

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204168Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

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NDA:	204168
Related IND:	104483
Generic Name:	Levomilnacipran
Trade Name:	Fetzima®
Strength and Dosage Form:	20 mg, 40 mg, 80 mg, and 120 mg Extended Release Capsules
Sponsor:	Forest Laboratories, Inc.
Indication:	Major Depressive Disorder
Submission Type:	Original NDA
Priority Classification:	Standard
Submission Date:	9/25/2012
OCP Division:	DCP1
OND Division:	DPP
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## 1.0 Executive Summary

The sponsor submitted an application requesting approval for Levomilnacipran, 20 mg, 40 mg, 80 mg and 120 mg Extended Release (ER) capsules for the treatment of Major Depressive Disorder (MDD). Levomilnacipran is the L-isomer present in racemate milnacipran (Savella<sup>®</sup>), which is approved for fibromyalgia. The clinical development program for levomilnacipran HCl consisted of 4 short-term placebo-controlled studies and 2 long-term studies (1 open-label and 1 randomized-withdrawal). Nineteen clinical pharmacology and biopharmaceutics studies, population pharmacokinetic, exposure-response analyses and 14 in vitro studies were included in the application. Office of Clinical Pharmacology (OCP) key findings are summarized as follows:

- Dose Adjustment:
  - Dose of Levomilnacipran ER in moderate renal impaired patients (Cl<sub>cr</sub>: 30 – 59 mL/min) should not exceed 60 mg daily. Levomilnacipran exposure (AUC) in moderate renal impaired patients increased by about 92% when compared to subjects with normal renal function (Cl<sub>cr</sub> ≥ 90 mL/min).
  - Dose of Levomilnacipran ER in severe renal impairment patients (Cl<sub>cr</sub>: < 30 mL/min) should not exceed 40 mg daily. Levomilnacipran exposure (AUC) in severe renal impaired patients increased by about 180% when compared to subjects with normal renal function (Cl<sub>cr</sub> ≥ 90 mL/min).
  - Dose adjustment is not recommended for hepatic impaired patients but caution should be exercised when dosing in severe hepatic impaired patients (Child Pugh C:10 - 15). Levomilnacipran exposure increased by about 30% in severe hepatic patients compared to subjects with normal hepatic function.
  - Levomilnacipran dose should not exceed 80 mg when levomilnacipran is co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole). Ketoconazole increased levomilnacipran exposure (AUC) by about 50%.
- Population Pharmacokinetics and Exposure-Response:
  - The identified dose range is appropriate based on exposure-efficacy and safety analyses.
  - Dose/exposure related changes in diastolic blood pressure, systolic blood pressure and heart rate were observed.
- General Pharmacokinetics and Biopharmaceutics:
  - The relative bioavailability of Levomilnacipran ER with levomilnacipran oral solution as a reference is 92%.
  - The To Be Marketed (TBM) formulation is bioequivalent to the formulation used in the pivotal clinical trials.
  - Levomilnacipran ER can be taken with or without food.
  - Levomilnacipran pharmacokinetics after administration of Levomilnacipran ER suggest it exhibits extended release characteristics.
  - Levomilnacipran pharmacokinetics is proportional to dose between 25 and 120 mg after single dose and 25 – 300 mg once daily after multiple dose administration. The elimination half-life is about 12 hours, protein binding is about 22% and approximately 58% of dosed levomilnacipran is excreted in urine as the unchanged compound.
- Pharmacodynamics:

- Marginal increase in QTc interval at both therapeutic and suprathreshold doses was identified in a thorough QT study with no apparent dose-response relationship.

*1.1 Recommendation*

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutic information submitted in NDA 204168 and supports a recommendation of approval for Levomilnacipran Extended Release capsules for the treatment of Major Depressive Disorder provided an agreement on the label can be reached with the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendations and Comments
Overall	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pending labeling agreements with the sponsor.
Evidence of Effectiveness	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pivotal safety and efficacy trials and supportive trials
Proposed dose for general population	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	The proposed starting dose is 20 mg daily for 2 days. Maintenance dose can be adjusted between 40 to 120 mg daily based on efficacy and tolerability
Proposed dose adjustment in specific patients or patients with comedications	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Recommendations: Levomilnacipran dose should not exceed 40 mg in severe renal impaired patients. Levomilnacipran dose should not exceed 60 mg in moderate renal impaired patients Dose adjustment is not recommended for hepatic impaired patients. Levomilnacipran dose should not exceed 80 mg when co-administered with strong inhibitors of CYP3A4 (e.g. ketoconazole). Dose adjustment of levomilnacipran is not recommended when co-administered with inducers (e.g. carbamazepine). No dose adjustment of levomilnacipran is recommended when levomilnacipran is coadministered with CYP3A4 substrates (e.g. alprazolam).
Pivotal bioequivalence studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	The to-be-marketing and clinical trial formulations are bioequivalent.
Labeling	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA	Pending satisfactory agreement with the sponsor.

## 1.2 Post Marketing Studies

No post-marketing studies are recommended by OCP.

## 1.3 Labeling Recommendations

- Dose of Levomilnacipran ER in moderate renal impaired patients (Clcr: 30 – 59 mL/min) should not exceed 60 mg daily.
- Dose of Levomilnacipran ER in severe renal impairment (Clcr: < 30 mL/min) should not exceed 40 mg daily.
- Dose adjustment is not recommended for hepatic impaired patients but caution should be exercised when dosing in severe hepatic impaired patients (Child Pugh C).
- Levomilnacipran dose should not exceed 80 mg when co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole)
- Dose-related changes in blood pressure and heart rate were found in a 24-day QTc study in healthy volunteers.

## 1.4 Summary of Clinical Pharmacology and Biopharmaceutic Findings

Levomilnacipran (1S, 2R) is the L- isomer in racemate milnacipran (Savella®) which is approved for the management of fibromyalgia. Levomilnacipran is reported to be the more active form of the two isomers (l- and d-milnacipran) present in milnacipran.

### Biopharmaceutics

The relative bioavailability of levomilnacipran after administration of Levomilnacipran Extended Release (ER) capsules with Levomilnacipran oral solution as a reference is about 92%. Administration of Levomilnacipran with food (800 to 1000 calories) did not have a significant effect on the exposure, but T<sub>max</sub> was prolonged by about two hours. The difference in T<sub>max</sub> is not expected to be clinically relevant.

The clinical trial material (CTM) formulation (Levomilnacipran 40 mg) used in the pivotal safety and efficacy trials and clinical pharmacology studies were demonstrated to be bioequivalent to the To Be Marketed (TBM) formulation. Table 1 contains the pharmacokinetic parameters and statistical analysis.

Table 1: Pharmacokinetic Parameters (Mean ± SD) of Levomilnacipran after a Single Oral Administration of 120 mg Levomilnacipran Sustained-Release Capsules in Healthy Subjects

PK Parameter	Treatment A To-Be-Marketed SR 1 x 120 mg (Fasted) (N = 34)	Treatment B Clinical SR 3 x 40 mg (Fasted) (N = 29)	Treatment C To-Be-Marketed SR 1 x 120 mg (Fed) (N = 34)	Statistical Comparison			
				Geometric Means Ratio, %		90% CI	
				Trt A/B	Trt C/A	Trt A/B	Trt C/A
C <sub>max</sub> , ng/mL	234.6 ± 51.9	226.7 ± 47.3	239.6 ± 51.3	100.5	102.3	95.04-106.21	97.13-107.79
AUC <sub>0-t<sub>e</sub></sub> , ng•h/mL	5084.4 ± 900.8	5154.0 ± 918.3	5180.2 ± 925.5	97.5	101.7	94.49-100.7	98.74-104.82
AUC <sub>0-∞</sub> , ng•h/mL	5298.7 ± 1013.0	5317.9 ± 998.6	5345.0 ± 1009.8	98.7	100.8	95.52-101.97	97.74-103.92
T <sub>max</sub> , h <sup>b</sup>	6.0 (4.0, 8.0)	6.5 (5.0, 16.0)	8.0 (5.0, 12.0)	—	—	0.0990 <sup>c</sup>	< 0.0001 <sup>c</sup>
T <sub>1/2</sub> , h	13.9 ± 3.8	12.7 ± 2.9	13.0 ± 2.9	—	—	—	—

### Effect of Intrinsic Factors

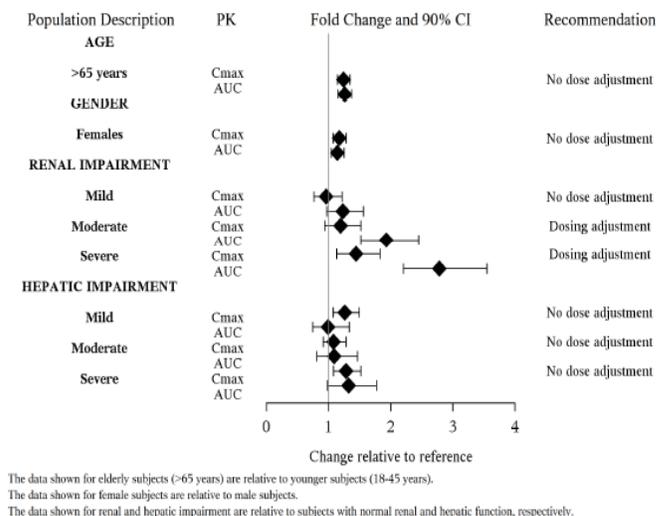
The major intrinsic factors evaluated were renal impairment, hepatic impairment, age, gender and race. Figure 1 depicts the impact of age, gender, renal and hepatic impairment on the exposure (C<sub>max</sub>, AUC) of levomilnacipran. Age and gender did not have a significant effect. Based on population pharmacokinetic analysis, ethnicity/race is not expected to have significant effect on the exposure of levomilnacipran.

Dosage adjustment is only recommended in patients with moderate to severe renal impairment by setting the maximal allowable doses. In the pivotal clinical efficacy and safety trials, patients were only given doses up to 120 mg/day, with no efficacy and safety information for doses beyond 120 mg/day. Even at the dose of 120 mg/day, the trial results suggested not all patients tolerated it well. It has been shown in the fixed dose trial that some patients, who were assigned to 120 mg /day dose group and completed the trial, only reached the dose up to 80 mg/day. In some patients prematurely discontinued from the same trial, the final dose was 80 mg/day or less. Therefore, it is advisable to prevent patients from unnecessarily being exposed to concentration levels with unknown safety profiles and potential tolerability issue.

**Hepatic:** Levomilnacipran exposure (AUC) increased by about 30% in severe hepatic impaired (Child Pugh C: 10 – 15) patients. Dose adjustment is not recommended because the exposure increase is minimal and optimal dose is always titrated for each patient. But caution should be exercised in patients with severe hepatic impairment.

**Renal:** Moderate (Cl<sub>cr</sub> = 30 -59 mL/min) and severe (Cl<sub>cr</sub> < 30 mL/min) renal impairment increased exposure (AUC) of levomilnacipran by 92% and 180%, respectively when compared with subjects with normal (Cl<sub>cr</sub> ≥ 90 mL/min) renal function. Dose adjustment is recommended for moderate and severe renal impaired patients. For moderate renal impaired patients, the dose should not exceed 60 mg daily and for severe renal impaired patients, it should not exceed 40 mg daily.

Figure 1: Impact of Intrinsic Factors on Levomilnacipran after Administration of Levomilnacipran ER

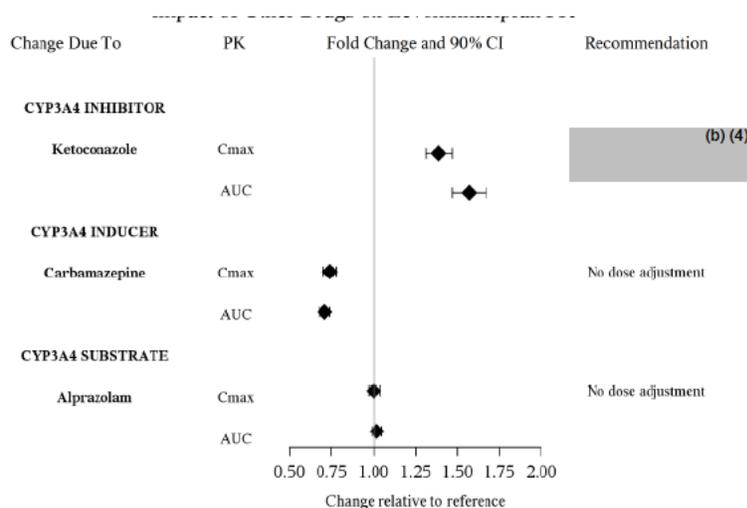


Source: sponsor's clinical pharmacology summary

### Effect of Extrinsic Factors (Drug-Drug Interactions)

Cytochrome P450 (CYP) 3A4 appears to be the major enzyme responsible for the biotransformation of levomilnacipran. Levomilnacipran does not significantly inhibit or induce CYP enzymes ((e.g. CYP 1A2, 2A6, 2C9, 2D6, 3A4/5) or membrane transporters (e.g. P-gp, BCRP, OAT1, OAT1B1). The sponsor evaluated the impact on levomilnacipran exposure when Levomilnacipran ER and either a strong CYP3A4 inhibitor (ketoconazole), an inducer (carbamazepine) or a substrate (alprazolam) was co-administered. The impact of ketoconazole, carbamazepine or alprazolam on the exposure (AUC, Cmax) is presented in Figure 2.

Figure 2: Impact of Other Drugs on Levomilnacipran Pharmacokinetics



Source: Sponsor's Clinical Pharmacology summary

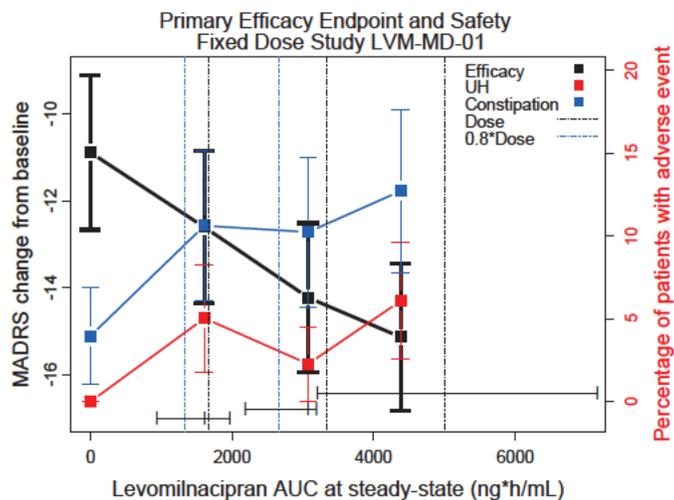
(b) (4)  
the reviewer is recommending that the dose of Levomilnacipran ER should not exceed 80 mg daily when it is administered with strong CYP3A4 inhibitors (e.g. ketoconazole). This recommendation can be understood from the following example. When a patient with a stabilized high dose of levomilnacipran (e.g., 120 mg) starts the treatment with a strong CYP3A4 inhibitor, the final exposure may exceed the average exposure seen under the dose of 120 mg. For the reasons discussed under *Effect of Intrinsic Factors* section, this may lead to potential safety or tolerability concern. Hence, a maximal of 80 mg dose appears to be able to avoid this situation. The decrease in levomilnacipran concentration when administered with carbamazepine is not expected to be clinically relevant. Dose adjustment is not recommended when Levomilnacipran ER is co-administered with carbamazepine or alprazolam.

### Exposure- Response (E-R)

E-R with respect to Efficacy and Adverse Events (AE)

Exposure-response relationship is shown in Figure 3. The exposure is steady-state AUC of mean daily levomilnacipran dose, the efficacy response is change from baseline in MADRS scores, and the safety response is the percentage of patients who experienced adverse events.

Figure 3: Primary Efficacy Scores (Black Lines and 95% CI Bars against Left Y axis) and Moderate/Severe Adverse Event Rates (Red Lines and 95% CI Bars against Right Y Axis) versus Levomilnacipran Exposure (X axis) in Major Depressive Disorder Patients in Study LVM-MD-01

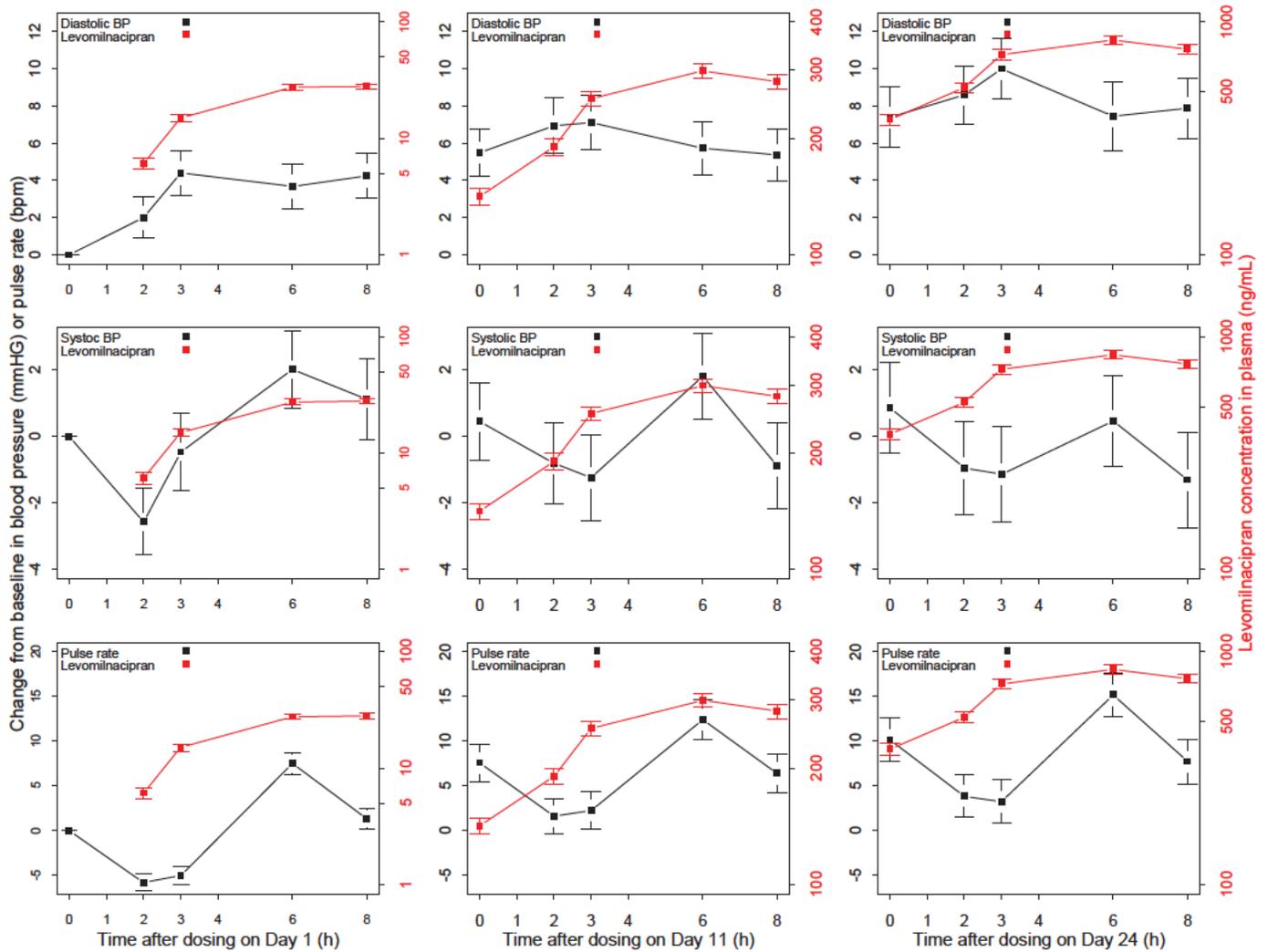


AEs: adverse events; AUCs: area under levomilnacipran concentration-time curve at steady-state; CI: confidence interval; MADRS: Montgomery Åsberg Depression Rating Scale; UH: urine hesitation  
 Source: exposure-response analysis of the Pharmacometrics Division

*E-R with respect to blood pressure and heart rate*

Dose related changes in diastolic blood pressure, systolic blood pressure and heart rate (or pulse rate) were observed in a 24-day QTc study in healthy volunteers (Figure 4).

Figure 4: Vital sign change from baseline versus plasma levomilnacipran concentration on Days 1, 11 and 24 for Doses of 20, 120 and 300 mg QD levomilnacipran (N=400) in Study LVM-PK-07



*Population Pharmacokinetics*

The sponsor conducted a population pharmacokinetic (PopPk) analysis using data from adults. The PopPk model developed is acceptable and may be used for further dosage determination in pediatric patients.

## *Absorption, Distribution, Metabolism and Excretion (ADME)*

### *Absorption*

The relative bioavailability of levomilnacipran after administration of Levomilnacipran Extended Release (ER) capsules with Levomilnacipran oral solution as a reference is about 92%. Pharmacokinetic profiles of levomilnacipran following the administration of Levomilnacipran ER and Levomilnacipran oral solution suggest that the ER formulation has extended release characteristic. This observation is supported by the half-life of 4-6 hours reported for levomilnacipran when administered as immediate release racemate, milnacipran (Savella®).

Single dosing of Levomilnacipran ER displayed a dose proportional increase in C<sub>max</sub> and AUC over the dose range of 25 to 120 mg. After multiple dose administration, a dose proportional increase in C<sub>max,ss</sub>, AUC(0-τ) and C<sub>min,ss</sub> was observed over a dose range 25 – 300 mg once daily. Steady state is reached by Day 4 following once daily dosing of Levomilnacipran ER.

### *Distribution*

Levomilnacipran is 22% bound to human plasma proteins.

### *Metabolism*

Levomilnacipran is metabolized to N-Desethyl Levomilnacipran, the major inactive metabolite, and other minor metabolites. CYP 3A4 is the major enzyme involved in this metabolism.

### *Excretion*

After oral administration of [14C]-levomilnacipran hydrochloride, renal excretion was the major elimination route of the dose. Total excretion of radioactivity in urine and feces was 93.6% and 3.8%, respectively. Approximately 58% of dosed levomilnacipran is excreted in urine as unchanged levomilnacipran, 18% as N-desethyl levomilnacipran (F17400), and each of the other metabolites less than 5%. The terminal elimination half-life for levomilnacipran after administration of Levomilnacipran ER was approximately 12 -13 hours.

## **2.0 Question Based Review (QBR)**

### 2.1 General Attributes

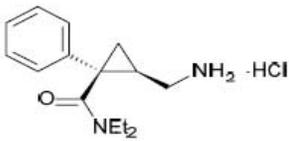
#### *2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

The sponsor submitted an original New Drug Application (NDA) for Levomilnacipran hydrochloride, Extended Release capsules for the treatment of major depressive disorder (MDD). Levomilnacipran (1S, 2R) is the levo- isomer of the two enantiomers present in the racemate Savella® (milnacipran), which was approved in 2009 for the management of fibromyalgia. Levomilnacipran is the more active form of the two isomers present in racemate milnacipran. The clinical development program for levomilnacipran HCl consisted of 5 short-term

placebo-controlled studies and 2 long-term studies (1 open-label and 1 randomized-withdrawal). Nineteen clinical pharmacology and biopharmaceutics studies, population pharmacokinetic and exposure-response analyses and 14 in vitro studies were included in the submission.

*2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?*

Levomilnacipran chemically is (1S, 2R)-2-(Aminomethyl)-N,N-diethyl-1-Phenylcyclopropanecarboxamide hydrochloride. It has the following properties

<i>Molecular Formula:</i>	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O·HCl
<i>Molecular Weight:</i>	282.81 g/mol
<i>Structural Formula:</i>	
<i>Log D:</i>	-0.39 (pH7.4)
<i>Solubility:</i>	> 5 mg/mL
<i>pKa:</i>	9.6

Source: Sponsor's Clinical Pharmacology Summary

The sponsor has developed and seeking approval for Levomilnacipran Extended Release (ER) capsules in the strengths of 20 mg, 40 mg, 80 mg and 120 mg. Table 2 contains the composition of the To Be Marketed (TBM) formulation.

Table 2: Composition of Levomilnacipran ER To-Be-Marketed Formulations

Ingredients	Function	% (w/w)	Quantity Unit (mg/capsule)				
			20 mg	40 mg	80 mg	120 mg	
Levomilnacipran HCl (F2695)	Drug substance	(b) (4)	23.0 <sup>b</sup>	45.9 <sup>b</sup>	91.8 <sup>b</sup>	137.8 <sup>b</sup>	
Sugar spheres, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Povidone, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Talc, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Ethylcellulose, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Triethyl citrate, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
<b>Total Filled Weight</b>	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
<b>Total Capsule Weight</b>	(b) (4)	—	—	89	148	264	379

<sup>b</sup> Expressed as hydrochloride equivalent to 20 mg, 40 mg, 80 mg and 120 mg base, respectively.

(b) (4)

Source: Sponsor's Clinical Overview

### 2.1.3 What are the proposed mechanism (s) of action and therapeutic indication(s)?

Levomilnacipran inhibits both norepinephrine (NE) and 5-hydroxytryptamine (serotonin [5-HT]) reuptake in vitro and in vivo and is approximately 2-fold more potent at inhibiting NE reuptake than 5-HT reuptake transporters.

Levomilnacipran ER 40 to 120 mg once daily is indicated for the treatment of major depressive disorder (MDD).

### 2.1.4 What are the proposed dosage and route of administration?

The recommended dose range for levomilnacipran is 40 mg to 120 mg once daily. Levomilnacipran should be initiated at 20 mg once daily for 2 days and then increased to 40 mg once daily. Based on efficacy and tolerability, levomilnacipran may then be increased in increments of 40 mg at intervals of 2 or more days. The maximum recommended dose is 120 mg once daily.

### 2.1.5 What drugs (substances, products) indicated for the same indication are approved in the US?

Table 3 contains examples of drugs that are approved for the treatment of major depressive disorder (MDD).

Table 3: Drugs Indicated for the Treatment of Major Depressive Disorder

<i>Pharmacologic Category</i>	<i>Brand Name (Generic Name)</i>	<i>Indication</i>
Aminoketone	Wellbutrin <sup>®</sup> (bupropion hydrochloride)	Treatment of major depressive disorder
Atypical Antipsychotic Agent	Abilify <sup>®</sup> (aripiprazole)	Adjunctive therapy to antidepressants for the treatment of major depressive disorder
Atypical Antipsychotic Agent	Seroquel XR <sup>®</sup> (quetiapine fumarate)	Adjunctive therapy to antidepressants for the treatment of major depressive disorder
Serotonin and Norepinephrine Reuptake Inhibitor	Cymbalta <sup>®</sup> (duloxetine hydrochloride)	Treatment of major depressive disorder
Serotonin and Norepinephrine Reuptake Inhibitor	Pristiq <sup>®</sup> (desvenlafaxine)	Treatment of major depressive disorder
Serotonin and Norepinephrine Reuptake Inhibitor	Effexor (venlafaxine)	Treatment of major depressive disorder
Selective Serotonin Reuptake Inhibitor	Celexa <sup>®</sup> (citalopram hydrobromide)	Treatment of depression.
Selective Serotonin Reuptake Inhibitor	Lexapro <sup>®</sup> (escitalopram oxalate)	Acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age
Selective Serotonin Reuptake Inhibitor	Paxil <sup>®</sup> (paroxetine hydrochloride)	Treatment of major depressive disorder
Selective Serotonin Reuptake Inhibitor	Pexeva <sup>®</sup> (paroxetine mesylate)	Treatment of major depressive disorder
Selective Serotonin Reuptake Inhibitor	Prozac <sup>®</sup> (fluoxetine hydrochloride)	Acute and maintenance treatment of Major Depressive Disorder in adult patients and in pediatric patients aged 8 to 18 years

<i>Pharmacologic Category</i>	<i>Brand Name (Generic Name)</i>	<i>Indication</i>
Selective Serotonin Reuptake Inhibitor/5-HT <sub>1A</sub> Receptor Partial Agonist	Viibryd <sup>™</sup> (vilazodone hydrochloride)	Treatment of major depressive disorder
Selective Serotonin Reuptake Inhibitor	Effexor (venlafaxine)	Treatment of major depressive disorder
Selective Serotonin Reuptake Inhibitors and Atypical Antipsychotic Agent	Symbyax <sup>®</sup> (olanzapine and fluoxetine hydrochloride)	Acute treatment of treatment resistant depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode)
Selective Serotonin Reuptake Inhibitor	Zoloft <sup>®</sup> (sertraline hydrochloride)	Major depressive disorder
Tricyclic antidepressant	Pamelor <sup>™</sup> (Nortriptyline)	Relief of symptoms of depression
Tricyclic antidepressant	Amitriptyline	Relief of symptoms of depression
Tetracyclic	Remeron <sup>®</sup> , RemeronSolTab <sup>®</sup> (mirtazapine)	Treatment of major depressive disorder

Source: Sponsor's Reviewer's Guide

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The effectiveness of levomilnacipran for the treatment of MDD was evaluated in 4 studies: 3 pivotal studies (LVM-MD-01, LVM-MD-10, and LVM-MD-03) conducted in the United States and Canada, and 1 supportive study (F02695 LP 2 02) conducted outside of the United States.

All 4 studies were placebo-controlled; no active comparator was included in these studies. Two of the studies were fixed-dose studies (LVM-MD-01: placebo, levomilnacipran 40, 80, and 120 mg/day and LVM-MD-10: placebo, levomilnacipran 40 and 80 mg/day) and 2 of the studies were flexible-dose studies (LVM-MD-03: placebo, levomilnacipran 40 to 120 mg/day and F02695 LP 2 02: placebo, levomilnacipran 75 to 100 mg/day). Clinical pharmacology studies including pharmacokinetic (PK) characterization, effect of intrinsic factors (e.g. renal and hepatic impairment), effect of extrinsic factors (e.g. ketoconazole, carbamazepine), and thorough QT study were conducted. A tabular listing providing a description of the pivotal clinical pharmacology and biopharmaceutics studies, clinical safety and efficacy studies are provided in the Appendix.

*2.2.2 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies*

The changes from baseline to endpoints in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and in the Sheehan Disability Scale (SDS) total score were used to assess effectiveness. The endpoints for Clinical Pharmacology studies were plasma and/or urine concentrations of levomilnacipran and /or metabolites measured by validated bioanalytical methods.

*2.2.3 What was the design features of the pivotal efficacy and safety trials*

The design features of the pivotal efficacy and safety trials are summarized in Table 4.

Table 4: Clinical Efficacy and Safety Trials

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>GROUP 1: SHORT-TERM, PLACEBO-CONTROLLED STUDIES IN PATIENTS WITH MDD</b>									
<b>Group 1A: US Short-term, Placebo-Controlled Studies</b>									
<i>Fixed-dose studies</i>									
Efficacy, safety, tolerability	LVM-MD-01	5.3.5.1	Evaluate the efficacy, safety, and tolerability of fixed doses of F2695 SR compared with placebo in the treatment of adult patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in 4 treatment groups; placebo control	F2695 SR 20-mg NT capsules; F2695 SR 40-mg NT capsules 4 parallel treatment groups: placebo, F2695 40 mg, F2695 80 mg, F2695 120 mg, all once daily. Patients fixed titrated to target dose	724	Patients with MDD	11 weeks: up to 1 week screening, 8 weeks double-blind treatment, 2 weeks down-taper	Complete Full
Efficacy, safety, tolerability	LVM-MD-10	5.3.5.1	Evaluate the efficacy, safety, and tolerability of fixed doses of F2695 SR compared with placebo in the treatment of adult patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study; placebo control	LVM SR 20- and 40-mg capsules Patients were assigned to placebo, LVM 40 mg, or LVM 80 mg once daily. The starting dose for patients randomized to the LVM groups was 20 mg. Patients were fixed-dose titrated to the target doses over a 7-day period	568	Patients with MDD	10 weeks: up to 1 week screening, 8 weeks double-blind treatment, 1 week down-taper	Complete Full

Flexible-dose studies									
Efficacy, safety, tolerability	LVM-MD-02	5.3.5.1	Evaluate the efficacy, safety, and tolerability of F2695 SR versus placebo in the treatment of patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study with 2 treatment groups; placebo control	F2695 SR 20-mg and 40-mg NT capsules Patients assigned to F2695 SR received 20 mg on Days 1 and 2 and 40 mg/day starting on Day 3. Dosage may have been increased from 40 to 80 mg/day at Visit 3 or Visit 4. At Visit 5, the dosage may have been increased from 40 to 80 mg/day or from 80 to 120 mg/day, based on response and tolerability	362	Patients with MDD	11 weeks; up to 1 week screening, 8 weeks double-blind treatment, 2 weeks down-taper	Complete Full
Efficacy, safety, tolerability	LVM-MD-03	5.3.5.1	Evaluate the efficacy, safety, and tolerability of F2695 SR versus that of placebo in the treatment of patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study; placebo control	F2695 SR 20- and 40-mg capsules Patients assigned to F2695 SR received 20 mg/day on Days 1 and 2 and 40 mg/day starting on Day 3. Dosage may have been increased from 40 to 80 mg/day at Visit 3 or Visit 4. At Visit 5, the dosage may have been increased from 40 to 80 mg/day or from 80 to 120 mg/day, based on response and tolerability	442	Patients with MDD	11 weeks; up to 1 week screening, 8 weeks double-blind treatment, 2 weeks down-taper	Complete Full

a N = number of subjects who received at least 1 dose of investigational product (safety population)

b Dose (mg) refers to the dose of levomilnacipran free base

AE = adverse events; AUC<sub>0-∞</sub> = area under the curve; AUC<sub>0-t</sub> = steady-state area-under-the-curve; BA = bioavailability; BE = bioequivalence; BID = twice daily; CL/F = apparent clearance; CGI-I = Clinical Global Impressions-Improvement (scale); CGI-S = Clinical Global Impressions-Severity (scale); C<sub>max,ss</sub> = peak plasma concentration; C<sub>min,ss</sub> = trough plasma concentration; CRCL = Creatinine Clearance; DBP = diastolic blood pressure; F = bioavailability; HAMD-17 = Hamilton Rating Scale for Depression, 17 items; HR = pulse rate; IR = immediate release (formulation); IV = intravenous; Ka = absorption rate constant; MADRS-CR = Montgomery-Åsberg Depression Rating Scale-Clinician Rated; MADRS-SR = Montgomery-Åsberg Depression Rating Scale-Self Rated; MD = multiple dose; MEI-SF = Motivation and Energy Inventory-Short Form; (LVM = levomilnacipran; PD = pharmacodynamic; PK = pharmacokinetic; PopPK = Population Pharmacokinetic; PKPD = Population Pharmacokinetic/Pharmacodynamic; RR = the time elapsing interval between two consecutive R waves in the electrocardiogram; SBP = systolic blood pressure; SD = single dose; SDS = Sheehan Disability Scale; SR = sustained release (formulation); ΔΔQTcNi = least square means difference of QTc from placebo for change from time-matched baseline after drug treatment using individual linear correction for RR, ΔΔQTcF = least square means difference of QTc from placebo for change from time-matched baseline after drug treatment using the Fridericia's formula for RR; ΔΔQTcL = least square means difference of QTc from placebo for change from time-matched baseline after drug treatment using logarithm transformed QT for logarithm transformed RR correction individually; VAS = Visual Analog Scale; V<sub>d</sub>/F = apparent volume of the central compartment.

Source: Sponsor's Clinical Overview

## 2.2.4 What are the evidences of efficacy provided by the sponsor in support of the application?

Tables 5 and 6 contain the results of the safety and efficacy trials based on the sponsor's analysis. Refer to FDA review for Agency's analysis and conclusions.

Table 5: Primary Efficacy Parameter: Change from Baseline in the MADRS Total Score (MMRM) – ITT Population

	<i>Baseline Mean ± SD</i>	<i>Change LS mean (SE)</i>	<i>LSMD (95% CI)</i>	<i>P-Value<sup>a</sup></i>
<b>LVM-MD-01</b>				
Placebo	35.6 ± 4.5	-11.6 (0.97)	—	—
40 mg/day	36.0 ± 4.1	-14.8 (0.99)	-3.23 (-5.92, -0.54)	0.0186
80 mg/day	36.1 ± 3.9	-15.6 (1.00)	-3.99 (-6.69, -1.29)	0.0038
120 mg/day	36.0 ± 3.9	-16.5 (1.02)	-4.86 (-7.59, -2.12)	0.0005
<b>LVM-MD-10</b>				
Placebo	31.0 ± 3.8	-11.3 (0.77)	—	—
40 mg/day	30.8 ± 3.4	-14.6 (0.79)	-3.30 (-5.46, -1.15)	0.0027
80 mg/day	31.2 ± 3.5	-14.4 (0.79)	-3.14 (-5.29, -0.99)	0.0043
<b>LVM-MD-03</b>				
Placebo	35.2 ± 3.8	-12.2 (0.78)	—	—
40-120 mg/day	35.0 ± 3.6	-15.3 (0.79)	-3.10 (-5.26, -0.94)	0.0051
<b>F02695 LP 2 02</b>				
Placebo	30.5 ± 3.7	-14.5 (0.56)	—	—
75-100 mg/day	30.9 ± 4.1	-18.7 (0.56)	-4.2 (-5.7, -2.6)	< 0.0001

Note: Endpoint was Week 8 in the 3 pivotal Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in the supportive Study F02695 LP 2 02.

a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SE = standard error.

Source: Sponsor's Efficacy Summary

Table 6: Secondary Efficacy Parameter: Change from Baseline in the SDS Total Score (MMRM) – ITT Population

	<i>Baseline Mean ± SD</i>	<i>Change LS mean (SE)</i>	<i>LSMD (95% CI)</i>	<i>P-Value<sup>a</sup></i>
<b>LVM-MD-01</b>				
Placebo	21.5 ± 4.8	-7.2 (0.74)	—	—
40 mg/day	21.1 ± 4.8	-8.6 (0.75)	-1.41 (-3.42, 0.60)	0.1687
80 mg/day	21.4 ± 4.9	-9.7 (0.77)	-2.51 (-4.54, -0.49)	0.0151
120 mg/day	21.3 ± 5.0	-9.7 (0.78)	-2.57 (-4.62, -0.52)	0.0141
<b>LVM-MD-10</b>				
Placebo	16.4 ± 6.1	-5.4 (0.66)	—	—
40 mg/day	16.7 ± 6.6	-7.3 (0.68)	-1.83 (-3.62, -0.03)	0.0459
80 mg/day	17.6 ± 6.0	-8.2 (0.66)	-2.72 (-4.49, -0.95)	0.0028
<b>LVM-MD-03</b>				
Placebo	19.7 ± 5.2	-5.4 (0.57)	—	—
40-120 mg/day	20.1 ± 5.0	-8.0 (0.58)	-2.63 (-4.19, -1.07)	0.0010
<b>F02695 LP 2 02</b>				
Placebo	20.8 ± 3.8	-7.7 (0.44)	—	—
75-100 mg/day	21.3 ± 3.9	-11.1 (0.43)	-3.4 (-4.6, -2.2)	< 0.0001

Note: Endpoint was Week 8 in the 3 pivotal Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in the supportive Study F02695 LP 2 02.

a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error.

