

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204168Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 204168
Related IND	104483
Priority or Standard	Standard
Submit Date(s)	September 24, 2012
Received Date(s)	September 25, 2012
PDUFA Goal Date	July 25, 2013
Division / Office	Division of Psychiatry Products (HFD-130)/ODE1
Reviewer Name(s)	Kavneet Kohli-Chhabra M.D. Tiffany Farchione M.D.
Review Completion Date	July 2, 2013
Established Name	levomilnacipran
(Proposed) Trade Name	Fetzima
Therapeutic Class	Antidepressant
Applicant	Forest Laboratories, Inc.
Formulation(s)	Capsule (Extended Release) of 20, 40, 80, and 120 mg strengths
Dosing Regimen	Once daily – oral
Indication(s)	Major Depressive Disorder
Intended Population(s)	Adults

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	10
2.1	Product Information	10
2.2	Tables of Currently Available Treatments for Proposed Indications	11
2.3	Availability of Proposed Active Ingredient in the United States	11
2.4	Important Safety Issues with Consideration to Related Drugs.....	11
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Post-Submission Regulatory Activity	12
2.7	Other Relevant Background Information	13
3	ETHICS AND GOOD CLINICAL PRACTICES.....	13
3.1	Submission Quality and Integrity.....	13
3.2	Compliance with Good Clinical Practices.....	13
3.3	Financial Disclosures	15
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	15
4.1	Chemistry Manufacturing and Controls	15
4.2	Clinical Microbiology	16
4.3	Preclinical Pharmacology/Toxicology	16
4.4	Clinical Pharmacology	17
4.4.1	Mechanism of Action	18
4.4.2	Pharmacodynamics.....	18
4.4.3	Pharmacokinetics.....	19
5	SOURCES OF CLINICAL DATA	21
5.1	Tables of Studies/Clinical Trials	21
5.2	Review Strategy	22
5.3	Discussion of Individual Studies/Clinical Trials.....	23
6	REVIEW OF EFFICACY	24
6.1	Indication – Treatment of Major Depressive Disorder (MDD).....	26
6.1.1	Rationale for Selection of Studies for Review	26
6.2	Study Summaries.....	26
6.2.1	Study LVM-MD-01	26
6.2.2	Study LVM-MD-10.....	35
6.2.3	Study LVM-MD-03.....	41
6.2.4	Study F02695 LP 2 02.....	48
6.2.5	Study LVM-MD-02.....	55
6.2.6	Randomized Withdrawal Study (Study LVM-MD-05).....	60

6.3	Cross-cutting issues.....	71
6.3.1	Subpopulations	71
6.3.2	Analysis of Clinical Information Relevant to Dosing Recommendations.....	73
6.3.3	Discussion of Persistence of Efficacy and/or Tolerance Effects	74
6.3.4	Additional Efficacy Issues/Analyses	74
7	REVIEW OF SAFETY.....	75
7.1	Methods.....	78
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	78
7.1.2	Categorization of Adverse Events	78
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	78
7.2	Adequacy of Safety Assessments.....	78
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	78
7.2.2	Explorations for Dose Response.....	79
7.2.3	Special Animal and/or In Vitro Testing.....	79
7.2.4	Routine Clinical Testing	79
7.2.5	Metabolic, Clearance, and Interaction Workup.....	80
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	81
7.3	Major Safety Results	81
7.3.1	Deaths	81
7.3.2	Nonfatal Serious Adverse Events	82
7.3.3	Dropouts and/or Discontinuations	95
7.3.4	Significant Adverse Events	97
7.3.5	Submission Specific Primary Safety Concerns	97
7.4	Supportive Safety Results	100
7.4.1	Common Adverse Events	100
7.4.2	Laboratory Findings	103
7.4.3	Vital Signs	105
7.4.4	Electrocardiograms (ECGs).....	108
7.4.5	Special Safety Studies/Clinical Trials	111
7.4.6	Immunogenicity.....	114
7.5	Other Safety Explorations	114
7.5.1	Dose Dependency for Adverse Events	114
7.5.2	Time Dependency for Adverse Events.....	116
7.5.3	Drug-Demographic Interactions	117
7.5.4	Drug-Disease Interactions	119
7.5.5	Drug-Drug Interactions.....	121
7.6	Additional Safety Evaluations.....	122
7.6.1	Human Carcinogenicity.....	122
7.6.2	Human Reproduction and Pregnancy Data.....	122
7.6.3	Pediatrics and Assessment of Effects on Growth.....	123
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	123
7.7	Additional Submissions / Safety Issues.....	124
7.7.1	Suicidality and Other Psychiatric Adverse Events	124
7.7.2	Sedative events	125
7.7.3	120-Day Safety Update	125

8	POSTMARKETING EXPERIENCE.....	126
9	APPENDICES	126
9.1	Literature Review/References	126
9.2	Labeling Recommendations	126
9.3	Advisory Committee Meeting	129
9.4	Additional Efficacy Results and Tables	129
9.5	Additional Safety Results and Tables.....	134

