enzymes/hepatic adverse events.

- Severe cutaneous reactions

MAH response

1. Hepatic Risk.

In Studies HMCK and HMCL, no patient had an SAE related to laboratory results, and no patient

discontinued due to abnormal laboratory values. A new analysis of spontaneously reported hepatic-related TEAEs was performed using pooled data from HMCK and HMCL. Based on this analysis, few patients were identified who experienced a hepatic-related TEAE during the 36 weeks of either study. Specifically, during the acute phase, 1 patient in each treatment group experienced 1 hepatic-related TEAE: In the duloxetine group, ALT increased; in the fluoxetine group, hepatic steatosis; in the placebo group, hepatic enzyme increased. During the extension phase, 1 (0.6%) patient who continued duloxetine in the extension phase (DLX/DLX group) and 2 (1.1%) patients who continued fluoxetine in the extension phase experienced ALT increase. One patient who switched from placebo to duloxetine for the extension phase experienced ALT increase. An analysis of mean change in chemistry and hematologic laboratory analytes was performed using the acute analyses set. For chemistry analytes related to hepatology, the difference between duloxetine and placebo was statistically significant ($p<.05$) only for GGT (-1.20, -0.32). However, this finding is not considered clinically meaningful since a decrease is not indicative of liver injury. No clinically meaningful differences were noted between duloxetine and fluoxetine. No patients met Hy's Rule criteria. Treatment-emergent ALT $\geqslant$3 times ULN was reported in the extension analyses set for 1 patient in the duloxetine group and 1 patient in fluoxetine group. The patient in the duloxetine group (17 year old male) was initially randomised to placebo and then transitioned to duloxetine for the extension period. The patient had an abnormal ALT value at baseline and experienced a treatment emergent ALT increase to $\geqslant$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. For the patient in the fluoxetine group, a 17 year old male, had a treatment-emergent ALT $\geqslant$3 times ULN that reached levels $\geqslant$5 times during ULN Study Period III. The patient's ALT elevation persisted for approximately 9 weeks reaching a maximum of 216 U/L (5 times ULN) approximately 6 weeks after the initial ALT elevation. The patient's ALT returned to normal at approximately the 28- and 32-week time points while the patient continued on fluoxetine 40 mg QD. Overall, therefore, no new hepatic-related safety concerns for duloxetine were noted within the paediatric population in these studies.

2. Severe Cutaneous Reactions

A standard MedDRA query was performed using the acute and long-term analyses sets. One possible case of Stevens-Johnson Syndrome was identified (this case was reported in the Risk Management Plan (RMP) v9 submitted in October 2011). As summarised in the HMCL Study Report, this 15-year-old male in the duloxetine group was hospitalized for suspected SJS 137 days after starting duloxetine, and discontinued treatment on the day of hospitalization. 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. The patient recovered from the event. The investigator judged the event to be possibly related to the drug. The risk of SJS is already a labeled adverse reaction in the SmPC and an important identified risk noted within the RMP.

Rapporteur's comments:

No new hepatic-related safety concerns for duloxetine were noted within the paediatric population in these studies. One possible case of Stevens-Johnson Syndrome was identified. The risk of SJS is already a labelled adverse reaction in the SmPC.

SmPC Related Request and Responses

The MAH should submit a proposal for the SmPC including modifications in the wording of the following sections: 4.2; 4.4; 4.8; 5.1; 5.2

Please refer to WS0334 procedure (Ariclaim-EMEA/H/C/000552/WS0334/0054/G, Cymbalta-EMEA/H/C/000572/WS0334/0056/G, Xeristar-EMEA/H/C/000573/WS0334/0059/G

Yentreve-EMEA/H/C/000545/WS0334/0043/G -Type II Variation: Safety Update to SmPC and Package Leaflet – Company Core Data Sheet (CCDS) Update & Addition of Clinically Relevant Paediatric Data) for the final SmPC wording.

VI. CONCLUSION

With the responses submitted by the MAH, all questions have now been resolved and this procedure could be considered finalized.

As a positive benefit for paediatric population has not been demonstrated with the submitted studies, the use of duloxetine in the paediatric population is not recommended.

However, changes in the PI other than section 4.1of the SmPC are being considered. These are being assessed within the procedure submitted in parallel: EMEA/H/C/ xxxx/WS/0334/G.