Source: Sponsor's Efficacy Summary

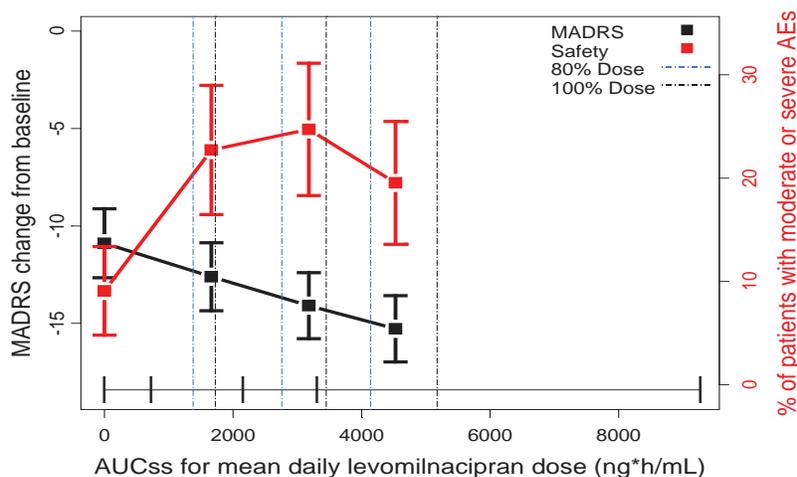
The sponsor reported that clinical efficacy for levomilnacipran 40 to 120 mg/day was demonstrated in 4 adequate and well-controlled studies in patients with MDD using the change from baseline in the MADRS total score and in the SDS total score (Tables 5 and 6). In the fixed-dose Study LVM-MD-01, which included all 3 doses of levomilnacipran (40, 80, and 120 mg/day), showed the effect of levomilnacipran was dose dependent, with increasing doses demonstrating increased efficacy (Refer to medical review for Agency's conclusions)

## 2.2.5 Exposure-Response

### 2.2.5.1 Is there evidence of an exposure-response relationship (dose-response, concentration-response) for efficacy or safety of Levomilnacipran?

Exposure-response relationship in the patient population of Study LVM-MD-01 conducted by the pharmacometric reviewer is shown in Figure 5. The exposure is steady-state AUC of mean daily levomilnacipran dose, the efficacy response is change from baseline in MADRS scores, and the safety response is the percentage of patients who experienced adverse events. Exposure Quartiles 1, 2, 3 and 4 in Figure 5 approximately represent the following 4 treatment arms: placebo, 10-40 mg, 41-80 mg and 81-120 mg QD levomilnacipran, respectively. The analyses showed that MADRS change (mean ± 95% CI) from the baseline for Quartiles 1-4 were -10.9±1.8 (n=176), -12.6±1.7 (n=176), -14.1± 1.7 (n=178) and -15.3± 1.7 (n=174), respectively. In addition, proportion of patients experienced moderate or severe adverse events (AEs) were 9.1±4.3%, 22.7±6.3%, 24.7±6.4% and 19.5±6.0% for Quartiles 1-4, respectively.

Figure 5: Primary Efficacy Scores (Black Lines and 95% CI Bars against Left Y Axis) and Moderate/Severe Adverse Event Rates (Red Lines and 95% CI Bars against Right Y Axis) versus Levomilnacipran Exposure (X Axis) in Major Depressive Disorder Patients in Study LVM-MD-01



AEs: adverse events; AUCss: area under levomilnacipran concentration-time curve at steady-state; CI: confidence interval; MADRS: Montgomery Åsberg Depression Rating Scale

Source: Pharmacometric Review

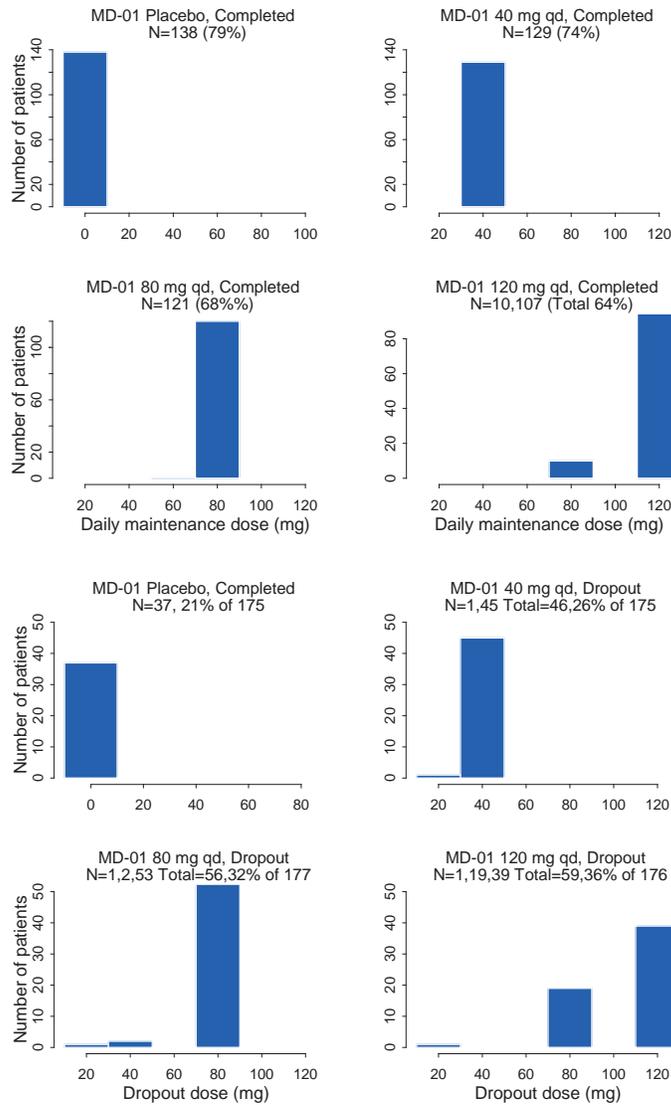
The sponsor reported that in the fixed-dose Study LVM-MD-01 (Table 7), which included all 3 doses of levomilnacipran (40, 80, and 120 mg/day), there was a dose-response effect with a higher magnitude of symptom improvement with increases in levomilnacipran dose. The sponsor reported that, the following AEs were examined for a relationship with exposure: nausea, vomiting, dizziness, headache, hyperhidrosis, constipation, dry mouth, urinary hesitation, and erectile dysfunction/related events. Two separate time-frames were examined: the initial run-in period of Days 1 and 2, when AEs were most frequent, and after Day 2. Most AEs examined in each time-frame did not show a relationship between exposure and incidence. Some statistically significant relationships between AE incidence and exposures were found, in alignment with the drug's mechanism of action and need for initial titration. For Days 1 and 2 of treatment, only nausea showed a relationship with exposure that was statistically significant and consistent with the observed data. In the maintenance phase, constipation and male urinary hesitation showed statistically significant relationships with exposure. However, their predicted absolute increases in incidence over the dose range of 40 to 120 mg were modest (< 7%).

2.2.5.2 *Is the proposed once daily dose of 40-120 mg levomilnacipran, by the sponsor, appropriate for major depressive disorder (MDD) patients?*

The proposed once daily dose of 40-120 mg Levomilnacipran ER is appropriate for major depressive disorder patients.

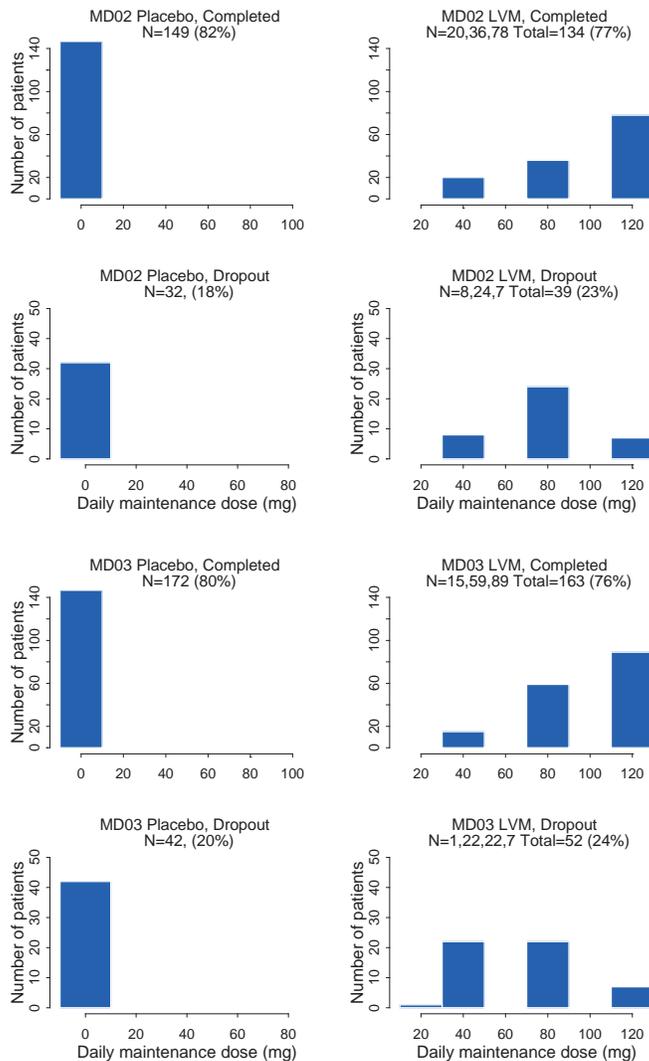
Figure 6: The distribution of mean daily levomilnacipran dose for patients of Study LVM-MD-01,

with Y axes represent frequencies of patients, X axes represents mean daily doses of levomilnacipran in mg for the duration of Days 8-56, and sub-titles represent treatment arms and outcomes



Source: Pharmacometric review

Figure 7: The distribution of mean daily levomilnacipran dose for patients of Study LVM-MD-02 and 03, with Y axes represent frequencies of patients, X axes represents mean daily doses of levomilnacipran in mg for the duration of Days 7-56, and sub-titles represent treatment arms and outcomes

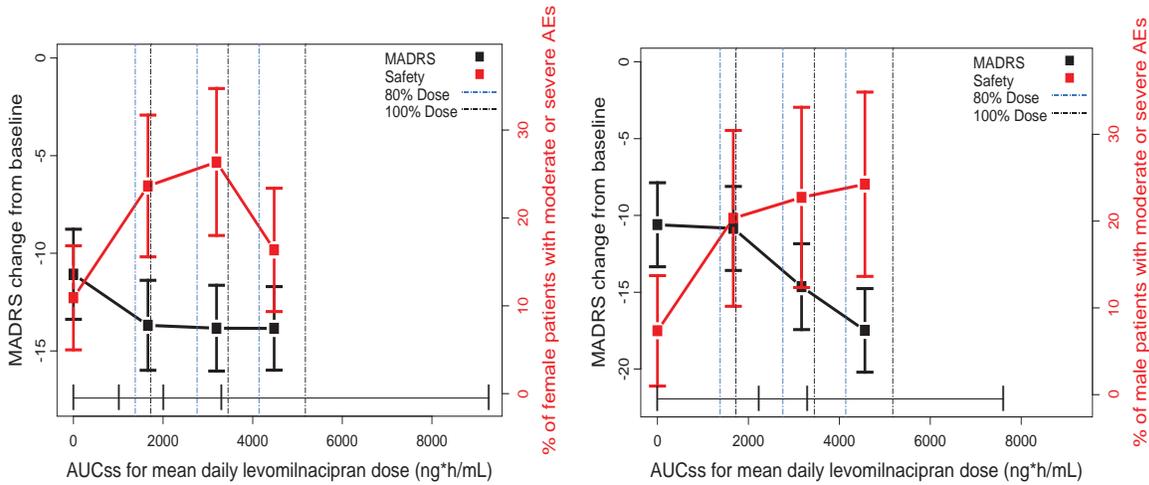


Source: Pharmacometric review

### 2.2.5.3 Is the exposure-response relationship for efficacy and safety endpoints similar by gender and race in major depressive disorder (MDD) patients?

Exposure-response relationship for efficacy and safety endpoints of levomilnacipran appears to be different based on gender (Figure 4) and race (Figure 5). It is not clear if there are any potential factors that can further explain these differences. At the current stage, the difference patterns of exposure-response relationships on efficacy and safety observed from different gender or race groups do not lead to further recommendations on dose adjustment.

Figure 8: Primary Efficacy Scores (Black Lines and 95% CI Bars Against Left Y Axis) and Moderate/Severe AE Rates (Red Lines and 95% CI Bars Against Right Y Axis) versus Levomilnacipran Exposure (X Axis) in Major Depressive Disorder Patients by Sex in Study LVM-MD-01

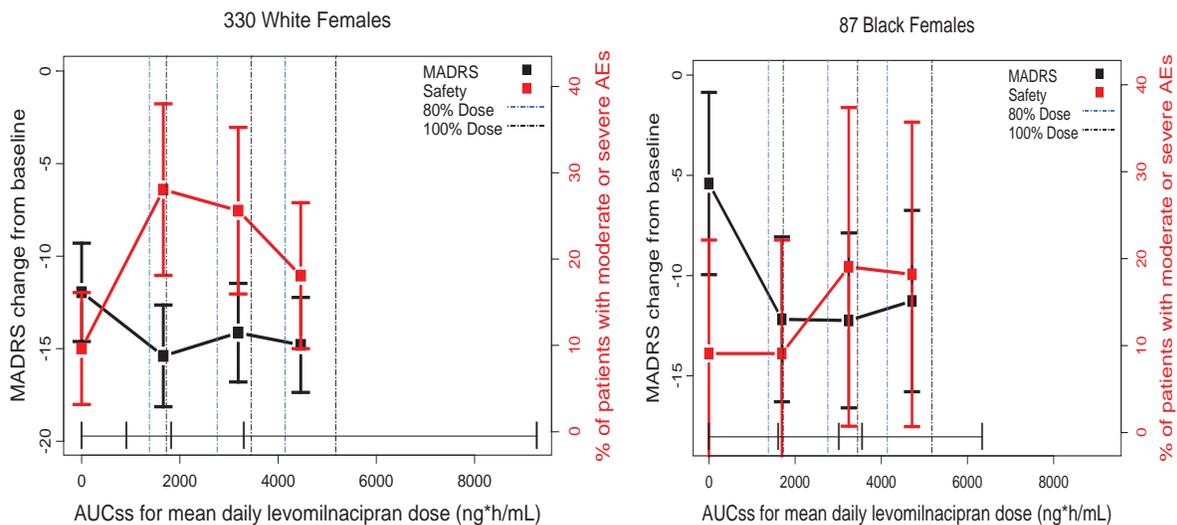


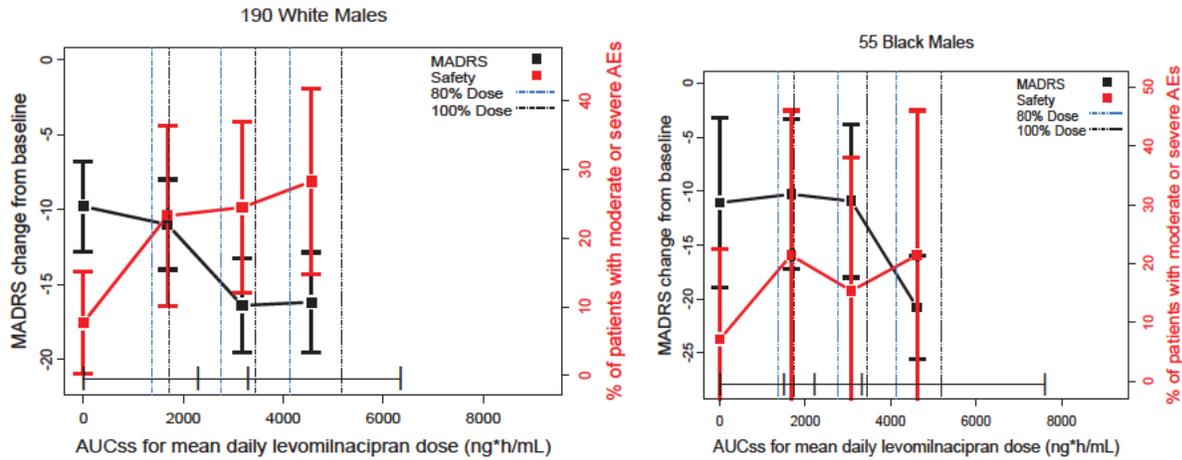
AEs: adverse events; AUCss: area under concentration-time curve at steady-state; CI: confidence interval; MADRS: Montgomery Åsberg Depression Rating Scale

Source: Pharmacometric review

Further, exposure-response relationship for both MADRS and AEs appeared different between white and black patients for each gender as shown in Figure 9.

Figure 9: Primary efficacy scores (black lines and 95% CI bars against left Y axis) and adverse event rates (red lines and 95% CI bars against right Y axis) versus levomilnacipran exposure (X axis) in patients with major depressive disorder by race and sex in Study LVM-MD-01





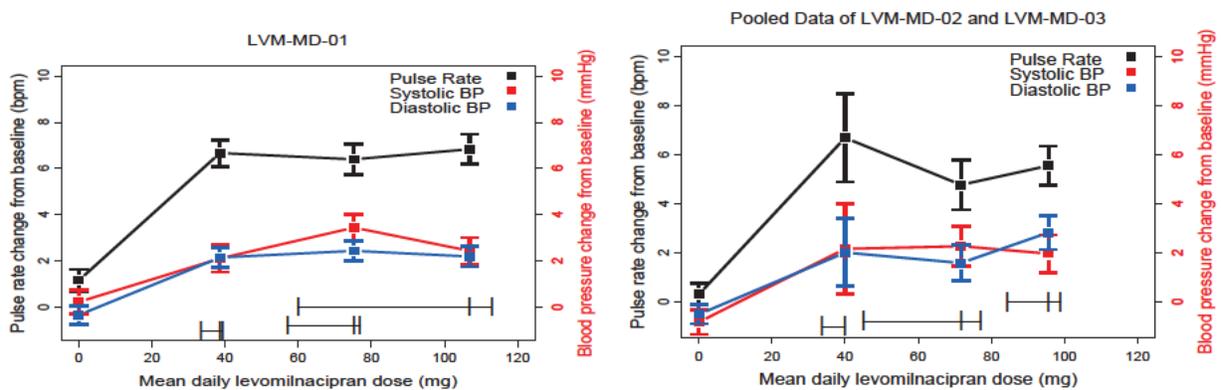
Source: Pharmacometric review

*2.2.5.4 Is there a relationship between levomilnacipran dose and changes in vital signs such as blood pressure, heart rate?*

In Phase III studies, for patients treated with placebo, the change from baseline of vital sign (pulse rate, systolic blood pressure and diastolic blood pressure) was negligible. For patients treated with levomilnacipran, the change from baseline of vital sign (pulse rate, systolic blood pressure and diastolic blood pressure) was similar amongst the dose range of 40 mg to 120 mg QD.

The relationship between dose and vital sign change from baseline is shown in Figure 6. The data for the Figure 6 were the mean results of 713 patients of Study LVM-MD-01, and 357 patients of Studies LVM-MD-02 and 03.

Figure 6: Pulse Rate Change From Baseline (Black Lines and 95% CI Bars Against Left Y Axis) and Blood Pressure Change from Baseline (Red, Blue lines and 95% CI Bars Against Right Y axis) versus Levomilnacipran Mean Dose (X Axis) in Major Depressive Disorder Patients of Phase III studies

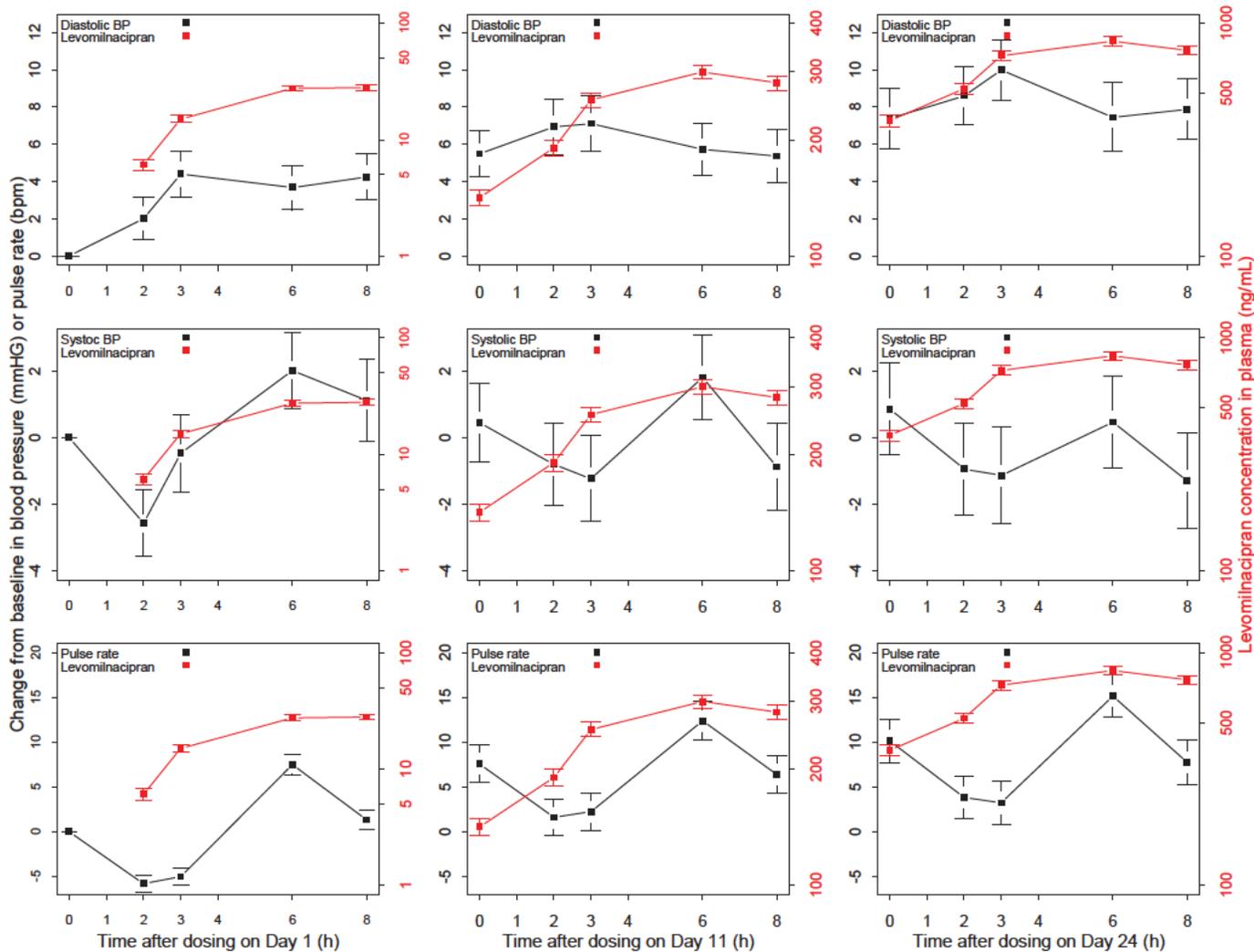


CI: confidence interval; The vertical bars represent 95% CI of the vital sign changes from baselines with mean change in the middle; The horizontal bars represent minimum and maximum dose with median dose in the middle.

Source: Pharmacometric review

Dose related changes in diastolic blood pressure, systolic blood pressure and heart rate (or pulse rate) were observed in Study LVM-PK-07 (Evaluation of the effects of sequential multiple-dose regimens of levomilnacipran on cardiac repolarization in healthy subjects). The findings are shown in Figure 7. Diastolic blood pressure (DBP), systolic blood pressure (SBP), and heart rate (HR) increased with levomilnacipran dose.

Figure 10: Vital sign change from baseline versus plasma levomilnacipran concentration on Days 1, 11 and 24 for Doses of 20, 120 and 300 mg QD levomilnacipran (N=400) in Study LVM-PK-07



Source: Pharmacometric review

Table 7: Vital Sign Change from Baseline at the Selected Time Point for Different Dose Levels (Mean ± 95% CI) of Study LVM-PK-07

Vital Sign	Time after Current Dose (h)	Change from Baseline		
		Day 1 Dose=20 mg	Day 11 Dose=120 mg	Day 24 Dose=300 mg
DBP (mmHG)	3	4.4 ± 1.2	7.1 ± 1.5	10.0 ± 1.8
SBP (mmHG)	0	0.0 ± 0.0	0.5 ± 1.2	0.9 ± 1.4
HR (bpm)	6	7.5 ± 1.2	12.4 ± 2.1	15.2 ± 2.4

DBP, diastolic blood pressure; SBP, systolic blood pressure; HR: heart rate; N, number of subjects contributed measurements to the mean data; Dose: levomilnacipran dose on Day 1 or at steady-state. Data are extracted from figure 7 at the corresponding time points.

**Dosing Schedule:** placebo for 2 days, LVM 20 mg for 1 day, 40 mg for 3 days, 80 mg for 3 days, 120 mg for 4 days, 160 mg for 3 days, 200 mg for 3 days, 260 mg for 3 days, and 300 mg for 4 days, placebo for 1 day.

#### 2.2.5.5 Does this drug prolong the QT or QTc interval?

Base on QT-IRT review, levomilnacipran marginally prolongs QTc interval. The QT effect following the administration of levomilnacipran HCl was evaluated in a thorough QT study (Study LVM-PK-07). Marginal QTc prolongation effect of 120 mg and 300 mg levomilnacipran HCl with no apparent dose-response relationship was detected in Study LVM-PK-07. The largest upper bounds of the 2-sided 90% CI for the mean difference between levomilnacipran 120 mg and placebo, and between levomilnacipran 300 mg and placebo were 10.8 and 10.5 ms observed at 8 and 16 hours post-dose, respectively.

In this randomized, blinded, parallel-crossover study, 170 healthy subjects received levomilnacipran HCl, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in Table 8.

Table 8: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Levomilnacipran HCl and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Levomilnacipran 120 mg	8	7.3	(3.9, 10.8)
Levomilnacipran 300 mg	16	7.5	(4.5, 10.5)
Moxifloxacin 400 mg*	3	9.5	(7.4, 11.6)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 6.6 ms.

Source: IRT QT Review team

## 2.3 General Pharmacokinetics

2.3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

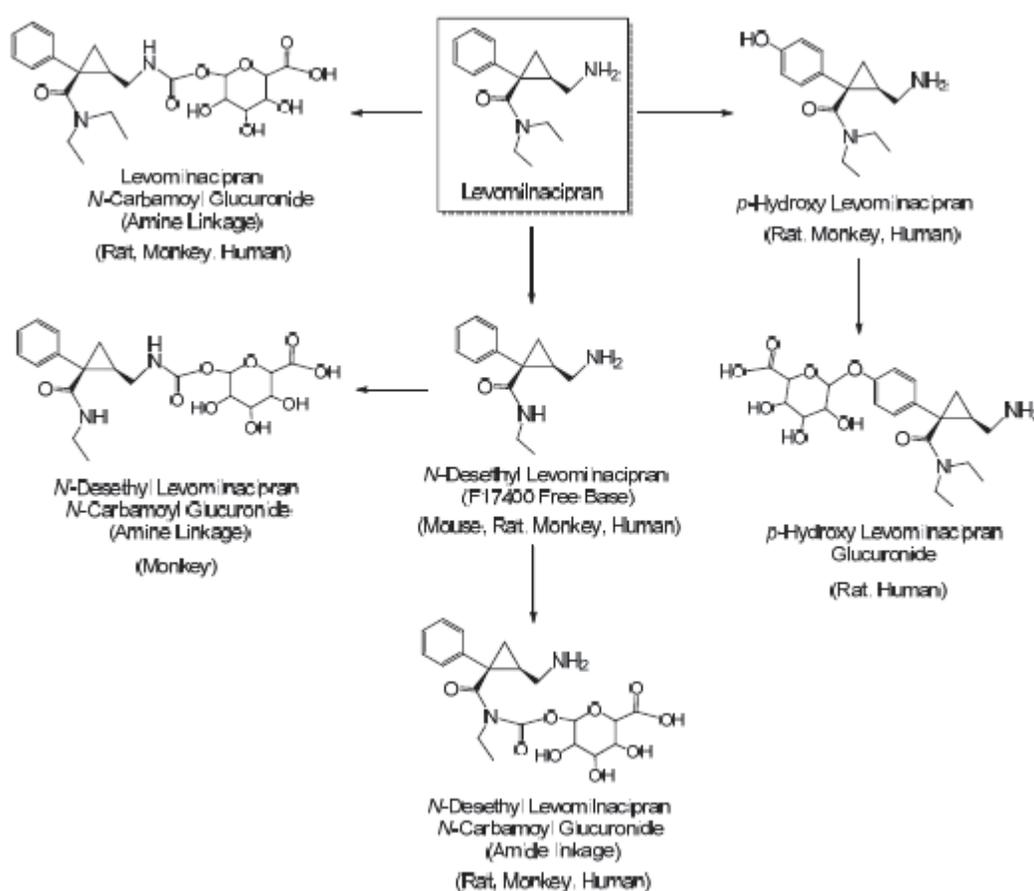
Yes, the active moiety, levomilnacipran, is identified. A selective and sensitive liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) method was developed for the determination of Levomilnacipran free base and F17400 free base in human plasma and/or urine. F17400 free base is the N-desethyl metabolite of F levomilnacipran free base (see Analytical Method section for details). The method provided accuracy, precision, selectivity, sensitivity, and reproducibility in the determination of levomilnacipran and its metabolite in human plasma and/or urine.

Levomilnacipran is the circulating active moiety based on in vitro activity. With a lower quantification limit of 1 ng/mL using validated LC-MS/MS methods, the plasma level could be detected 72 hours postdose, the last sampling time point. As apparent terminal  $T_{1/2}$  of levomilnacipran after administration of Levomilnacipran ER is observed to be approximate 12 hours, the sampling duration of 72 hours covers more than 5 times the  $T_{1/2}$  value. In addition, the extrapolated AUC estimated by  $T_{1/2}$  and the last detectable concentration for individual subject in regular PK studies was less than 20%, suggesting the sufficient sensitivity of the assay for levomilnacipran determination.

### *2.3.2 What is the proposed metabolic scheme and enzymes involved in the metabolism of levomilnacipran?*

Figure 11 is the proposed metabolism pathway for levomilnacipran.

Figure 11: Proposed Biotransformation Pathways for Levomilnacipran



After oral administration of [14C]-levomilnacipran hydrochloride, renal excretion was the major elimination route of the dose. Total excretion of radioactivity in urine and feces was 93.6% and 3.8%, respectively. Individual cumulative recoveries in urine and feces ranged from 87.6% to 102%.

In vitro evidence indicated that the metabolites of levomilnacipran (e.g., N-desethyl levomilnacipran) are not pharmacologically active. All the identifiable metabolites found in

humans are also found in animal species. Approximately 58% of dosed levomilnacipran is excreted in urine as unchanged form. Hence, the maximal contribution of metabolism is expected to be 50% of overall elimination of levomilnacipran.

Cytochrome P450 (CYP) 3A4 was identified as the major enzyme involved in the metabolism of levomilnacipran to its major inactive metabolite, F17400 (N-Desethyl Levomilnacipran).

### 2.3.3 What are the PK characteristics of the Levomilnacipran?

#### 2.3.3.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dosing of Levomilnacipran ER capsules displayed a dose-proportional increase in C<sub>max</sub> (R<sup>2</sup> = 0.9638) and AUC<sub>0-∞</sub> (R<sup>2</sup> = 0.9808) of levomilnacipran over the dose range of 25-100 mg. In another single dose study to characterize the pharmacokinetics of levomilnacipran following the administration 40 mg, 80 mg and 120 mg extended release capsules, C<sub>max</sub> and AUC<sub>0-∞</sub> were proportional to dose (C<sub>max</sub> (R<sup>2</sup> = 0.8439) and AUC<sub>0-∞</sub> (R<sup>2</sup> = 0.9434)

Table 9 contains the pharmacokinetic parameters after single dose administration of 40 mg, 80 mg and 120 mg Levomilnacipran ER.

Table 9: Mean (SD) Plasma Pharmacokinetic Parameters for Levomilnacipran

<i>PK Parameter (unit)</i>	<i>Cohort I Levomilnacipran 40 mg (N = 10)</i>	<i>Cohort II Levomilnacipran 80 mg (N = 9)</i>	<i>Cohort III Levomilnacipran 120 mg (N = 7)</i>
AUC <sub>0-t</sub> (ng•h/mL)	1757.5 (417.8)	3293.6 (562.9)	5219.2 (1527.0)
AUC <sub>0-∞</sub> (ng•h/mL)	1812.9 (441.5)	3404.7 (562.9)	5363.2 (1623.2)
C <sub>max</sub> (ng/mL)	71.5 (17.1)	148.6 (41.6)	231.2 (58.1)
T <sub>max</sub> (h) <sup>a</sup>	7.00 (5.00, 12.00)	6.00 (5.00, 12.00)	8.00 (5.00, 10.00)
T <sub>1/2</sub> (h)	12.4 (2.3)	12.9 (3.5)	12.7 (1.9)
CL/F (L/h)	23.5 (6.7)	24.2 (4.8)	23.6 (5.0)
V <sub>d</sub> /F (L)	405.1 (70.8)	444.3 (138.4)	428.6 (89.0)

Single-dose administration of Levomilnacipran ER capsules resulted in detectable exposure of F17400, a pharmacologically inactive metabolite (the N-desethylated form of levomilnacipran), in plasma and urine. The plasma C<sub>max</sub> and AUC<sub>0-∞</sub> of F17400 were proportional to the administered dose of levomilnacipran (R<sup>2</sup> = 0.8231 and R<sup>2</sup> = 0.8739, respectively).

#### Multiple Dose Pharmacokinetics

Treatment with multiple escalating doses of Levomilnacipran ER capsules showed a dose-proportional increase in maximum plasma concentration at steady state (C<sub>max,ss</sub>), area under the plasma concentration versus time curve from time zero to dose-interval time τ (AUC<sub>0-τ</sub>); and minimum plasma concentration at steady state (C<sub>min,ss</sub>) of levomilnacipran over the dose range

of 25-300 mg, QD, with  $R^2$  values of 0.9743, 0.9808, and 0.9665, respectively. The pharmacokinetics of levomilnacipran were time-independent as comparable  $AUC_{0-\infty}$  and  $AUC_{0-\tau}$  values were observed after single and multiple-dose administration of 25, 50, and 100 mg levomilnacipran. Median  $T_{max}$  of levomilnacipran was 5-6 hours, similar to what was observed following single-dose administration. Consistent with single dosing, multiple-dosing had a  $T_{1/2}$  of levomilnacipran of 11.3-15.0 hours. Comparable trough concentrations between days 3 to 4 at these dose levels were observed, indicating the steady state was reached by day 4 of daily dosing dose. Multiple-dose administration of levomilnacipran ER capsules in the dose range of 25-300 mg daily resulted in a dose-proportional increase in plasma exposure of F17400 as indicated by  $R^2$  values of 0.9683, 0.9623, and 0.9340, respectively, for  $C_{max,ss}$ ,  $AUC_{0-\tau}$ , and  $C_{min,ss}$ .

Table 10: Mean (SD) Pharmacokinetic Parameters of Levomilnacipran and F17400 in Healthy Male and Female Subjects after Escalating Multi-Dose Oral Administration of Levomilnacipran ER Capsules

Levomilnacipran							
PK Parameter	Cohort B1			Cohort B2			
	25 mg, QD (N = 9)	50 mg, QD (N = 9)	100 mg, QD (N = 9)	150 mg, QD (N = 7)	200 mg, QD (N = 7)	250 mg, QD (N = 7)	300 mg, QD (N = 6)
$C_{max,ss}$ , ng/mL	63.1 (11.6)	128.5 (14.5)	299.0 (55.4)	393.8 (74.5)	585.2 (108.5)	716.1 (138.8)	872.8 (118.6)
$T_{max}$ , h <sup>a</sup>	5 (5, 6)	5 (4, 6)	5 (4, 5)	5 (5, 6)	5 (4, 6)	6 (4, 6)	5 (4, 6)
$AUC_{0-\tau}$ , ng·h/mL	988.1 (166.1)	2047.0 (303.0)	4520.1 (893.9)	6300.0 (1098.6)	8967.4 (1658.1)	10964.5 (1651.0)	12829.3 (1242.7)
$C_{min,ss}$ , ng/mL	24.1 (4.6)	50.9 (10.9)	97.7 (22.3)	135.3 (29.0)	197.0 (49.5)	227.9 (51.0)	271.6 (26.3)
$C_{av,ss}$ , ng/mL	41.2 (6.9)	85.3 (12.6)	188.3 (37.2)	262.5 (45.8)	373.6 (69.1)	456.9 (68.8)	534.6 (51.8)
Fluctuation, %	95.2 (15.8)	92.4 (13.8)	107.3 (7.6)	98.7 (11.9)	104.5 (11.4)	106.8 (14.2)	112.1 (12.3)
Swing, %	165.3 (38.0)	159.5 (39.4)	210.7 (41.0)	194.0 (32.4)	202.4 (34.9)	218.2 (41.1)	221.5 (31.6)
$T_{1/2}$ , h	—	—	15.0 (4.7)	—	—	—	11.3 (2.2)
Accumulation Index	1.491 (0.123)	1.457 (0.135)	1.500 (0.260)	1.353 (0.072)	1.340 (0.089)	1.336 (0.068)	1.300 (0.113)

F17400 <sup>b</sup>							
PK Parameter	Cohort B1			Cohort B2			
	25 mg, QD (N = 9)	50 mg, QD (N = 9)	100 mg, QD (N = 9)	150 mg, QD (N = 7)	200 mg, QD (N = 7)	250 mg, QD (N = 7)	300 mg, QD (N = 6)
$C_{max,ss}$ , ng/mL	8.9 (4.2)	16.6 (4.0)	34.7 (8.9)	48.2 (9.1)	71.8 (14.0)	83.3 (13.5)	95.1 (17.4)
$T_{max}$ , h <sup>a</sup>	6 (6, 12)	8 (6, 8)	6 (5, 8)	6 (6, 8)	8 (5, 8)	6 (6, 12)	8 (5, 12)
$AUC_{0-\tau}$ , ng·h/mL	153.0 (56.3)	299.8 (74.0)	626.9 (175.6)	902.3 (182.8)	1283.4 (275.8)	1510.1 (274.3)	1763.2 (381.5)
$C_{min,ss}$ , ng/mL	3.7 (1.1)	7.6 (2.1)	15.2 (5.2)	22.3 (5.4)	31.4 (8.7)	34.5 (8.3)	43.0 (13.6)
$C_{av,ss}$ , ng/mL	6.4 (2.3)	12.5 (3.1)	26.1 (7.3)	37.6 (7.6)	53.5 (11.5)	62.9 (11.4)	73.5 (15.9)
Fluctuation, %	78.5 (18.5)	73.1 (8.0)	76.6 (11.3)	69.6 (10.3)	76.6 (12.5)	78.5 (10.3)	72.8 (14.1)
Swing, %	139.2 (55.4)	122.9 (22.7)	142.0 (56.2)	120.1 (28.9)	133.9 (32.6)	146.2 (30.3)	130.5 (40.2)
$T_{1/2}$ , h	—	—	15.2 (5.2)	—	—	—	11.1 (2.0)
Accumulation Index	1.542 (0.124)	1.589 (0.134)	1.502 (0.236)	1.557 (0.108)	1.463 (0.159)	1.522 (0.212)	1.289 (0.100)

a Median (minimum, maximum).

b For F17400, dose represents levomilnacipran dose.