Table of Tables

Table 1: Sites selected for OSI inspection with their final results.....	14
Table 2: Financial disclosure could not be obtained for the following sub investigators.....	15
Table 3: Vital sign change from baseline to selected time point for different doses (Mean ± 95% CI) of Study LVM-PK-07.....	18
Table 4: Maximal QTc Changes - Study LVM-PK-07.....	18
Table 5: Items utilized in the review.....	21
Table 6: Phase I Clinical Pharmacology and Biopharmaceutic studies in healthy volunteers.....	21
Table 7: Phase 2 and 3 safety and efficacy clinical studies.....	22
Table 8: Patient baseline demographic characteristics (Study LVM-MD-01).....	31
Table 9: Patient baseline efficacy assessments (Study LVM-MD-01).....	31
Table 10: Patient populations (Study LVM-MD-01).....	32
Table 11: Patient disposition and reasons for discontinuations (Study LVM-MD-01).....	32
Table 12: Concomitant medications taken by > 10% of patients (Study LVM-MD-01).....	33
Table 13: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-01).....	34
Table 14: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-01).....	34
Table 15: Patient baseline demographic characteristics (Study LVM-MD-10).....	38
Table 16: Patient baseline efficacy assessments - ITT populations (Study LVM-MD-10).....	38
Table 17: Patient populations (Study LVM-MD-10).....	39
Table 18: Patient disposition and reasons for discontinuations (Study LVM-MD-10).....	39
Table 19: Concomitant medications taken by > 10% of patients (Study LVM-MD-10).....	40
Table 20: Summary of protocol deviations — safety population (Study LVM-MD-10).....	40
Table 21: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-10).....	41
Table 22: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-10).....	41
Table 23: Patient baseline demographic characteristics (Study LVM-MD-03).....	44
Table 24: Patient baseline efficacy assessments - ITT populations (Study LVM-MD-03).....	45
Table 25: Patient populations (Study LVM-MD-03).....	45
Table 26: Patient disposition and reasons for discontinuations (Study LVM-MD-03).....	46
Table 27: Concomitant medications taken by > 10% of patients (Study LVM-MD-03).....	46
Table 28: Summary of protocol deviations — safety population (Study LVM-MD-03).....	47
Table 29: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-03).....	47
Table 30: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-03).....	48
Table 31: Patient baseline demographic characteristics (Study F02695 LP 2 02).....	52
Table 32: Patient baseline efficacy assessments (Study F02695 LP 2 02).....	52
Table 33: MADRS at inclusion by strata [FAS] (Study F02695 LP 2 02).....	52
Table 34: Patient populations (Study F02695 LP 2 02).....	53
Table 35: Patient disposition and reasons for discontinuations - randomized patient set (Study F02695 LP 2 02).....	54
Table 36: Primary efficacy analysis - change from baseline to day 70 (MMRM) - FAS - (Study F02695 LP 2 02).....	55
Table 37: Secondary efficacy analysis - change from baseline to day 70 (LOCF) – FAS - (Study F02695 LP 2 02).....	55
Table 38: Patient populations (Study LVM-MD-02).....	58
Table 39: Patient disposition and reasons for discontinuations (Study LVM-MD-02).....	59
Table 40: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-02).....	60
Table 41: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-02).....	60
Table 42: Patient baseline demographic characteristics - safety populations (Study LVM-MD-05).....	64
Table 43: Patient baseline disease characteristics - ITT populations (Study LVM-MD-05).....	64
Table 44: Patient populations (Study LVM-MD-05).....	65
Table 45: Patient disposition - Safety populations (Study LVM-MD-05).....	66
Table 46: Concomitant medications taken by > 10% of patients — safety populations (Study LVM-MD-05).....	66
Table 47: Summary of protocol deviations — double-blind, randomized population (Study LVM-MD-05).....	67
Table 48: Primary efficacy parameter: Time to relapses - double-blind ITT population (Study LVM-MD-05).....	68
Table 49: Summary of relapse rates during the double-blind treatment, ITT population (Study LVM-MD-05).....	69
Table 50: Analysis of time to relapse – exploratory analysis, double-blind ITT Population (Study LVM-MD-05).....	69
Table 51: Post-hoc Analysis: Relapse rate by MADRS at Screening and Open-label Baseline (Study LVM-MD-05).....	70
Table 52: Change from baseline to EOT in MADRS by gender in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02.....	71
Table 53: Change from baseline to EOT in the MADRS by age in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02.....	72
Table 54: Change from baseline to EOT in MADRS by race in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02.....	72
Table 55: Change from baseline to EOT in MADRS by baseline MADRS in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02.....	73
Table 56: Efficacy results from three pivotal (Studies LVM-MD-01, -10, and -03) and 1 supportive study (Study F02695 LP 2 02).....	74
Table 57: Clinical laboratory tests.....	80
Table 58: Incidence of serious adverse events in short-term clinical trials of levomilnacipran - safety population.....	82
Table 59: List of patients with SAEs in short-term clinical trials of levomilnacipran - safety population.....	83
Table 60: Dr. Kohli-Chhabra’s review of the case narratives of the SAEs of patients who received the drug.....	87
Table 61: Incidence of SAEs in LVM-MD-04 - safety population.....	89
Table 62: Incidence of SAEs during the open-label and double-blind treatment periods of Study LVM-MD-05 - safety populations.....	93
Table 63: Incidence of discontinuation due to AEs in short-term trials - safety population.....	95

Clinical Review
Kavneet Kohli-Chhabra M.D. /Tiffany Farchione M.D.
NDA 204168
Levomilnacipran Extended Release Capsule

Table 64: SMQ preferred terms for discontinuation syndrome query.....	99
Table 65: TEAEs reported in >2% of levomilnacipran-treated patients and at a greater rate than placebo in short term trials -- safety population	101
Table 66: Number (%) of patients with potentially clinically significant liver function test result in short term trials (US and Canada) - safety population	103
Table 67: Changes from baseline to end of treatment period in liver function parameters in short term studies (US and Canada) - safety population	104
Table 68: Changes from baseline to end of double-blind treatment in SBP and DBP in fixed-dose studies - safety population.....	106
Table 69: Number and percentage of patients with orthostatic hypotension in short term trials (US and Canada) - safety population.....	107
Table 70: Changes from baseline to end of double-blind treatment in heart rate in fixed-dose studies - safety population	108
Table 71: Change from baseline to endpoint in ECG parameters (Short Term Trials, US and Canada) - safety population.....	109
Table 72: Summary of potentially clinically significant ECG values in short term trials (US and Canada) - safety population	110
Table 73: Summary of postbaseline QTc values > 30 msec or > 450 msec in short term trials (US and Canada) - safety population.....	111
Table 74: Categorical Analysis for QTcI.....	113
Table 75: Categorical Analysis for \square QTcI.....	113
Table 76: Common TEAEs (>2% in any levomilnacipran group and at a greater rate than in the placebo group) in short term, fixed-dose studies - safety population	115
Table 77: TEAEs reported in >5% of patients in the levomilnacipran treatment group and at twice the rate of the placebo group in either sex category in short term trials - safety population	117
Table 78: TEAEs reported in >5% of patients in the levomilnacipran treatment group and at twice the rate of the placebo group in either age category in short term trials - safety population	118
Table 79: TEAEs reported in >5% of patients in the levomilnacipran treatment group and at twice the rate of the placebo group in either race category in short term trials - safety population	119
Table 80: Incidence of TEAEs associated with suicidal thoughts and behaviors in short term trials - safety population.....	124
Table 81: Number (percentage) of patients with most severe suicidal ideation and most severe suicidal behavior as reported in the C-SSRS (short term trials) - safety populations	125
Table 82: Change from baseline to week 8 in additional efficacy parameters (MMRM), ITT population (Study LVM-MD-01)	129
Table 83: Response rates for MADRS-CR at week 8 (LOCF), ITT population	130
Table 84: Change from baseline to week 8 in additional efficacy parameters Study LVM-MD-10 (MMRM), ITT population	130
Table 85: Response and remission rates for additional efficacy parameters at week 8 Study LVM-MD-10 (LOCF), ITT population.....	130
Table 86: Change from baseline to week 8 in additional efficacy parameters (MMRM), ITT population (Study LVM-MD-03)	131
Table 87: Response and remission rates at week 8 (LOCF), ITT population (Study LVM-MD-03)	131
Table 88: Change from baseline to week 8 in additional efficacy parameters (MMRM), ITT population (Study LVM-MD-02)	133
Table 89: Response and remission rates at week 8 (LOCF), ITT Population (Study LVM-MD-02).....	133
Table 90: Change from baseline to end of open-label and double-blind treatment periods for additional efficacy parameters - ITT populations (Study LVM-MD-05).....	134
Table 91: Levomilnacipran clinical studies	135
Table 92: List of pregnancies in the levomilnacipran development program	136

Table of Figures

Figure 1: Study design for Study LVM-MD-01 27
Figure 2: Study design for Study LVM-MD-10 36
Figure 3: Study design for Study LVM-MD-03 42
Figure 4: Study design for Study F02695 LP 2 02..... 49
Figure 5: Study Design of Study LVM-MD-02..... 56
Figure 6: Study design for Study LVM-MD-05 62
Figure 7: Kaplan-Meier estimates of rate of relapse during DB treatment period - Study LVM-MD-05 .. 68

Template Version: March 6, 2009

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, approval is recommended (with revisions to the proposed label) of NDA 204168 Fetzima (levomilnacipran 40 -120 mg once daily oral administration) for the treatment of Major Depressive Disorder (MDD) in adult patients.