$AUC_{0-\tau}$  = area under the plasma concentration versus time curve from time zero to dose-interval time  $\tau$ ;

$C_{max,ss}$  = maximum plasma concentration at steady state;  $C_{min,ss}$  = minimum plasma concentration at steady state;

$C_{av,ss}$  = average plasma concentration at steady state; PK = pharmacokinetic;  $T_{1/2}$  = terminal elimination half-life;

$T_{max}$  = time of maximum plasma concentration.

### 2.3.3.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

In the population pharmacokinetic analysis, conducted by the sponsor and verified by the pharmacometric reviewer, using data from healthy subjects and patients with MDD, healthy/patient status was a not statistically significant covariate. Thus, no difference was found

in the pharmacokinetics of levomilnacipran in healthy subjects and patients with MDD, apart from differences attributable to the identified covariates of renal function and body weight.

#### *2.3.3.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?*

Inter- and intra-subject variability is relatively low. In healthy subjects, the overall inter-subject variability was about 20% for C<sub>max</sub> and AUC (ranged from 10.5-34.4%). The intra-subject variability was assessed to be less than 20%. In the population PK analysis which was based on data from 13 Phase 1 studies and 3 phase 3 studies, interindividual variability was estimated to be 26% for apparent clearance (CL/F) and apparent volume of the central compartment (V<sub>c</sub>/F) and 55% for the absorption rate constant (K<sub>a</sub>).

#### *2.3.3.4 What are the characteristics of drug absorption?*

The relative bioavailability was 82% in reference to an IR formulation and 92% in reference to a solution formulation. The ER formulation delays absorption with a lag time of approximately 1-2 hours. Absolute bioavailability of levomilnacipran ER was observed ranged from 82% - 101%, but the studies were conducted using developmental formulations. The oral bioavailability is not significantly affected after administration with a high fat meal (800 – 1000 calories). A median T<sub>max</sub> of levomilnacipran ER capsule is 6 to 8 hours after oral administration and declines with a T<sub>1/2</sub> of approximately 12 hours.

#### *2.3.3.5 What are the characteristics of drug distribution?*

Levomilnacipran is widely distributed with an apparent volume of distribution of 387 to 473 L. Following a 2-hour incubation of [<sup>14</sup>C] levomilnacipran over the concentration range of 10 to 1000 ng/mL, approximately 21.7% ± 3.4% of the levomilnacipran in the human plasma was bound to plasma proteins and the binding to plasma proteins was independent of the levomilnacipran concentration. Following a 2-hour incubation of levomilnacipran, the binding of levomilnacipran to Human Serum Albumin (HSA) (12.8% ± 3.6% of levomilnacipran in samples), Alpha1-acid-Glycoprotein (AAG) (6.3% ± 3.2% of levomilnacipran in samples), and Gamma Globulin (GG) (3.1% ± 3.1% of levomilnacipran in samples) was also independent of the levomilnacipran concentration.

#### *2.3.3.6 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?*

The total radioactivity in urine and feces recovered over the sample collection period was 97.4% of the radioactivity administered to subjects who did not vomit in the study. Total excretion of radioactivity in urine and feces was 93.6% and 3.8%, respectively, with 58% of the total dosed radioactivity being the parent compound, indicating that the principal route of elimination of levomilnacipran/metabolites is through urinary excretion.

Table 11: Mean Excretion Following Oral Administration of a 60 mg [<sup>14</sup>C] Levomilnacipran in Healthy Male Subjects (n = 4, without emesis)

<i>Subject</i>	<i>Recovery (% of total dosed radioactivity)</i>		
	<i>Urine</i>	<i>Feces</i>	<i>Total</i>
0901003	97.6	3.1	100.7
0901004	97.3	4.8	102.0
0901009	96.4	2.9	99.3
0901021	83.2	4.4	87.6
<b>Mean</b>	<b>93.6</b>	<b>3.8</b>	<b>97.4</b>
<b>SD</b>	<b>7.0</b>	<b>0.9</b>	<b>6.6</b>
<b>CV (%)</b>	<b>7</b>	<b>25</b>	<b>7</b>

SD = standard deviation

### 2.3.3.7 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is no evidence that enterohepatic recirculation takes place for levomilnacipran. No double peak phenomenon was ever observed in PK studies for levomilnacipran administered under conditions either with food intake or without.

### 2.3.3.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

The relationship between dose and the parameters AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> for single dose administration (dose range tested was 25-100 mg and 40-120 mg) and AUC<sub>0-τ</sub>, C<sub>max,ss</sub> and C<sub>min,ss</sub> for multiple dose administration (dose range tested was 25-300 mg/day) was evaluated. These results indicated the dose-linearity and dose-proportionality of levomilnacipran pharmacokinetics (Figures 12 - 15).

Figure 12: Linear Regression Analysis of Levomilnacipran C<sub>max</sub> (Top Panel), C<sub>min</sub> (Middle Panel), and AUC<sub>0-τ</sub> (Bottom Panel) Following Escalating Multiple Oral Dose Administration of 25, 50, and 100-mg (B1) or 150, 200, 250, and 300-mg (B2) of Levomilnacipran ER in Healthy Human Male and Female Subjects

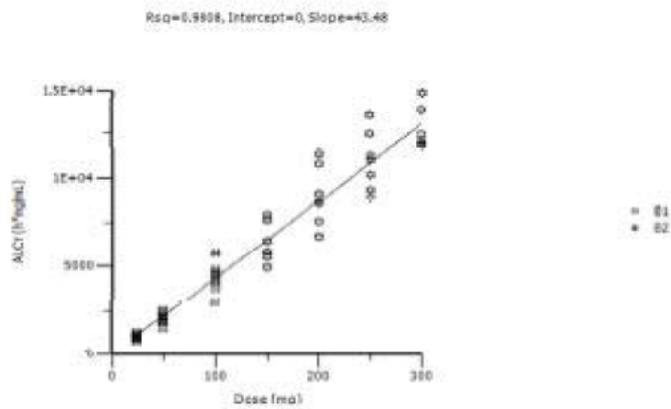
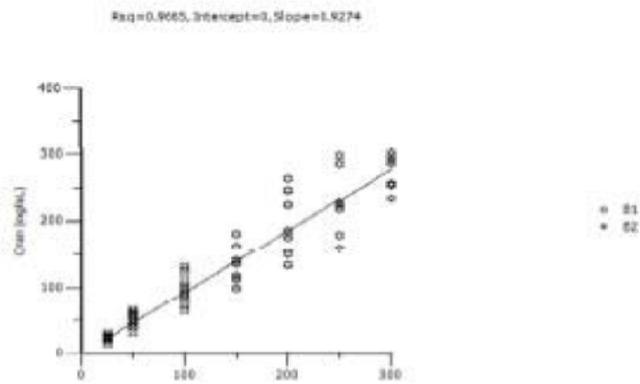
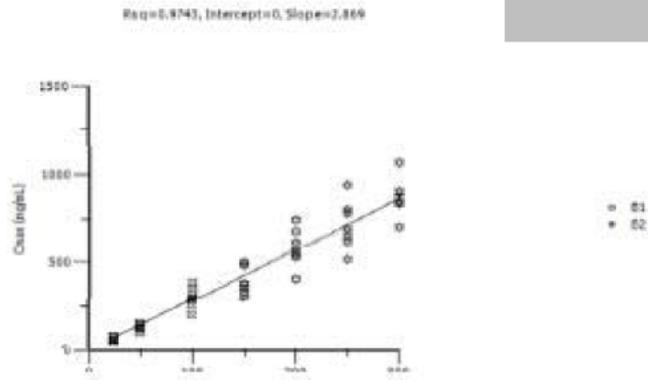


Figure 13: LVM-PK-01: Linear Regression Analysis of Levomilnacipran Cmax (Upper Panel) and AUC0-∞ (Lower Panel) Following a Single Oral Dose Administration of 25-mg (A1), 50-mg (A2), or 100-mg (A3) of Levomilnacipran SR in Healthy Human Male and Female Subjects

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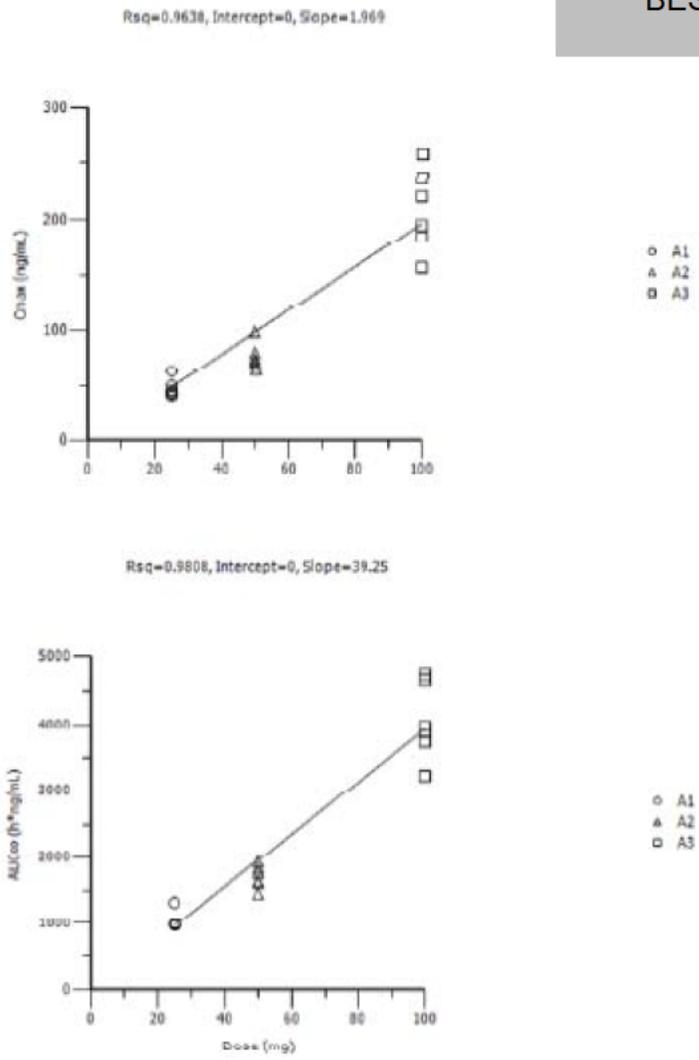


Figure 14: Linear Regression Analysis of Levomilnacipran Cmax (Top Panel), AUC0-t (Middle Panel), and AUC0-∞ (Bottom Panel) Following a Single Oral Dose Administration of 40, 80, and 120-mg of Levomilnacipran SR in Healthy Human Male and Female Subjects

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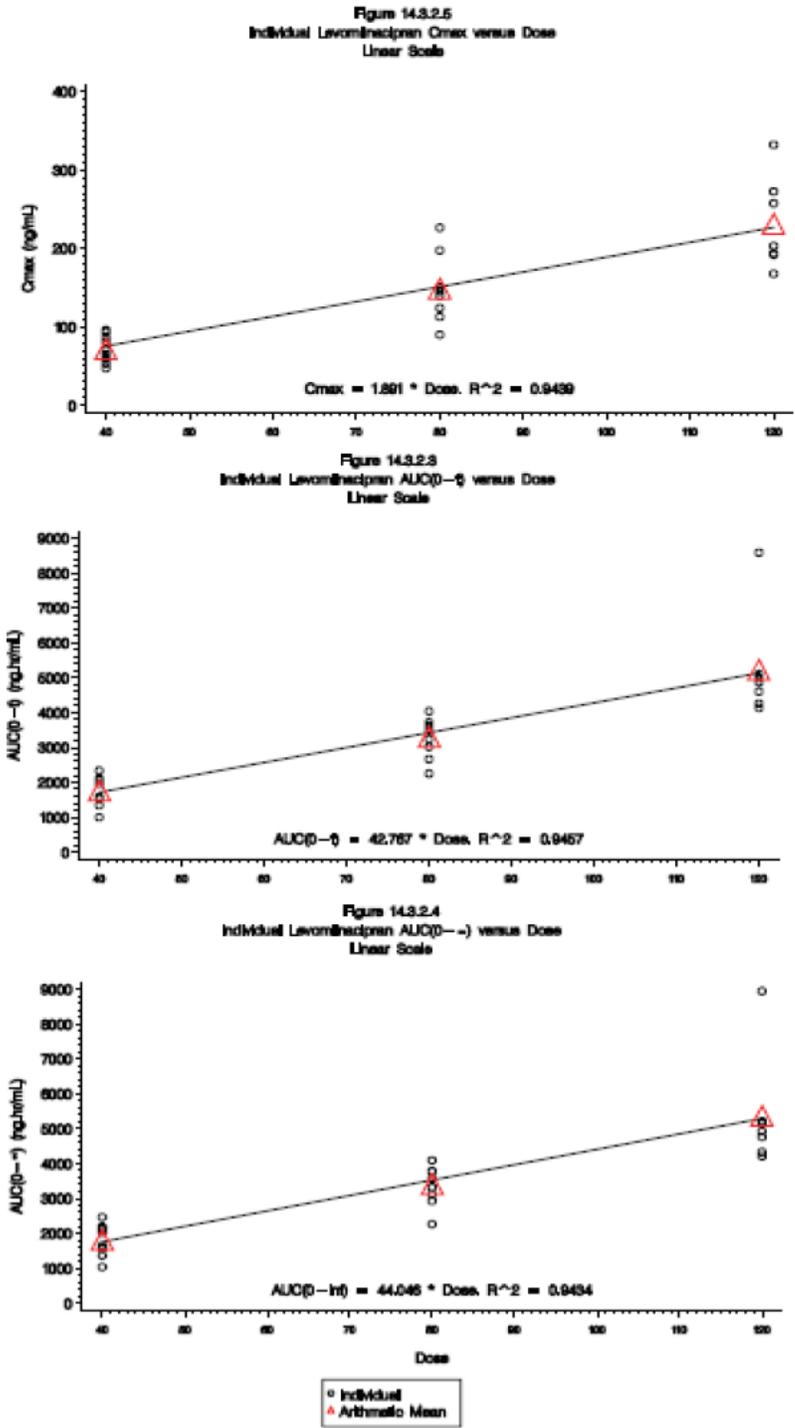
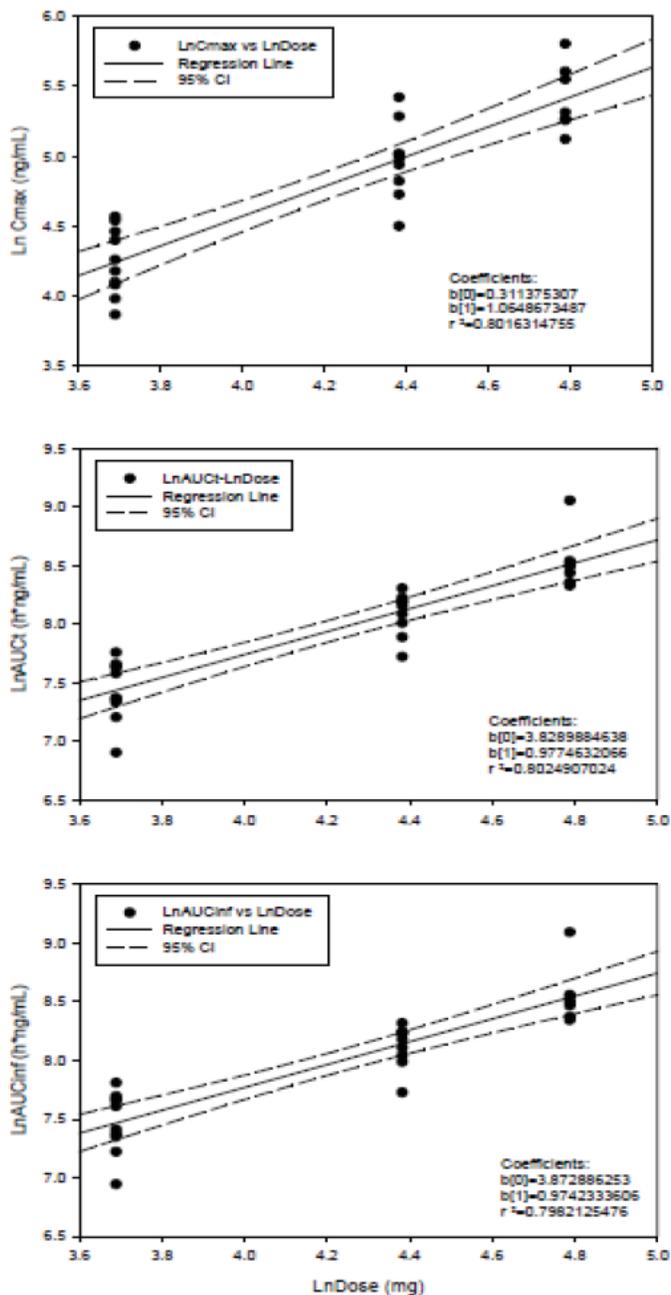


Figure 15: Regression Analysis between Dose and PK Parameters Following a Single Dose Administration Using Power Model

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2.3.3.9 Is there evidence for a circadian rhythm of the PK?

The effect of circadian rhythm on the PK was not formally evaluated. However, it is not expected that circadian rhythm will affect the PK of levomilnacipran.

### 2.3.3.10 How do the PK parameters change with time following chronic dosing?

The PK behavior of levomilnacipran following multiple-dose administration is predictable from single-dose data. Levomilnacipran AUC<sub>0-∞</sub> after single-dose administration was similar to steady-state AUC<sub>0-τ</sub> as demonstrated in the following table (Table 12). T<sub>1/2</sub> remained unchanged after multiple-dose administration relative to single-dose administration.

Table 12: Comparison of Mean (SD) AUC<sub>0-∞</sub> Following Single-Dose Administration and AUC<sub>0-τ</sub> Following Multiple-Dose Administration

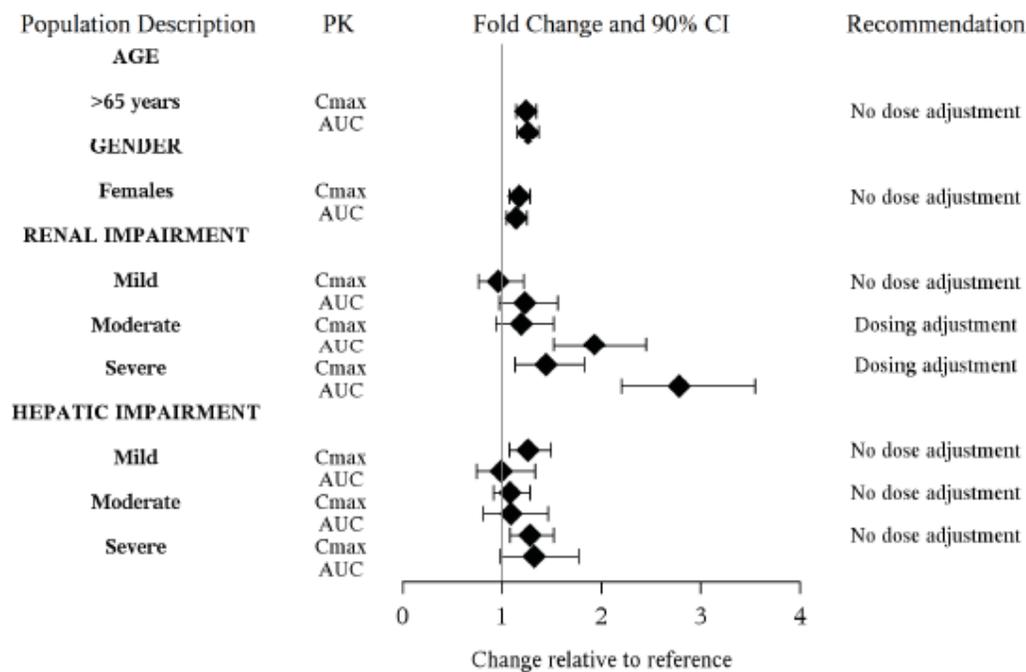
	<i>Dose (mg)</i>	<i>AUC<sub>0-∞</sub> (h•ng/mL)</i>	<i>AUC<sub>0-τ</sub> (h•ng/mL)</i>
LVM-PK-01	25	1043.9 (142.1)	988.1 (166.1)
LVM-PK-01	50	1713.2 (168.4)	2047.0 (303.0)
LVM-PK-01	100	4034.0 (575.9)	4520.1 (893.9)
LVM-PK-16	120	4978.8 (1309.8)	5752.0 (871.2)

### 2.3.4 Intrinsic Factors

2.3.4.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in subjects and how much of the variability is explained by the identified covariates?

The major intrinsic factors evaluated for impact on the inter-subject variability in exposure (AUC, C<sub>max</sub>) were age, gender, renal and hepatic function. Age and gender did not significantly affect inter-subject variability (Figure 13). Mild (Child Pugh : 1-6), moderate (Child Pugh: 7 -9) and severe (Child Pugh: 10 -13) hepatic impairment also did not significantly affect inter subject variability in exposure (Figure 13 ). Mild (Cl<sub>cr</sub>: 50 – 79 mL/min) renal impairment also did not significantly affect Levomilnacipran exposure. However, moderate (30 – 49 mL/min) and severe (< 30 mL/min) renal impairment significantly affected the exposure of Levomilnacipran in these patients. Figure 16 is the Forest plot presenting the impact of intrinsic factors on the pharmacokinetics of Levomilnacipran.

Figure 16: Impact of Intrinsic Factors on Levomilnacipran PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (18-45 years).  
 The data shown for female subjects are relative to male subjects.  
 The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

In the covariate analysis conducted by the sponsor using population PK methods, statistically significant and clinically relevant effects of creatinine clearance on CL/F and body weight on Vc/F were identified. In the final PopPK model, creatinine clearance explained 34% of the interindividual variability in CL/F while body weight explained 13% of the interindividual variability in Vc/F.

*2.3.4.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?*

Dose adjustment is recommended for patients with moderate and severe renal impairment. For moderate renal impaired patients, Levomilnacipran dose should not exceed 60 mg daily. For severe renal impaired patients, Levomilnacipran dose should not exceed 80 mg daily. The following table (Table 13) contains the pharmacokinetic parameters for Levomilnacipran in renal impaired patients after administration of 40 mg Levomilnacipran ER.

Table 13: Mean (SD) PK Parameters of Levomilnacipran after a Single Dose Administration of 40-mg Levomilnacipran SR to Subjects with Varied Degrees of Renal Function

PK Parameter	Group I (Normal), (N = 8)	Group II (Mild) (N = 8)	Group III (Moderate) (N = 8)	Group IV (Severe) (N = 8)	Ratio of Geometric Means (90% CI)		
					Mild/ Normal	Moderate/ Normal	Severe/ Normal
<b>Levomilnacipran</b>							
C <sub>max</sub> , ng/mL	83.9 (21.0)	81.8 (23.4)	98.7 (18.1)	122.1 (35.1)	96.1 (75.5-122.4)	119.3 (93.7-151.8)	143.5 (112.8-182.7)
AUC <sub>0-t</sub> , h•ng/mL	2054.3 (500.1)	2506.3 (630.2)	3820.6 (863.4)	5240.1 (1343.2)	121.8 (96.9-153.1)	187.9 (149.5-236.2)	256.1 (203.8-321.9)
AUC <sub>0-∞</sub> , h•ng/mL	2101.0 (516.9)	2587.8 (649.9)	4016.4 (995.4)	5900.8 (1799.3)	123.1 (96.9-156.3)	192.5 (151.6-244.5)	279.7 (220.2-355.2)
T <sub>max</sub> <sup>a</sup> , h	5.5 (4, 8)	7 (6, 12)	9 (6, 12)	7 (6, 24)			
T <sub>1/2</sub> , h	13.5 (2.8)	17.3 (3.5)	19.1 (4.6)	27.7 (7.4)			
CL/F, L/h	20.5 (7.1)	16.7 (5.9)	10.5 (2.5)	7.3 (1.9)			
V <sub>z</sub> /F, L	387.2 (107.0)	422.0 (202.9)	280.3 (59.3)	283.1 (77.7)			
V <sub>ss</sub> /F, L	462.3 (121.8)	492.7 (203.7)	355.3 (72.5)	315.3 (81.4)			
Ae, mg	20.8 3.7	16.9 4.6	15.7 4.3	8.7 3.6			
%Dose, %	51.9 (9.3)	42.3 (11.6)	39.2 (10.7)	21.9 (9.0)			
CL <sub>r</sub> , mL/min	175.9 (42.7)	114.7 (24.3)	69.9 (17.9)	28.6 (11.6)			

Subjects were grouped based on serum creatinine clearance value: Group I (normal renal function)  $\geq 80$  mL/min; Group II (mild renal impairment) 50-79 mL/min; Group III (moderate renal impairment) 30-49 mL/min; and Group IV (severe renal impairment)  $< 30$  mL/min.

a Median (Minimum, Maximum)

Dose adjustment is also not recommended for patients with hepatic impairment. Age, gender, body weight, and ethnicity/race do not have a significant effect on exposure so no dose adjustment is needed based on population PK and population PK-PD analyses.

Information was not supplied by the sponsor to address if there is a need for dose adjustment for pediatric patients. The sponsor is seeking a waiver for children under 7 years of age and a deferral for children 7 to 17 years.

#### 2.3.4.3 Does genetic variation impact exposure and/or response?

The sponsor did not evaluate the impact of genetic variation on exposure and/or response.

#### 2.3.5 Extrinsic Factors

##### 2.3.5.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

CYP3A4 appears to be the major CYP responsible for the metabolism of levomilnacipran. Biotransformation of levomilnacipran was low for other CYPs (e.g. CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1). CYP2C8, 2C19, 2D6, 2J2 appear to be involved to a minor extent in the transformation of levomilnacipran to F17400. Levomilnacipran did not demonstrate a significant inhibition of major CYPs in human liver microsomes ( $IC_{50} > 30 \mu M$ ) or induction of major CYPs and UDP-glucuronosyltransferase 1A6 enzyme in freshly isolated human hepatocytes (up to  $10 \mu M$ ). *In vitro* studies did not indicate significant interactions of levomilnacipran with transporters (BCRP, OAT1, OAT3, OATP1B, OCT2) except for a reduction in organic cation transporter 2 (OCT2) activity by 77% at  $140 \mu M$ . Levomilnacipran was a weak P-gp substrate. These *in vitro* data suggest that levomilnacipran has a low potential for drug-drug interactions except possible with inhibitors or inducers of CYP3A.

##### 2.3.5.2 Is the drug a substrate of CYP enzymes?

CYP3A4 is the major enzyme responsible for the biotransformation of levomilnacipran.

##### 2.3.5.3 Is the drug an inhibitor and/or an inducer of enzymes?

Therapeutic use of levomilnacipran is unlikely to have inhibitory effects on the activity of CYP isozymes.

The inhibition potential of levomilnacipran on the activities of human CYP enzymes (CYP 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5) was evaluated over the concentration range of 3 to  $30 \mu M$  using pooled human liver microsomes pre-incubated in the absence or presence of NADPH. No inhibition on the activities of these CYP enzymes was observed at  $3 \mu M$  of levomilnacipran. At  $10 \mu M$  of levomilnacipran, a slight inhibition (approximately 20%) was observed for CYP3A4/5 after preincubation with NADPH only when nifedipine was the substrate, but inhibition on metabolism of midazolam and testosterone was not observed. The other CYP enzymes were not inhibited at  $10 \mu M$  of levomilnacipran. At  $30 \mu M$  of levomilnacipran, a slight inhibition was observed for CYP2C9 (approximately 20% after preincubation with NADPH) and CYP3A4 (approximately 20 to 30% on all three substrates after preincubation), but the other CYP enzymes were not inhibited at  $30 \mu M$  of levomilnacipran.

The  $IC_{50}$  of levomilnacipran on the activity of the isozymes was always greater than  $30 \mu M$ , a concentration much higher than steady state  $C_{max}$  ( $1.4 \mu M$ ) attained after oral administration of maximum therapeutic dose at 120 mg, QD levomilnacipran ER.

The induction potential of levomilnacipran on the activities of CYP enzymes (CYP 1A2, 2C9, 2C19, 3A4/5) and UGT1A6 was evaluated using human hepatocyte cultures. Following daily treatment of human hepatocyte cultures for three consecutive days with 1, 3, and 10  $\mu\text{M}$  of levomilnacipran, the activities of these CYP enzymes as well as UGT1A6 were not induced and were similar to those without the treatment of levomilnacipran (i.e. negative control).

*2.3.5.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?*

Levomilnacipran is a weak P-gp substrate. It is not a substrate of BCRP, OAT1, OAT3, OATP1B1, OATP1B3 and OCT2. Levomilnacipran is a poor inhibitor of P-gp ( $\text{IC}_{50} = 423 \pm 99 \mu\text{M}$ ). Levomilnacipran did not significantly inhibit the other transporters.

*2.3.5.5 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?*

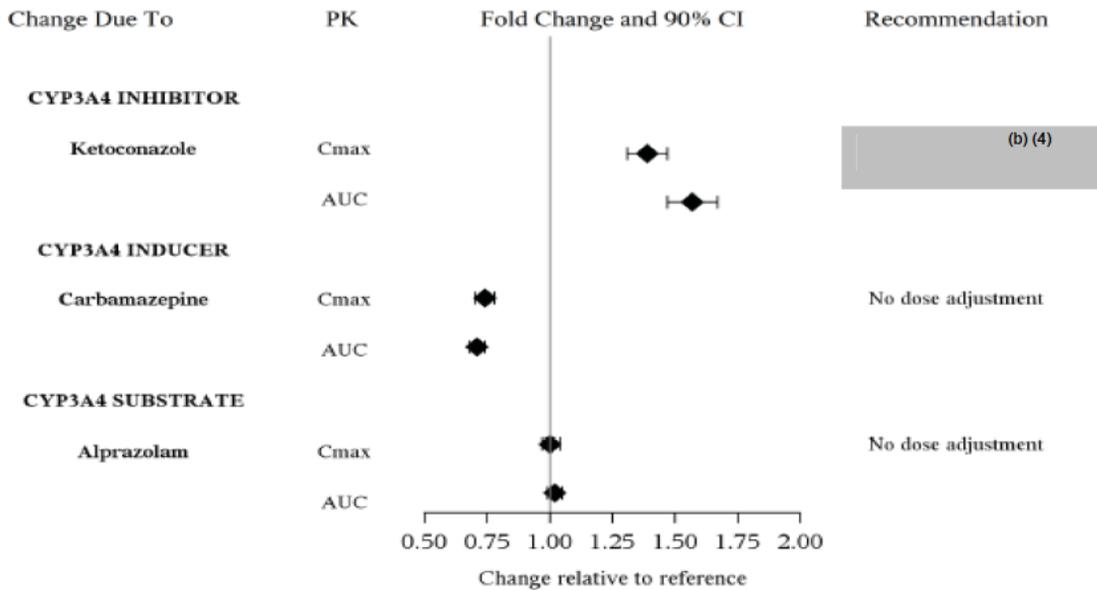
The potential of extrinsic factors significantly affecting exposure of levomilnacipran and other drugs being affected by levomilnacipran co-administration is low based on in vitro findings except for inhibitors or inducers of CYP3A4 (see Section J below).

*2.3.5.6 What are the drug-drug interactions?*

*Is Drug of interest impacted by co-administered other drugs?*

Figure 17 summarizes the findings from the drug interaction studies submitted in the application.

Figure 17: Impact of Other Drugs on Levomilnacipran Pharmacokinetics



Levomilnacipran dose should not exceed 80 mg when co-administered with ketoconazole or other strong inhibitors of CYP3A4.

Table 14: Pharmacokinetic Parameters (Mean  $\pm$  SD) for Levomilnacipran and F17400 Following a Single-Dose Administration of 80-mg Levomilnacipran Alone (Treatment A) and in Combination with 400-mg Ketoconazole at Steady State (Treatment B)

PK Parameter	LVM alone (Treatment A) (n = 33)	LVM + Ketoconazole (Treatment B) (n = 33)	Ratio of Geometric Means (TrtB/TrtA), %	90% CI or p-Value
<b>Levomilnacipran</b>				
C <sub>max</sub> , ng/mL	162.97 $\pm$ 27.83	230.96 $\pm$ 60.05	138.7	130.72-147.07
AUC <sub>0-t</sub> , ng•h/mL	3684.25 $\pm$ 552.37	5910.65 $\pm$ 1350.27	156.8	147.17-167.09
AUC <sub>0-∞</sub> , ng•h/mL	3730.19 $\pm$ 565.01	5976.10 $\pm$ 1370.96	156.6	146.93-166.89
T <sub>max</sub> , h	6.00 (5.00-12.00) <sup>a</sup>	8.00 (5.00-12.00) <sup>a</sup>	133.3 <sup>b</sup>	p < 0.0001 <sup>c</sup>
T <sub>1/2</sub> , h	12.21 $\pm$ 2.54	13.13 $\pm$ 2.42	—	—
CL/F, L/h	21.93 $\pm$ 3.31	14.32 $\pm$ 4.66	—	—
V <sub>ss</sub> /F, L	469.59 $\pm$ 74.81	339.03 $\pm$ 85.29	—	—
<b>F17400</b>				
C <sub>max</sub> , ng/mL	16.60 $\pm$ 5.93	14.66 $\pm$ 6.59	85.8	79.96-91.98
AUC <sub>0-t</sub> , ng•h/mL	447.15 $\pm$ 167.27	566.45 $\pm$ 247.69	122.2	112.86-132.25
AUC <sub>0-∞</sub> , ng•h/mL	492.75 $\pm$ 167.14	606.92 $\pm$ 243.79	120.0	111.21-129.50
T <sub>max</sub> , h	12.00 (5.00-12.00) <sup>a</sup>	12.00 (12.00-24.00) <sup>a</sup>	—	p < 0.0001 <sup>c</sup>
T <sub>1/2</sub> , h	14.27 $\pm$ 2.86	15.56 $\pm$ 3.70	—	—

Note: — indicates not calculated

a Median (Minimum, Maximum)

b Ratio of arithmetic mean using the median T<sub>max</sub>

c Based on Wilcoxon signed-rank test using the median T<sub>max</sub>

### 2.3.5.7 Does Drug of interest impact other co-administered drugs?

Levomilnacipran did not significantly affect alprazolam or carbamazepine in in vivo studies, consistent with in vitro data indicating Levomilnacipran has low potential to be an inhibitor or inducer of CYP enzymes or membrane transporters.

### 2.3.5.8 Does the label specify co-administration of another drug?

No. Levomilnacipran is indicated as a monotherapy for MDD. Therefore, other than potential drug-drug interactions the label does not specify adjunctive therapy.

### 2.3.5.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

The sponsor states that there is no known mechanistic basis for pharmacodynamic drug-drug interactions.

## 2.4 General Biopharmaceutics

2.4.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Levomilnacipran HCl possesses a high solubility and high permeability. The absolute bioavailability using developmental formulations ranged from 82% to 101%. The relative bioavailability of Levomilnacipran ER was 92% when compared to an oral solution. About 93% of radioactivity was recovered in urine. The solubility was > 5 mg/mL in the pH range of 1-7.5. At least 50% of Levomilnacipran ER is dissolved in 4 hours and at least 98% in 24 hours. Thus, there is a suggestion that levomilnacipran could be a BCS 1 drug. However, an official determination was not undertaken during the review because BCS classification was not requested and was not the basis for a biowaiver request. However, a request was submitted for milnacipran when it was reviewed and classified as BCS 1.

2.4.2 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

Bioequivalence was established between 120 mg (3 capsules x 40 mg) of the Clinical Trial Material (CTM) ER capsule formulation used in Phase 3 trials and 120 mg (1 capsule x 120 mg) of the To-Be-Marketed ER (TBM) formulation manufactured by the primary facility and by the alternate facility in male and female healthy subjects following an oral single-dose administration under fasted conditions.

The composition of Levomilnacipran ER (120 mg) To be Marketed Capsule and Clinical Trial formulation (40 mg ER capsule) are provided in Table 15.

Table 15: Composition of Levomilnacipran ER Capsules Clinical and To Be Marketed Formulations

Manufacturing Site		Pierre Fabre Medicament, France		Forest Laboratories, Ireland, Limited (b) (4)	
Formulation Type		Clinical formulation		To-be-marketed formulation <sup>d</sup>	
Process	Ingredients	Quantity Unit (mg/capsule)		Quantity Unit (mg/capsule)	
		40 mg	% w/w	120 mg	% w/w
(b) (4)	Levomilnacipran HCl (F2695)	45.9 <sup>b</sup>	(b) (4)	137.8 <sup>c</sup>	(b) (4)
	Sugar spheres, (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Povidone, (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Talc (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Ethylcellulose, (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Triethyl citrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Talc (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total filled weight		100		100	
Capsule (b) (4)		Size 3		Size 1	

b Expressed as levomilnacipran hydrochloride salt equivalent to 40 mg base.

c Expressed as levomilnacipran hydrochloride salt equivalent to 120 mg base.

The levomilnacipran capsules to be marketed have been formulated as an ER formulation in which levomilnacipran ER beads are (b) (4) filled in different capsule sizes to produce 20, 40, 80 and 120 mg strengths. The Levomilnacipran ER capsules consist of sugar spheres (b) (4)

Levomilnacipran capsules with the desired strengths are produced (b) (4) (refer to ONDQA review for Agency's evaluation).

Table 16: Composition of Levomilnacipran ER Capsules To Be Marketed Formulation

Ingredients	Function	% (w/w)	Quantity Unit (mg/capsule)			
			20 mg	40 mg	80 mg	120 mg
Levomilnacipran HCl (F2695)	Drug substance	(b) (4)	23.0 <sup>b</sup>	45.9 <sup>b</sup>	91.8 <sup>b</sup>	137.8 <sup>b</sup>
Sugar spheres, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Povidone, (b) (4) USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Talc, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Ethylcellulose (b) (4) USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Triethyl citrate, USP/NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
<b>Total Capsule Weight</b>	(b) (4)	(b) (4)	<b>89</b>	<b>148</b>	<b>264</b>	<b>379</b>

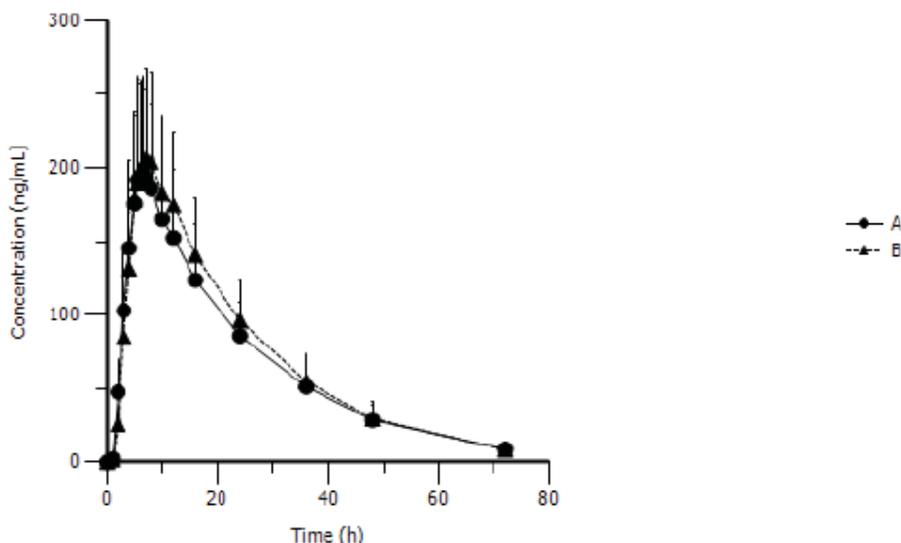
b Expressed as hydrochloride equivalent to 20 mg, 40 mg, 80 mg and 120 mg base, respectively.

2.4.3 Are equal doses of Levomilnacipran ER To Be Marketed formulation bioequivalent to the Clinical Trial Formulation?

Bioequivalence was established between 120 mg (3 capsules x 40 mg) of the clinical ER capsule formulation used in Phase 3 trials and 120 mg (1 capsule x 120 mg) of the to-be-marketed ER formulation in male and female healthy subjects following an oral single-dose administration under fasted conditions.

This study was a single-center, randomized, open-label, crossover, single-dose study in 40 healthy male and female subjects, aged 19 through 45 years. Pharmacokinetics, safety and tolerability were evaluated. Subjects were randomly assigned to 1 of 2 treatment sequences to receive the following 2 treatments under fasted conditions with a 7-day washout period between treatments: Treatment A: Single oral dose of 120 mg levomilnacipran (1 x 120 mg to-be-marketed SR capsule) under fasted conditions or Treatment B: Single oral dose of 120 mg levomilnacipran (3 x 40 mg clinical SR capsules) under fasted conditions. The following figure (Figure 18) and table contain the mean levomilnacipran plasma concentration time profile and the statistical analysis of the pharmacokinetic parameters, respectively.

Figure 18: Mean (SD) Levomilnacipran Plasma Concentrations versus Time Profile following a Single Oral Administration of Levomilnacipran under Fasted Conditions as Either the To-Be-Marketed Capsule (A) or Clinical ER Capsules (B) to Healthy Subjects (N=21)



- a Treatment A, to-be-marketed levomilnacipran SR formulation 120 mg (1 x 120 mg) administered under fasted conditions (N = 21);  
 b Treatment B, clinical levomilnacipran SR formulation 120 mg (3 x 40 mg) administered under fasted conditions (N = 21)

Subjects who experienced vomiting within 24 hours post dose administration were excluded.

Table 17: Pharmacokinetic Parameters (Mean  $\pm$  SD) of Levomilnacipran after a Single Oral Administration of 120 mg Levomilnacipran ER in Healthy Subjects

PK Parameter, Unit	Treatment A To-Be-Marketed SR 1 x 120 mg (N = 21)	Treatment B Clinical SR 3 x 40 mg (N = 21)	Treatment A/Treatment B	
			Ratio of Geometric Means, %	90% CI
$C_{max}$ , ng/mL	201.3 $\pm$ 69.3	215.6 $\pm$ 60.7	92.1	85.99 - 98.62
$AUC_{0-t}$ , h•ng/mL	4760.5 $\pm$ 1318.6	5114.1 $\pm$ 1353.2	92.9	89.37 - 96.63
$AUC_{0-\infty}$ , h•ng/mL	4948.7 $\pm$ 1390.2	5280.8 $\pm$ 1416.8	93.6	90.00 - 97.26
$T_{max}$ , h <sup>a</sup>	6.5 (5.5, 10.0)	7.0 (5.0, 12.0)	—	p = 0.5001 <sup>b</sup>
$T_{1/2}$ , h	13.9 $\pm$ 2.6	13.1 $\pm$ 1.9	—	—

a Median (minimum, maximum).

b p-Value is based on Signed Rank Test.

The 90% confidence intervals (CI) for the geometric mean ratios of  $C_{max}$ ,  $AUC(0-t)$  and  $AUC(0-\infty)$  meet the regulatory criteria for bioequivalence; therefore, the two products are considered bioequivalent. However, it must be noted that the 90% CI for  $C_{max}$  and  $AUC$  did not encompass 100%.  $T_{max}$  was similar. The to-be-marketed product for this study was produced by Forest Ireland facility, the primary site of manufacturing.

The sponsor conducted another bioequivalence study using Levomilnacipran 120 mg ER capsule ( (b) (4) To Be Marketed Levomilnacipran ER) manufactured at an alternate site comparing it to the CTM that was used in the clinical pharmacology and Phase 3 studies for MDD. The TBM product was produced by (b) (4)

The study was a single-center, randomized, open-label, crossover, single-dose study in healthy male and female subjects, aged 18 through 45 years. The pharmacokinetics, safety and tolerability were evaluated. Subjects were randomly assigned to 1 of 2 treatment sequences to receive the following 2 treatments under fasted conditions with a 7-day washout period between treatments: Treatment A: Single oral dose of 120 mg levomilnacipran (1 × 120-mg (b) (4) site SR capsule) under fasted conditions and Treatment B: Single oral dose of 120 mg levomilnacipran (3 × 40-mg clinical SR capsules) under fasted conditions. Table 18 contains the statistical analysis.

Table 18: Pharmacokinetic Parameters (Mean ± SD) of Levomilnacipran after a Single Oral Administration of 120 mg Levomilnacipran Extended -Release Capsules in Healthy Subjects

PK Parameter, Unit	Treatment A To-Be-Marketed SR 1x120 mg (N = 25)	Treatment B Clinical SR 3x40 mg (N = 25)	Treatment A/Treatment B	
			Ratio of Geometric Means, %	90% CI
C <sub>max</sub> , ng/mL	193.6 ± 35.9	195.5 ± 31.8	98.5	92.84 - 104.50
AUC <sub>0-t</sub> , ng•h/mL	4327.7 ± 853.8	4473.5 ± 787.7	96.3	92.10 - 100.63
AUC <sub>0-∞</sub> , ng•h/mL	4484.6 ± 985.1	4611.1 ± 925.7	96.8	92.54 - 101.23
T <sub>max</sub> , h <sup>a</sup>	6.0 (5.0, 10.0)	7.0 (5.0, 12.0)	—	p = 0.0374 <sup>b</sup>
T <sub>1/2</sub> , h	13.4 ± 2.9	12.3 ± 2.7	—	—

a Median (minimum, maximum).

b p-Value is based on Signed Rank Test.

AUC<sub>0-∞</sub> = area under the plasma concentration versus time curve from time zero to infinity; AUC<sub>0-t</sub> = area under the plasma concentration versus time curve from time zero to time t (time of last measurable concentration);

CI = confident interval; C<sub>max</sub> = maximum plasma drug concentration; T<sub>1/2</sub> = terminal elimination half-life;

T<sub>max</sub> = time of maximum plasma concentration; — = not available.

The 90% confidence intervals for the geometric mean ratios of C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> were within the range of 80% to 125%, indicating the two formulations are bioequivalent. Median T<sub>max</sub> of the clinical levomilnacipran SR capsule was 1 hour longer than that of the to-be-marketed levomilnacipran SR capsule. The difference in T<sub>max</sub> after administration of the two formulations is not expected to be clinically relevant.

#### 2.4.4 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

There were two food effect studies conducted: one using the clinical formulation of Levomilnacipran 40 mg ER capsule (Study LVM-PK-06) and the other using the TBM formulation of levomilnacipran 120 mg ER capsule (LVM-PK-12). Both study results demonstrated no food effect on the bioavailability of levomilnacipran ER.

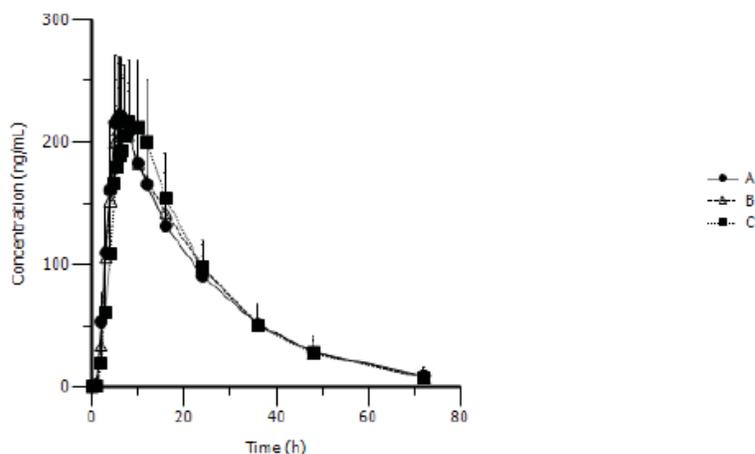
The study using the TBM formulation (LVM-PK-12) was a single-center, randomized, open-label, crossover, single-dose study in 50 healthy male and female subjects. The effect of food on

the oral bioavailability of levomilnacipran 120 mg administered as the to-be-marketed ER capsule (1 × 120 mg) was assessed. Subjects were randomly assigned to 1 of 6 treatment sequences to receive 3 treatments with a 7-day washout period between treatments.

The high-fat breakfast derived approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat, a total of approximately 900 to 1000 calories.

Mean (SD) levomilnacipran plasma concentrations versus time profile following a 120 mg single oral administration of levomilnacipran ER capsules to healthy human male and female subjects are presented in Figure 19.

Figure 19: Mean (SD) Levomilnacipran Plasma Concentrations (ng/mL) Versus Time (h) Following a 120 mg Single Oral Administration of Levomilnacipran SR Capsules to Healthy Human Male and Female Subjects -



- a Treatment A, to-be-marketed levomilnacipran SR formulation 120 mg (1 x 120 mg) administered under fasted conditions (N = 34);
- b Treatment B, clinical levomilnacipran SR formulation 120 mg (3 x 40 mg) administered under fasted conditions (N = 29);
- c Treatment C, to-be-marketed levomilnacipran SR formulation 120 mg (1 x 120 mg) administered under fed conditions (N = 34)

The Pharmacokinetic parameters and statistical analysis are provided in the Table19.

Table 19: Pharmacokinetic Parameters (Mean ± SD) of Levomilnacipran after a Single Oral Administration of 120 mg Levomilnacipran Sustained-Release Capsules in Healthy Subjects

PK Parameter	Treatment A To-Be-Marketed SR 1 x 120 mg (Fasted) (N = 34)	Treatment B Clinical SR 3 x 40 mg (Fasted) (N = 29)	Treatment C To-Be-Marketed SR 1 x 120 mg (Fed) (N = 34)	Statistical Comparison			
				Geometric Means Ratio, %		90% CI	
				Trt A/B	Trt C/A	Trt A/B	Trt C/A
C <sub>max</sub> , ng/mL	234.6 ± 51.9	226.7 ± 47.3	239.6 ± 51.3	100.5	102.3	95.04-106.21	97.13-107.79
AUC <sub>0-t</sub> , ng·h/mL	5084.4 ± 900.8	5154.0 ± 918.3	5180.2 ± 925.5	97.5	101.7	94.49-100.7	98.74-104.82
AUC <sub>0-∞</sub> , ng·h/mL	5298.7 ± 1013.0	5317.9 ± 998.6	5345.0 ± 1009.8	98.7	100.8	95.52-101.97	97.74-103.92
T <sub>max</sub> , h <sup>b</sup>	6.0 (4.0, 8.0)	6.5 (5.0, 16.0)	8.0 (5.0, 12.0)	—	—	0.0990 <sup>c</sup>	< 0.0001 <sup>c</sup>
T <sub>1/2</sub> , h	13.9 ± 3.8	12.7 ± 2.9	13.0 ± 2.9	—	—	—	—

Tmax = median (range)

Food increased the concentration of levomilnacipran by about 1 -3%. The ratios of geometric means for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> were between 100.8-102.3% and 90% CIs of the ratios were in the range of 97.13-107.79%, suggesting the food has no effect on the bioavailability of the to-be-marketed levomilnacipran ER formulation. T<sub>max</sub> of the to-be-marketed ER formulation appeared to be delayed by the high fat meal for about 2 hours. T<sub>1/2</sub> was quite similar when the formulation was taken with food compared to without. The difference in T<sub>max</sub> is not expected to be clinically relevant.

The food effect study using the Levomilnacipran ER 40 mg capsules clinical trial formulation was a single-center, randomized, open-label, 2 × 2 crossover, single-dose study in 24 healthy male and female subjects 18 to 45 years of age. Table 20 contains the pharmacokinetic parameters with statistical analysis.

Table 20: Mean ± SD Pharmacokinetic Parameters of Levomilnacipran After a Single Oral Administration of a 40-mg Levomilnacipran Sustained-Release Capsule Under Fasted (Treatment A) and Fed Conditions

PK Parameter	Treatment A (Fasted) Mean ± SD (N = 22)	Treatment B (Fed) Mean ± SD (N = 22)	Ratio of Geometric Means, %	90% CI (%) or p-Value
C <sub>max</sub> , ng/mL	69.38 ± 14.22	77.87 ± 21.36	110.5	100.63-121.39
AUC <sub>0-t</sub> , ng·h/mL	1647.13 ± 327.77	1632.87 ± 377.65	98.5	89.18-108.75
AUC <sub>0-∞</sub> , ng·h/mL	1686.75 ± 329.75	1668.16 ± 370.38	98.4	89.34-108.36
T <sub>max</sub> , h	6.68 ± 1.62 6.0 (4.0, 12.0) <sup>b</sup>	8.18 ± 2.42 8.0 (5.0, 12.0) <sup>b</sup>	—	p = 0.0174 <sup>c</sup>
T <sub>1/2</sub> , h	11.39 ± 1.68	10.95 ± 1.23	—	—

a Two subjects excluded from PK analysis due to vomiting (1 subject) and withdrawing consent (1 subject).

b Median (minimum, maximum).

c Based on the Wilcoxon signed-rank test.

Mean C<sub>max</sub> was 10.5% higher in the fed group than in the fasted group. Mean AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were similar between the 2 treatments. The 90% CI of the geometric mean ratios of C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> were all within the range of 80% to 125% suggesting food does not have an effect.

2.4.5 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested?  
If so, were they bioequivalent or not?

Bioequivalence between the clinical and to-be-marketed formulations was only tested for Levomilnacipran 120 mg ER capsule, the highest to-be-marketed strength. The clinical and to-be-marketed formulations were bioequivalent. The sponsor is requesting a biowaiver for Levomilnacipran 20 mg, 40 mg and 80 mg ER strengths based on (b) (4) strengths and linear pharmacokinetics of Levomilnacipran. Refer to ONDQA-Biopharmaceutics review for the Agency's evaluation and decision on the biowaiver request.

2.4.6 What is the bioavailability of Levomilnacipran ER product relative to an intravenous (IV) formulation, immediate release (IR) and an oral solution?

The sponsor intends to market only the ER formulations. An IR formulation was made only in the initial stage of the developmental program. A total 3 ER formulations were developed and compared with the IR formulation during drug development. One formulation (SR2) was chosen for further development. Relative bioavailability of the ER formulation in reference to the IR formulation is 82%. The relative bioavailability of the levomilnacipran ER formulation referenced to the solution formulation was 92.5%. In these studies, pharmacokinetics between the IR and ER formulations were compared following a single dose administration. In addition, the 3 SR formulations were compared with an IV infusion following a single dose administration. Absolute bioavailability for the SR2 formulation was 101%.

The bioavailability of levomilnacipran following the administration of an IR and IV levomilnacipran formulations are presented in Tables 21 and 22. These studies were conducted using developmental formulations

Table 21: Mean (SD) Pharmacokinetic Parameters of Levomilnacipran Following Oral Administration of Levomilnacipran IR and ER Formulations in Healthy Male Subjects (N = 10)

Formulation (Dose)	$C_{max}$ , ng/mL	$T_{max}$ <sup>a</sup> , h	$AUC_{0-\infty}$ , h•ng/mL	$T_{1/2}$ , h	F, %
IR (25 mg)	64.4 (15.6)	2.5 (1, 6)	861 (207)	8.3 (0.7)	—
SR1 (50 mg)	89.5 (20.4)	6 (5, 8)	1611 (406)	10.9 (1.4)	93.6 (8.8)
SR2 (50 mg)	69.2 (21.6)	8 (5, 10)	1404 (338)	11.9 (1.5)	82.2 (11.5)
SR3 (50 mg)	62.0 (15.7)	7 (5, 12)	1318 (308)	12.8 (1.9)	76.9 (5.4)

a Median (minimum, maximum).

$AUC_{0-\infty}$  = area under the plasma concentration vs time curve from time 0 to infinity;  $C_{max}$  = maximum plasma drug concentration; F = relative bioavailability; IR = immediate release (formulation); SR = sustained release (formulation);  $T_{max}$  = time to maximum plasma drug concentration;  $T_{1/2}$  = terminal elimination half-life.

Table 22: Mean (SD) Pharmacokinetic Parameters of Levomilnacipran After 1-hour Intravenous Infusion of 20 mg and Oral Administration of Three Sustained-Release Formulations of 50-mg Levomilnacipran

Formulation (Dose)	$C_{max}$ , ng/mL	$T_{max}^a$ , h	$AUC_{0-\infty}$ , h•ng/mL	$T_{1/2}$ , h	CL, L/h	$V_z$ , L	$V_{3\beta}$ , L
IV (20 mg)	78.3 (18.3)	1 (0.75, 1)	602 (94)	8.82 (0.92)	34 (5.8)	431 (71.4)	408 (68.9)
Formulation (Dose)	$C_{max}$ , ng/mL	$T_{max}^a$ , h	$AUC_{0-\infty}$ , h•ng/mL	$T_{1/2}$ , h	$T_{lag}$ , h	F, %	
SR1 (50 mg)	84.9 (18.8)	5 (5, 7)	1610 (282)	12.1 (1.3)	0.25 (0-0.5)	107 (5.6)	
SR2 (50 mg)	71.7 (16.5)	6 (5, 7)	1495 (236)	12.8 (1.6)	0.5 (0-1)	101 (10.9)	
SR3 (50 mg)	59 (9.2)	7 (5, 8)	1344 (187)	13 (1.85)	1 (0-1)	90 (8.0)	

a Median (minimum, maximum).

$AUC_{0-\infty}$  = area under the plasma concentration vs time curve from time 0 to infinity; CL = total plasma body clearance;

$C_{max}$  = maximum plasma drug concentration; F = bioavailability; IV = intravenous; SR = sustained release;

$T_{1/2}$  = terminal elimination half-life;  $T_{lag}$  = absorption lag time;  $T_{max}$  = time to maximum plasma drug

concentration;  $V_z$  = volume of distribution at steady state;  $V_z$  = volume of distribution based on terminal phase.

#### 2.4.7 Relative Bioavailability with Oral Solution as Reference

The sponsor conducted a single-center, randomized, open-label,  $2 \times 2$  crossover, single and multiple-dose study to compare the pharmacokinetics of levomilnacipran ER capsule and levomilnacipran oral solution formulation after single- and multiple-dose administration. Subjects were randomized to 1 of 2 treatment sequences in which they received each of the treatments, with a 7-day washout period between treatments.

The pharmacokinetic parameters after single and multiple dose administration are provided in Table 23.

Table 23: PK Parameters (Mean  $\pm$  SD) for Levomilnacipran in Healthy Male and Female Subjects After Oral Single-Dose Administration of Levomilnacipran Oral Solution and Capsule Formulations

PK Parameter	Levomilnacipran Oral Solution, 40 mg (Treatment A) (N = 11)	Levomilnacipran SR Capsule, 120 mg (Treatment B) (N = 15)	Treatment B/Treatment A
			Ratio of Geometric Means %, (90% CI) <sup>a</sup>
$C_{max}$ , ng/mL	125.3 $\pm$ 27.4	213.3 $\pm$ 70.4	59.6 (52.7-67.4)
$AUC_{0-t}$ , ng•h/mL	1759.9 $\pm$ 369.4	4802.0 $\pm$ 1266.3	91.0 (86.6-95.6)
$AUC_{0-\infty}$ , ng•h/mL	1794.9 $\pm$ 372.9	4978.8 $\pm$ 1309.8	92.5 (89.0-96.1)
$T_{max}$ , h <sup>b</sup>	4.0 (1.0, 5.0)	6.0 (5.0, 12.0)	$p < 0.01^c$
$T_{1/2}$ , h	10.6 $\pm$ 3.3	13.7 $\pm$ 2.6	NA

a Based on dose-normalized parameter values

b Median (minimum, maximum).

c Wilcoxon signed rank test (N = 8, only subjects who had values for both treatments were included).

$AUC_{0-\infty}$  = area under the plasma concentration versus time curve from time zero to infinity;  $AUC_{0-t}$  = area under the

plasma concentration versus time curve from time zero to time t; CI = confidence interval;  $C_{max}$  = maximum

plasma drug concentration; h = hour(s); NA = not available; PK = pharmacokinetic; SR = sustained release;

$T_{1/2}$  = terminal elimination half-life;  $T_{max}$  = time of maximum plasma drug concentration.

Table 24: PK Parameters (Mean ± SD) for Levomilnacipran in Healthy Male and Female Subjects After Oral Multiple-Dose Administration of Levomilnacipran Oral Solution and Capsule Formulations

PK Parameter	Levomilnacipran Oral Solution, 40 mg (Treatment A) (N = 19)	Levomilnacipran SR Capsule, 120 mg (Treatment B) (N = 22)	Treatment B/Treatment A
			Ratio of Geometric Means %, (90% CI) <sup>a</sup>
C <sub>max,ss</sub> , ng/mL	185.0 ± 32.6	384.6 ± 66.1	69.7 (65.9-73.8)
AUC <sub>0-τ</sub> , ng•h/mL	2097.5 ± 220.7	5752.0 ± 871.2	91.2 (86.9-95.7)
C <sub>min,ss</sub> , ng/mL	31.5 ± 7.2	144.9 ± 25.1	155.2 (143.3-168.0)
T <sub>max,ss</sub> , h <sup>b</sup>	2.0 (1.0, 5.0)	5.0 (4.0, 6.0)	p < 0.01 <sup>c</sup>
C <sub>av,ss</sub> , ng/mL	87.4 ± 9.2	239.7 ± 36.3	NA
T <sub>1/2</sub> , h	12.0 ± 2.7	13.5 ± 3.3	
Fluctuation, %	175.5 ± 34.6	100.0 ± 19.7	
Swing, %	525.1 ± 207.7	170.6 ± 54.0	

a Based on dose-normalized parameter values

b Median (minimum, maximum).

c Wilcoxon signed rank test (N = 19, only subjects who had values for both treatments were included).

AUC<sub>0-τ</sub> = area under the plasma concentration versus time curve from time zero to dose-interval time τ; C<sub>av,ss</sub> = average plasma drug concentration at steady state; C<sub>max,ss</sub> = maximum plasma concentration at steady state; C<sub>min,ss</sub> = plasma concentration during a dosing interval at steady state; CI = confidence interval; h = hour(s); NA = not available; PK = pharmacokinetic; SR = sustained release; T<sub>1/2</sub> = terminal elimination half-life; T<sub>max,ss</sub> = time of maximum plasma concentration at steady state.

Table 25: PK Parameters (Mean ± SD) for Levomilnacipran in Healthy Male and Female Subjects After Oral Single-Dose Administration of Levomilnacipran Oral Solution and Capsule Formulations

PK Parameter	Levomilnacipran Oral Solution, 40 mg (Treatment A) (N = 11)	Levomilnacipran SR Capsule, 120 mg (Treatment B) (N = 15)	Treatment B/Treatment A
			Ratio of Geometric Means %, (90% CI) <sup>a</sup>
C <sub>max</sub> , ng/mL	125.3 ± 27.4	213.3 ± 70.4	59.6 (52.7-67.4)
AUC <sub>0-t</sub> , ng•h/mL	1759.9 ± 369.4	4802.0 ± 1266.3	91.0 (86.6-95.6)
AUC <sub>0-∞</sub> , ng•h/mL	1794.9 ± 372.9	4978.8 ± 1309.8	92.5 (89.0-96.1)
T <sub>max</sub> , h <sup>b</sup>	4.0 (1.0, 5.0)	6.0 (5.0, 12.0)	p < 0.01 <sup>c</sup>
T <sub>1/2</sub> , h	10.6 ± 3.3	13.7 ± 2.6	NA

a Based on dose-normalized parameter values

b Median (minimum, maximum).

c Wilcoxon signed rank test (N = 8, only subjects who had values for both treatments were included).

AUC<sub>0-∞</sub> = area under the plasma concentration versus time curve from time zero to infinity; AUC<sub>0-t</sub> = area under the plasma concentration versus time curve from time zero to time t; CI = confidence interval; C<sub>max</sub> = maximum plasma drug concentration; h = hour(s); NA = not available; PK = pharmacokinetic; SR = sustained release; T<sub>1/2</sub> = terminal elimination half-life; T<sub>max</sub> = time of maximum plasma drug concentration.

The result (T<sub>1/2</sub>, T<sub>max</sub>) of the comparison of the ER formulation with oral solution suggests that the ER formulation possesses extended release characteristics. Based on the single dose AUC data, the relative bioavailability of the levomilnacipran SR formulation referenced to the solution formulation was 92.5%.

#### 2.4.8 Does the ER product show dose dumping?

The potential of alcohol-mediated dose dumping of ER formulation was assessed in an *in vitro* alcohol dose dumping study. The sponsor submitted a request to waive an *in vivo* interaction study with alcohol and the Agency responded to the request stating that the waiver was appropriate.

The *in vitro* dissolution study in the presence of various amounts of alcohol was conducted on the intended commercial formulation of levomilnacipran SR capsules, 20 mg, 40 mg, 80 mg and 120 mg. All strengths of the ER capsules are dose-proportional (b) (4)

Dissolution media with alcohol concentrations of 5%, 20% and 40% were used. The sponsor stated that Levomilnacipran ER capsules, 20 mg, 40 mg, 80 mg and 120 mg exhibited no or little dose-dumping in alcohol. However, OCP reviewed, under IND 1004483, an *in vitro* dose dumping study for levomilnacipran SR capsules, 20 mg, 40 mg, 80 mg and 120 mg. Dissolution media with alcohol concentrations of 5%, 20% and 40% were evaluated. The most pronounced dose dumping was observed in 40% v/v alcohol. The results of this *in vitro* study confirmed that an interaction existed between levomilnacipran ER capsules and alcohol. In the presence of 40% alcohol, nearly the entire dose would be released in 4 hours although the formulation was designed to release the drug over a period of 24 hours. The issue of potential dose depending when Levomilnacipran is taken with 40% alcohol will be discussed with ONDQA- Biopharmaceutics and addressed in the label. (Refer to ONDQA Biopharm review for Agency's evaluation).

#### 2.4.9 What is the evidence that the ER formulation *in vivo* consistently shows claimed ER characteristics?

The ER formulation displays characteristics of sustained release (lower C<sub>max</sub>, longer time T<sub>max</sub>, and longer T<sub>1/2</sub> relative to oral solution following either single- or multiple-dose administration). Compared with the levomilnacipran SR capsule formulation, dose-normalized C<sub>max</sub> was significantly higher for the levomilnacipran oral solution. Following multiple dose treatment, dose-normalized C<sub>min</sub> was higher by 55.2% in subjects receiving the ER capsule than those receiving the oral solution (Tables 24, 25). T<sub>max</sub> and T<sub>1/2</sub> were shorter with the levomilnacipran oral solution compared to the SR capsule formulation.

There is a suggestion based on the comparison of the ER formulation to the oral solution that the ER formulation possesses sustained release characteristics.

## 2.5 Analytical Methods

*What bioanalytical methods are used to assess concentrations of Levomilnacipran and its metabolite, N-desethyl-levomilnacipran (F17400) and is the validation complete and acceptable?*

Levomilnacipran and its metabolite, N-desethyl levomilnacipran (F17400) were measured using a selective and sensitive LC-MS/MS method (electrospray ionization (ESI) mass spectrometry in

the positive ion multiple reaction monitoring (MRM) mode). The analytical methods were adequately validated and acceptable. The list of all assays used and brief descriptions are summarized in Tables 25 and 26.

Table 25: Summary of Bioanalytical Methods for determination of Levomilnacipran (free base) and the metabolite, F17400, used in Clinical Studies

<i>Bioanalytical Method</i>	<i>Method 1</i>	<i>Method 2</i>	<i>Method 3</i>
<b>Report Number(s)</b>	FRI Report Number PRD-RPT-BDM-00290	FRI Report Number PRD-RPT-BDM-00297	(b) (4)
<b>Location (laboratory or CRO)</b>	Farmingdale, NY, USA	Farmingdale, NY, USA	
<b>Year</b>	2009	2009	2003
<b>Matrix</b>	plasma	urine	plasma and urine
<b>Anticoagulant</b>	dipotassium EDTA		lithium heparin
<b>Sample Preparation</b>	liquid-liquid extraction	liquid-liquid extraction	on-line SPE
<b>Method Type</b>	LC-MS/MS	LC-MS/MS	TFC-LC/MS-MS
<b>Mass Spec Platform</b>	MDS SCIEX API3000	MDS SCIEX API3000	cohesive HTLC
<b>Analyte</b>	levomilnacipran and F17400	levomilnacipran and F17400	levomilnacipran
<b>Internal Standard</b>	[ <sup>2</sup> H <sub>10</sub> ]levomilnacipran and [ <sup>2</sup> H <sub>5</sub> ]F17400	[ <sup>2</sup> H <sub>10</sub> ]levomilnacipran and [ <sup>2</sup> H <sub>5</sub> ]F17400	[ <sup>2</sup> H <sub>10</sub> ]levomilnacipran
<b>Matrix Sample Size</b>	100 µL	50 µL	50 µL
<b>Calibration curve range (ng/mL), curve fit</b>	both: 1 to 200 (original), 1/x2 F2695: 1 to 500 (modified), 1/x2 F17400: 1-200 (modified), 1/x2	100 to 5000, 1/x2	plasma: 0.5 to 1500, 1/x2 urine: 50 to 50000, 1/x2
<b>Validation dilution fold</b>	10	10	plasma: 5, 10 urine: 5,10,20,50,100
<b>Matrix Stability, room temperature</b>	24 hours	24 hours	4 hours
<b>Matrix Stability, stored at temperature</b>	777 days at -30°C and -70°C	372 days, -30°C and -70°C	ca. 6 months, -20°C
<b>Extract Stability, stored at autosampler temperature</b>	88 hours, at 10°C	45 hours, at 10°C	39 hours, at 4°C
<b>Matrix Freeze/Thaw Stability, temperature</b>	5 cycles, -30°C and -70°C	4 cycles, -70°C 3 cycles, -30°C	3 cycles, -20°C
<b>Studies Supported</b>	LVM-PK-01, LVM-PK-02, LVM-PK-04, LVM-PK-05, LVM-PK-06, LVM-PK-07, LVM-PK-08, LVM-PK-09, LVM-PK-10, LVM-PK-12, LVM-PK-14, LVM-PK-15, LVM-PK-16, LVM-PK-19, LVM-MD-01, LVM-MD-02, LVM-MD-03	LVM-PK-01 LVM-PK-02 LVM-PK-05	F02695 GE 1 01 F02695 GE 1 02 F02695 LP 1 01

CRO = contract research organization ; TFC = turboflow chromatography; NA = not available  
LC = liquid chromatography; MS = mass spectrometry; FL = fluorescence; FRI = Forest Research Institute.

Table 26: Summary of Bioanalytical Methods Used in Clinical Studies contd.

<i>Bioanalytical Method</i>	<i>Method 4</i>	<i>Method 5</i>	<i>Method 6</i>
Report Number(s)	(b) (4)		
Location (laboratory or CRO)	(b) (4)		
Year	2005	2005	2009
Matrix	plasma	serum	plasma
Anticoagulant	lithium heparin		dipotassium EDTA
Sample Preparation	on-line SPE	on-line SPE	Protein Precipitation
Method Type	TFC-LC/MS-MS	TFC-LC/MS-MS	LC-FL
Mass Spec Platform	cohesive HTLC	cohesive HTLC	
Analyte	levomilnacipran and F2696	levomilnacipran	moxifloxacin
Internal Standard	[ <sup>2</sup> H <sub>10</sub> ]levomilnacipran	[ <sup>2</sup> H <sub>10</sub> ]levomilnacipran	(b) (4)
Matrix Sample Size	50 µL	50 µL	50 µL
Calibration curve range (ng/mL), curve fit	1 to 500, 1/x <sup>2</sup>	0.5 to 500, 1/x <sup>2</sup>	40 to 3000, 1/x <sup>2</sup>
Validation dilution fold	5, 10	5, 10	10
Matrix Stability, room temperature	4 hours	48 hours	24 hours
Matrix Stability, stored at temperature	ca. 1 year, -20°C	NA	38 days at -30°C and -70°C
Extract Stability, stored at autosampler temperature	ca. 7 days, at 4°C	45 hours, at 5°C ca. 3 days at -20 °C	97 hours, at 20°C
Matrix Freeze/Thaw Stability, temperature	NA	NA	4 cycles, -30°C
Studies Supported	F02695 LP 1 02	F02695 LP 2 01	LVM-PK-07

CRO= contract research organization ; TFC= turboflow chromatography; NA= not available  
 LC = liquid chromatography; MS = mass spectrometry; FL= fluorescence; FRI = Forest Research Institute.

Table 26 contd: Summary of Bioanalytical Methods Used in Clinical Studies contd.

<i>Bioanalytical Method</i>	<i>Method 7</i>	<i>Method 8</i>	<i>Method 9</i>
Report Number(s)	(b) (4)		
Location (laboratory or CRO)	(b) (4)		
Year	2006	2002	2010
Matrix	plasma	plasma	plasma
Anticoagulant	sodium heparin	sodium heparin	lithium heparin
Sample Preparation	liquid-liquid extraction	liquid-liquid extraction	liquid-liquid extraction
Method Type	LC-MS/MS	LC-MS/MS	LC-MS/MS
Mass Spec Platform	SCIEX API3000	SCIEX API3000 or Micromass Quattro	Micromass Quattro
Analyte	carbamazepine and carbamazepine 10, 11-epoxide	alprazolam	Levomilnacipran and F17400
Internal Standard	(b) (4)		[ <sup>3</sup> H <sub>10</sub> ]levomilnacipran and [ <sup>3</sup> H <sub>5</sub> ]F17400
Matrix Sample Size	50 µL	500 µL	0.2 mL
Calibration curve range (ng/mL), curve fit	both analytes: 0.05 to 37.5 µg/mL, quadratic	0.25 to 40 ng/mL, 1/x	1 to 250 ng/mL, 1/x
Validation dilution fold	NA	NA	50
Matrix Stability, room temperature	24 hours	27 hours	NA
Matrix Stability, stored at temperature	1110 days at -20°C	356 days, -20°C	7 months, -20°C
Extract Stability, stored at autosampler temperature	102 hours, at ambient	85 hours, at ambient	72 hours, at 10°C
Matrix Freeze/Thaw Stability, temperature	4 cycles, -20°C	3 cycles, -20°C	3 cycles, -20°C
Studies Supported	LVM-PK-09	LVM-PK-10	LVM-PK-03 (F02695 PO 1 01)

CRO= contract research organization ; TFC= turboflow chromatography; NA= not available

LC = liquid chromatography; MS = mass spectrometry; FL= fluorescence; FRI = Forest Research Institute.

2.5.1 Which metabolites have been selected for analysis and why?

N-Desethyl levomilnacipran (F17400), a pharmacologically inactive metabolite, was selected for analysis in some PK studies to understand its PK behavior and formation after administration of levomilnacipran SR in healthy subjects. This metabolite was found in plasma and urine after single- and multiple-dose administration of levomilnacipran, presenting approximately 15% of dosed levomilnacipran.

2.5.2 For all moieties measured, is free, bound, or total measured?

Total concentrations (bound+unbound) of levomilnacipran and F17400 were measured. About 22% of levomilnacipran bound to plasma proteins.

2.5.3 What are the lower and upper limits of quantitation?

Refer to summary Tables for analytical methods.

2.5.4 What are the accuracy, precision, and selectivity at these limits?

The inter-day and intra-day precision and accuracy for levomilnacipran and F17400 for Method 1, which was used in supporting most of the clinical studies in this submission are presented in Tables 27 and 28.

Table 27: Precision and Accuracy of Levomilnacipran QC Samples

<i>Method Validation</i>	<i>Observation</i>	<i>QC.1 (3 ng/mL)</i>	<i>QC.2 (50 ng/mL)</i>	<i>QC.3 (160 ng/mL)</i>
Accuracy (% deviation)	Intra-day	within $\pm 3.7$	within $\pm 1.1$	within $\pm 3.1$
	Inter-day	-2.7	-0.6	-2.1
Precision (% CV)	Intra-day	$\leq 3.5$	$\leq 1.8$	$\leq 1.7$
	Inter-day	3.0	1.4	2.1

CV = coefficient of variation; QC = quality control.

Table 28: Precision and Accuracy of F17400 QC Samples

<i>Method Validation</i>	<i>Observation</i>	<i>QC.1 (3 ng/mL)</i>	<i>QC.2 (50 ng/mL)</i>	<i>QC.3 (160 ng/mL)</i>
Accuracy (% deviation)	Intra-day	within $\pm 4.7$	within $\pm 0.7$	within $\pm 3.5$
	Inter-day	-3.3	-0.1	-2.2
Precision (% CV)	Intra-day	$\leq 3.8$	$\leq 1.3$	$\leq 3.5$
	Inter-day	2.9	1.2	2.6

CV = coefficient of variation; QC = quality control.

The following tablet (Table 29) gives the precision (CV%) and accuracy (%RE) for each analyte in studies that used Method 1 that was used to assay most of the clinical pharmacology studies.