1.2 Risk Benefit Assessment

Levomilnacipran is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). Levomilnacipran extended release 40 to 120 mg once daily oral administration was effective in the treatment of adult outpatients with MDD. The efficacy of levomilnacipran has been established through two pivotal double-blind, placebo-controlled fixed dose studies (Studies LVM-MD-01 and -10), one pivotal flexible dose study (Study LVM-MD-03), and one supportive non-US flexible dose study (Study F02695 LP 2 02). Among these four studies, the observed treatment effect (difference of levomilnacipran – placebo), least square mean difference (LSMD) change from baseline to week 8 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (primary efficacy endpoint), was in the range of –3 to –5.

The safety of levomilnacipran was evaluated in 2,655 patients (18-78 years of age) diagnosed with MDD. In controlled, short-term trials 1583 patients were exposed to levomilnacipran. The total levomilnacipran exposure in clinical studies was 899.5 patient-years. Six hundred ninety-one patients were exposed for at least 24 weeks, with 324 patients exposed for at least 48 weeks.

The safety profile is similar to other approved SNRIs. Two deaths occurred during the clinical development program; neither appeared to be related to treatment with levomilnacipran. Approximately 0.07% of the patients receiving levomilnacipran in short-term studies experienced a non-fatal serious adverse event (SAE), compared to 1.3% of patients receiving placebo. Four patients experienced SAEs thought to be related to levomilnacipran; the SAEs of seminal vesiculitis/prostatitis, and premature baby/small for dates baby were not necessarily expected AEs in this drug class. The most frequently reported adverse events (AEs) ($\geq 5\%$ in the levomilnacipran group and twice the rate of the placebo group) in the short-term, placebo-controlled studies included nausea, constipation, hyperhidrosis, heart rate increased, erectile dysfunction, tachycardia, vomiting, and palpitations. Erectile dysfunction and urinary hesitation were dose-related AEs. The AE profile for long-term treatment of up to 1 year was generally similar, except for a single case of convulsion/encephalopathy for which the causal relationship cannot be ruled out.

Like other SNRIs levomilnacipran has been associated with increases in blood pressure and heart rate. In the short-term, placebo-controlled MDD studies, the mean increase from initiation of treatment in systolic and diastolic BP was greater than the placebo treatment group, though no dose-related changes were observed. The incidence of orthostatic hypotension between the levomilnacipran and placebo treatment group was similar. For the fixed dose studies, the percentage of patients with orthostatic hypotension was higher in all three levomilnacipran dose groups relative to placebo but there was no clear trend suggesting a dose-dependent increase. A mean increase in heart rate was observed with levomilnacipran versus a mean decrease in placebo-treated patients. This increase was considered dose-related.

The sponsor conducted a thorough QT study, which was reviewed by the Interdisciplinary Review Team (IRT) for QT Studies. Overall, the IRT team concluded that a significant, but modest, QTc prolongation effect was detected.

Based on the cardiovascular side effects observed with levomilnacipran treatment, the proposed recommendations included in the levomilnacipran Package Insert (PI) are to monitor blood pressure and heart rate prior to initiating and during the treatment course, and to control hypertension before initiating treatment.

Drug-disease interactions were observed in patients with moderate and severe renal impairment. Recommendations in the PI include reductions in maximum daily levomilnacipran dose for patients with moderate (b) (4) and severe (40 mg) renal impairment. Drug-drug interactions were detected when levomilnacipran was co-administered with strong inhibitors of CYP3A4 such as ketoconazole. Dosing recommendations in the PI state that levomilnacipran should not exceed 80 mg once daily when co-administered with a strong CYP3A4 inhibitors.

Post-marketing commitments will investigate safety, efficacy and dose-response relationship of levomilnacipran at lower doses, longer-term maintenance efficacy, and further explore sexual dysfunction adverse events through a validated and reliable instrument.

Overall, in view of the potential clinical benefit, the risk-benefit assessment is favorable for levomilnacipran 40-120 mg/day for the treatment of MDD in the adult population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No specific risk management steps beyond the product labeling are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

We will ask the sponsor to conduct another longer-term (i.e., maintenance) efficacy of levomilnacipran in the treatment of adults with major depressive disorder as part of their post-marketing commitment. This trial must be placebo-controlled, utilize a randomized withdrawal design, and include an adequate period of stabilization (at least 12 weeks) during the open label-treatment prior to double-blind randomization.

The lower dose-response of levomilnacipran's efficacy and safety has not been adequately characterized. Some important adverse reactions are dose-related. Therefore, the sponsor should conduct a trial to assess the treatment of levomilnacipran in adults with MDD using fixed doses of levomilnacipran (20 mg and 40 mg), and placebo in an adequate and well controlled trial. In this study they can also include a validated and reliable outcome measure to assess for sexual dysfunction.

Erectile dysfunction was one of the dose related sexual dysfunction adverse events observed with levomilnacipran. However, we do not have quantified sexual dysfunction data. Thus, we recommend sponsor to employ a validated and reliable outcome measure to assess for sexual dysfunction in the lower dose to be conducted as part of their post marketing commitments. An active control for assay sensitivity is essential when designing trials to assess for sexual dysfunction.

The pediatric study requirement for ages 0 to 6 years old in the treatment of MDD were waived, because studies are highly impractical due to the low prevalence of this disorder in this age range. Pediatric studies for ages 7 to 17 years old in the treatment of MDD are deferred, as levomilnacipran for use in adults with MDD is ready for approval. We will ask the sponsor, as post-marketing requirement, to conduct two pediatric efficacy and safety studies, and a juvenile animal study to support a clinical trial in pediatrics less than 12 years of age as well.

2 Introduction and Regulatory Background

2.1 Product Information

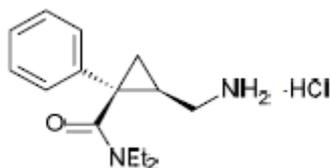
NDA 204168 is being submitted by Forest Laboratories, Inc. under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for levomilnacipran extended release for the treatment of MDD. Levomilnacipran is developed for the treatment of MDD under a Phase 3 clinical development plan (IND #104,483).

Levomilnacipran is one of the 2 enantiomers present in the racemate milnacipran approved by the FDA on January 14, 2009 for the management of fibromyalgia under the trade name Savella. Milnacipran was first approved in France in 1996 for the treatment of depression. Since then it has been approved for the treatment of depression in many foreign countries except the United States.

International Nonproprietary Name (INN):
United States Approved Name (USAN):

levomilnacipran
levomilnacipran (base) and
levomilnacipran hydrochloride (salt)
F2695 and F02695
 $C_{15}H_{22}N_2O \cdot HCl$

Company Codes:
Molecular Formula:
Structural Formula:



Proposed Trade Name (established name):
Chemical Name:

Fetzima
(1S,2R)-2-(aminomethyl)-N,N-diethyl-1-
Phenylcyclopropanecarboxamide
Hydrochloride

Pharmacologic Class:
Proposed Indications:
Proposed Age Group:
Proposed Dose:
Proposed Dosing Regimen:

Serotonin Norepinephrine Reuptake Inhibitor
Treatment of Major Depressive Disorder
Adults
40 to 120 mg once-daily oral administration
Initiate with 20 mg/day x 2 days, increased to 40
mg/day, and from thereon increased at 40
mg/day intervals of not less than 2 days based on
efficacy and tolerability
120 mg once daily

Maximum Recommended Dose:

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of antidepressant medications are available for the treatment of MDD, including:

Tricyclic Antidepressants (TA)	imipramine, desipramine, amitriptyline, Nortriptyline, doxepin, amoxapine, trimipramine, protryptiline, maprotiline.
Monoamine Oxidase Inhibitors (MAOI)	phenylzine, tranylcypramine, isocarboxazid, maprotiline, selegiline patch
Selective Serotonin Reuptake Inhibitors (SSRI)	fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, Escitalopram, vilazodone
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	venlafaxine, duloxetine, desvenlafaxine
Other Antidepressants	bupropion HCl, bupropion, trazodone, nefazodone, mirtazapine

Electroconvulsive therapy is also available for the treatment of MDD.

2.3 Availability of Proposed Active Ingredient in the United States

This product is under development for licensing by the sponsor and is currently not marketed in the United States. The sponsor indicates that the drug product would be readily available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Levomilnacipran is in the therapeutic class of SNRI. The following are the major class related AEs listed under the Warnings and Precautions section of the class labels: suicidality, serotonin syndrome, increasing effects on blood pressure and heart rate, mydriasis, seizure, abnormal bleeding, activation of mania or hypomania, hyponatremia, and discontinuation syndrome.

These issues are specifically addressed in section 7, Review of Safety.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 104,483 was submitted on February 05, 2009 for the MDD clinical development program for levomilnacipran. Sponsor requested four meetings during the presubmission regulatory Phase. The dates and the main discussion topics are listed below.

End of Phase 2 (EOP2) Meeting

The Division sent the EOP2 preliminary comments to the sponsor on 05/15/09, the sponsor then elected to conduct the EOP2 meeting as a teleconference on 05/18/09, rather than a face-face meeting. In the teleconference meeting the sponsor noted that they are going to develop the sustained-release (SR) formulation and not the immediate release (IR) formulation. They agreed to incorporate C- SSRS (Columbia-Suicide Severity Rating Scale) in all their studies, and Sheehan Disability Score (SDS) was determined to be a key secondary endpoint. (b) (4) the Arizona Sexual Experience Scale (ASEX) scale (b) (4). The Division suggested including it in the one fixed dose study as well. In the meeting minutes, it stated that the Division had suggested to the

sponsor to include ASEX as key secondary parameter if they believed that levomilnacipran would be lacking sexual side effects.

(b) (4)



Pre-NDA CMC Meeting

This meeting occurred on 01/25/12. The sponsor sought to gain the Division's agreement on chemistry, manufacturing and controls data to support the NDA for levomilnacipran.

Pre-NDA Submission Meeting

At this meeting on 05/04/12, the sponsor stated they are submitting 2 positive well-controlled efficacy studies (LVM-MD-01 and -03). Safety data from ongoing studies LVM-MD-04 and -06 will be included in the 120-day safety update. The sponsor clarified that the data supporting this NDA application will be stand-alone, i.e., only levomilnacipran data.

2.6 Post-Submission Regulatory Activity

The 74-day filing letter was sent to the sponsor on 11/27/2012. No filing issues were identified for this NDA submission. Communication to the sponsor in that letter included a request for comprehensive literature search, editorial and formatting comments on labeling, and a specific comment from the

Biopharmaceutics Division requesting that the increased GI adverse events with alcohol be appropriately labeled in product labeling.

On February 20, 2013, I requested the sponsor to identify the time period utilized for their literature search, provide a summary of the 9 relevant articles noted by the sponsor in the literature search, and provide the names of the specific concomitant medications used under the categories “psychoanaleptic” and “psycholeptics” for all short-term controlled studies.

On April 29, 2013, I requested if the sponsor has applied for approval of levomilnacipran in any other country, and the second request was regarding BP categorical shift changes data for “at any time” interval.

Over this NDA review period, the sponsor has responded to these information requests. I discussed the items under the relevant sections throughout this NDA review.

A 4-Month Safety Update (4MSU) to the NDA was submitted on 01/16/2013. The data cutoff date for this safety update was September 24, 2012. It included two studies:

- Additional safety data from Study LVM-MD-04, a 48 week open label extension study in patients with MDD
- [REDACTED] (b) (4)

The full safety analysis of these two studies will be included in the integrated safety summary section 7.

2.7 Other Relevant Background Information

The clinical development of levomilnacipran is the result of a partnership between Forest Laboratories, Inc. (Forest) of New York, New York, and Pierre Fabre Médicament (Pierre Fabre) of France.

The sponsor did not report on a submission of marketing authorization applications of levomilnacipran to foreign regulatory agencies for the MDD indication or any withdrawal of this product in other countries.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission was appropriately organized to allow information to be reviewed in an acceptable manner. I conducted a brief audit of adverse event safety data by comparing case report forms, narratives and line listings for consistency on reporting. Overall, there was good consistency of adverse event information across these sources of data. Adverse event coding (verbatim to preferred terms) appeared to be appropriate. No significant deficiencies were noted.

3.2 Compliance with Good Clinical Practices

Protocols were reviewed and approved by the Institutional Review Boards and informed consent was obtained from participants in the clinical trials. In each of the study protocols, the sponsor stated that the trials were conducted as per good clinical practice and applicable regulatory requirements.

A consult dated November 9, 2012 was sent to the Office of Scientific Investigations (OSI) requesting to inspect a number of clinical sites from the pivotal clinical trials. Dr. John Lee was the assigned reviewer from Division of Good Clinical Practice Compliance, OSI. We requested them to audit four sites among the three pivotal studies. These sites were selected by me and Dr. Thomas Birkner, the assigned reviewer of this NDA from Biometrics Division. Our selection of these particular sites to be inspected was based on the following reasons: multiple studies conducted at the same site and large numbers of subjects were enrolled with significant contribution towards efficacy results.

The OSI review was completed on May 23, 2013, table 1 list the name of the investigator at each of the sites selected, study name, number of subjects at the sites, and OSI inspection dates with results.

Table 1: Sites selected for OSI inspection with their final results

Inspection Outcome	Studies, Sites, and Subject count	Inspection Date and Outcome
Nick G. Vatakis, MD Social Psychiatry Research Institute, Brooklyn, NY	LVM-MD-01 Site 32, 19 subjects (3% of total study enrollment)	December 19 - 21, 2012 – NAI
Zinoviy Benzar, MD, PhD Brooklyn Medical Institute Brooklyn, NY	LVM-MD-03 Site 51, 28 subjects (6% of total study enrollment)	December 4 -13, 2012 - NAI
	LVM-MD-10 Site 04, 12 subjects (2% of total study enrollment)	
Alexander Horwitz, MD Oregon Center for Clinical Investigations, Salem, OR	LVM-MD-03 Site 58, 31 subjects (7% of total study enrollment)	December 3 -14, 2012 - VAI
	LVM-MD-10 Site 17, 24 subjects (4% of total study enrollment)	
Arifulla Khan, MD Northwest Clinical Research Center Bellevue, WA	LVM-MD-10 Site 22, 33 subjects (6% of total study enrollment)	March 12 - April 10, 2013 - Pending (preliminary VAI)*

Please Note: This table is extracted from Dr. Lee’s review

NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations);

*Pending: Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report EIR had not been received from the field office and OSI’s complete review of the EIR remains pending as of this clinical inspection summary.