Table 29: Accuracy and Precision of Standards and QC Samples in Studies Which Used Method 1

Protocol No. (Bioanalytical Study Report)	Analytes	Accuracy (% Deviation)		Precision (% CV)	
		Standards	QC Samples	Standards	QC Samples
LVM-PK-01 (PRD-RPT-BDM-00303)	levomilnacipran	within $\pm$ 3.6	within $\pm$ 5.5	$\leq$ 4.0	$\leq$ 2.4
	F17400	within $\pm$ 3.6	within $\pm$ 4.7	$\leq$ 4.0	$\leq$ 2.7
LVM-PK-02 (PRD-RPT-BDM-00311)	levomilnacipran	within $\pm$ 3.0	within $\pm$ 6.0	$\leq$ 3.6	$\leq$ 4.1
	F17400	within $\pm$ 2.6	within $\pm$ 4.9	$\leq$ 3.6	$\leq$ 2.8
LVM-PK-04 (PRD-RPT-BDM-00381)	levomilnacipran	within $\pm$ 2.5	within $\pm$ 3.3	$\leq$ 3.6	$\leq$ 12.6
	F17400	within $\pm$ 3.4	within $\pm$ 1.9	$\leq$ 5.0	$\leq$ 7.0
LVM-PK-05 (PRD-RPT-BDM-00370)	levomilnacipran	within $\pm$ 1.6	within $\pm$ 0.9	$\leq$ 2.8	$\leq$ 6.0
	F17400	within $\pm$ 2.7	within $\pm$ 4.3	$\leq$ 4.2	$\leq$ 7.0
LVM-PK-06 (PRD-RPT-BDM-00312)	levomilnacipran	within $\pm$ 3.7	within $\pm$ 9.5	$\leq$ 3.6	$\leq$ 3.2
	F17400	NA	NA	NA	NA
LVM-PK-07 (PRD-RPT-BDM-00450)	levomilnacipran	within $\pm$ 2.9	within $\pm$ 5.9	$\leq$ 3.8	$\leq$ 5.4
	F17400	within $\pm$ 3.2	within $\pm$ 4.2	$\leq$ 5.0	$\leq$ 7.1
LVM-PK-08 (PRD-RPT-BDM-00368)	levomilnacipran	within $\pm$ 2.4	within $\pm$ 6.1	$\leq$ 2.5	$\leq$ 9.5
	F17400	within $\pm$ 2.8	within $\pm$ 5.2	$\leq$ 2.5	$\leq$ 6.2
LVM-PK-09 (PRD-RPT-BDM-00379)	levomilnacipran	within $\pm$ 3.6	within $\pm$ 5.2	$\leq$ 4.9	$\leq$ 6.5
	F17400	within $\pm$ 3.8	within $\pm$ 5.3	$\leq$ 5.4	$\leq$ 7.2
LVM-PK-10 (PRD-RPT-BDM-00382)	levomilnacipran	within $\pm$ 3.2	within $\pm$ 3.7	$\leq$ 6.2	$\leq$ 8.7
	F17400	NA	NA	NA	NA
LVM-PK-12 (PRD-RPT-BDM-00412)	levomilnacipran	within $\pm$ 3.3	within $\pm$ 6.0	$\leq$ 4.0	$\leq$ 8.0
	F17400	NA	NA	NA	NA
LVM-PK-14 (PRD-RPT-BDM-00528)	levomilnacipran	within $\pm$ 4.1	within $\pm$ 3.7	$\leq$ 3.0	$\leq$ 13.0
	F17400	NA	NA	NA	NA
LVM-PK-15 (PRD-RPT-BDM-00390)	levomilnacipran	within $\pm$ 2.5	within $\pm$ 5.8	$\leq$ 3.9	$\leq$ 5.9
	F17400	NA	NA	NA	NA
LVM-PK-16 (PRD-RPT-BDM-00454)	levomilnacipran	within $\pm$ 1.7	within $\pm$ 3.5	$\leq$ 5.0	$\leq$ 4.8
	F17400	NA	NA	NA	NA
LVM-PK-19 (PRD-RPT-BDM-00441)	levomilnacipran	within $\pm$ 7.1	within $\pm$ 7.1*	$\leq$ 4.0	$\leq$ 3.3*
	F17400	NA	NA	NA	NA
LVM-MD-01 (PRD-RPT-BDM-00449)	levomilnacipran	within $\pm$ 5.0	within $\pm$ 2.6	$\leq$ 5.3	$\leq$ 5.8
	F17400	NA	NA	NA	NA
LVM-MD-02 (PRD-RPT-BDM-00401)	levomilnacipran	within $\pm$ 2.4	within $\pm$ 1.7	$\leq$ 4.4	$\leq$ 3.1
	F17400	NA	NA	NA	NA
LVM-MD-03 (PRD-RPT-BDM-00527)	levomilnacipran	within $\pm$ 5.1	within $\pm$ 4.1	$\leq$ 3.5	$\leq$ 4.0
	F17400	NA	NA	NA	NA

CV = coefficient of variation; \*excluding outliers

NA: Not Available, only levomilnacipran concentrations were determined.

The following table (Table 30) contains the Incurred Sample Reanalysis (ISR) data that was performed for studies using Method 1. The acceptance criteria was that for chromatographic

analysis, two-thirds (2/3) of the ISR results for each compound should be within  $\pm 20\%$  of the original value.

Table 30: Incurred Sample Reanalysis (ISR)

<i>Protocol No. (Bioanalytical Study Report)</i>	<i>Number of ISR Samples</i>		<i>Percentage of ISR samples passing the Acceptance criteria (%)</i>	
	<i>Levomilnacipran</i>	<i>F17400</i>	<i>Levomilnacipran</i>	<i>F17400</i>
LVM-PK-01 (PRD-RPT-BDM-00303)	77 (out of 1253)	77 (out of 1253)	98.7	98.7
LVM-PK-02 (PRD-RPT-BDM-00311)	24 (out of 479)	24 (out of 479)	100	100
LVM-PK-04 (PRD-RPT-BDM-00381)	51 (out of 512)	51 (out of 512)	98.0	98.0
LVM-PK-05 (PRD-RPT-BDM-00370)	40 (out of 480)	40 (out of 480)	100	95.0
LVM-PK-06 (PRD-RPT-BDM-00312)	32 (out of 623)	NA	100	NA
LVM-PK-07 (PRD-RPT-BDM-00450)	212 (out of 3123)	212 (out of 3123)	100	97.6
LVM-PK-08 (PRD-RPT-BDM-00368)	94 (out of 952)	94 (out of 952)	98.9	100
LVM-PK-09 (PRD-RPT-BDM-00379)	100 (out of 995)	100 (out of 995)	96.0	97.0
LVM-PK-10 (PRD-RPT-BDM-00382)	48 (out of 480)	NA	97.9%	NA

The ISR procedure, computation and results are acceptable.

#### 2.5.5 What is the sample stability under conditions used in the study?

The samples were stable for 24 hours at room temperature.

The long-term storage stability for levomilnacipran and F17400 are summarized in Table 31 below.

Table 31: Levomilnacipran and F17400 Stability in Human Plasma and Urine when stored at -70°C and -30°C

<i>Biomatrix</i>	<i>Levomilnacipran Storage Stability (days)</i>	<i>F17400 Storage Stability (days)</i>
Human plasma	778	778
Human urine	462	462

2.5.6 *Are there any analytical issues identified? If so, what is the status?*

No significant analytical issues were identified. The Office of Scientific Investigation (OSI) conducted an inspection of the pivotal bioequivalence studies linking the clinical trial formulations to the TBM formulations. No significant deficiency was reported and they recommended acceptance of the clinical pharmacology studies inspected.

## 3.0 Appendix

### 3.1 Clinical Pharmacology and Biopharmaceutics Studies

BA (food effect)	LVM-PK-06	5.3.1.1	Evaluate the effect of food on the BA of 40-mg F2695 capsules	Phase 1, single-center, randomized, open-label, 2 × 2 crossover, single-dose study; no control	F2695 SR 40-mg capsules <b>Treatment A:</b> Single 40-mg dose (fasted conditions); <b>Treatment B:</b> Single 40-mg dose (fed conditions)	24	Healthy male and female volunteers	2 dosing days, each followed by a 7-day washout	Complete Full
BE (TBM 120-mg capsule), BA (food effect)	LVM-PK-12	5.3.1.1	Objectives: evaluate 1) the BE of LVM 120 mg administered as the TBM 120-mg SR capsule and as the clinical SR capsules and 2) the effect of food on the oral BA of the TBM LVM 120-mg SR capsule	Phase 1, single-center, randomized, open-label, crossover, single-dose study; no control	TBM formulation of LVM SR 120-mg capsules; clinical formulation of LVM SR, 40-mg capsules <b>Treatment A:</b> Single dose of the TBM formulation of LVM, one 120-mg capsule (fasted conditions); <b>Treatment B:</b> Single dose of the clinical formulation of LVM, three 40-mg capsules (fasted conditions); <b>Treatment C:</b> Single oral dose of the TBM formulation of LVM, one 120-mg capsule (fed conditions)	50	Healthy male and female volunteers	1 day in each of 3 treatment periods, separated by a washout of 7 days	Complete Full
BE (TBM (b) (4) formulation)	LVM-PK-14	5.3.1.2	Evaluate the BE of LVM 120 mg administered as the TBM (b) (4) SR capsule (1 × 120 mg) and as the clinical SR capsules (3 × 40 mg)	Phase 1, single-center, randomized, open-label, crossover, single-dose study; no control	(b) (4) site formulation of LVM, 120-mg SR capsules; clinical formulation of LVM, 40-mg SR capsules <b>Treatment A:</b> Single dose of LVM (b) (4) site formulation, one 120-mg capsule; <b>Treatment B:</b> Single dose of clinical LVM, three 40-mg capsules	61	Healthy male and female volunteers	1 day in each of 2 treatment periods, separated by a washout of 7 days	Complete Full

BA (food effect)	LVM-PK-06	5.3.1.1	Evaluate the effect of food on the BA of 40-mg F2695 capsules	Phase 1, single-center, randomized, open-label, 2 × 2 crossover, single-dose study; no control	F2695 SR 40-mg capsules <b>Treatment A:</b> Single 40-mg dose (fasted conditions); <b>Treatment B:</b> Single 40-mg dose (fed conditions)	24	Healthy male and female volunteers	2 dosing days, each followed by a 7-day washout	Complete Full
BE (TBM 120-mg capsule), BA (food effect)	LVM-PK-12	5.3.1.1	Objectives: evaluate 1) the BE of LVM 120 mg administered as the TBM 120-mg SR capsule and as the clinical SR capsules and 2) the effect of food on the oral BA of the TBM LVM 120-mg SR capsule	Phase 1, single-center, randomized, open-label, crossover, single-dose study; no control	TBM formulation of LVM SR 120-mg capsules; clinical formulation of LVM SR, 40-mg capsules <b>Treatment A:</b> Single dose of the TBM formulation of LVM, one 120-mg capsule (fasted conditions); <b>Treatment B:</b> Single dose of the clinical formulation of LVM, three 40-mg capsules (fasted conditions); <b>Treatment C:</b> Single oral dose of the TBM formulation of LVM, one 120-mg capsule (fed conditions)	50	Healthy male and female volunteers	1 day in each of 3 treatment periods, separated by a washout of 7 days	Complete Full
BE (TBM (b) (4) formulation)	LVM-PK-14	5.3.1.2	Evaluate the BE of LVM 120 mg administered as the TBM (b) (4) SR capsule (1 × 120 mg) and as the clinical SR capsules (3 × 40 mg)	Phase 1, single-center, randomized, open-label, crossover, single-dose study; no control	(b) (4) site formulation of LVM, 120-mg SR capsules; clinical formulation of LVM, 40-mg SR capsules <b>Treatment A:</b> Single dose of LVM (b) (4) site formulation, one 120-mg capsule; <b>Treatment B:</b> Single dose of clinical LVM, three 40-mg capsules	61	Healthy male and female volunteers	1 day in each of 2 treatment periods, separated by a washout of 7 days	Complete Full

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
<b>Pharmacokinetic Studies (Continued)</b>									
Safety, tolerability, PK	LVM-PK-01	5.3.3.1	Evaluate safety and tolerability and characterize the PK of F2695	Phase 1, single-center, randomized, double-blind, placebo-controlled, single (part A) and multiple-dose (part B); placebo control	F2695 SR, 25- and 50-mg capsules Part A: single-dose F2695 25, 50, or 100 mg or placebo; Part B: multiple escalating dose F2695 25, 50, 75, and 100 mg or placebo; or F2695 25, 50, 100, 125, 150, 200, 250, and 300 mg or placebo	48	Healthy male and female volunteers	Part A: 1 day Part B, Cohort B1: Up to 16 days Part B, Cohort B2: Up to 36 days	Complete Full
PK, tolerability, mass balance (liquid formulation)	LVM-PK-03 (F02695 PO 1 01)	5.3.3.1	Determine in healthy male subjects, the rate and route of excretion of a single oral dose of [ <sup>14</sup> C]-F2695, explore PK parameters of radioactivity, F2695 and F17400 following a single oral dose of [ <sup>14</sup> C]-F2695, collect samples in order to characterize and/or quantify the metabolites of F2695 in plasma and excreta following a single oral dose of [ <sup>14</sup> C]-F2695, and assess the clinical and biological tolerability of [ <sup>14</sup> C]-F2695 administered as single 60-mg oral dose in healthy subjects	Phase 1, single-dose study; no control	[ <sup>14</sup> C]-F2695 solution A 5-g single oral dose (approximately 5 mL) solution containing 60 mg of [ <sup>14</sup> C]-F2695 with 100 µCi radioactivity)	9	Healthy male volunteers	1 day	Complete Full
Safety, tolerability, PK	LVM-PK-15	5.3.3.1	Characterize the PK of LVM following oral administration of 40-, 80-, or 120-mg LVM SR capsules	Phase 1, single-center, randomized, open-label, parallel-group, single-dose study; no control	LVM 40-mg SR capsules Cohort I: Single dose of one 40-mg LVM capsule; Cohort II: Single dose of two 40-mg LVM capsules; Cohort III: Single dose of three 40-mg LVM capsules	30	Healthy male and female volunteers	1 day	Complete Full
<b>Intrinsic Factors</b>									
Safety, PK (renal impairment)	LVM-PK-02	5.3.3.3	Evaluate the PK characteristics and safety profile of F2695 and its nonactive metabolite F17400 after a single dose of 40 mg F2695 in subjects with various degrees of impaired renal function	Phase 1, single-dose, open-label, parallel-group design in 4 groups; no control	F2695 SR, 40-mg capsule, single dose	32	Healthy and renal impaired male and female volunteers	1 day	Complete Full
Safety, PK (age and gender effect)	LVM-PK-04	5.3.3.3	Evaluate 1) the effects of age and gender on the PK of F2695 and its metabolite F17400 following multiple-dose administration and 2) the safety profile of multiple doses of F2695 SR in healthy young adult and elderly male and female subjects	Phase 1, open-label, parallel-group study in 2 groups of subjects; no control	F2695 SR, 20- and 40-mg capsules Day 1: 20-mg single dose; Days 2 through 4: 40 mg once daily; Days 5 through 9: 80 mg (2 × 40 mg) once daily	33	Healthy male and female volunteers	9 dosing days	Complete Full

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
<b>Intrinsic Factors (Continued)</b>									
Safety, PK (hepatic impairment)	LVM-PK-05	5.3.3.3	Evaluate the PK characteristics and safety profile of F2695 and its nonactive metabolite F17400 after a single oral dose of 40 mg F2695 SR in male and female patients with various degrees of impaired hepatic function compared with healthy subjects with normal hepatic function	Phase 1, single-dose, open-label, parallel-group study; no control	F2695 SR, 40-mg capsule, single dose	32	Healthy and hepatic impaired male and female volunteers	1 day	Complete Full
<b>Extrinsic Factors</b>									
Safety, tolerability, PK, drug interaction (ketoconazole)	LVM-PK-08	5.3.3.4	Assess the effects of ketoconazole at steady state on the PK of a single dose of F2695	Phase 1, single-center, randomized, open-label, 2 × 2 crossover, drug-drug interaction study; no control	F2695 SR 40-mg capsules); ketoconazole, 200-mg tablets <b>Treatment A:</b> F2695 alone (single oral dose of F2695 80 mg); <b>Treatment B:</b> F2695 coadministered with ketoconazole 400 mg once daily for 5 days; ketoconazole 400 mg plus F2695 80 mg for 1 day, then ketoconazole 400 mg once daily for 3 days	34	Healthy male and female volunteers	2 days (2 doses separated by a washout period of at least 6 days)	Complete Full
Safety, tolerability, PK, drug interaction (alprazolam)	LVM-PK-10	5.3.3.4	Assess the effect of a F2695 SR capsule at steady state on the PK of alprazolam following single-dose administration of an alprazolam XR tablet	Phase 1, single-center, randomized, open-label, 2 × 2 crossover, drug-drug interaction study; no control	F2695 SR 20- and 40-mg capsules; alprazolam XR 1-mg tablet <b>Treatment A:</b> Single dose of alprazolam 1 mg under fasted conditions; <b>Treatment B:</b> F2695 20 mg for 1 day, 40 mg once daily for 3 days, 80 mg once daily for 3 days, and 120 mg once daily for 4 days; coadministration of F2695 120 mg plus alprazolam 1 mg for 1 day (fasted conditions), followed by F2695 120 mg once daily for 2 days	30	Healthy male and female volunteers	1 day in Treatment A, 14 days in Treatment B, separated by a washout period of at least 7 days	Complete Full
<b>Pharmacokinetic/Pharmacodynamic Study</b>									
Thorough QT	LVM-PK-07	5.3.4.1	Assess the effects of the investigated maximum therapeutic dose (120 mg/day) and a supratherapeutic dose (300 mg/day) of LVM on cardiac repolarization as determined by manual measurement of QTc on repeated digitally recorded 12-lead electrocardiograms	Phase 1, multicenter, randomized (stratified by sex), double-blind, placebo- and positive-controlled, parallel-group, multiple-dose study; placebo and positive controls	LVM 20- and 40-mg capsules. <b>Group 1:</b> placebo for 2 days; LVM 20 mg for 1 day, 40 mg for 3 days, 80 mg for 3 days, 120 mg for 4 days, 160 mg for 3 days, 200 mg for 3 days, 260 mg for 3 days, and 300 mg for 4 days, placebo for 1 day; <b>Group 2:</b> placebo for 2 days; moxifloxacin 400 mg for 1 day; and placebo for 24 days; <b>Group 3:</b> placebo for 26 days and moxifloxacin 400 mg for 1 day. All doses administered once daily	170 Group 1: 94 Group 2: 39 Group 3: 37	Healthy male and female volunteers	27 days	Complete Full

## In vitro pharmacokinetic studies

<i>Study No.</i>	<i>Title Objective</i>	<i>Test Substance</i>	<i>Materials Used</i>
CEPC 05-0164 <sup>a</sup>	Determination of the <i>In-Vitro</i> Binding of [ <sup>14</sup> C]-F2695 to the Plasma Proteins and Blood Cells of Human <b>Objective:</b> to identify which human plasma proteins are involved in the binding of F2695, and to determine the free fraction available in order to show if the plasma protein binding is restrictive or not for the tissue distribution of the drug.	LVM	<ul style="list-style-type: none"> <li>• <b>Blood:</b> human blood obtained from 3 healthy donors (2 males and 1 female, 15-65 years)</li> <li>• <b>Plasma:</b> human plasma obtained from previous bloods</li> <li>• <b>Protein solutions:</b> Albumin from human, (Solution 30%) (HSA + FFA), <math>\alpha</math>-1 glycoprotein, <math>\gamma</math>-globulin</li> </ul>
PK07MXH1	Characterization of Human Cytochrome P450 Isoenzymes Involved in the Metabolism of Milnacipran Enantiomers <b>Objective:</b> to get a better knowledge of the <i>in vitro</i> metabolism of milnacipran (F2207) enantiomers and to determine which cytochromes P450 were involved in the biotransformation of milnacipran enantiomers. This knowledge allows to predict drug-drug interaction risks in clinical use.	LVM (F2695) F2696	<ul style="list-style-type: none"> <li>• <b>Human liver microsomes:</b> a pool prepared with 5 batches of human liver microsomes (1st experiment) then 15 batches of human liver microsomes)</li> <li>• <b>Cryopreserved human hepatocytes:</b> hepatocyte cultures prepared from 3 human subjects (a 55-year old woman, a 30-year old woman and a 41-year old man)</li> <li>• <b>cDNA-expressed human P450 enzymes (Supersomes™):</b> human CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 Supersomes™</li> </ul>
LVM-PR-52 <sup>a</sup> (XT104114)	<i>In Vitro</i> Cytochrome P450 Reaction Phenotyping of F2695 in Human Liver Microsomes <b>Objective:</b> to determine the role of human cytochrome P450 (CYP) enzymes in the N-dealkylation of F2695 to F17400.	LVM, LVM metabolite (F17400 oxalate salt)	<ul style="list-style-type: none"> <li>• Human liver microsomes from non-transplantable, donated livers from a pool of 200 individuals</li> <li>• Recombinant human CYP enzymes (Bactosomes) expressed in <i>Escherichia Coli</i> as the control</li> <li>• Monoclonal antibodies (ascites fluid) against CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4</li> </ul>
CEPC 05-017 <sup>a</sup>	Evaluation of Human Drug-Metabolizing Enzyme Induction Properties of F2695: <i>In Vitro</i> Experiments <b>Objective:</b> to evaluate the hepatic enzymes induction properties of F2695, in order to anticipate potential changes in the pharmacokinetics of F2695 and other co-administered drugs in clinical use.	LVM	Human hepatocytes from 5 individuals (3 males and 2 females, 31-75 years)

<i>Study No.</i>	<i>Title Objective</i>	<i>Test Substance</i>	<i>Materials Used</i>
CEPC 05-0174 <sup>a</sup>	Evaluation of Human Cytochrome P450 Inhibitory Properties of F2695: <i>In Vitro</i> Experiments <b>Objective:</b> to evaluate <i>in vitro</i> the human CYP inhibitory properties of F2695 in order to predict the risk of drug-drug interactions of this type.	LVM	Human hepatocytes from 2 individuals
LVM-PR-53 (XT10512)	<i>In Vitro</i> Evaluation of F17400 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes <b>Objective:</b> : to evaluate <i>in vitro</i> the human CYP inhibitory properties of F17400	F17400	Human liver microsomes from 16 individuals
PRD-RPT-EXP-00070 <sup>a</sup>	Investigation of P-Glycoprotein Inhibitory Potential of F17400 Using Caco-2 Cell Monolayers <b>Objective:</b> to evaluate the P-gp inhibitory potential of F17400 using the Caco-2 cell model.	F17400	Caco-2 cell monolayer
PRD-RPT-EXP-00071 <sup>a</sup>	Investigation of P-Glycoprotein Inhibitory Potential of Levomilnacipran Using Caco-2 Cell Monolayers <b>Objective:</b> to evaluate the P-gp inhibitory potential of Levomilnacipran using the Caco-2 cell model.	LVM	Caco-2 cell monolayer
PRD-RPT-EXP-00072 <sup>a</sup>	Investigation of P-Glycoprotein Substrate Potential of F17400 Using Caco-2 Cell Monolayers <b>Objective:</b> to evaluate the P-gp substrate potential of F17400 using the Caco-2 cell model.	F17400	Caco-2 cell monolayer
PRD-RPT-EXP-00073 <sup>a</sup>	Investigation of P-Glycoprotein Substrate Potential of Levomilnacipran Using Caco-2 Cell Monolayers <b>Objective:</b> to evaluate the P-gp substrate potential of Levomilnacipran using the Caco-2 cell model.	LVM	Caco-2 cell monolayer
PRD-RPT-EXP-00079 <sup>a</sup>	Assessment of F17400 as Substrate of Human OAT1-, OAT3- or OCT2-Mediated Transport <b>Objective:</b> to assess whether F17400 was transported by human transporters OAT1, OAT3, and OCT2.	F17400	<ul style="list-style-type: none"> <li>• MDCK-II cells expressing human solute carrier transporter OAT1, OAT3, or OCT2</li> <li>• MDCK-II control cells transfected with a control vector</li> </ul>

<i>Study No.</i>	<i>Title Objective</i>	<i>Test Substance</i>	<i>Materials Used</i>
PRD-RPT-EXP-00080 <sup>a</sup>	Assessment of F2695 as substrate of human OCT2-, OAT1-, OAT3-, OATP1B1- and OATP1B3-mediated transport. <b>Objective:</b> to assess whether F2695 was transported by human transporters OCT2, OAT1, OAT3, OATP1B1 and OATP1B3.	LVM	<ul style="list-style-type: none"> <li>• MDCK-II cells expressing human solute carrier transporter OAT1, OAT3, OCT2, OATP1B1, or OATP1B3</li> <li>• MDCK-II control cells transfected with a control vector</li> </ul>
PRD-RPT-EXP-00081 <sup>a</sup>	Assessment of F17400 as potential inhibitor of human OCT2, OAT1 or OAT3- mediated transport. <b>Objective:</b> to determine whether or not F17400 inhibits the transport of substrate by OAT1, OAT3 or OCT2.	F17400	<ul style="list-style-type: none"> <li>• MDCK-II cells expressing human solute carrier transporter OAT1, OAT3, OCT2, OATP1B1, or OATP1B3</li> <li>• MDCK-II control cells transfected with a control vector</li> </ul>
PRD-RPT-EXP-00082 <sup>a</sup>	Assessment of F2695 as potential inhibitor of human OCT2, OAT1, OAT3, OATP1B1 or OATP1B3- mediated transport. <b>Objective:</b> to determine whether or not F2695 inhibits the transport of substrate by OAT1, OAT3, OCT2, OATP1B1 or OATP1B3.	LVM	<ul style="list-style-type: none"> <li>• MDCK-II cells expressing human solute carrier transporter OAT1, OAT3, OCT2, OATP1B1, or OATP1B3</li> <li>• MDCK-II control cells transfected with a control vector</li> </ul>
PRD-RPT-EXP-00087	Evaluation of Levomilnacipran based on Biopharmaceutics Classification System Guidance <b>Objective:</b> to evaluate the pH-solubility of Levomilnacipran and its stability in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) according to the FDA's BCS guidance; to determine the permeability of levomilnacipran in the Caco-2 cell model, and to assign to Levomilnacipran an appropriate BCS class.	LVM	Dissolution media and Caco-2 cell monolayer
PRD-RPT-EXP-00091 <sup>a</sup>	Investigation of Breast Cancer Resistance Protein (BCRP) Substrate and Inhibitory Potential of Levomilnacipran Using Caco-2 Cell Monolayers <b>Objective:</b> to evaluate the BCRP substrate and inhibitory potential of levomilnacipran using the Caco-2 cell model.	LVM	Caco-2 cell monolayer

<sup>a</sup> Study supporting the label  
F17400 = N-desethyl-levomilnacipran; LVM = levomilnacipran

Source: Clinical Pharmacology Summary

### 3.2 Pharmacometric Review

## OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

NDA Number	204168
Drug Name	Levomilnacipran
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Sponsor	Forest Laboratories Inc.

## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following five key questions:

1.1.1 Is the proposed once daily dose of 40-120 mg levomilnacipran, by the sponsor, appropriate for major depressive disorder (MDD) patients?

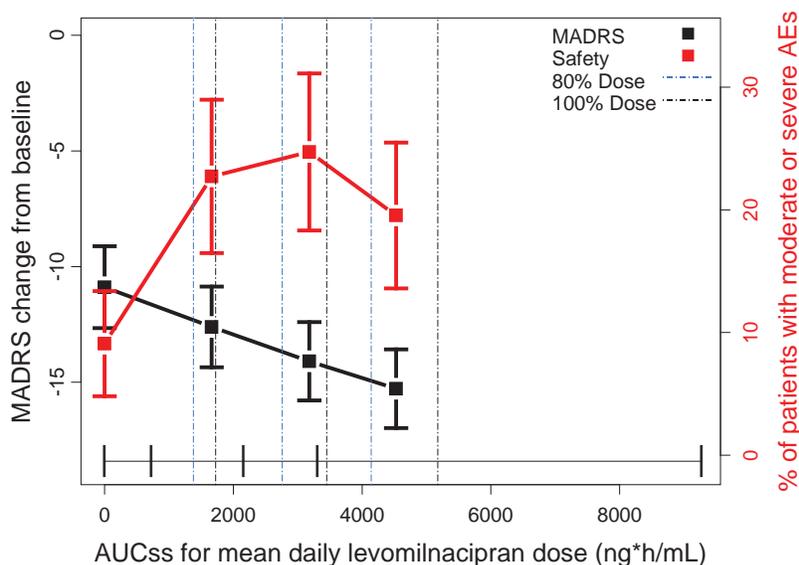
The proposed dose range of 40-120 mg once daily (QD) is appropriate for patients with MDD.

- Benefit and risk plot supports the proposed dose regimen of 40-120 mg QD in MDD patients (**Figure 1**).
- Although the dose compliance data and patient dropout data of LVM-MD-01 (the Phase III fixed dose study) indicated tolerability issue in the MDD patients, the overall outcome still supports the proposed daily dose of 40-120 mg (**Figure 2**).
- Dose compliance data and patient dropout data of LVM-MD-02 and LVM-MD-03 (the two Phase III flexible dose studies with 40-120 mg QD designed as optimal dose range) are also supportive to the proposed dose range of 40-120 mg QD (**Figure 3**).

Exposure-response relationship in the patient population of Study LVM-MD-01 is shown in **Figure 1**. The exposure is steady-state AUC of mean daily levomilnacipran dose, the efficacy response is change from baseline in MADRS scores, and the safety response is the percentage of patients who experienced adverse events. Exposure Quartiles 1, 2, 3 and 4 in **Figure 1** approximately represent the following 4 treatment arms: placebo, 10-40 mg, 41-80 mg and 81-120 mg QD levomilnacipran, respectively.

- MADRS changes (mean  $\pm$  95% CI) from the baselines for Quartiles 1-4 were  $-10.9 \pm 1.8$  (n=176),  $-12.6 \pm 1.7$  (n=176),  $-14.1 \pm 1.7$  (n=178) and  $-15.3 \pm 1.7$  (n=174), respectively.
- Proportion of patients experienced moderate or severe adverse events (AEs) were  $9.1 \pm 4.3\%$ ,  $22.7 \pm 6.3\%$ ,  $24.7 \pm 6.4\%$  and  $19.5 \pm 6.0\%$  for Quartiles 1-4, respectively.

**Figure 1: Primary efficacy scores (black lines and 95% CI bars against left Y axis) and moderate/severe adverse event rates (red lines and 95% CI bars against right Y axis) versus levomilnacipran exposure (X axis) in major depressive disorder patients in Study LVM-MD-01**



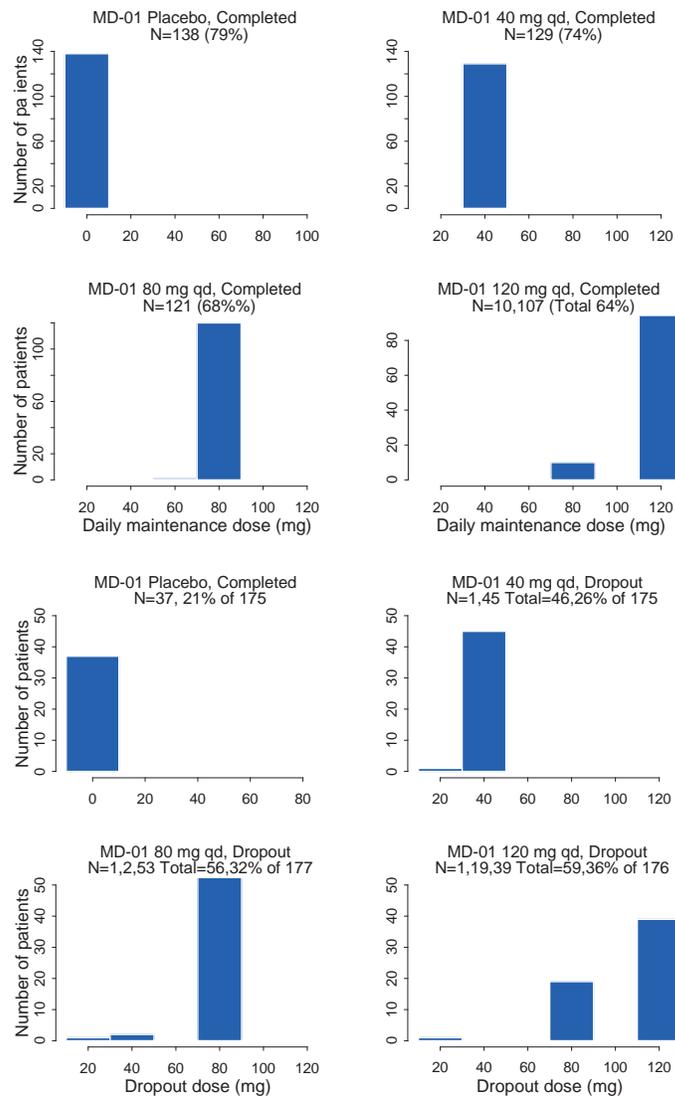
AEs: adverse events; AUCss: area under levomilnacipran concentration-time curve at steady-state; CI: confidence interval; MADRS: Montgomery Åsberg Depression Rating Scale

Regarding levomilnacipran dose compliance and dropout data in Study LVM-MD-01, **Figure 2** demonstrated:

- The completion rates of patients in placebo, 40, 80 and 120 mg arms were 79%, 74%, 68% and 64%, respectively.
- The dropout rates of patients in placebo, 40, 80 and 120 mg arms were 21%, 26%, 32% and 36%, respectively.
- Amongst patients completed the study, 10 patients of 120 mg arm had 80 mg QD as the highest administered dose.

Of 207 (29% of 713) dropout patients in LVM-MD-01, 55 (7.7%) were due to withdrawal of consent, 54 (7.6%) were due to adverse events, 47 (6.6%) were lost to follow-up, 33 (4.6%) were due to protocol violation, 15 (2.1%) were due to insufficient therapeutic response and 3 (0.4%) were due to other reasons (Source: Page 3 of the study report).

**Figure 2: Levomilnacipran Dose Distribution in Study LVM-MD-01**



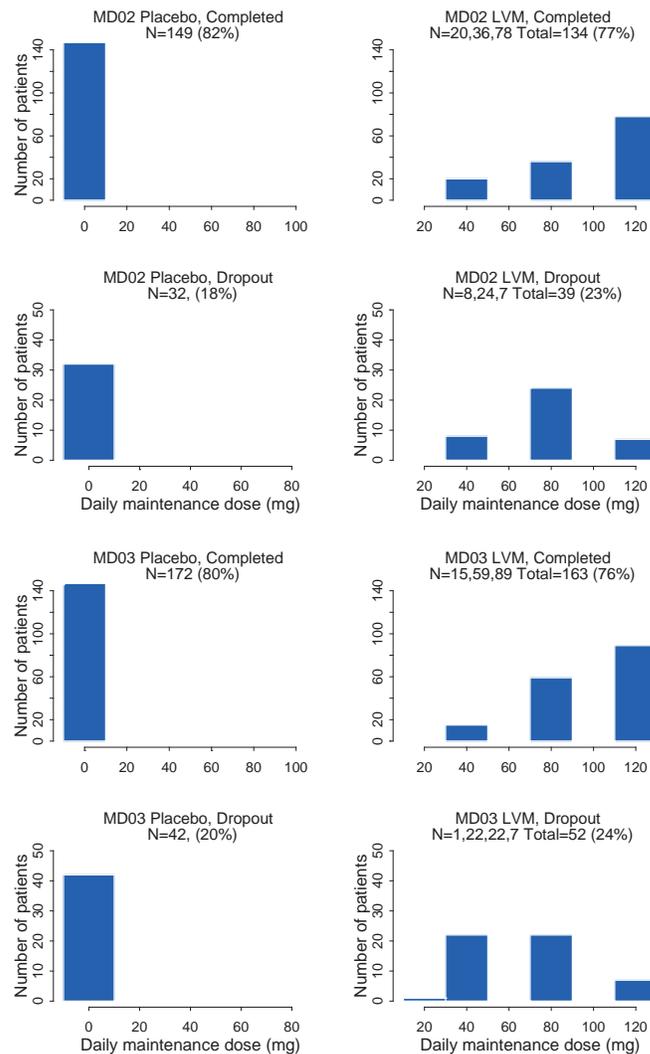
Regarding levomilnacipran dose compliance and dropout data in Studies LVM-MD-02 and LVM-MD-03 (the two Phase III flexible dose studies) for study Days 8-56, **Figure 3** demonstrated:

- Dropout rate was about 4-5% higher in levomilnacipran arm than placebo arm.
- Completion rate was about 4-5% lower in levomilnacipran arm than placebo arm.
- The ratio was 1:3:5 for 40, 80 and 120 mg arms for patients who completed Studies LVM-MD-02 and 03. In LVM-MD-02, there were 20, 36 and 78 patients on 40, 80 and 120 mg arms, respectively, completed the study. In LVM-MD-03, there were 15, 59 and 89 on 40, 80 and 120 mg arms, respectively, completed the study.

Of 73 (20.4% of 357) dropout patients in LVM-MD-02, 22 (6.2%) were due to withdrawal of consent, 18 (5.0%) were due to adverse events, 9 (2.5%) were lost to follow-up, 21 (5.9%) were due to protocol violation, 2 (0.6%) were due to insufficient therapeutic response and 1 (0.3%) was due to other reason (Source: Page 82 of the study report).

Of 99 (22.8% of 335) dropout patients in LVM-MD-03, 17 (3.9%) were due to withdrawal of consent, 24 (5.5%) were due to adverse events, 30 (6.9%) were lost to follow-up, 17 (3.9%) were due to protocol violation, 8 (1.8%) were due to insufficient therapeutic response and 3 (0.7%) were due to other reason (Source: Page 86 of the study report).

**Figure 3: : Levomilnacipran Dose Distribution in Studies LVM-MD-02 and LVM-MD-03**



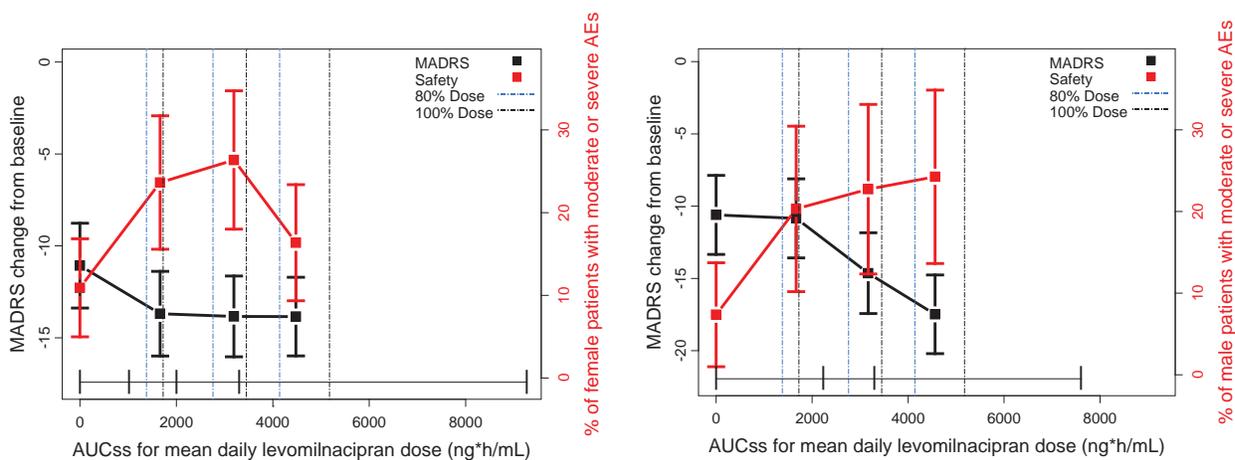
In summary, 40-120 mg QD is appropriate for MDD patients based on efficacy and safety data from the three Phase III Studies LVM-MD-01, LVM-MD-02 and LVM-MD-03.

**1.1.2 Is the exposure-response relationship for efficacy and safety endpoints similar by gender and race in major depressive disorder (MDD) patients?**

Gender and race appeared to be covariates of exposure-response relationship for efficacy and safety endpoints. **Figure 4** shows the exposure-response relationship for both MADRS and AEs in males and females:

- Primary efficacy maximized at Quartile 1 for female patients (N=440); MADRS changes (mean  $\pm$  95% CI) from the baselines for Quartiles 1-4 were  $-11.1 \pm 2.3$ ,  $-13.7 \pm 2.3$ ,  $-13.4 \pm 2.2$  and  $-14.3 \pm 2.2$ , respectively.
- Primary efficacy maximized at Quartile 4 for male patients (N=264); MADRS changes (mean  $\pm$  95% CI) from the baselines for Quartiles 1-4 were  $-10.6 \pm 2.7$ ,  $-10.8 \pm 2.7$ ,  $-14.8 \pm 2.8$  and  $-17.3 \pm 2.8$ , respectively.
- The highest proportion of patients experienced moderate/severe AEs were observed at Quartile 3 for the females (N=440), and Quartile 4 for male patients (N=264).