Following is a summary of field office inspection results written in Dr. Lee’s review with his opinion on the acceptability of the sites data’ reliability.

Drs. Vatakis and Benzar’s sites had no significant deficiencies observed and no Form FDA 483 was issued. Minor deficiencies were verbally discussed with the investigators. Overall, Data from this study site appears reliable as reported in the NDA. No action indicated (NAI).

For one of the two Dr. Horwitz’s sites inspected, a Form FDA 483 was issued for failing to adhere to the protocol for Study LVM-MD-03. Other minor deficiencies were verbally discussed with the investigator. All observed deficiencies (cited and not cited on Form FDA 483) appear to be minor, isolated, and unlikely to importantly affect the study outcome at this study site. For both audited studies, data from these study sites appear reliable as reported in the NDA.

Dr. Khan’s site was inspected; a Form FDA 483 was issued for failing to adhere to the protocol for Study LVM-MD-10. The reasons for issuing the Form 483 were: 6 patients had inconsistent data between the source records and the CRFs, 8 mild AEs not reported on the CRFs, the study kits received from the sponsor did not match the number returned at the end of the study, no documentation of evaluation of exclusion criteria related to use of psychotropic drugs, prior vagus nerve stimulation or experimental procedure for CNS, and for 10 subjects the MINI assessment did not rule out non psychiatric causes for all disorders. All observed deficiencies appear to be relatively minor, isolated, and unlikely to importantly affect the study outcome at this study site. Data from this study site appear reliable as reported in the NDA.

Overall, it is Dr. Lee’s opinion as stated in his review, that these deficiencies are unlikely to have significant impact on the outcome of this NDA’s clinical studies. I have reviewed the OSI consult report and I concur with Dr. Lee that these sites field inspection results have no effect on the reliability of the clinical results of this NDA’s.

3.3 Financial Disclosures

Among the clinical investigators in all the studies, none were identified by the sponsor as having financial arrangements that require disclosure. However, there were 4 sub investigators for study LVM-MD-01 and 3 sub investigators for Study LVM-MD-04 that have not provided financial disclosure information. The sponsor states they made a thorough attempt to reach out to these sub investigators but with no success; thus, they have provided a Certificate of Due Diligence. See table 2 below.

Table 2: Financial disclosure could not be obtained for the following sub investigators

Study/Site #	Principal Investigator	Sub-Investigators (b) (6)	Reason
Study LVM-MD-01 Site 19	Shishuka Malhotra, MD		Incomplete form
Study LVM-MD-01 Site 23	Arthur Mollen, DO		An oversight error by staff to not get the forms completed in its entirety
Study LVM-MD-04 Site 25	Shishuka Malhotra, MD		Incomplete form
Study LVM-MD-04 Site 39	Ram Shrivistava, MD		An oversight error by staff to not get the forms completed in its entirety
Study LVM-MD-04 Site 62	Tracy Schillerstrom, MD		Incomplete form

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pei-I Chu, Ph.D., is the CMC reviewer for this NDA submission. The review team held many review update meetings during the course of this NDA evaluation, and no significant issues were identified by the Dr. Chu. In her review (review dated 6/24/2013) she noted that the Office of Regulatory Affairs has completed the inspections of all the manufacturing facilities in (b) (4) 2013. Overall, she states in her review, that levomilnacipran is recommended for approval from the CMC perspective as the Office of Compliance made the acceptable recommendation of the facilities in EES. No postmarketing studies are recommended by CMC.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology data was reviewed by Arippa Ravindran, Ph.D. The review team held many review update meetings during the course of this NDA evaluation, and no significant issues were identified by the Dr. Ravindran. Overall, Dr. Ravindran's recommendation is in support to approve this NDA. No postmarketing studies are recommended by Pharmacology/Toxicology.

In the sections below, I have highlighted important findings related to the Toxicology and Safety Pharmacology Studies, these findings are as per Dr. Arippa Ravindran's review (review dated 6/17/2013).

Toxicology Studies

Repeat-dose toxicology

Studies were conducted in rats (up to 6 month duration) and cynomolgus monkeys (up to 1 year). Exposures that resulted in convulsions and/or deaths in animals were well above those in humans at therapeutic doses. The liver was identified as the primary target organ of toxicity as increased liver weights and hepatocellular hypertrophy were observed, findings of which were reversible in both species upon dosing cessation, and found to be clinically non-significant.

Carcinogenicity

Studies were conducted in a standard two-year study in Sprague-Dawley rats and in a short-term study in transgenic mice. Sprague-Dawley rats were dosed with levomilnacipran at doses of 10, 30 and 90 mg/kg for 104 weeks. There was no evidence of carcinogenicity in this study. Transgenic mice were dosed with levomilnacipran at 15, 50 and 150 mg/kg for 26 weeks. There was a numerical increase in the incidence of splenic hemangiosarcomas in males and females dosed at 150 mg/kg; however, the incidence was within the historical control range. Interpretation of all carcinogenic data in totality indicates that levomilnacipran is not carcinogenic.

Genotoxicity

Genotoxic potential of levomilnacipran was evaluated in vitro in the bacterial mutagenicity study, mouse lymphoma assay and in vivo in the rat micronucleus assay. The result of each genetic toxicology study was negative.

Reproductive toxicity

Toxicology studies were conducted in rats and/or rabbits to evaluate the potential for effects on fertility, embryonic development and peri-/post-natal development. In a fertility study conducted in rats, there was no effect on parental gonadal function, mating behavior or fertility at doses of levomilnacipran up to 100 mg/kg. In the embryo-fetal development studies, there were no fetal malformations in pregnant rats or rabbits dosed with levomilnacipran via oral (gavage) up to 100 mg/kg in both species. In a peri-/post-natal development study, rats were dosed with levomilnacipran at 7, 20, or 60 mg/kg. Reduced maternal body weight gain during gestation and lactation, reduced pup body weight and a slight delay in some developmental milestones were observed. These findings were considered to represent a secondary effect

related to reductions in maternal body weight during gestation and lactation, which are crucial periods for pup development and not considered relevant risk for humans.

Dr. Ravindran's review states levomilnacipran is not genotoxic, carcinogenic or a reproductive toxicant.

Safety Pharmacology Studies

Safety pharmacology assessments included in vitro and in vivo effects of levomilnacipran on central nervous system, cardiovascular system and respiratory system in multiple non-clinical species.

CNS

Oral levomilnacipran doses in the range of 10-256 mg/kg in rodents resulted in decrease in body temperature, mydriasis, decreased arousal, decreased motor activity, and increased sedation.

Respiratory

An oral administration of levomilnacipran (20 or 63 mg/kg) in male rats had no respiratory effects.

CVS

In conscious beagle dogs, levomilnacipran (10 mg/kg/day; PO) produced a significant increase in heart rate (max effect occurred at 1-2 hours of ~125 bpm on average) and diastolic blood pressure (increase of ~ 30 mmHg [single dose] and 15 mmHg [5-day dosing]) without effects on the ECG. In 3M/3F conscious cynomolgus monkeys (telemetry), a single oral dose of levomilnacipran (5, 15, and 45 mg/kg) caused significant increases in mean systolic and diastolic arterial blood pressure (~15 to 21 mmHg from pretest).

hERG (human ether-a-go-go-related gene) channel

In vitro study using a hERG expressing HEK293 cell line, effects on rapidly activated delayed rectifier potassium current (IKr) were investigated with a patch-clamp technique. Levomilnacipran (0.001, 0.01, 0.1, 1, and 10 μ M) produced a concentration-dependent inhibition of the hERG tail current amplitude (14%, 15%, 16%, 22%, and 31%, respectively), with an estimated IC₅₀ > 10 μ M (> 8-fold the C_{max} associated with the highest clinical dose of 120 mg).

Renal and Gastrointestinal

No studies were provided.

Dr. Ravindran's review states results from nonclinical safety pharmacology studies suggest that levomilnacipran is like other SNRIs with antidepressant-like activity and has an acceptable safety pharmacology profile.

4.4 Clinical Pharmacology

The Clinical Pharmacology was reviewed by Kofi Kumi, Ph.D. and the Pharmacometric review conducted by Hongshan Li, Ph.D. Nineteen clinical pharmacology and biopharmaceutics studies, population pharmacokinetic and exposure-response analyses were included in the NDA submission. The review team held many review update meetings during the course of this NDA evaluation. OCP's recommendation is in support to approve this NDA pending labeling agreements to be made with the sponsor. No postmarketing studies are recommended by OCP.

In the sections below, I have highlighted important findings from Drs. Kumi and Li's review (review dated 6/17/2013) that are included in their evaluation of the Clinical Pharmacology and Pharmacometric sections.

4.4.1 Mechanism of Action

Levomilnacipran is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). Although the precise mechanisms underlying MDD are unknown, both the norepinephrine and serotonin neurotransmitter systems play a role in treating the disease.

4.4.2 Pharmacodynamics

Levomilnacipran lacked significant affinity for numerous receptors and ion channels, including serotonergic (5HT₁₋₇), α - and β -adrenergic, muscarinic, or histaminergic receptors and Ca²⁺, Na⁺, K⁺ or Cl⁻ channels in vitro. Levomilnacipran also lacked monoamine oxidase (MAO) inhibitor activity.

Key findings from Study LVM-PK-07 (Thorough QTc Study)

Pharmacometric review of Study LVM-PK-07 was conducted by Hongshan Li, Ph.D. Study LVM-PK-07 was a randomized, blinded, parallel-crossover study, 170 healthy subjects received levomilnacipran 120 mg and 300 mg, placebo, and a single oral dose of moxifloxacin 400 mg.

Table 3 highlights the SBP, DBP, and heart rate results from Dr. Li's review (table extracted from his review, review dated 6/17/2013).

Study LVM-PK-07 was also reviewed by Janice B. Brodsky, from Interdisciplinary Review Team (IRT) for QT Studies and her consult review findings are presented in section 7.4.4 of the safety section. Table 4 is extracted from the QT-IRT consult analysis that highlights maximal QTc changes observed in the Thorough QTc (T QTc) study.

Table 3: Vital sign change from baseline to selected time point for different doses (Mean \pm 95% CI) of Study LVM-PK-07

Vital Sign	Time after 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 \pm 1.2	7.1 \pm 1.5	10.0 \pm 1.8
SBP (mmHg)	0	0.0 \pm 0.0	0.5 \pm 1.2	0.9 \pm 1.4
HR (bpm)	6	7.5 \pm 1.2	12.4 \pm 2.1	15.2 \pm 2.4

Source: extracted from Dr. Li's Pharmacometric analysis review

Table 4: Maximal QTc Changes - Study LVM-PK-07

Treatment	Time (Hour)	QTcI (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)

Source: extracted from the QT-IRT consult review

*90% CIs corresponding to the largest upper bounds for LVM and the largest lower bound for moxifloxacin

4.4.3 Pharmacokinetics

Absorption

The T_{max} of oral levomilnacipran capsule is 6 to 8 hours and declines with a $T_{1/2}$ of ~ 12 hours. The oral bioavailability of levomilnacipran capsule is >82% and is not affected by food. However, food appears to delay T_{max} for about 2 hours, but this difference is not expected to be clinically relevant. After once daily administration of levomilnacipran capsules, steady-state levels were reached within 3 days.

Linear and dose-proportional pharmacokinetics were observed, after administration of levomilnacipran capsules between 25 and 120 mg/day, and following multiple doses between 25 and 300 mg/day.

Distribution

Levomilnacipran is widely distributed with 22% binding to plasma proteins.

Metabolism

There were five metabolites identified in human urine following an oral dose administration of levomilnacipran SR: N-desethyl levomilnacipran (F17400), levomilnacipran N-carbamoyl glucuronide, N-carbamoyl glucuronide, p-hydroxy levomilnacipran glucuronide, and p-hydroxy levomilnacipran. CYP3A4 is likely a major enzyme involved in the transformation.

Excretion

Levomilnacipran and its metabolites after oral administration are predominately excreted through urine (94%) and feces (4%), with ~ 58% of levomilnacipran excreted in urine as an unchanged drug and ~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 was approximately 12 hours.

PK related to intrinsic factors

Age: No age-related dose adjustment is considered necessary.

Gender: No dose adjustment is needed.

See table below that highlights the study results of the studies conducted in patients to assess for hepatic and renal impairment. These findings presented in the table below are adopted by Dr. Kumi OCP review (review dated 6/21/2013). In the table you will see the labeling recommendations proposed by the Dr. Kumi for the PI.

Hepatic Impairment	Renal Impairment
Study LVM-PK-05 entitled “A Single Dose Pharmacokinetic Study of F2695 SR in Subjects with Normal Hepatic Function and Patients with Impaired Hepatic Function” was reviewed.	Study LVM-PK-02 entitled “A Single Dose Pharmacokinetic Study of F2695 in Subjects with Normal or Mild to Severe Impaired Renal Function” was reviewed.
<u>Results:</u> Levomilnacipran exposure (AUC) increased by about 30% in severe hepatic impaired (Child Pugh C: 10 – 15) patients.	<u>Study results:</u> Excretion of unchanged drug in urine in subjects with normal renal function represented about 52% of administered dose and was decreased to 42%, 39%, and 22% of the dose in subjects with mild, moderate, and severe renal impairment. AUC _{0-∞} in subjects with mild (creatinine clearance 50-79 mL/min), moderate (creatinine clearance 30-49 mL/min), and severe (creatinine clearance <30 mL/min) renal impairment was 23%, 93%, and 180% compared to subjects with normal renal function (creatinine clearance ≥ 80 mL/min).
<u>Sponsor’s proposed labeling language:</u> The sponsor has indicated that no dose adjustment is necessary for hepatically impaired patients.	<u>Sponsor’s proposed labeling language:</u> Based on these results the sponsor has stated that a renal dose adjustment is necessary for patients with moderate and severe renal impairment.
<u>Dr. Kumi’s PI recommendation:</u> “Dose adjustment is not recommended for hepatic impaired patients but caution should be exercised when dosing in severe hepatic impaired patients (Child Pugh C).”	<u>Dr. Kumi’s PI recommendation:</u> “levomilnacipran dose should not exceed 40 mg daily and 60 mg daily for patients with severe and moderate renal impairments, respectively.”