**Figure 4: Primary efficacy scores (black lines and 95% CI bars against left Y axis) and moderate/severe AE rates (red lines and 95% CI bars against right Y axis) versus levomilnacipran exposure (X axis) in major depressive disorder patients by sex in Study LVM-MD-01**



AEs: adverse events; AUCss: area under concentration-time curve at steady-state; CI: confidence interval; MADRS: Montgomery Åsberg Depression Rating Scale

Further, exposure-response relationship for both MADRS and AEs appeared different between white and black patients for each gender as shown in **Figure 5**:

- Efficacy of both white and black females maximized at Quartile 2. Efficacy maximized at Quartile 3 for white males, and it maximized at Quartile 4 for black males.
- About 10%, 30%, 25% and 20% white females reported moderate or severe AEs for Quartiles 1, 2, 3 and 4, respectively. About 20% black females reported AEs in Quartiles 3-4, and the rates went down to about 10% for Quartiles 1 and 2.
- About 8%, 25%, 27% and 30% white males reported moderate or severe AEs for Quartiles 1, 2, 3 and 4, respectively. About 8%, 20%, 15% and 20% black males reported moderate or severe AEs for Quartiles 1, 2, 3 and 4, respectively.

In summary, exposure-response relationship for efficacy and safety endpoints of levomilnacipran appears to be different based on gender and race. It is not clear if there are any potential factors that can further explain these differences.

1.1.3 Are the proposed dose adjustment guidelines for patients with renal impairment (b) (4) appropriate?

No. The proposed dose adjustment guidelines by sponsor and FDA are shown in **Table 1**.

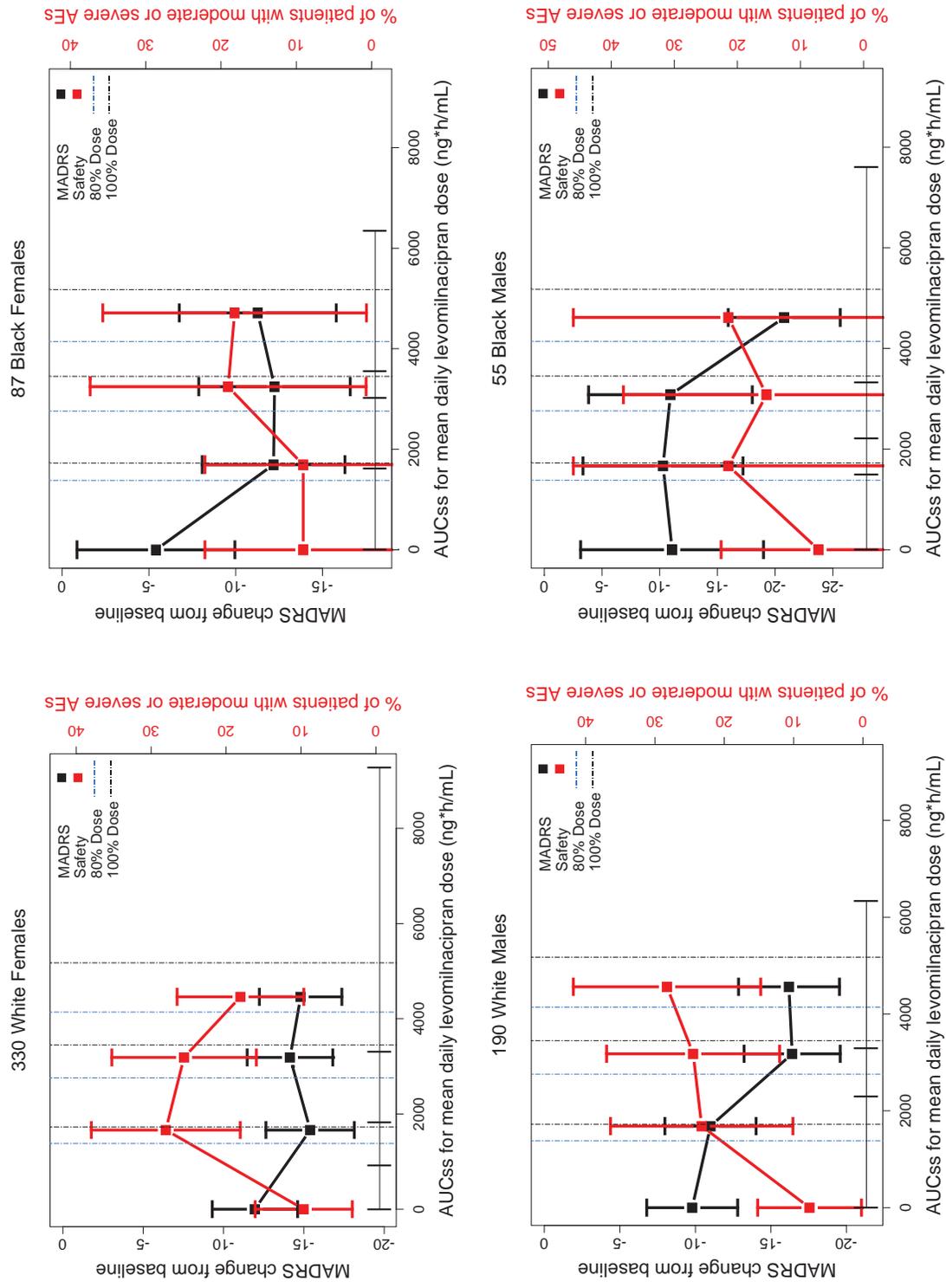
**Table 1: Daily Dose (mg) Proposed by the Sponsor and the FDA Reviewer for Patients with Different Renal Functions**

	Normal Renal Patients		Mild Renal Impaired		Moderate Renal Impaired		Severe Renal Impaired	
	Sponsor	FDA	Sponsor	FDA	Sponsor	FDA	Sponsor	FDA
Day 1	20	20	20	20	20	20	20	20
Day 2	20	20	20	20	0	0	0	0
Day 3	40	40	40	40	20	20	20	20
Day 4	40	40	40	40	20	20	20	20
Day 5	80	80	80	80	60	60	40	40
Day 6	80	80	80	80	60	60	40	40
Day 7	120	120	120	100	60	60	40	40
Day 8-21	120	120	120	100	80	60	<span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>	40

The proposed dose reduction was based on that 120 mg levomilnacipran is the maintenance dose at steady-state. If steady-state maintenance dose is not 120 mg QD, the dose reduction should be in the same proportion.

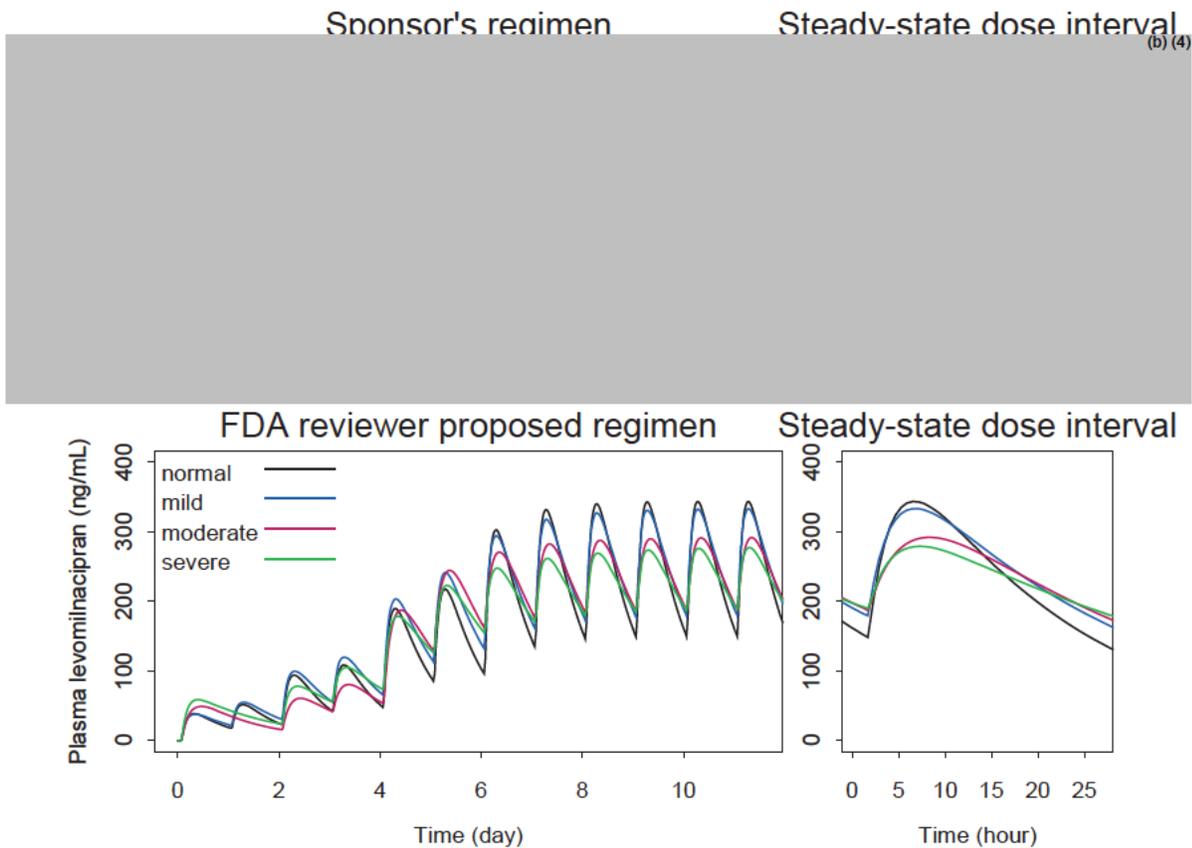
To visualize the dose adjustment guidelines of the sponsor, mean steady-state exposures of the sponsor's dosing plans in patients with different renal functions are simulated and shown in the upper panel of **Figure 7**.

**Figure 5: Primary efficacy scores (black lines and 95% CI bars against left Y axis) and adverse event rates (red lines and 95% CI bars against right Y axis) versus levomilnacipran exposure (X axis) in patients with major depressive disorder by race and sex in Study LVM-MD-01**



The simulations were conducted based on 1-compartment PK model. The model was described by the following 4 PK parameters: first order absorption rate constant  $ka$ , first order elimination rate constant  $ke$ , apparent distribution volume  $V/F$  and absorption lag time  $t_{lag}$ . The values of  $ka$ ,  $ke$ ,  $V/F$  and  $t_{lag}$  used for simulation are the mean results (as shown in **Figure 15**) of the 1-compartmental analysis of PK data of Study LVM-PK-02 (the Phase I PK study in healthy subjects with normal and impaired renal function). The PK parameters obtained from sponsor's population PK analysis were not used for simulations due to the limitation of the population PK analysis as discussed in Section 5.1.

**Figure 6: Simulated levomilnacipran concentration versus time courses for sponsor and FDA reviewer proposed regimens for patients with normal, moderate impaired and severely-impaired renal functions using PK estimates from LVM-PK-02. Left panels are for titration to steady-state and the right panels are for steady-state only.**



Simulations are for dose regimen in Table 1. and PK parameter values are from LVM-PK-02

For sponsor's regimen as visualized in the upper two panels of **Figure 6**,

In contrast, the simulations based on FDA reviewer's proposed regimen resulted in comparable steady-state exposure between patients with different renal

functions as shown in the lower panels of **Figure 6**. Please refer to Section 8 for the alternative simulations by the FDA reviewer.

1.1.4 Is the proposed dose adjustment guideline for patients with hepatic impairment (no dose reduction for any hepatic impairment patients) appropriate?

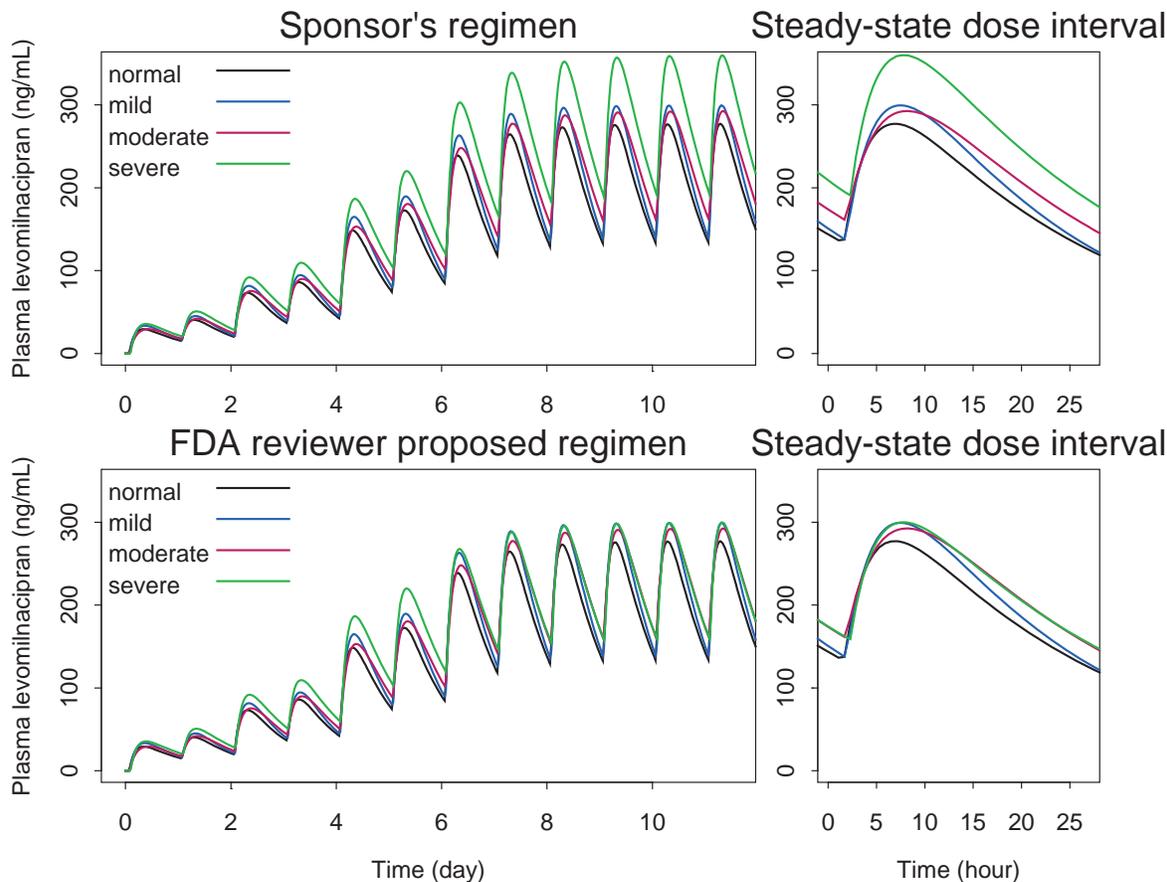
The guideline that no dose adjustment is needed for a severe hepatic impairment patient needs doctor's caution in execution. For severe hepatic impairment patients, the FDA pharmacometrics reviewer thinks daily maintain dose of levomilnacipran should be 3/4 of the maintain dose in normal patients. The rationale of dose adjustment is depicted in **Figure 7**. The simulation was based on PK parameter values from Study LVM-PK-05 (A single dose pharmacokinetic study of levomilnacipran in subjects with normal hepatic function and patients with impaired hepatic function).

**Table 2: Daily Dose (mg) Proposed by the Sponsor and the FDA Reviewer for Patients with Different Hepatic Functions**

	Normal, Mild and Moderate Hepatic Impaired		Severe Hepatic Impaired	
	Sponsor	FDA	Sponsor	FDA
Day 1	20	20	20	20
Day 2	20	20	20	20
Day 3	40	40	40	40
Day 4	40	40	40	40
Day 5	80	80	80	80
Day 6	80	80	80	80
Days 7-21	120	120	120	100

The proposed dose reduction was based on that 120 mg levomilnacipran is the maintenance dose at steady-state. If steady-state maintenance dose is not 120 mg QD, the dose reduction should be in the same proportion.

**Figure 7: Simulated levomilnacipran concentration versus time courses for sponsor and FDA reviewer proposed regimens for patients with normal, moderate impaired and severely-impaired hepatic functions using PK estimates from LVM-PK-05. Left panels are for titration to steady-state and the right panels are for steady-state only**



**Simulations are for dose regimen in Table 2 and PK parameter values are from LVM-PK-05**

### 1.1.5 Is there a relationship between levomilnacipran dose and changes in vital signs such as blood pressure, heart rate?

Yes, dose related changes in diastolic blood pressure, systolic blood pressure and heart rate (or pulse rate) were observed in Study LVM-PK-07 (Evaluation of the effects of sequential multiple-dose regimens of levomilnacipran on cardiac repolarization in healthy subjects). The findings are shown in **Figure 8**. Diastolic blood pressure (DBP), systolic blood pressure (SBP), and heart rate (HR) increased with levomilnacipran dose (**Table 3**).

For Phase III studies, the relationship between dose and vital sign change from baseline is shown in **Figure 9**. The data for the figure were the mean results of 713 patients of Study LVM-MD-01, and 357 patients of Studies LVM-MD-02 and 03, as presented in **Table 4** and **Table 5**, respectively. For patients treated with placebo, the change from baseline of vital sign (pulse rate, systolic blood pressure and diastolic blood pressure) was negligible. For patients

treated with levomilnacipran, the change from baseline of vital sign (pulse rate, systolic blood pressure and diastolic blood pressure) was similar amongst the dose range of 38.6 mg to 106.9 mg QD. The actual vital sign change might have been underestimated because no circadian rhythms were considered during the data collection.

**Table 3: Vital sign change from baseline at the selected time point for different dose levels (mean ± 95% CI) of Study LVM-PK-07**

Vital Sign	Time after Current Dose (h)	Change from Baseline		
		Day 1 Dose=20 mg	Day 11 Dose=120 mg	Day 24 Dose=300 mg
DBP (mmHg)	3	4.4 ± 1.2	7.1 ± 1.5	10.0 ± 1.8
SBP (mmHg)	0	0.0 ± 0.0	0.5 ± 1.2	0.9 ± 1.4
HR (bpm)	6	7.5 ± 1.2	12.4 ± 2.1	15.2 ± 2.4

DBP, diastolic blood pressure; SBP, systolic blood pressure; HR: heart rate; N, number of subjects contributed measurements to the mean data; Dose: levomilnacipran dose on Day 1 or at steady-state. Data are extracted from **Figure 8** at the corresponding time points.

**Dosing Schedule:** placebo for 2 days, LVM 20 mg for 1 day, 40 mg for 3 days, 80 mg for 3 days, 120 mg for 4 days, 160 mg for 3 days, 200 mg for 3 days, 260 mg for 3 days, and 300 mg for 4 days, placebo for 1 day.

**Table 4: Vital sign change from baselines for different treatment arms of Study LVM-MD-01 (mean ± 95% CI)**

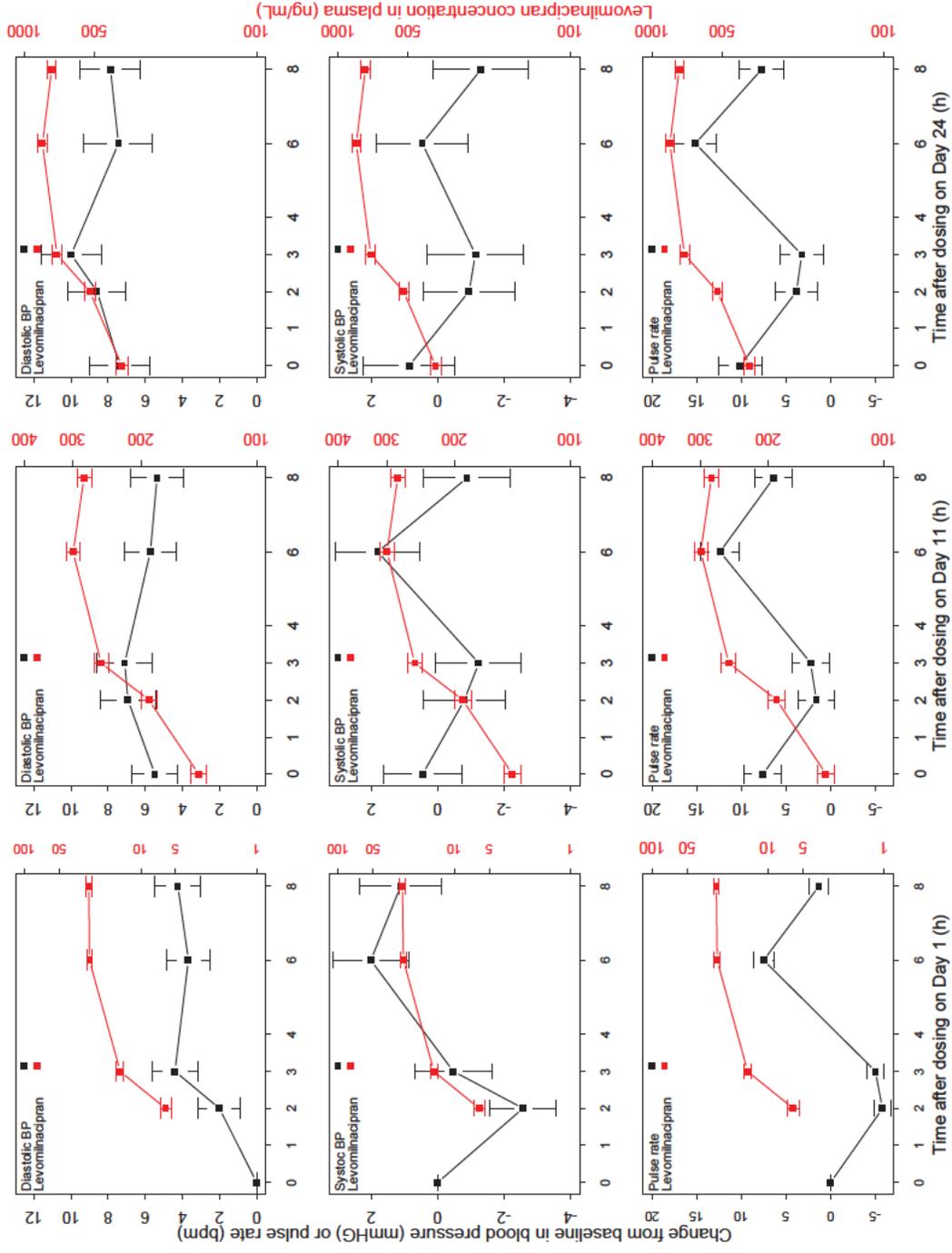
Arm	Median (minimum, maximum) of mean daily dose in mg , patient number	Change from baseline and 95% confidence interval		
		Pulse rate (bpm)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
1	0 (0, 0), N=176	1.2±0.5	0.2±0.5	-0.3±0.4
2	38.6 (33.3, 39.3), N=178	6.7±0.6	2.1±0.6	2.2±0.4
3	75.2 (57.1, 76.8), N=179	6.4±0.7	3.5±0.6	2.4±0.4
4	106.9 (60.0, 113.0), N=180	6.8±0.6	2.4±0.6	2.2±0.4

**Table 5: Vital sign change from baselines for different mean daily doses of pooled data of Studies LVM-MD-02 and LVM-MD-03 (mean ± 95% CI)**

Arm	Median (minimum, maximum) of mean daily dose in mg , patient number	Change from baseline and 95% confidence interval		
		Pulse rate (bpm)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
1	0 (0, 0), N=182	0.3±0.4	-0.8±0.5	-0.5±0.4
2	40.0 (33.6, 40.0), N=24	6.7±1.8	2.2±1.8	2.0±1.4
3	71.7 (45.0, 77.0), N=65	4.8±1.0	2.3±0.8	1.6±0.7
4	95.6 (84.3, 98.9), N=86	5.6±0.8	2.0±0.8	2.8±0.7

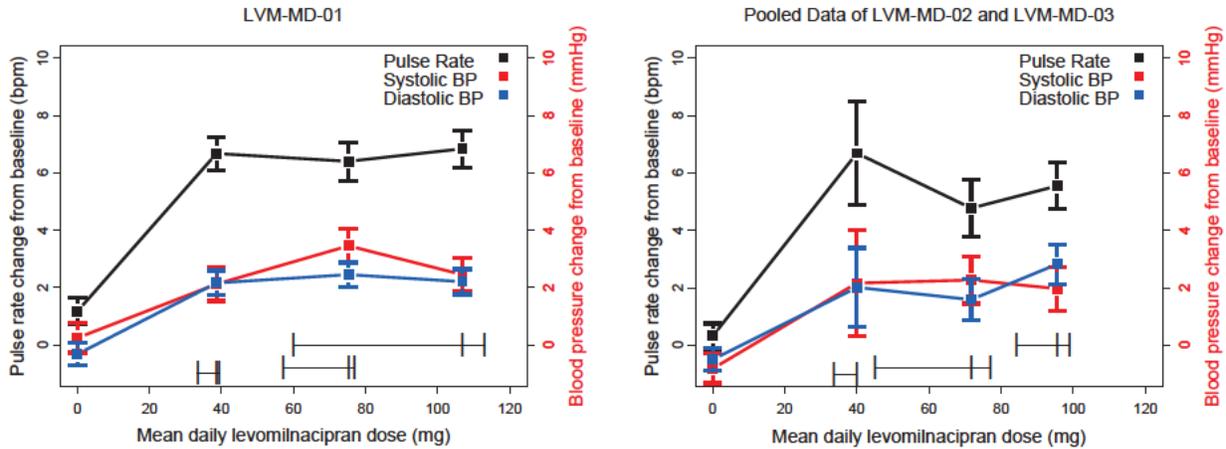
These results appeared consistent with results from Integrated Summary of Safety submitted by the sponsor. The following text, highlighted in light grey, about cardiovascular effect of levomilnacipran is cited from sponsor's Integrated Summary of Safety.

**Figure 8: Vital sign change from baseline versus plasma levomilnacipran concentration on Days 1, 11 and 24 for Doses of 20, 120 and 300 mg QD levomilnacipran (N=400) in Study LVM-PK-07**



APPEARS THIS WAY ON ORIGINAL

**Figure 9: Pulse rate change from baseline (black lines and 95% CI bars against left Y axis) and blood pressure change from baseline (red, blue lines and 95% CI bars against right Y axis) versus levomilnacipran mean dose (X axis) in major depressive disorder patients of Phase III studies**



CI: confidence interval; The vertical bars represent 95% CI of the vital sign changes from baselines with mean change in the middle; The horizontal bars represent minimum and maximum dose with median dose in the middle.

### Key Findings Reported for Cardiovascular Effect of Levomilnacipran (5.3.5.3 Integrated Summary of Safety):

In the short-term, placebo-controlled studies, a total of 1583 patients were randomized to levomilnacipran (mean age 43 years and mean BMI 28.7 kg/m<sup>2</sup>) and 1040 patients were randomized to placebo (mean age 44 years and mean BMI 28.2 kg/mg<sup>2</sup>). Approximately 10% of patients in both treatment groups were taking an antihypertensive agent at baseline. After completing the short-term, placebo-controlled studies, a total of 779 patients continued into the open-label treatment period of the long-term extension study. A total of 341 patients completed the 48-week open-label treatment period. No deaths were reported during the treatment periods. No events of cardiac failure or myocardial infarction were reported. The following are key results from the cardiovascular analyses of the short-term, placebo-controlled and long-term, extension studies:

#### Blood-pressure in the short-term, placebo-controlled studies:

- Mean increases of 3.0 mm Hg in SBP and 3.2 mm Hg in DBP were noted among levomilnacipran patients compared to a mean decrease (0.4 mm Hg) in SBP and no change in DBP among placebo-treated patients. The incidences of PCS BP changes among levomilnacipran-treated patients were low and similar to those observed in placebo (less than 1% of patients).
- Based on BP readings at the end of the double-blind treatment period, 89.6% of levomilnacipran patients who had normal or pre-hypertensive BP readings at baseline had a BP reading that remained normal or pre-hypertensive compared with 92.9% for placebo patients. 10.4% of the levomilnacipran-treated patients who had normal or prehypertensive BP readings at baseline had a hypertensive reading at the end of the treatment period compared with 7.1% of placebo patients.
- The rate of sustained hypertension (defined by the relatively sensitive criterion of SBP  $\geq$  140 mm Hg and increase  $\geq$  15 mm Hg **OR** DBP  $\geq$  90 mm Hg and increase  $\geq$  10 mm Hg for at least 3 consecutive visits) was 1.8% in the levomilnacipran group compared with 1.2% in the placebo group. The rate of sustained hypertension using the more specific criterion (SBP  $\geq$  140 mm Hg and increase  $\geq$  15 mm Hg **AND** DBP  $\geq$  90 mm Hg and increase  $\geq$  10 mm Hg for at least 3

consecutive visits) was 0.3% in the levomilnacipran group compared with 0.1% in the placebo group.

- In subset of fixed-dose studies, no dose-dependent relationship to the above-mentioned BP changes was observed among patients in the levomilnacipran 40 mg, 80 mg, and 120 mg groups.

**Blood-pressure in the long-term extension study,**

- In the cohort of patients who received open-label levomilnacipran for at least 48 weeks, mean increases of 4.1 mm Hg in SBP and 3.0 mm Hg in DBP were noted, increases not substantially different from increases seen with levomilnacipran in the short-term, placebo-controlled studies. These results were similar to those observed in the entire Open-Label Safety Population (increases of 4.0 mm Hg and 3.2 mm Hg in SBP and DBP, respectively).
- PCS increases in DBP were observed in 2% of patients. No patient met the PCS-high criterion for SBP during the long-term extension study.
- 86.6% of patients who had a normal or prehypertensive baseline BP reading remained normal or prehypertensive.
- The sustained hypertension criterion was met by 5.9% of patients.

**Heart rate in the short-term, placebo-controlled studies,**

- A mean increase of 7.4 bpm in HR was noted among levomilnacipran patients compared to a mean decrease of 0.3 bpm among placebo patients.
- Very few levomilnacipran-treated patients (0.4%) met the PCS-high criterion for heart rate.
- In the subset of fixed-dose studies, mean increases in HR were 7.2 bpm in the levomilnacipran 40 mg and 80 mg groups and 9.1 bpm in the levomilnacipran 120 mg dose group. No consistent pattern of HR changes was observed to suggest a dose-effect.

**Heart rate in the long-term extension study,**

- In the cohort of patients who received open-label levomilnacipran for at least 48 weeks, a mean increase of 9.1 bpm in HR was noted, an increase not substantially different from increases seen with levomilnacipran in the short-term, placebo-controlled studies. This result was the same as that observed in the Open-Label Safety Population.
- Very few patients (0.4%) met the PCS-high criterion for HR in the long-term extension studies.
- Most AEs related to cardiovascular disorders reported in levomilnacipran-treated patients were mild or moderate in intensity. None resulted in death. Very few of these AEs were SAEs or led to premature discontinuation.
- In the short-term placebo-controlled studies, AEs related to the SMQ of hypertension were observed in 5.3% of levomilnacipran patients compared with 2.3% of placebo patients. In the long-term extension study, AEs related to the SMQ of hypertension were reported in 11.6% of patients.
- One non-serious event within the MACE composite was reported in the levomilnacipran group in the short-term, placebo-controlled studies. No MACE composite events were reported in the long-term extension study.

**1.2 Recommendations**

Please refer to the label statements below.

**1.3 Label Statements**

The recommendation for labeling change from pharmacometrics perspective:

-----**WARNINGS AND PRECAUTIONS**-----

(b) (4)

(b) (4)

### 5.3 (b) (4) *Blood Pressure*

(b) (4)

In patients (b) (4) exposed to one-year, open-label treatment of TRADENAME (doses range from 40-120 mg once daily), the mean change from initiation of treatment in systolic BP was (b) (4) mm Hg and diastolic BP was (b) (4) mm Hg.

Concomitant use of TRADENAME with drugs that increase blood pressure and heart rate has not been evaluated and such combinations should be used with caution. Effects of TRADENAME on blood pressure in patients with significant hypertension or cardiac disease have not been systematically evaluated. TRADENAME should be used with caution in these patients.

(b) (4)

For patients who experience a sustained increase in blood pressure while receiving TRADENAME, discontinuation or other appropriate medical intervention should be considered.

### 5.4 (b) (4) *Heart Rate*

SNRIs (b) (4) TRADENAME have been associated with increased heart rate. (b) (4) TRADENAME treatment was associated with a mean increase in heart rate of 7.4 beats per minute (bpm) compared to a mean decrease of 0.3 bpm in placebo-treated patients. Heart rate increase in TRADENAME (b) (4)

(b) (4)

(b) (4)

TRADENAME has not been systematically evaluated in patients with a cardiac rhythm disorder.

Heart rate should be measured prior to initiating treatment and periodically measured throughout TRADENAME treatment. ~~Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with TRADENAME.~~ (b) (4)

For patients who experience an increase in heart rate while receiving TRADENAME discontinuation or other appropriate medical intervention should be considered.

## 2 PERTINENT REGULATORY BACKGROUND

Levomilnacipran has been studied for the treatment of MDD under IND104483 that was submitted to the Division of Psychiatry Products on 05 Feb 2009. The sponsor (Forest Laboratories Inc.) met with the FDA on 18 May 2009 (Type B End-of-Phase-2 meeting).

## 3 SPONSOR'S POPULATION PK ANALYSIS (REPORT LVM-MS-01)

### 3.1 Data and Study Population

Data of 3 Phase III studies and 13 Phase I studies were used in the PPK analysis (**Table 7**). Of drug-drug interaction studies, only data from the levomilnacipran monotherapy arms were included. Of hepatic impairment study, only data from subjects with normal hepatic function were included. In addition, administrations of placebo, treatments other than levomilnacipran and formulations other than the sustained release clinical formulation were excluded in the PPK dataset. Outliers were identified as any samples having an absolute conditional weighted residual (CWRES) greater than or equal to 6 in the assessment of the final structural model.

### 3.2 Methods

#### Model Development

The concentration-time data was described using 1-compartment model. The residual errors were assumed to be normally distributed with two components, additive and proportional to the predicted plasma concentrations. Between-subject variability (interindividual variability, IIV) in the pharmacokinetic parameters took the general form where appropriate. As is general practice, random effects were only included if they provided improvements in individual fits and/or numerical stability to the model. Additionally, allometric scaling of apparent clearance (CL/F) and apparent volume of the central compartment (Vc/F) by subject body weight was evaluated in the course of structural model development.

#### Covariate Analysis

Exploratory graphical and regression analyses using generalized additive models (GAM) were used to identify significant parameter – covariate relationships ( $p < 0.05$ ). The following relationships were evaluated in the exploratory analyses:

- CL/F: creatinine clearance (CLCR) at baseline, age, metrics of body size, including body weight (WT), body mass index (BMI), ideal body weight (IBW), and body surface area (BSA), gender, race, and liver function markers (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin).
- Vc/F: age, metrics of body size (including WT, BMI, IBW, and BSA), gender, food, and race.
- Absorption rate constant (Ka) and relative bioavailability (F): food, race and dose. In addition, influences of vomiting and number of capsules were examined as covariates on Ka.

Selected covariates were screened one at a time and selected using a stepwise forward-selection, backward-elimination method on the likelihood ratio test. Specifically, during the forward selection process, covariates were added to the model in decreasing order of their influence on

the NONMEM objective function value (OFV,  $-2 \times \log\text{-likelihood (LL)}$ ), including only parameter-covariate relationships that were significant at the 1% significance level ( $p < 0.01$ ). In the backward elimination process, covariates were excluded sequentially from the model if they were not significant at 0.1% significance level ( $p < 0.001$ ). The resultant model was termed the full statistical model. Subsequently, covariates that were not clinically significant, defined as covariates demonstrating less than 20% effect on PK parameters or negligible explanatory impact on the relevant intersubject omega ( $\omega_2$ ) term ( $< 10\%$ ), were removed from the model. Finally, parameter estimates were examined to ensure that they were well-estimated and plausible, and the resultant model was considered the final model.

### Model Assessment

Model evaluation was based on statistical criteria (i.e., the model with the lowest objective function value), numerical stability of the minimization and graphical presentations of goodness of fit. Standard goodness-of-fit graphs including population and individually predicted concentration versus observed concentration, conditional weighted residuals versus time after dose, and conditional weighted residuals versus predicted plasma concentrations of levomilnacipran were examined to assess the performance of the models. Parameter estimates were examined to ensure they were well estimated (relative standard error (RSE)  $< 50\%$ ) and plausible. Precision in parameter estimation was evaluated using bootstrapping. ETA shrinkage ( $1\text{-SD}(\eta)/\omega$ ) (where SD is standard deviation) and epsilon shrinkage ( $1\text{-SD}(\text{IWRES})$ ) (where IWRES is individual weighted residuals) were assessed during the model development process to determine if the available data were adequate for estimating interindividual variability as specified in the model. Visual predictive checks were performed on the final structural model to assess model qualification.

### Simulation of Dose Adjustment Scenarios in Renal Impairment

Simulations of the final PPK model were performed to identify dose adjustment strategies for subjects with varying degrees of renal impairment. The effects of different dose adjustment criteria on levomilnacipran exposures during the titration period and at steady-state were examined. Dosage reduction strategies were developed on the basis of comparison to exposures in subjects with normal renal function ( $\text{CLCR} \geq 90 \text{ mL/min}$ ). For subjects with normal renal function, the nominal dose titration schedule was as follows: 20 mg daily on days 1 and 2, 40 mg daily on days 3 and 4, 80 mg daily on days 5 through 7 followed by a maintenance dose of 120 mg daily.

**Table 6: Clinical Studies Used in the Population PK Analyses**

Study (Phase)	Brief Study Description	Treatment(s)	Population	Number of Subjects/Observations
PK-01 (I)	Single and multiple escalating doses	Single doses of placebo, 25, 50 or 100 mg SR; Escalating doses of 25 – 300 mg SR or placebo daily for up to 36 days	Healthy subjects who received levomilnacipran	35/885
PK-02 (I)	Single dose in renal impairment	40 mg SR	Subjects with normal and mild to severe renal impairment	32/423
PK-04 (I)	Multiple dose study	Escalating doses of 20 – 80 mg SR daily for 9 days	Healthy adult and elderly subjects	32/478
PK-05 (I)	Single dose in hepatic impairment	40 mg SR	Subjects with normal hepatic function (exclude hepatic impairment)	8/98

PK-06 (I)	Food effect study	40 mg SR either fasted or with food	Healthy subjects	24/523
PK-07 (I)	TQT study	Multiple escalating doses of 20 – 300 mg SR daily for 24 days then placebo on Day 25; or moxifloxacin 400 mg on Day 1 then placebo on Days 2-25; or placebo on Days 1-24 and moxifloxacin 400 mg on Day 25	Healthy subjects who received levomilnacipran	92/2941
PK-08 (I)	Drug-drug interaction study with ketoconazole	80 mg SR daily with and without ketoconazole	Healthy subjects; levomilnacipran alone period	34/421
PK-09 (I)	Drug-drug interaction study with carbamazepine	Multiple escalating doses of 20 – 120 mg SR daily with and without carbamazepine	Healthy subjects; levomilnacipran alone period	34/502
PK-10 (I)	Drug-drug interaction study with alprazolam	Multiple escalating doses of 20 – 120 mg SR daily with and without alprazolam	Healthy subjects; levomilnacipran alone period	30/240
PK-12 (I)	Bioequivalence and food effect study	120 mg to-be-marketed SR with food or fasted or 120 mg clinical formulation fasted	Healthy subjects; clinical formulation only	49/814
PK-15 (I)	Single ascending dose study	40, 80 or 120 mg SR	Healthy subjects	30/371
PK-16 (I)	Bioequivalence study	20 – 40 mg oral solution daily or 20 – 120 mg SR daily for 14 days	Healthy subjects; SR formulation only	23/613
PK-19 (I)	Bioequivalence study	120 mg to-be-marketed SR or 120 mg clinical formulation	Healthy subjects; clinical formulation only	37/619
MD-01 (III)	Randomized, double-blind, fixed dose, placebo controlled, parallel group study	40, 80 or 120 mg SR daily for 8 weeks	Adults with MDD who received levomilnacipran	443/1795
MD-02 (III)	Randomized, double-blind, flexible dose, placebo-controlled, parallel-group study	40, 80 or 120 mg SR daily for 8 weeks (flexible dose)	Adults with MDD who received levomilnacipran	157/501
MD-03 (III)	Randomized, double-blind, flexible dose, placebo-controlled, parallel-group study	40, 80 or 120 mg SR daily for 8 weeks (flexible dose)	Adults with MDD who received levomilnacipran	198/639

### 3.3 Results

#### Structure Model

The structure model for levomilnacipran was parameterized in terms of apparent systemic clearance (CL/F), apparent central compartment volume (Vc/F), an absorption rate constant (Ka) and absorption lag time (Tlag). Interindividual variability was estimated to be 26% for CL/F and Vc/F and 55% for Ka. Covariance (cov) between CL/F and Vc/F was modeled.

#### Final Model

The final 1-compartment model was parameterized as follows:

$$CL_i/F = 24.0 \cdot \left( \frac{CLCR_i}{120 \text{ mL/min}} \right)^{(0.525 \cdot I_{(CLCR < 50)}} + (0.475 \cdot I_{(CLCR \geq 50)l}) \cdot e^{\eta_{CL/Fi}}$$

$$Vc_i/F = 495 \cdot \left( \frac{Wt_i}{79 \text{ kg}} \right)^{0.605} \cdot e^{\eta_{Vc/Fi}}$$

$$Ka_i = 0.519 \cdot e^{\eta_{Ka_i}}$$

$$Tlag_i = 1.73$$

$$C_{ij} = C + \sqrt{(21.4 + 0.352 \cdot C) \cdot I_{sparse} + (2.71 + 0.15 \cdot C) \cdot I_{phase1}}$$

where subscript  $i$  represents the  $i^{\text{th}}$  subject, subscript  $j$  represents the  $j^{\text{th}}$  plasma concentration,  $I(.)$  represents a binary indicator variable which may have values of 0 or 1, CLCR is creatinine clearance (truncated to 150 ml/min), Wt is body weight,  $C_{ij}$  represents an observed plasma concentration and  $C$  represents a predicted plasma concentration.  $I_{(CLCR < 50)}$  has a value of 1 for  $CLCR < 50$  ml/min,  $I_{(CLCR \geq 50)}$  has a value of 1 for  $CLCR \geq 50$  ml/min,  $I_{\text{sparse}}$  has a value of 1 for sparse sampling and  $I_{\text{phase1}}$  has a value of 1 for intensive sampling in phase I studies; otherwise value is 0.

**Table 7: Parameter estimate for the final levomilnacipran PK model**

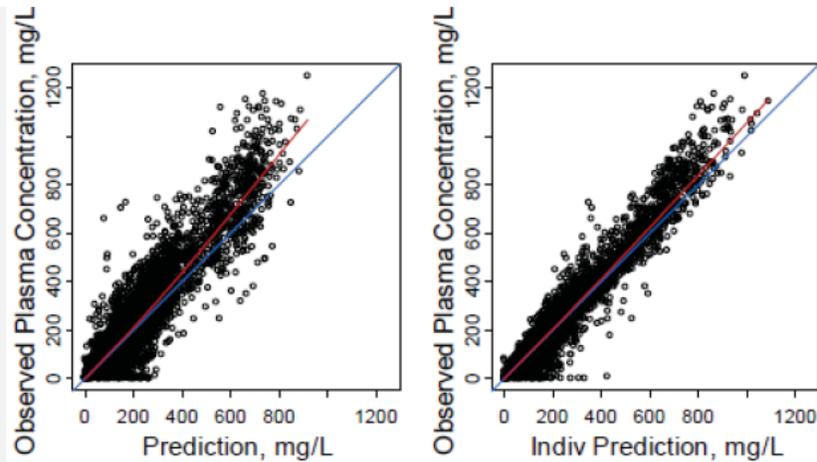
Parameter	Unit	Estimate	SE	RSE	%CV
CL/F	L/h	24.0	0.224	0.93	
Vc/F	L	495	6.12	1.24	
Ka	1/h	0.519	0.0137	2.64	
Tlag	h	1.73	0.0101	0.58	
CLCR $\geq$ 50 ml/min on CL/F		0.475	0.0402	8.46	
CLCR $<$ 50 ml/min on CL/F		0.525	0.039	7.43	
WT on Vc/F		0.605	0.0676	11.2	
<b>Intersubject Variability</b>					
CL/F		0.0674	0.00691	10.3	26.0
Vc/F		0.0657	0.00585	8.90	25.6
cov CL/F-Vc/F		0.0260	0.00602	23.2	
correlation CL/F-Vc/F		0.391			
Ka		0.307	0.0269	8.76	55.4
<b>Residual Error</b>					
Ph I - prop		0.150	0.00593	3.95	15.0
Ph I - add	ng/mL	2.71	0.215	7.93	
Sparse - prop		0.352	0.0159	4.52	35.2
Sparse - add	ng/mL	21.4	2.60	12.1	

SE = standard error, RSE = relative standard error, %CV = coefficient of variation, prop = proportional, add = additive. ETA shrinkage estimates for CL/F, Vc/F and Ka were 14.3%, 36.1% and 39.3%, respectively; EPS shrinkage was 7.7%

## Model Assessment

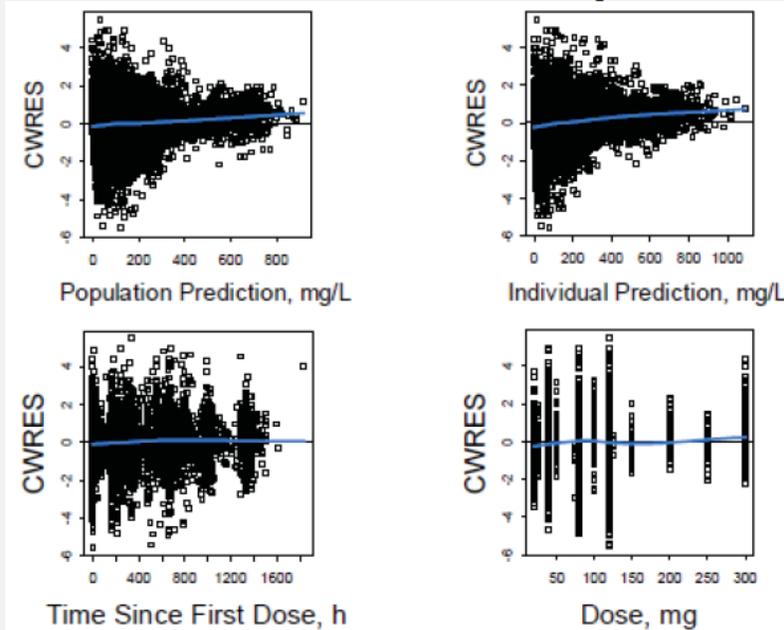
**Figure 10** shows that the individual predicted concentrations match the observed concentrations satisfactorily for levomilnacipran, while some bias was apparent in the population predictions. Although additional exploration of alternative models did not remove the pattern seen for the population predictions, the model was judged to be satisfactory overall, as individual fits showed good accordance between fitted and observed. CWRES plotted versus population and individual predictions, time since first dose and dose indicated adequate model fits (**Figure 11**).

**Figure 10: Observed plasma concentrations of levomilnacipran versus population predictions (left panel) and individual predictions (right panel) for the final PPK model. Red line represents loess smooth and blue line is the line of identity**



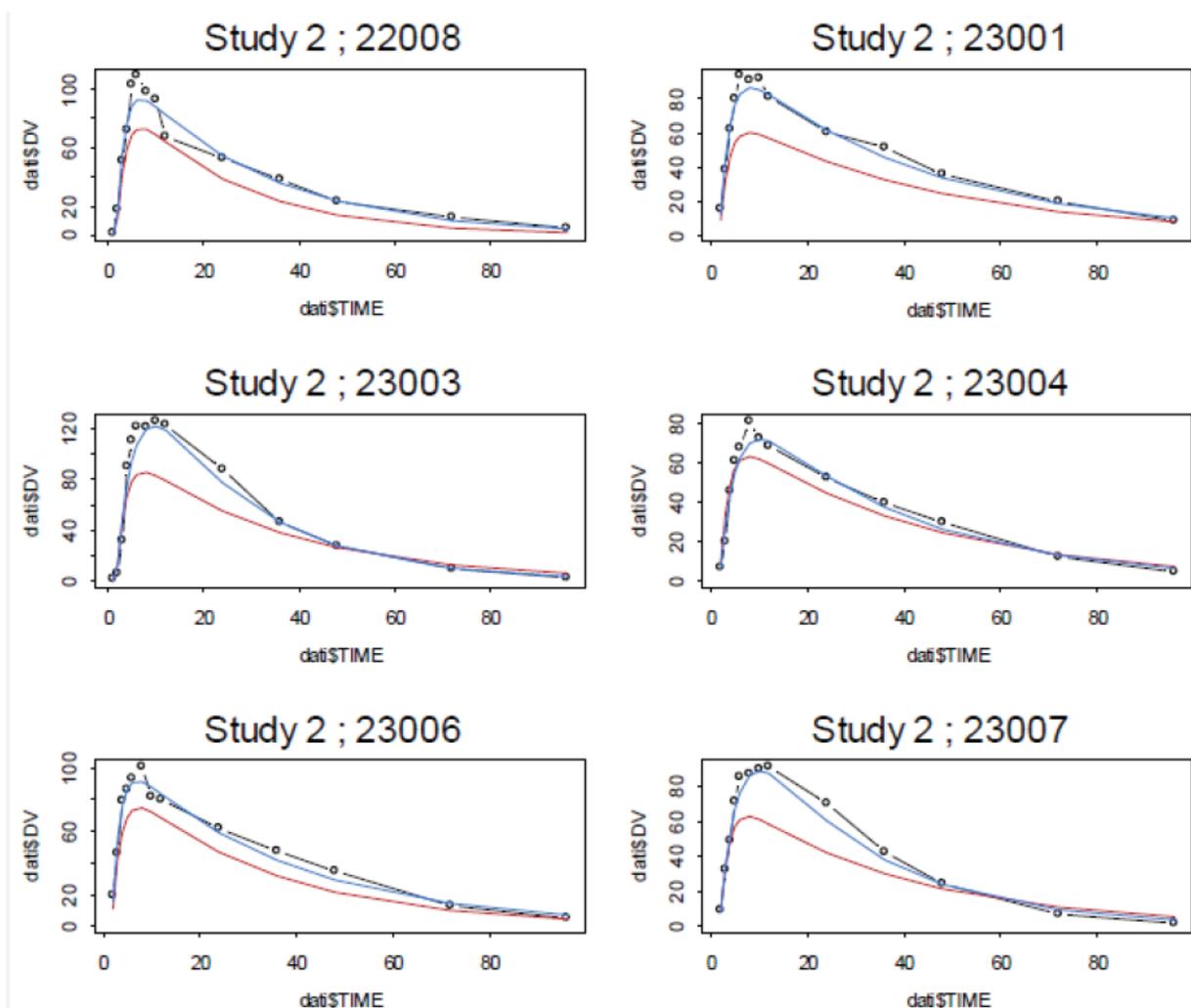
Source: Page 31 of sponsor's population PK report LVM-MS-01

**Figure 11: Conditional weighted residuals vs. population and individual predictions, time since first dose and dose for the final PPK model. Blue line represents loess smooth**



Source: Page 32 of sponsor's population PK report LVM-MS-01

**Figure 12: Examples of individual fits of Phase I studies where circles and black lines represent observations, red line is the population prediction and blue line is the individual prediction. X label is time in hours and Y label is plasma levomilnacipran concentration in ng/mL.**



Source: Page 84 of sponsor's population PK report LVM-MS-01

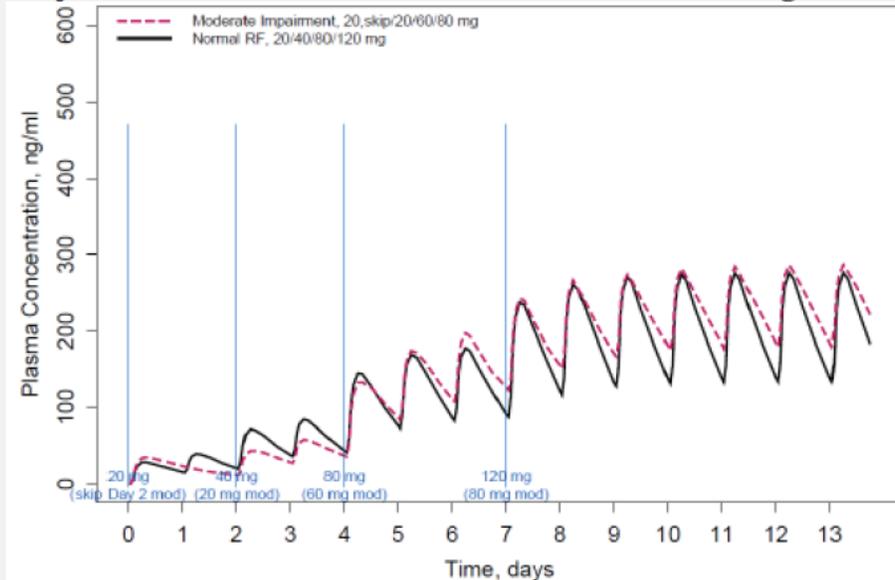
### Implications of Significant Covariate Effects

The final PPK model was used to simulate median plasma concentration versus time profiles to characterize the influences of statistically significant, clinically relevant covariates on steady state exposures to levomilnacipran under various dosing scenarios. The impact of renal function (Creatinine Clearance; CLCR) on levomilnacipran exposures are shown in **Table 9**. Based on relative AUC<sub>ss</sub> in **Table 9**, renal impairment resulted in 136%, 64% and 23% median increases in exposure for severe, moderate and mild impairment, respectively, relative to a typical subject with normal renal function. Similarly, C<sub>max,ss</sub> and C<sub>min,ss</sub> were increased in renal impairment groups. Levomilnacipran exposures resulting from dose reduction strategies are shown in **Figure 13** and **Figure 14** for moderate and severe renal impairment, respectively. The dose on Day 2 is skipped to reduce C<sub>max</sub> during the first four days of dosing.

**Table 8: Impact of CLCR on steady-state exposures**

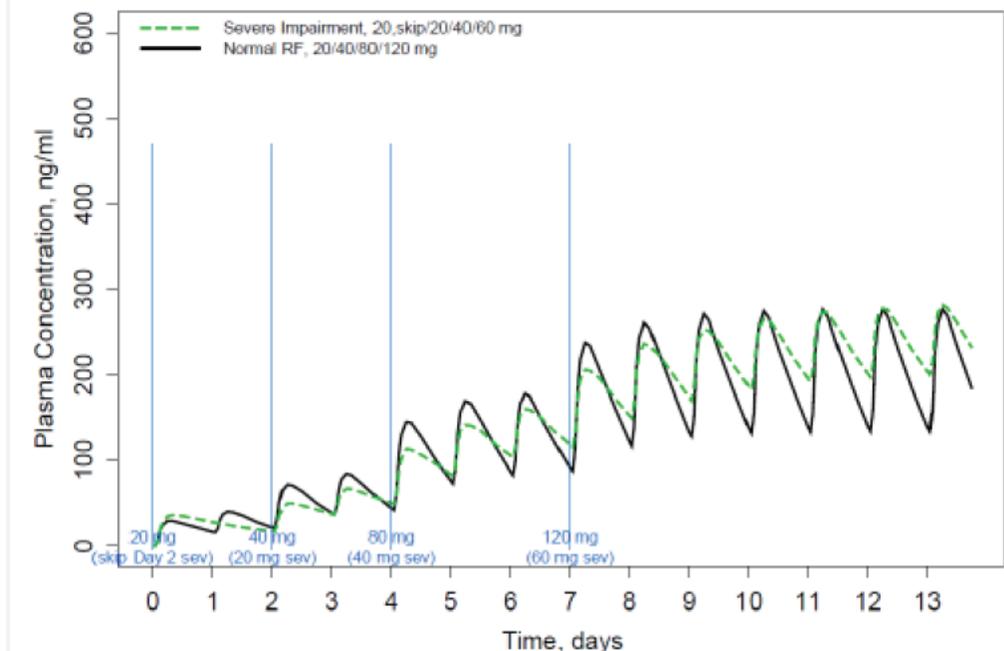
Dose (mg)	CLCR (mL/min)	Weight (kg)	C <sub>max,ss</sub> (ng/mL)	C <sub>min,ss</sub> (ng/mL)	AUC <sub>0-24,ss</sub> (ng.h/mL)
80	22.5	79	384.5	270.8	8027.0
80	45.0	79	283.3	170.6	5578.5
80	75.0	79	225.3	113.8	4167.1
80	115.0	79	194.1	83.7	3401.4

**Figure 13: Median plasma concentration vs. time profile following modified dose titration schedule in a typical subject with moderate renal impairment compared with the profile for a typical subject with normal renal function for the nominal dosing schedule.**



Nominal dosing schedule in normal renal function: 20 mg daily on days 1 and 2, 40 mg daily on days 3 and 4, 80 mg daily on days 5 through 7 followed by a maintenance dose of 120 mg daily. Modified schedule in moderate renal impairment: 20 mg daily on days 1, 3 and 4, 60 mg daily on days 5 through 7 followed by a maintenance dose of 80 mg daily.

**Figure 14: Median plasma concentration vs. time profile following modified dose titration schedule in a typical subject with severe renal impairment compared with the profile for a typical subject with normal renal function for the nominal dosing schedule.**



Nominal dosing schedule in normal renal function: 20 mg daily on days 1 and 2, 40 mg daily on days 3 and 4, 80 mg daily on days 5 through 7 followed by a maintenance dose of 120 mg daily. Modified schedule in severe renal impairment: 20 mg daily on days 1, 3 and 4, 40 mg daily on days 5 through 7 followed by a maintenance dose of 60 mg daily.

#### 4 POPULATION PK/PD ANALYSIS (REPORT LVM-MS-04)

##### 4.1 Data and Population

Summarized in **Table 10** are studies included in this PKPD analysis. Each study's objective was to evaluate the efficacy, safety, and tolerability of levomilnacipran versus placebo.

**Table 9: Clinical Studies Used in the Population PK Analyses**

Study (Phase)	Brief Study Description	Treatment(s)	Population	Number of Patients (Observations)		
				PKPD	Efficacy (ITT)	Safety
MD-01 (III)	Randomized, double-blind, fixed dose, placebo controlled, parallel-group study	40, 80 or 120 mg SR daily for 8 weeks	Adults with MDD who received levomilnacipran	724 (4498)	704 (4458)	713 (4476)
MD-02 (III)	Randomized, double-blind, flexible dose, placebo-controlled, parallel-group study	40, 80 or 120 mg SR daily for 8 weeks (flexible dose)	Adults with MDD who received levomilnacipran	362 (2338)	355 (2324)	357 (2328)
MD-03 (III)	Randomized, double-blind, flexible dose, placebo-controlled, parallel-group study	40, 80 or 120 mg SR daily for 8 weeks (flexible dose)	Adults with MDD who received levomilnacipran	442 (2802)	429 (2776)	434 (2786)

The PKPD analysis set included 9638 observations from 1528 patients (570 males, 958 females), of which 1488 patients, with 9558 total observations, were part of the intent-to-treat (ITT) population included in the efficacy analysis. The safety analysis set (vital signs and binary AEs) was comprised of 1504 patients and 9590 observations. Screening data (1531 observations) were

excluded from exploratory analyses and model development for efficacy and vital sign endpoints. Data from unscheduled visits were included in the ITT and safety analysis sets. The AE dataset included a total of 1938 events in 1504 patients.

The sponsor proposed a variety of PD models to capture MADRS, vital sign data (including pulse rate, DBP and SBP), and AEs (including nausea, vomiting, dizziness, headache, hyperhidrosis, dry mouth, constipation, urinary hesitation, erection and ejaculation disorder). Details are not copied here.

## 5 FDA REVIEWER'S COMMENTS ON SPONSOR'S ANALYSIS

### 5.1 FDA Reviewer's Comments on Sponsor's Population PK Analysis

- For the renal impairment subjects, the population PK estimate of  $CL/F$  was higher than NCA (the renal impairment PK study LVM-PK-02). As a result,  $V/F$  was also over-estimated for those subjects so that the model can capture the PK data at the elimination phase (as demonstrated in **Figure 12** and **Figure 15**). (b) (4)



## 6 FDA REVIEWER'S ANALYSIS

The purpose of FDA reviewer's analysis was to

- Evaluate if the proposed daily dose of 40-120 mg appropriate for MDD patients based on efficacy and safety data observed in three Phase III studies, LVM-MD-01, LVM-MD-02 and LVM-MD-03.
- Evaluate if sponsor's levomilnacipran dose adjustment regimens for moderate and severe renal impairment patients are appropriate or not.
- Evaluate if sponsor's levomilnacipran dose regimen for severe hepatic impairment patients is appropriate or not.
- Evaluate if levomilnacipran effect on vital sign was related to dose levels based on data collected in LVM-PK-07 (evaluation of the effects of sequential multiple-dose regimens of levomilnacipran on cardiac repolarization in healthy subjects).

### 6.1 Analysis about Proposed Maintenance Dose Range of 40-120 mg at Steady-State

To evaluate the appropriateness of the proposed dose range of 40-120 mg QD levomilnacipran, FDA reviewer first reproduced sponsor's population PK analysis of levomilnacipran using the final PK model as reported in LVM-MS-01. FDA reviewer second explored possible relationships between efficacy/safety and exposure data of LVM-MD-01 to establish possible benefit/risk profiles of levomilnacipran for male and female patients separately. Third, the distributions of mean daily doses of the MDD patients were plotted for the three Phase III studies, LVM-MD-01, LVM-MD-02 and LVM-MD-03. And finally, an optimal dose range was proposed for MDD patients. The results and conclusion are presented in Sections 1.1.1 and 1.1.2.

### 6.3 Analysis about Dose Adjustment for Renal Impairment Patients

To evaluate the appropriateness of sponsor's dose regimen for renal impaired patients, modeling and simulations were executed on PK data of LVM-PK-02 (PK study in renal impairment

patients) by WinNonlin 6.3 of Pharsight. The model used for analysis was 1-compartment extravenous 1<sup>st</sup> order absorption PK model with absorption lag time. Further, the goodness of fits was compared to that of the population PK analysis by the sponsor. The results and conclusion are presented in **Figure 15**. Finally, the sponsor's dose regimens for impairment patients were evaluated by PK simulations. In the simulation, the values of 1-compartment PK parameters were generated based on LVM-PK-02 by WinNonlin. The results and conclusion are presented in Section 1.1.3.

#### **6.4 Analysis about Dose Adjustment for Severe Hepatic Impairment Patients**

To evaluate the appropriateness of sponsor's dose regimen for hepatic impaired patients, modeling and simulations were executed on PK data of LVM-PK-05 (PK study in hepatic impairment patients) by WinNonlin 6.3 of Pharsight. The model used for analysis was 1-compartment extravenous 1<sup>st</sup> order absorption PK model with absorption lag time. Finally, the sponsor's dose regimens for patients with hepatic impairment were evaluated by PK simulations. In the simulation, the values of 1-compartment PK parameters were generated based on LVM-PK-05 by WinNonlin. The results and conclusion are presented in Section 1.1.4.

#### **6.5 Analysis about the Effect of Levomilnacipran on Vital Sign Data**

The levomilnacipran effect on vital sign was evaluated based on data for 20, 120 and 300 mg QD from Study LVM-PK-07 (the QT prolongation study). In addition, the effect of levomilnacipran on vital sign was evaluated based on data for 40-120 mg QD from three Phase III studies (LVM-MD-01, LVM-MD-02 and LVM-MD-03). The results are presented in Section 1.1.5.

**Figure 15: Comparison of goodness of fit between pop-PK analysis and WinNonlin analysis on observed plasma levomilnacipran concentrations of LVM-PK-02, the renal impairment PK study**

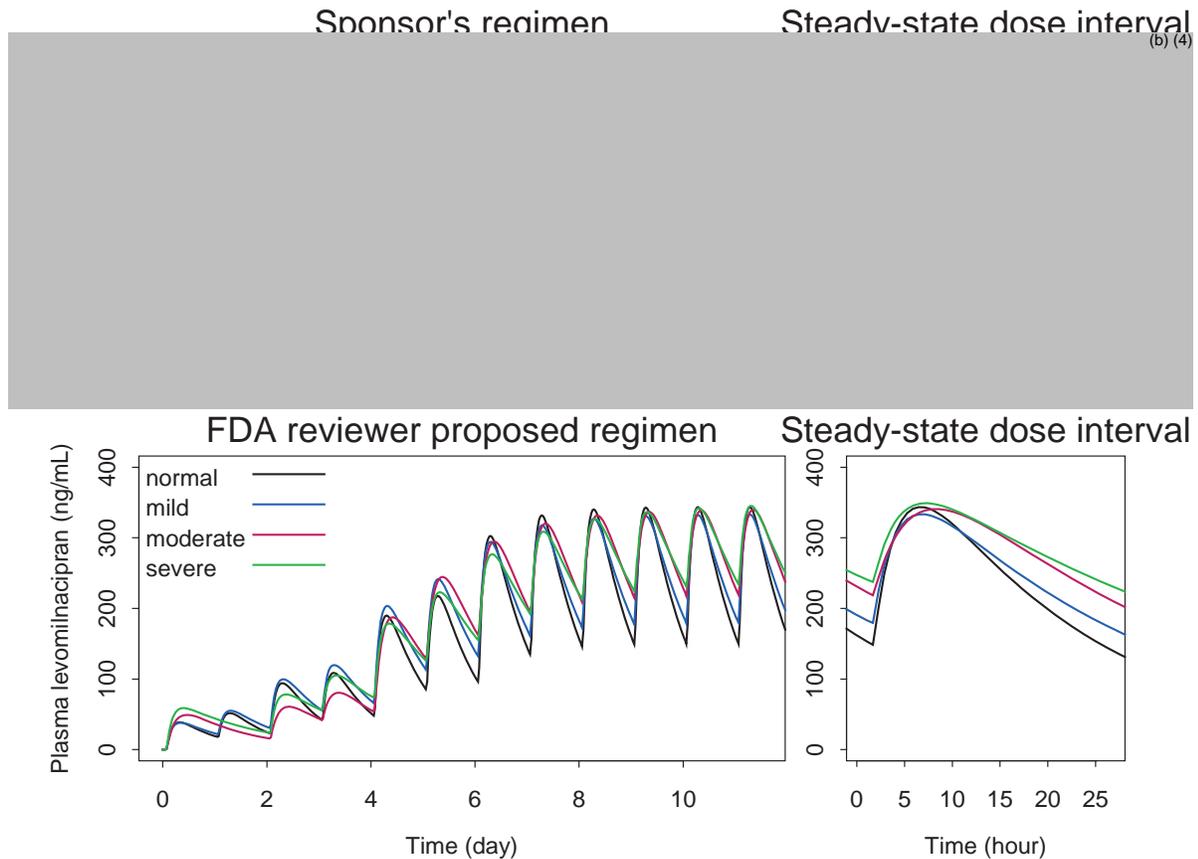
**7 LISTING OF ANALYSES CODES AND OUTPUT FILES**

File Name	Description	Location in \\cdsnas\pharmacometrics\
FDA population PK analysis	Reproducing sponsor's final population PK model with modified code	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Levomilnacipran_NDA_204168_HL\PPK Analysis\FDA ppk analysis
FDA Exposure Response Analysis	S-Plus codes for data merging and exposure response analysis	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Levomilnacipran_NDA_204168_HL\ER Analysis\Final Model

**8 Appendix**

The lower panels of **Figure 16** present alternative regimens, as described in **Table 10**, proposed by the FDA reviewer. Additional strength, 10 mg levomilnacipran per capsule, might be needed for the regimens.

**Figure 16: Simulated levomilnacipran concentration versus time courses for sponsor and FDA reviewer proposed regimens for patients with normal, moderate impaired and severely-impaired renal functions using PK estimates from LVM-PK-02. Left panels are for titration to steady-state and the right panels are for steady-state only**



Simulations are for dose regimen in **Table 10** and PK parameter values are from LVM-PK-02

**Table 10: Daily Dose (mg) Proposed by the Sponsor and the FDA Reviewer for Patients with Different Renal Functions**

	Normal Renal Patients		Mild Renal Impaired		Moderate Renal Impaired		Severe Renal Impaired	
	Sponsor	FDA	Sponsor	FDA	Sponsor	FDA	Sponsor	FDA
Day 1	20	20	20	20	20	20	20	20
Day 2	20	20	20	20	0	0	0	0
Day 3	40	40	40	40	20	20	20	20
Day 4	40	40	40	40	20	20	20	20
Day 5	80	80	80	80	60	60	40	40
Day 6	80	80	80	80	60	60	40	40
Day 7	120	120	120	100	60	70	40	50
Day 8-21	120	120	120	100	80	70	(b) (4)	50

The proposed dose reduction was based on that 120 mg levomilnacipran is the maintenance dose at steady-state. If steady-state maintenance dose is not 120 mg QD, the dose reduction should be in the same proportion.

**3.3 OSI Report**

**MEMORANDUM  
DEPARTMENT OF HEALTH  
AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE**

**FOOD AND DRUG  
ADMINISTRATION CENTER FOR DRUG  
EVALUATION AND RESEARCH**

DATE: May 30, 2013

TO: Mitchell V. Mathis, M.D.  
Director,  
Division of Psychiatry Products

FROM: Arindam Dasgupta Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
(DBGLPC)  
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.  
Chief, Bioequivalence Branch,  
Division of Bioequivalence and GLP Compliance

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI A KUMI  
06/17/2013

HONGSHAN LI  
06/17/2013

VENKATESH A BHATTARAM  
06/17/2013

HAO ZHU  
06/17/2013

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 204-168	<b>Reviewer:</b> Akm Khairuzzaman, Ph.D.	
<b>Submission Date:</b>	25-Sept-2012		
<b>Division:</b>	Division of Psychiatry Products	<b>Team Leader:</b> Angelica Dorantes, PhD	
<b>Sponsor:</b>	Forest Laboratories Inc.		
<b>Trade Name:</b>	None	<b>Date Assigned:</b>	10/17/2012
<b>Established Name:</b>	Levomilnacipran (base) and Levomilnacipran hydrochloride (salt)	<b>Date of Review:</b>	05/20/2013
<b>Indication:</b>	Major depressive disorder (MDD)	<b>Type of Submission:</b> Original NDA 505(b)1	
<b>Formulation/strengths</b>	Sustained Release Capsule, 20 mg, 40 mg, 80 mg & 120 mg		
<b>Route of Administration</b>	Oral		
<b>PDUFA V Timeline:</b>	<b>MILESTONES</b>	<b>MILESTONE DEADLINES</b>	
	Receipt Date	Sep. 25, 2012 [Tue.]	
	Day 45	Nov. 9, 2012 [Fri.]	
	Day 60 (Filing Date)	Nov. 24, 2012 [Sat.]	
	Day 74 Letter Due	Dec. 8, 2012 [Sat.]	
	Month 5	Feb. 25, 2013 [Tue.]	
	Primary Review due to TL	Jun. 20, 2013 [Thu.]	
	Secondary Review due to CDTL	Jun. 27, 2013 [Thu.]	

### **EXECUTIVE SUMMARY:**

Levomilnacipran HCl is a selective serotonin and norepinephrine reuptake inhibitor and is claimed to be approximately 2-fold more potent since it is the more active of the 2 enantiomers present in the racemate of milnacipran which was approved by the FDA on January 14, 2009 for the management of fibromyalgia under the trade name Savella®. Levomilnacipran HCl has an aqueous solubility of 0.7 g/mL. The pH of the 1% w/v aqueous solution is between 5.2 and 5.9. Levomilnacipran HCl (F2695) drug substance could possibly be classified as a BCS Class 1 compound based on the solubility and permeability. The dissolution was found to be one of the critical quality attribute in the application. The dissolution method development report showed sufficient data for its robustness. The dissolution limit set was justified based on comparative individual clinical batch dissolution data, individual tablet dissolution data from stability and approved IVIVC. Bioequivalence studies were conducted to link formulation changes between phase III and “to be marketed” formulation. Additional bioequivalence studies were also conducted to support site (two) equivalence. The biowaver request for the dose proportional lower strength can be granted. The applicant has conducted in vitro alcohol dose dumping studies; the agency has approved a biowaver for in vivo alcohol dose dumping. Currently there is no pending issue with this NDA from biopharmaceutics point of view.

**RECOMMENDATION**

The NDA is recommended for APPROVAL from the Biopharmaceutics perspective.

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Akm Khairuzzaman, Ph.D.  
**Interdisciplinaire Scientist, ONDQA**

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Date

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John Duan, Ph.D.  
**Biopharmaceutics Lead, ONDQA**

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Date

cc: NDA 204168

**SUBMISSION:** This NDA was submitted under the Section 505(b)(1) of the Food, Drug and Cosmetic Act for the treatment of Major Depressive Disorder (MDD). Levomilnacipran HCl inhibits both norepinephrine (NE) and 5- hydroxytryptamine (serotonin [5-HT]) reuptake in vitro and in vivo and is approximately 2-fold more potent at inhibiting NE reuptake than 5-HT reuptake transporters. Levomilnacipran is the more active of the 2 enantiomers present in the racemate of milnacipran which was approved by the FDA on 14-JAN-2009 for the management of fibromyalgia under the trade name Savella® (NDA 022256, film coated tablets, Cypress Bioscience Inc., Approved, 14-JAN-2009). The highest marketed strength of Savella is 100 mg tablet.

**1. The reviewer’s analyses on the formulation development:**

*Evaluation: Acceptable.*

Levomilnacipran SR Capsules (20 mg, 40 mg, 80 mg & 120 mg) are formulated as a sustained-release (SR) capsule formulation intended for once-daily oral administration. The commercial drug products are supplied (b) (4)

(b) (4)

(b) (4)

Formulation is dose proportional across all the strengths. The drug product has been developed by utilizing Quality by Design strategy whereby the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQA) have been identified by the Applicant. Dissolution is identified as one of the drug product CQA. A risk assessment on formulation & manufacturing variability has also been conducted.

**Table 1.** Comparative formulation composition between the Phase III and to be marketed commercial formulation:

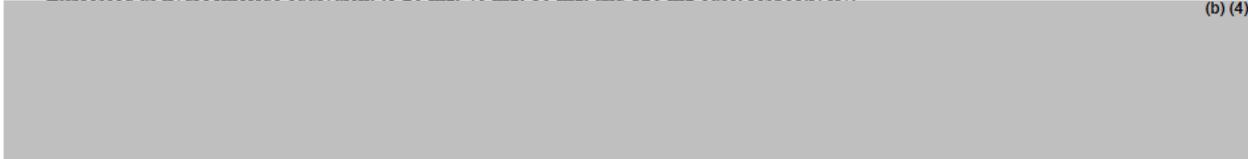
<i>Ingredient</i>	<i>Phase III Formulation (%w/w)</i>	<i>NDA Registration<sup>a</sup> (%w/w)</i>
F2695	(b) (4)	
Sugar spheres		
Povidone (b) (4) USP		
Talc, USP		
Ethylcellulose, NF		
Triethyl citrate, NF		
Talc, USP		
Total		

a Proposed Commercial Formulation

**Table 2.** Commercial formulation composition for each strength

Ingredients	Function	% (w/w)	Quantity Unit (mg/capsule)			
			20 mg	40 mg	80 mg	120 mg
Levomilnacipran HCl	Drug substance	(b) (4)	(b) (4)			
Sugar spheres, (b) (4) USP/NF	(b) (4)					
Povidone, (b) (4) USP/NF						
Talc, USP/NF						
(b) (4)						
Ethylcellulose, (b) (4) USP/NF						
Triethyl citrate, USP/NF						
<b>Total Filled Weight</b>		<b>100</b>				
Empty (b) (4) capsule	Capsule shell <sup>c</sup>	—				
<b>Total Capsule Weight</b>	—	—	<b>89</b>	<b>148</b>	<b>264</b>	<b>379</b>

<sup>c</sup>Expressed as hydrochloride equivalent to 20 mg, 40 mg, 80 mg, and 120 mg base, respectively.



PK studies were conducted to establish bioequivalence between the clinical SR formulation and the commercial SR formulation. Results showed acceptable PK parameters (The 90% CIs of the geometric mean ratios of  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were all within the range of 80% to 125%) but this is subject to be reviewed by the Office of Clinical Pharmacology. Additionally, the following dissolution profile shows that there were no differences between the phase III product and the “to be marketed” formulation:



**Fig. 1.** Dissolution Profile for Levomilnacipran SR Capsules 120 mg, FLI NDA Registration Batches in Comparison to Clinical Reference

**2. The reviewer’s analyses on the biowaver request**

***Evaluation: Acceptable.***

Biowaver for lower strength: Based on the (b) (4) formulation (see above table for formulation composition) of the drug products of different strengths and the demonstration of linear pharmacokinetics of the levomilnacipran SR formulation, applicant’s request for biowaver for conducting bioequivalence studies on the lower strengths (20 mg, 40 mg, and 80 mg) can be granted.

Site change biowaver: A submission dated 7/26/11 (ref. IND # 104483, reviewed by Dr. John Duan dated 01/06/2013), included a biowaiver request for conducting a BE study between the clinical and the to-be-marketed formulations and a biowaiver request for a level 3 manufacturing site change. However, the sponsor conducted the corresponding BE studies and bioequivalence was demonstrated (see below); therefore, the BE waivers previously requested are not longer necessary. Dr. John Duan however, has approved the IVIVC submitted under this IND and can be found in the same review. On 03 Jan 2012, FDA informed Forest that the biowaiver for the lower dose strengths may be granted if the bioequivalence and dose proportionality are confirmed after the final review of the data.

### **3. The reviewer's analyses on the manufacturing site change**

*Evaluation: Acceptable.*

There are two manufacturing sites. The clinical batches (Phase III) were manufactured in Forest Ireland and the "to be marketed" formulation is in [REDACTED] (b) (4) studies were conducted to establish bioequivalence between the clinical batch manufacture site (Forest Laboratories Ireland, Ltd) and the commercial batch manufacturing facility [REDACTED] (b) (4) Results showed acceptable PK parameters but this is subject to be reviewed by the Office of Clinical Pharmacology.