PK related to extrinsic factors

Cytochrome P450 (CYP) 3A4 appears to be the major enzyme responsible for the biotransformation of levomilnacipran. The sponsor evaluated the impact on levomilnacipran exposure when levomilnacipran is co-administered with a strong CYP3A4 inhibitor (ketoconazole), an inducer (carbamazepine) or a substrate (alprazolam). Population PK analysis did not identify any clinically relevant and statistically significant increases in levomilnacipran exposures in patients who were taking concomitant medications in the following classes: inducers and substrates of major CYP enzymes.

Study LVM-PK-08 entitled “A Single-Center, Randomized, Open-Label, 2 × 2 Crossover, Drug-Drug Interaction Study between F2695 Sustained-Release Capsules and Ketoconazole in Healthy Subjects” was conducted. The results as per Dr. Kumi’s review found if a potent inhibitor of CYP3A4 and levomilnacipran were co-administered, it increased the levomilnacipran plasma exposure C_{max} by 39% and AUC by 57% at the 80 mg levomilnacipran dose.

No dosing adjustment was proposed by the sponsor in regards to co-administration of ketoconazole and levomilnacipran. Thus, for the PI Dr. Kumi is recommending the dose of levomilnacipran should not exceed 80 mg daily when it is administered with strong CYP3A4 inhibitors (e.g. ketoconazole).

5 Sources of Clinical Data

Table 5: Items utilized in the review

Submission Date	Items Reviewed
September 24, 2012	Clinical Study Reports, Proposed Labeling, Application Summary, Financial Disclosure Certification, Case Report Tabulations (.xpt files), Case Report Forms

5.1 Tables of Studies/Clinical Trials

The following table 6 lists the Clinical Pharmacology and Biopharmaceutic studies in healthy volunteers.

Table 6: Phase I Clinical Pharmacology and Biopharmaceutic studies in healthy volunteers

Protocol/Country	Study Design/Duration	Treatment arms mg/day	N	Subjects
BA/BE Studies				
LVM-PK-06 USA	R, OL,SD, crossover, SR, food BA	Placebo, 25 and 50 SR	23	HV, M/F
LVM-PK-14 USA	R, OL,SD, crossover study BE of SR capsules	40, 120 SR	50	HV, M/F
LVM-PK-16 USA	PK study comparing SR capsule to oral solution	2 mg/ml 20, 40, 80 and 120 SR	Oral – 22 SR - 23	HV, M/F
LVM-PK-19 USA	R, SD, OL, Crossover to assess BE of LVM	40, 120 SR	SR – 21	HV, M/F
PK studies				
F02695 GE 1 01 France	R,DB,PC,S, and T	SD: 12.5, 25, 50 and 75 IR QD, MD: 12.5, 25, 50 and 75 IR BID	Total: 41, LVM: 33 Placebo: 8	HV, M
F02695 LP 1 02 France	OL, S, T, SD,	50 SR	13	HV, M
LVM-PK-01 USA	R,DB,PC,S, and T	SD: 25, 50, 100 SR, MD: 25, 50, 75, 100, 125, 150, 200, 50, 300	Total: 48, LVM: 36 Placebo: 12	HV, M/F
LVM-PK-03 Netherlands	OL, NR, to assess ADME	60 Solution	9	HV, M
LVM-PK-15 USA	R,OL,PG,SD, PK and dose proportionality	40 80, and 120 SR	30	HV, M/F
Intrinsic Factors				
LVM-PK-02 USA	SD,OL,PG effects of renal function on PK of LVM	40 SR	32	HV, and renally Impaired M/F
LVM-PK-04 USA	OL, PG, assess PK of LVM on young and elderly	80 SR QD	33	HV, and Young and elderly M/F
LVM-PK-05 USA	SD,OL,PG effects of hepatic function on PK of LVM	40 SR	32	HV, and hepatically Impaired M/F
Extrinsic Factors				
LVM-PK-08 USA	R,OL, crossover, drug-drug interaction study to assess effect of ketoconazole on PK of LVM	80 SR	34	HV, M/F
LVM-PK-09 USA	OL, MD, fixed, 4-period study to assess effect of carbamazepine on PK of	120 SR QD	34	HV, M/F

Clinical Review
 Kavneet Kohli-Chhabra M.D./Tiffany Farchione M.D.
 NDA 204168
 Levomilnacipran Extended Release Capsule

	LVM			
LVM-PK-10 USA	OL, MD, crossover, drug-drug interaction study to assess effect of alprazolam on PK of LVM	120 SR QD	30	HV, M/F
PK/Pharmacodynamics (PD) Studies				
LVM-PK-07 USA	R stratified by sex, DB, PC, PG, effect of LVM on measurement of QTc	120 and 300, SR QD	Total: 170, LVM: 94 Placebo: 76	HV, M/F

F=female, M=male, HV=healthy volunteer, SR= sustained release, IR=immediate release, QD= once daily, PK= pharmacokinetic, LVM= levomilnacipran, SD=single dose, MD=multiple dose, BA=bioavailability, BE=bioequivalence, BID=twice daily, R= randomized, DB= double-blind, PC=placebo-controlled, DT= down taper, OL=open label, PG=parallel group, S=safety, T=Tolerability, NR=Non Randomized,

Following table 7 lists the safety and efficacy clinical trials conducted under levomilnacipran clinical development program.

Table 7: Phase 2 and 3 safety and efficacy clinical studies

Study(Country)	Study Design, Duration, Subject	Treatment arm/N
LVM-MD-01 (US) Phase 3	DB, PC, R,P, Fixed dose, S, E study of LVM patients with MDD x 8 weeks (Adults 18- 65 y/o), 2 week down taper period	LVM 40 mg =178, LVM 80 mg = 179, LVM 120 mg = 180, Pbo=176
LVM-MD-02 (US) Phase 3	DB, PC, R,P, flexible dose, S, E study of LVM patients with MDD x 8 weeks (Adults 18-80 y/o), 2 week down taper period	LVM 40-120 mg =175, Pbo =182
LVM-MD-03 (US) Phase 3	DB, PC, R,P, flexible dose, S, E study of LVM patients with MDD x 8 weeks (Adults 18-80 y/o), 2 week down taper period	LVM 40-120 mg =217, Pbo =217
LVM-MD-04 (US) Phase 3	OL flexible dose, 52 week extension study of patients from studies LVM-MD-01,-02 and-0.3 patients with MDD (Adults), 4 week down taper	LV N= 825
LVM-MD-05 (US & Canada) Phase 3	R, OL-12 weeks, DB-24 weeks, PC, PG, Relapse-Prevention Study with LVM in patients with MDD (Adults), 2 week down taper period	LVM 40-120 mg in OL=734, LVM 40-120 mg in DB=233, Pbo=112
(b) (4)		
LVM-MD-10 (US & Canada) Phase 3	DB, PC, R,P, Fixed dose, S, E study of LVM patients with MDD x 8 weeks (Adults 18-75 y/o), 1 week down taper period, 1 week down taper	LVM 40 mg =188 ,LVM 80 mg =188, Pbo =186
(b) (4)		
F02695 LP 2 02 (Non-US) Phase 2	DB, PC, R,P 10-week study assessing the efficacy and safety of LVM flexible Dose (75, 100 mg/day) in patients with MDD x 10 weeks (Adults 18-70 y/o) 1 week down taper period	LVM 75-100 mg =278, Pbo =279