### **4. The reviewer's analyses on the manufacturing process development :**

*Evaluation: Acceptable.*



(b) (4)



**5. Reviewer's evaluation on dissolution method development:**  
*Evaluation: Acceptable.*

(b) (4)



6. Reviewer's evaluation on the propose dissolution method and acceptance criteria :

**Evaluation: Not Acceptable.**

Apparatus	Medium	Volume	Speed	UV detection	Sampling time points	Acceptance criteria
(b) (4)						

**Reviewer's comment:** The dissolution limits for levomilnacipran HCl sustained-release (SR) capsules established for the 4 hr time point was slightly higher than the (b) (4). Although, such limit is covered in the clinical trial batches used in the primary efficacy and safety studies (LVM-MD-01, LVM-MD-02, LVM-MD-03, LVM-MD-04, LVM-MD-05, and LVM-MD-10) and the applicant has IVIVC (approved by a different Biopharm reviewer, Dr. John Duan, under the IND # 104483, Review date 01/06/2013), such limit is not sufficiently justified. The following question was sent out to eh Applicant on 8/28/2013.

**Question sent out to the Applicant:** Justify your proposed dissolution acceptance criteria using your IVIVC model. Otherwise tighten the dissolution acceptance criteria to the target  $\pm$  (b) (4) at 2 h and 4 h. Provide updated drug product specification.

**Response:** The proposed limits were established at 1, 4, 8 and 24 h. The 1 h interval ensures that no dose-dumping occurs. The 4 h and 8 h time points provide control over intermediate release levels, and the 24-hour time ensures that (b) (4) of the product releases. This is consistent with the approach outlined in the FDA *Guidance for Industry, Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*, where a minimum of three time points is recommended to set the specifications; and these time points should cover the early, middle, and late stages of the dissolution profile. The sponsor does not propose setting a dissolution limit at the 2 h interval as the 4 proposed time intervals adequately characterize the drug product dissolution profile and ensure batch-to-batch consistency. The specification is as follows:

Dissolution <sup>a</sup>	1-hour	(b) (4)
	4-hours	
	8-hours	
	24-hours	

Reviewer's final evaluation: **Acceptable.**

**7. Reviewer's evaluation on dissolution data and IVIVC in support of dissolution limit :  
*Evaluation: Acceptable.***



**Fig. 5.** Dissolution data (mean, min and max) of Batch BN0006491 used in clinical studies LVM-MD-01, LVM-MD-02, LVM-MD-03 & LVM-MD-04



**Fig. 6.** Dissolution data (mean, min and max) of Batch L0003424 used in clinical studies LVM-MD-05 Phase I



Fig. 7. In vitro datasets used to construct the IVIVC (Ref. Dr. John Duan's review on the IND # 104483, dated 01/06/2013)

Formulation	PE Cmax(%)	PE AUC (%)
(b) (4)		

(b) (4)

The dissolution limit was found to be acceptable to this reviewer based on the acceptable IVIVC.

**8. Reviewer's evaluation on dissolution stability during product shelf life :**

*Evaluation: Acceptable.*

Individual tablet dissolution data from the accelerated as well as from the long term study showed that dissolution profile is stable over the duration of the stability and does not fall outside of the limit.

**9. Reviewer's evaluation on the alcohol dose dumping (in vitro):**

*Evaluation: Acceptable.*

Dissolution media with alcohol concentrations of 5%, 20% and 40% v/v were used. Levomilnacipran SR Capsules, 20 mg, 40 mg, 80 mg, and 120 mg exhibited no or little release in 5% v/v alcohol relative to the water control at 30 minutes. Minimal release was observed in 20% v/v alcohol with an average of 6% of the drug dissolved at 30 minutes (the control was  $\approx$  3%). A pronounced drug release was observed in 40% v/v alcohol. About 26% of the drug dissolved at 30 minutes. The results of this in vitro study confirmed that an interaction exists between levomilnacipran SR capsules and alcohol. An *in vivo* simulation (assumes a complete levomilnacipran SR dose dump in the presence of alcohol) demonstrated a  $C_{max}$  of 435 ng/mL which is more than 50% lower than 873 ng/mL that was reached at 300 mg daily, the highest dose tested and tolerated in healthy subjects. Therefore, on January 20, 2012, the Agency informed Forest that the waiver for an in vivo alcohol dose-dumping study is appropriate. (b) (4)

## 10. Reviewer's evaluation on the Sustained Release Designation:

### *Evaluation: Acceptable.*

The SR formulation displays characteristics of sustained release (lower maximum plasma drug concentration [C<sub>max</sub>], longer time of maximum plasma drug concentration [T<sub>max</sub>], and longer terminal elimination half-life [T<sub>1/2</sub>] relative to oral solution following either single- or multiple-dose administration. The study number was LVM-PK-16/ A and the purpose of this study was to compare the pharmacokinetics of levomilnacipran sustained-release formulation (SR capsule) and levomilnacipran oral solution formulation after single- and multiple-dose administration. The following table summarizes comparative PK parameters from multiple dose study between SR and solution formulations:

**Table 3.** PK Parameters (Mean ± SD) for Levomilnacipran in Healthy Male and Female Subjects After Oral Multiple-Dose Administration of Levomilnacipran Oral Solution and SR Capsule Formulations — PK Analysis Population

PK Parameter	Levomilnacipran Oral Solution, 40 mg (Treatment A) (N = 19)	Levomilnacipran SR Capsule, 120 mg (Treatment B) (N = 22)	Treatment B/Treatment A
			Ratio of Geometric Means (90% CI) <sup>a</sup> , %
C <sub>max,ss</sub> , ng/mL	185.0 ± 32.6	384.6 ± 66.1	69.7 (65.9-73.8)
AUC <sub>0-t</sub> , ng•h/mL	2097.5 ± 220.7	5752.0 ± 871.2	91.2 (86.9-95.7)
C <sub>min,ss</sub> , ng/mL	31.5 ± 7.2	144.9 ± 25.1	155.2 (143.3-168.0)
T <sub>max,ss</sub> , h <sup>b</sup>	2.0 (1.0, 5.0)	5.0 (4.0, 6.0)	p < 0.01 <sup>c</sup>
C <sub>av,ss</sub> , ng/mL	87.4 ± 9.2	239.7 ± 36.3	NA
T <sub>1/2</sub> , h	12.0 ± 2.7	13.5 ± 3.3	
Fluctuation, %	175.5 ± 34.6	100.0 ± 19.7	
Swing, %	525.1 ± 207.7	170.6 ± 54.0	

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/s/  
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AKM KHAIRUZZAMAN

05/20/2013

This NDA is recommended for APPROVAL from the Biopharmaceutics perspective

JOHN Z DUAN

05/20/2013

BIOPHARMACEUTICS INITIAL ASSESSMENT and FILING REVIEW Office of New Drugs Quality Assessment			
<b>Application No.:</b>	NDA 204-168	<b>Reviewer:</b> Akm Khairuzzaman, Ph.D.	
<b>Submission Date:</b>	25-Sept-2012		
<b>Division:</b>	Division of Psychiatry Products	<b>Team Leader:</b> Angelica Dorantes, PhD	
<b>Sponsor:</b>	Forest Laboratories Inc.		
<b>Trade Name:</b>	None	<b>Date Assigned:</b>	10/17/2012
<b>Established Name:</b>	Levomilnacipran (base) and l Levomilnacipran hydrochloride (salt)	<b>Date of Review:</b>	11/06/2012
<b>Indication:</b>	Major depressive disorder (MDD)	<b>Type of Submission:</b> Original NDA 505(b)1	
<b>Formulation/strengths</b>	Capsule, 20 mg, 40 mg, 80 mg & 120 mg		
<b>Route of Administration</b>	Oral		
<b>PDUFA V Timeline:</b>	<b>MILESTONES</b>	<b>MILESTONE DEADLINES</b>	
	Receipt Date	Sep. 25, 2012 [Tue.]	
	Day 45	Nov. 9, 2012 [Fri.]	
	Day 60 (Filing Date)	Nov. 24, 2012 [Sat.]	
	Day 74 Letter Due	Dec. 8, 2012 [Sat.]	
	Month 5	Feb. 25, 2013 [Tue.]	
	Primary Review due to TL	Jun. 20, 2013 [Thu.]	
	Secondary Review due to CDTL	Jun. 27, 2013 [Thu.]	

**SUBMISSION:**

This NDA was submitted under the Section 505(b)(1) of the Food, Drug and Cosmetic Act for the treatment of Major Depressive Disorder (MDD). Levomilnacipran HCl inhibits both norepinephrine (NE) and 5- hydroxytryptamine (serotonin [5-HT]) reuptake in vitro and in vivo and is approximately 2-fold more potent at inhibiting NE reuptake than 5-HT reuptake transporters. Levomilnacipran is the more active of the 2 enantiomers present in the racemate of milnacipran which was approved by the FDA on 14-JAN-2009 for the management of fibromyalgia under the trade name Savella® (NDA 022256, film coated tablets, Cypress Bioscience Inc., Approved, 14-JAN-2009). The highest marketed strength of Savella is 100 mg tablet.

Levomilnacipran SR Capsules (20 mg, 40 mg, 80 mg & 120 mg) are formulated as a sustained-release (SR) capsule formulation intended for once-daily oral administration. The commercial drug products are supplied (b) (4)

Formulation is dose proportional across all the strengths. The drug product has been developed by utilizing Quality by Design strategy whereby the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQA) have been identified by the Applicant. Dissolution is identified as one of the drug product CQA. A risk assessment on formulation & manufacturing variability has also been conducted.

There are two manufacturing sites. The clinical batches (Phase III) were manufactured in Forest Ireland and the “to be marketed” formulation is in (b) (4). Two PK studies were conducted to establish bioequivalence between the clinical SR formulation and the commercial SR formulation manufactured by Forest Laboratories Ireland, Ltd (LVM-PK-19) and (b) (4) (LVM-PK-14) using the highest strength of 120 mg. Based on the (b) (4) formulation of the drug products of different strengths and the demonstration of linear pharmacokinetics of the levomilnacipran SR formulation, a request for biowaiver for conducting bioequivalence studies on the lower strengths (20 mg, 40 mg, and 80 mg) of the commercial formulation is included in this NDA.

**BIOPHARMACEUTIC INFORMATION:** In support of approval, this NDA includes the following Biopharmaceutics data for review and evaluation:

- Critical Quality Attributes: Dissolution
- Proposed dissolution method and acceptance criteria, with justification
- Comparative dissolution data including all clinical batches
- Drug product dissolution stability data.
- Biowaver (BE) for the lower strength
- Biowaver for in vivo alcohol dose dumping potential

**COMMENTS & RECOMMENDATION:** From a biopharmaceutics perspective, NDA 204-168 for Levomilnacipran Hydrochloride SR capsule is considered fileable. There are sufficient Biopharmaceutics data to permit a substantive review. The following two (2) comments should be communicated to the Applicant:

1. Based on your PK simulation, it can be anticipated a very high drug exposure with the 120 mg SR formulation in an alcohol dose dumping situation; therefore, we recommend that the increased GI adverse events with alcohol be appropriately described in the product’s labeling.
2. Note that any biowaiver request based on IVIVC at a post-approval stage (*for a future Level 3 site change or any other significant manufacturing/formulation change*) will not be granted if the validity of your IVIVC model can not be confirmed.

**Akm Khairuzzaman, Ph.D.**  
Biopharmaceutics Reviewer, ONDQA

**Angelica Dorantes, Ph.D.**  
Biopharmaceutics Team Leader, ONDQA

**ONDQA-BIOPHARMACEUTICS Initial** overview of the NDA application for filing

	<b>Parameter</b>			<b>Comment</b>
1.	Is the QTPP (Quality Target Product Profile) defined for drug release? (3.2.P.2)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
2.	Has the risk assessment been performed to evaluate the criticality of the in vitro release? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
3.	Is there any manufacturing parameter evaluated using in vitro release as an end point?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	No manufacturing parameters were evaluated using the dissolution method. However, applicant has evaluated the method for its capability to distinguish formulation variability such as effect of rate controlling polymer.
4.	Is there any design space proposed using in vitro release as an end point?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	
5.	Is the control strategy related to in vitro dissolution/drug release? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
6.	Solubility	High <input checked="" type="checkbox"/>	Low <input type="checkbox"/>	
7.	Permeability	High <input checked="" type="checkbox"/>	Low <input type="checkbox"/>	Based on urinary clearance (% unchanged drug) from PK mass balance study
8.	BCS Class	I <input checked="" type="checkbox"/> II <input type="checkbox"/>	III <input type="checkbox"/> IV <input type="checkbox"/>	Claimed as BCS I
9.	Is the study report included for the development of the in vitro release method? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
10.	In the study report, are the individual data, the mean, the standard deviation and the plots provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
11.	Has the discriminating ability been shown for the in vitro release methodology using formulation variants? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
12.	Is the justification provided for the acceptance criteria of the in vitro release? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
13.	Are the proposed acceptance criteria adequate? (3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	Acceptance criteria appear to be reasonable. However, it requires further review in order to make a final decision
14.	Is the to-be-marketed formulation the same as that used in pivotal clinical trials?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	Formulation is same but to me marketed product has different site. BE study was conducted to site equivalence.
15.	Are all the to-be-marked strengths used in the pivotal clinical trials?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	A biowaver has been requested for the lower strengths

16.	Have any biowaivers been requested? (1.12/2.7.1)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	A request for biowaiver for conducting bioequivalence studies on the lower strengths (20 mg, 40 mg, and 80 mg) of the commercial formulation is included in this NDA. On 03 Jan 2012, FDA informed Forest that the biowaiver for the lower dose strengths may be granted if the bioequivalence and dose proportionality are confirmed after the final review of the data. Applicant has reported a liner PK between 25 mg and 120 mg. Therefore the lowest dose 20 mg falls outside of the liner PK range.
17.	If it is a Sustained Release Formulation, then is there any in vitro alcohol dose dumping study?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
18.	Is there any IVIVC information submitted? (5.3.1)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	IVIVC was submitted as a part of applicant's IND # 104483. The IVIVC was reviewed by Dr. John Duan and it was found to be not acceptable.
19.	If the IVIVC information presented, are the study report and data provided?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	No details of the IVIVC has been submitted in this NDA
20.	Is the Extended release designation supported by the steady state study?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	The steady-state was achieved at the end of the study (Day 16). However, there is not commercially IR tablets in the market.

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
21.	<b>IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	<ul style="list-style-type: none"> <li>➤ The NDA is filable from the Biopharmaceutics Perspective</li> <li>➤ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue.</li> </ul>
22.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not applicable.
23.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not applicable.
24.	Are there any potential review issues identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>	None at this stage
25.	Are there any comments to be included in the 74-Day letter?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	The reviewer comments listed in page 2 should be conveyed to the Applicant in the 74-Day letter.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AKM KHAIRUZZAMAN

11/19/2012

Thsi NDA is Fileable from Biopharmaceutics point of view

ANGELICA DORANTES

11/19/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	204168	Brand Name	TBD
OCP Division (I, II, III, IV, V)	I	Generic Name	Levomilnacipran
Medical Division	DPP	Drug Class	SNRI
OCP Reviewer	Kofi Kumi	Indication(s)	Treatment of Major Depressive Disorder (MDD)
OCP Team Leader	Hao Zhu	Dosage Form	Extended Release Capsules (20 mg, 40 mg, 80 mg, 120 mg)
Pharmacometrics Reviewer	Hongshan Li	Dosing Regimen	40 – 120 mg daily
Date of Submission	9/24/12	Route of Administration	Oral
Estimated Due Date of OCP Review	6/25/13	Sponsor	Forest Laboratories
Medical Division Due Date	7/4/12	Priority Classification	Standard
PDUFA Due Date	7/25/13		

**Summary**

The sponsor has submitted an original NDA for Levomilnacipran hydrochloride (LVM) sustained release capsules, 20 mg, 40 mg, 80 mg and 120 mg, for treatment of MDD. LVM is a selective serotonin (5HT) and norepinephrine (NE) reuptake inhibitor (SNRI) with 2-fold greater potency for NE than 5HT receptors. LVM is the levo-enantiomer of milnacipran (Savella®) tablets approved in 2009 for the treatment of fibromyalgia.

The submission contains 19 clinical pharmacology and biopharmaceutics studies, 2 population pharmacokinetic (PopPK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses and 14 in vitro pharmacokinetic studies. The sponsor reported that efficacy for MDD was demonstrated in 3 positive pivotal Phase III studies (LVM-MD-01, LVM-MD-03, LVM-MD-10) and supported by 1 positive Phase II study (F02695 LP 2 02).

**Clin. Pharm. and Biopharm. Information**

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	Original NDA			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x	27		
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	9		
I. Clinical Pharmacology	x			

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Mass balance:	X	1		
Isozyme characterization:	X	3		
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -	X	12		
<b>Healthy Volunteers-</b>				
single dose:	X	4		
multiple dose:	X	3		
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	3		
fasting / non-fasting multiple dose:	X	2		
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:	X	1		
In-vitro:	X	14		
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>	X	1		
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X			
<b>Population Analyses -</b>	X	1		
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>	X			
<b>Absolute bioavailability</b>	X	1		
<b>Relative bioavailability -</b>	X			
solution as reference:	X	1		
alternate formulation as reference:	X	1		
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	3		
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>	X	2		
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>	X	1		
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>	X	1		
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>	X			
<b>Literature References</b>	X			
<b>Total Number of Studies</b>		41		

On **initial** review of the NDA/BLA application for filing:

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?				x

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

  Yes  

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Clinical Pharmacologist

Kofi Kumi, Ph.D.

Date 10/31/12

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# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Appendix

A listing of all clinical studies is provided in the table below.

<i>Type of Study</i>	<i>Study Identifier</i>	<i>Module Location of Study Report</i>	<i>Primary Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dose Regimen; Route of Administration<sup>a</sup></i>	<i>Number of Subjects<sup>b</sup></i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment<sup>c</sup></i>	<i>Study Status; Type of Report</i>
<b>GROUP 1: SHORT-TERM, PLACEBO-CONTROLLED STUDIES IN PATIENTS WITH MDD</b>									
<b>Group 1A: US Short-term, Placebo-Controlled Studies</b>									
<i>Fixed-dose studies</i>									
Efficacy, safety, tolerability	LVM-MD-01	5.3.5.1	Evaluate the efficacy, safety, and tolerability of fixed doses of F2695 SR compared with placebo in the treatment of adult patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in 4 treatment groups; placebo control	F2695 SR 20-mg NT capsules; F2695 SR 40-mg NT capsules 4 parallel treatment groups: placebo, F2695 40 mg, F2695 80 mg, F2695 120 mg, all once daily. Patients fixed titrated to target dose	724	Patients with MDD	<u>11 weeks:</u> up to 1 week screening, 8 weeks double-blind treatment, 2 weeks down-taper	Complete Full
Efficacy, safety, tolerability	LVM-MD-10	5.3.5.1	Evaluate the efficacy, safety, and tolerability of fixed doses of F2695 SR compared with placebo in the treatment of adult patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study; placebo control	LVM SR 20- and 40-mg capsules Patients were assigned to placebo, LVM 40 mg, or LVM 80 mg once daily. The starting dose for patients randomized to the LVM groups was 20 mg. Patients were fixed-dose titrated to the target doses over a 7-day period	568	Patients with MDD	<u>10 weeks:</u> up to 1 week screening, 8 weeks double-blind treatment, 1 week down-taper	Complete Full

<i>Type of Study</i>	<i>Study Identifier</i>	<i>Module Location of Study Report</i>	<i>Primary Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dose Regimen; Route of Administration<sup>a</sup></i>	<i>Number of Subjects<sup>b</sup></i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment<sup>c</sup></i>	<i>Study Status; Type of Report</i>
<i>Flexible-dose studies</i>									
Efficacy, safety, tolerability	LVM-MD-02	5.3.5.1	Evaluate the efficacy, safety, and tolerability of F2695 SR versus placebo in the treatment of patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study with 2 treatment groups; placebo control	F2695 SR 20-mg and 40-mg NT capsules Patients assigned to F2695 SR received 20 mg on Days 1 and 2 and 40 mg/day starting on Day 3. Dosage may have been increased from 40 to 80 mg/day at Visit 3 or Visit 4. At Visit 5, the dosage may have been increased from 40 to 80 mg/day or from 80 to 120 mg/day, based on response and tolerability	362	Patients with MDD	<u>11 weeks:</u> up to 1 week screening, 8 weeks double-blind treatment, 2 weeks down-taper	Complete Full
Efficacy, safety, tolerability	LVM-MD-03	5.3.5.1	Evaluate the efficacy, safety, and tolerability of F2695 SR versus that of placebo in the treatment of patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study; placebo control	F2695 SR 20- and 40-mg capsules Patients assigned to F2695 SR received 20 mg/day on Days 1 and 2 and 40 mg/day starting on Day 3. Dosage may have been increased from 40 to 80 mg/day at Visit 3 or Visit 4. At Visit 5, the dosage may have been increased from 40 to 80 mg/day or from 80 to 120 mg/day, based on response and tolerability	442	Patients with MDD	<u>11 weeks:</u> up to 1 week screening, 8 weeks double-blind treatment, 2 weeks down-taper	Complete Full

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>Group 1B: Non-US Short-term, Placebo-Controlled Study</b>									
Efficacy, safety	F02695 LP 2 02	5.3.5.1	Study the clinical efficacy of F2695 SR (dose 75 or 100 mg/day) compared with placebo in patients with MDD after 10 weeks of treatment	Phase 2, double-blind, randomized, placebo-controlled, parallel-group study; placebo control	F2695 SR, 25- and 50-mg capsules Patients randomized to F2695 received 25 mg on Days 1-3, 50 mg on Days 4-7, and 75 mg on Days 8-11; on Day 12, based on tolerance, the dose was increased to 100 mg or maintained at 75 mg. All doses administered once daily	563	Patients with MDD	<u>11 weeks:</u> 10 weeks double-blind treatment, 1 week down-taper	Complete Full
<b>GROUP 2: LONG-TERM, OPEN-LABEL STUDY IN PATIENTS WITH MDD</b>									
Safety, tolerability	LVM-MD-04	—	Evaluate the long-term safety and tolerability of F2695 SR in the treatment of adult patients with MDD	Phase 3, multicenter, open-label, flexible-dose, 52-week extension of studies LVM-MD-01, LVM-MD-02, and LVM-MD-03; no control	F2695 SR 20- and 40-mg capsules Patients will take F2695 20 mg on Days 1 and 2. On Day 3, the dose will be increased to 40 mg. From Visit 2 onward, the dosage may be increased in 40-mg increments at weekly intervals based on patient response and absence of dose-limiting adverse events. Minimum F2695 SR dose is 40 mg, and maximum is 120 mg. All doses administered once daily	850 planned	Patients with MDD	<u>52 weeks:</u> 48-week open-label treatment, 4-week down-taper	Ongoing

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>GROUP 3: RELAPSE-PREVENTION STUDY IN PATIENTS WITH MDD</b>									
Safety, efficacy (relapse prevention)	LVM-MD-05	5.3.5.1	Evaluate the safety and efficacy of F2695 SR relative to placebo in the prevention of depression relapse in patients with MDD	Phase 3, multicenter, randomized, double-blind, placebo-controlled relapse prevention study; placebo control during the double-blind phase	F2695 SR 20- and 40-mg capsules <b>Open-label phase:</b> Eligible patients will receive F2695 SR starting at 20 mg. After 2 days, the dosage will be increased to 40 mg and may be further increased at the end of Week 2 to 80 and/or 120 mg based on patient response and tolerability. After Week 4, patients will remain on the maximum effective and tolerated dose for the remaining open-label treatment phase. <b>Double-blind phase:</b> Patients meeting responder criteria will be randomized to F2695 SR treatment or placebo. The F2695 group will continue on the same dosage (40, 80, or 120 mg) that they were receiving at the end of the open-label treatment phase. The placebo group will be tapered off F2695 over 1 week and receive placebo thereafter. All doses administered once daily	Open-label phase: 734 Double-blind phase: 348	Patients with MDD	<u>39 weeks:</u> up to 1 week screening 12 weeks open-label treatment, 24 weeks double-blind treatment, 2 weeks double-blind down-taper	Complete Full

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>GROUP 4: CLINICAL PHARMACOLOGY AND BIOPHARMACEUTIC STUDIES IN HEALTHY SUBJECTS</b>									
<b>Bioavailability/Bioequivalence Studies</b>									
PK, BA, tolerability	F02695 GE 102	5.3.1.2	Evaluate the PK of 3 MR formulations of F2695 administered as single 50-mg oral doses and to compare their relative BA to that of the reference IR capsule	Phase 1, open-label, single-dose, randomized, 4-period crossover study; no control	F2695 25-mg IR capsules; F2695 50-mg MR capsules in 3 different formulations (MR1, MR2, MR3) Single dose of 25-mg IR F2695 or 50-mg F2695 MR1, MR2 or MR3 on Day 1 of each of 4 periods. Each dose was followed by a 7-day washout	16	Healthy male volunteers	1 day every 7 days for each of the 4 study periods	Complete Full
PK, BA, tolerability	F02695 LP 101	5.3.1.3	Evaluate whether a level A correlation exists for extended release formulations of F2695 between the fraction dissolved in vitro and the fraction absorbed in vivo. If such a correlation is evidenced, to validate the corresponding model. Develop a multiple level C correlation, in order to evaluate the dissolution limits for SR2 formulation to fulfill the bioequivalence criteria	Phase 1, single-center, open label, single dose, 4-period study; no control	F2695 20-mg IV formulation (25 mg/5 mL of isotonic saline solution); F2695 50-mg SR capsules in 3 different formulations (SR1, SR2, SR3) On Day 1 of Period 1, all subjects received a 1-hour IV infusion of F2695 20-mg IV formulation. SR1, SR2, and SR3 were administered on Day 1 of Periods 2, 3, and 4 according to a randomized cross-over design. Each dose was followed by a 7-day washout IV and oral administration	12	Healthy male volunteers	1 day for each of the 4 study periods; each single dose was separated by a 7-day interval	Complete Full

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>Bioavailability/Bioequivalence Studies (Continued)</b>									
BA (food effect)	LVM-PK-06	5.3.1.1	Evaluate the effect of food on the BA of 40-mg F2695 capsules	Phase 1, single-center, randomized, open-label, 2 × 2 crossover, single-dose study; no control	F2695 SR 40-mg capsules Treatment A: Single 40-mg dose (fasted conditions); Treatment B: Single 40-mg dose (fed conditions)	24	Healthy male and female volunteers	2 dosing days, each followed by a 7-day washout	Complete Full
BE (TBM 120-mg capsule), BA (food effect)	LVM-PK-12	5.3.1.1	Objectives: evaluate 1) the BE of LVM 120 mg administered as the TBM 120-mg SR capsule and as the clinical SR capsules and 2) the effect of food on the oral BA of the TBM LVM 120-mg SR capsule	Phase 1, single-center, randomized, open-label, crossover, single-dose study; no control	TBM formulation of LVM SR 120-mg capsules; clinical formulation of LVM SR, 40-mg capsules Treatment A: Single dose of the TBM formulation of LVM, one 120-mg capsule (fasted conditions); Treatment B: Single dose of the clinical formulation of LVM, three 40-mg capsules (fasted conditions); Treatment C: Single oral dose of the TBM formulation of LVM, one 120-mg capsule (fed conditions)	50	Healthy male and female volunteers	1 day in each of 3 treatment periods, separated by a washout of 7 days	Complete Full
BE (TBM (b) (4) formulation)	LVM-PK-14	5.3.1.2	Evaluate the BE of LVM 120 mg administered as the TBM (b) (4) SR capsule (1 × 120 mg) and as the clinical SR capsules (3 × 40 mg)	Phase 1, single-center, randomized, open-label, crossover, single-dose study; no control	(b) (4) site formulation of LVM, 120-mg SR capsules; clinical formulation of LVM, 40-mg SR capsules Treatment A: Single dose of LVM (b) (4) site formulation, one 120-mg capsule; Treatment B: Single dose of clinical LVM, three 40-mg capsules	61	Healthy male and female volunteers	1 day in each of 2 treatment periods, separated by a washout of 7 days	Complete Full

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Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>Pharmacokinetic Studies</b>									
Tolerability, PK (IR capsule)	F02695 GE 1 01	5.3.3.1	Assess the tolerability of increasing single and repeated oral doses of F2695 in healthy young male subjects	Phase 1, single-center, double-blind, randomized, placebo-controlled, single and repeated increasing oral dose study in 4 level groups of 10 healthy male subjects each; placebo control	F2695 12.5-mg and 25-mg capsules Day 1: single administration (after breakfast) of the randomized dose (ie, 1 dose of 12.5, 25, 50, or 75 mg); Days 3 to 15: BID administration (after breakfast and dinner) of the randomized dose (ie, 12.5, 25, 50, or 75 mg BID); Day 16: single administration (after breakfast) of the randomized dose. Dosage in the 2 highest dose groups was up-titrated over the first week to improve digestive tolerability	41 (8 each in placebo, 12.5-mg, 25-mg, and 75 mg groups; 9 in 50-mg group)	Healthy male volunteers	15 days (Dosing on Day 1 and on Days 3-16)	Complete Full
PK, tolerability	F02695 LP 1 02	5.3.3.1	Evaluate the potential interconversion of F2695 to F2696 by dosing both compounds in human plasma after a single 50-mg oral dose of F2695 in healthy male subjects	Phase 1, single-center, open-label, single-dose study; no control	Single dose of 1 F2695 50-mg SR capsule	13	Healthy male volunteers	1 day	Complete Full

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<b>Pharmacokinetic Studies (Continued)</b>									
Safety, tolerability, PK	LVM-PK-01	5.3.3.1	Evaluate safety and tolerability and characterize the PK of F2695	Phase 1, single-center, randomized, double-blind, placebo-controlled, single (part A) and multiple-dose (part B); placebo control	F2695 SR, 25- and 50-mg capsules Part A: single-dose F2695 25, 50, or 100 mg or placebo; Part B: multiple escalating dose F2695 25, 50, 75, and 100 mg or placebo; or F2695 25, 50, 100, 125, 150, 200, 250, and 300 mg or placebo	48	Healthy male and female volunteers	Part A: 1 day Part B, Cohort B1: Up to 16 days Part B, Cohort B2: Up to 36 days	Complete Full
PK, tolerability, mass balance (liquid formulation)	LVM-PK-03 (F02695 PO 1 01)	5.3.3.1	Determine in healthy male subjects, the rate and route of excretion of a single oral dose of [ <sup>14</sup> C]-F2695, explore PK parameters of radioactivity, F2695 and F17400 following a single oral dose of [ <sup>14</sup> C]-F2695, collect samples in order to characterize and/or quantify the metabolites of F2695 in plasma and excreta following a single oral dose of [ <sup>14</sup> C]-F2695, and assess the clinical and biological tolerability of [ <sup>14</sup> C]-F2695 administered as single 60-mg oral dose in healthy subjects	Phase 1, single-dose study; no control	[ <sup>14</sup> C]-F2695 solution A 5-g single oral dose (approximately 5 mL) solution containing 60 mg of [ <sup>14</sup> C]-F2695 with 100 µCi radioactivity)	9	Healthy male volunteers	1 day	Complete Full

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<i>Type of Study</i>	<i>Study Identifier</i>	<i>Module Location of Study Report</i>	<i>Primary Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dose Regimen; Route of Administration<sup>a</sup></i>	<i>Number of Subjects<sup>b</sup></i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment<sup>c</sup></i>	<i>Study Status; Type of Report</i>
<b>Pharmacokinetic Studies (Continued)</b>									
Safety, tolerability, PK	LVM-PK-15	5.3.3.1	Characterize the PK of LVM following oral administration of 40-, 80-, or 120-mg LVM SR capsules	Phase 1, single-center, randomized, open-label, parallel-group, single-dose study; no control	LVM 40-mg SR capsules Cohort I: Single dose of one 40-mg LVM capsule; Cohort II: Single dose of two 40-mg LVM capsules; Cohort III: Single dose of three 40-mg LVM capsules	30	Healthy male and female volunteers	1 day	Complete Full
<b>Intrinsic Factors</b>									
Safety, PK (renal impairment)	LVM-PK-02	5.3.3.3	Evaluate the PK characteristics and safety profile of F2695 and its nonactive metabolite F17400 after a single dose of 40 mg F2695 in subjects with various degrees of impaired renal function	Phase 1, single-dose, open-label, parallel-group design in 4 groups; no control	F2695 SR, 40-mg capsule, single dose	32	Healthy and renal impaired male and female volunteers	1 day	Complete Full
Safety, PK (age and gender effect)	LVM-PK-04	5.3.3.3	Evaluate 1) the effects of age and gender on the PK of F2695 and its metabolite F17400 following multiple-dose administration and 2) the safety profile of multiple doses of F2695 SR in healthy young adult and elderly male and female subjects	Phase 1, open-label, parallel-group study in 2 groups of subjects; no control	F2695 SR, 20- and 40-mg capsules Day 1: 20-mg single dose; Days 2 through 4: 40 mg once daily; Days 5 through 9: 80 mg (2 × 40 mg) once daily	33	Healthy male and female volunteers	9 dosing days	Complete Full
<b>Intrinsic Factors (Continued)</b>									
Safety, PK (hepatic impairment)	LVM-PK-05	5.3.3.3	Evaluate the PK characteristics and safety profile of F2695 and its nonactive metabolite F17400 after a single oral dose of 40 mg F2695 SR in male and female patients with various degrees of impaired hepatic function compared with healthy subjects with normal hepatic function	Phase 1, single-dose, open-label, parallel-group study; no control	F2695 SR, 40-mg capsule, single dose	32	Healthy and hepatic impaired male and female volunteers	1 day	Complete Full
<b>Extrinsic Factors</b>									
Safety, tolerability, PK, drug interaction (ketoconazole)	LVM-PK-08	5.3.3.4	Assess the effects of ketoconazole at steady state on the PK of a single dose of F2695	Phase 1, single-center, randomized, open-label, 2 × 2 crossover, drug-drug interaction study; no control	F2695 SR 40-mg capsules); ketoconazole, 200-mg tablets Treatment A: F2695 alone (single oral dose of F2695 80 mg); Treatment B: F2695 coadministered with ketoconazole 400 mg once daily for 5 days; ketoconazole 400 mg plus F2695 80 mg for 1 day, then ketoconazole 400 mg once daily for 3 days	34	Healthy male and female volunteers	2 days (2 doses separated by a washout period of at least 6 days)	Complete Full

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<b>Extrinsic Factors (Continued)</b>									
Safety, tolerability, PK, drug interaction (carbamazepine)	LVM-PK-09	5.3.3.4	Evaluate the effect of carbamazepine XR on the PK of F2695 SR	Phase 1, single-center, open-label, multiple-dose, fixed-sequence, 4-period study; no control	F2695 SR 20- and 40-mg capsules; carbamazepine XR 100- and 200-mg tablets <b>Treatment A:</b> F2695: 20 mg for 1 day, 40 mg once daily for 3 days, 80 mg once daily for 3 days, and 120 mg once daily for 4 days; <b>Treatment B:</b> carbamazepine: 100 mg twice daily for 4 days, 200 mg twice daily for 17 days; <b>Treatment C:</b> continuing carbamazepine 200 mg twice daily for the entire period and F2695 20 mg for 1 day, 40 mg once daily for 3 days, 80 mg once daily for 3 days, and 120 mg once daily for 4 days; <b>Treatment D:</b> carbamazepine 200 mg and 100 mg for 1 day, 100 mg twice daily for 2 days, and 100 mg once a day for 1 day	34	Healthy male and female volunteers	4 treatment periods: 11 days, 21 days, 11 days, and 4 days; 6-day washout after period 1; F2695 given during period 1 and 3	Complete Full

Type of Study	Study Identifier	Module Location of Study Report	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration <sup>a</sup>	Number of Subjects <sup>b</sup>	Healthy Subjects or Diagnosis of Patients	Duration of Treatment <sup>c</sup>	Study Status; Type of Report
<b>Extrinsic Factors (Continued)</b>									
Safety, tolerability, PK, drug interaction (alprazolam)	LVM-PK-10	5.3.3.4	Assess the effect of a F2695 SR capsule at steady state on the PK of alprazolam following single-dose administration of an alprazolam XR tablet	Phase 1, single-center, randomized, open-label, 2 x 2 crossover, drug-drug interaction study; no control	F2695 SR 20- and 40-mg capsules; alprazolam XR 1-mg tablet <b>Treatment A:</b> Single dose of alprazolam 1 mg under fasted conditions; <b>Treatment B:</b> F2695 20 mg for 1 day, 40 mg once daily for 3 days, 80 mg once daily for 3 days, and 120 mg once daily for 4 days; coadministration of F2695 120 mg plus alprazolam 1 mg for 1 day (fasted conditions), followed by F2695 120 mg once daily for 2 days	30	Healthy male and female volunteers	1 day in Treatment A, 14 days in Treatment B, separated by a washout period of at least 7 days	Complete Full
<b>Pharmacokinetic/Pharmacodynamic Study</b>									
Thorough QT	LVM-PK-07	5.3.4.1	Assess the effects of the investigated maximum therapeutic dose (120 mg/day) and a supratherapeutic dose (300 mg/day) of LVM on cardiac repolarization as determined by manual measurement of QTc on repeated digitally recorded 12-lead electrocardiograms	Phase 1, multicenter, randomized (stratified by sex), double-blind, placebo- and positive-controlled, parallel-group, multiple-dose study; placebo and positive controls	LVM 20- and 40-mg capsules. <b>Group 1:</b> placebo for 2 days; LVM 20 mg for 1 day, 40 mg for 3 days, 80 mg for 3 days, 120 mg for 4 days, 160 mg for 3 days, 200 mg for 3 days, 260 mg for 3 days, and 300 mg for 4 days, placebo for 1 day; <b>Group 2:</b> placebo for 2 days; moxifloxacin 400 mg for 1 day; and placebo for 24 days; <b>Group 3:</b> placebo for 26 days and moxifloxacin 400 mg for 1 day. All doses administered once daily	170 Group 1: 94 Group 2: 39 Group 3: 37	Healthy male and female volunteers	27 days	Complete Full

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<b>GROUP 5: STUDIES IN OTHER INDICATIONS</b>									
(b) (4)									

<i>Type of Study</i>	<i>Study Identifier</i>	<i>Module Location of Study Report</i>	<i>Primary Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dose Regimen; Route of Administration<sup>a</sup></i>	<i>Number of Subjects<sup>b</sup></i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment<sup>c</sup></i>	<i>Study Status; Type of Report</i>
(b) (4)									

a All doses given orally except in Study F02695 LP 1 01.

b Randomized.

c Treatment duration includes lead-in and down-taper periods.

BA = bioavailability; BE = bioequivalence; F2695 = levomilnacipran hydrochloride; IR = immediate release; IV = intravenous; LVM = levomilnacipran hydrochloride; MDD = major depressive disorder; MR = modified release; NT = nontrade; PK = pharmacokinetic, pharmacokinetics; QTc = QT interval corrected for heart rate; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; TBM = to be marketed; XR = extended release.

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KOFI A KUMI  
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HAO ZHU  
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