Source: Table 4.3.1-1 in ISS, Source: Appendix I, Tables 2.1.2 and 12.1.1; ISS in-text Table 5.2-1 and ISS Section 14.2.2

F=female, M=male, HV=healthy volunteer, SR= sustained release, IR=immediate release, QD= once daily, PK=pharmacokinetic, LVM= levomilnacipran, SD=single dose, MD=multiple dose, BA=bioavailability, BE=bioequivalence, BID=twice daily, R= randomized, DB= double-blind, PC=placebo-controlled, DT= down taper, OL=open label, PG=parallel group, S=safety, T=Tolerability, NR=Non Randomized, Safety database comprised of : Group 1- short controlled study, Group 2- open label extension study, Group 3-relapse prevention study, Group 4 (not listed above)- PK/PD studies, Group 5- early terminated (b) (4) study

5.2 Review Strategy

For the assessment of efficacy, I focused on the three pivotal double-blind, placebo-controlled positive efficacy clinical trials (Studies LVM-MD-01, LVM-MD-01-03, and LVM-MD-01-10) conducted in USA

and Canada. I also reviewed the foreign study (Study F02695 LP 2 02) with positive efficacy signal in depth, however, the sponsor has not claimed the results of this study in their PI. There was no active comparator utilized among these 4 studies. I have also briefly summarized the two failed studies (Study LVM-MD-02 and Relapse-prevention Study LVM-MD-05) with their study designs and efficacy findings. I was unable to complete the entire review, thus, on June 4, 2013; Tiffany Farchione, M.D. was assigned to complete the safety review.

The safety review focuses primarily on findings of five short term, placebo-controlled, Phase 3 studies. Four of these studies were conducted in the United States and Canada (LVM-MD-01, LVM-MD-02, LVM-MD-03, LVM-MD-10); an additional study was conducted in Europe, South Africa, and India (F02695 LP 2 02).

The sponsor has also submitted data from a long-term, open-label study (LVM-MD-04) and a relapse-prevention study (LVM-MD-05); these subjects are included in the overall safety population. In addition, the sponsor submitted data from several early Phase clinical pharmacology and biopharmaceutic studies in healthy subjects. For the purposes of this review, information regarding adverse events at the more serious end of the spectrum (deaths, non-fatal serious adverse events, and adverse events that led to dropout) from the Phase I, long-term, and relapse prevention studies was examined.

5.3 Discussion of Individual Studies/Clinical Trials

Following is a list of positive efficacy and failed efficacy studies under the clinical development for levomilnacipran. Most of these studies were short term studies; however, there were two long term studies (open label Study LVM-MD-04 and relapse prevention Study LVM-MD-5).

Three pivotal studies and one supportive efficacy study for treatment in MDD

1. Study LVM-MD-01: pivotal, 8 week, adults 18-65 y/o, double-blind, randomized, placebo-controlled with MADRS as primary and SDS as key secondary efficacy measure. Dosing groups were 40, 80, and 120 mg fixed dose compared to placebo.
2. Study LVM-MD-10: pivotal, 8 week, adults 18-75 y/o, double-blind, randomized, placebo-controlled with MADRS as primary and SDS as key secondary efficacy measure. Dosing groups were 40 and 80 mg fixed dose compared to placebo.
3. Study LVM-MD-03: pivotal, 8 week, adults 18-80 y/o, double-blind, randomized, placebo-controlled with MADRS as primary and SDS as key secondary efficacy measure. Dosing groups were 40-120 mg flexible dose compared to placebo.
4. Study F02695 LP 2 02: Phase 2, supportive, 10 week, Pierre Fabre Médicament, Non-US study, adults 18-70 y/o, double-blind, randomized, placebo-controlled with MADRS as primary and SDS was one of the many secondary efficacy measures. Dosing groups were 75-100 mg flexible dose compared to placebo.

Two studies with failed efficacy results:

1. Study LVM-MD-02: 8 week, adults 18-80 y/o, treatment of MDD, double-blind, randomized, placebo-controlled with MADRS as primary and SDS as key secondary efficacy measure. Dosing groups were 40-120 mg flexible dose compared to placebo.

2. Study LVM-MD-05: this is a relapse-prevention study to study maintenance potential of levomilnacipran in MDD, 12 week open label flexible dosing 40-120 mg levomilnacipran treatment period followed by 24 week fixed dosing double-blind period and 2 week down taper, primary efficacy was Time to Relapse.

6 Review of Efficacy

Efficacy Summary

The data that establish the efficacy of levomilnacipran for the indication of MDD in adults aged 18 years and older arises from three pivotal, randomized, double-blind, placebo-controlled, 8-week Phase 3 trials (Studies LVM-MD-01, -10 and -03) conducted in US and Canada, and 1 randomized, double-blind, placebo-controlled, international, 10-week Phase 2 trial (Study F02695 LP 2 02). There were two other trials conducted; Study LVM-MD-02 was a randomized, double-blind, placebo-controlled, 8-week Phase 3 trials to assess to the efficacy in MDD, and Study LVM-MD-05 was a randomized withdrawal design to evaluate the role of levomilnacipran in maintenance of depression. Both of these studies were considered as failed studies by the sponsor.

My clinical review primarily focused on the study designs and efficacy findings from the four adequate, well-controlled positive efficacy studies in a comprehensive manner. The two failed studies (Studies LVM-MD-02 and LVM-MD-05) are briefly summarized in regards to their study designs, efficacy findings and reasons for failure.

Studies LVM-MD-01 and -10 were fixed dose studies, Study LVM-MD-01 utilized the 40, 80 and 120 mg/day levomilnacipran treatment and Study LVM-MD-10 utilized the 40 and 80 mg/day levomilnacipran treatment. Study LVM-MD-03 was a flexible dose study of 40-120 mg/day oral levomilnacipran treatment. Study F02695 LP 2 02 was a flexible dose study with levomilnacipran 75-100mg/day, this study was identified by the sponsor as a “supportive” study based on doses tested in this study were different, though within the range of doses tested in the US studies. The sponsor is not claiming efficacy results from supportive study to be included in the PI.

The primary efficacy parameter instituted in all the studies was the change from baseline to week 8 in MADRS. The pre-specified key secondary parameter was the change from baseline to week 8 for SDS in the all the pivotal studies except Study F02695 LP 2 02. In Study F02695 LP 2 02, SDS was measured along with multiple other secondary efficacy parameters. Additional efficacy parameters assessed in all the studies were change from baseline to week 8 in HAMD-subscales, CGI-I and CGI-S, as well response and remission rates of MADRS, HAMD-17, and CGI-I.

Titration schedule in all four studies included patients initially starting with a levomilnacipran 20 mg dose for 2 days. In the fixed dose studies the patients were randomized to different dose groups and titrated up to 40 mg dose by days 3-4, 80 mg dose by days 5-7 and 120 mg dose after day 8. In the flexible dose studies the patients were dosed at 40 mg on days 3-7, 80 mg by days 8-28 and 120 mg after day 29, dose increase was not allowed after week 4 (Visit 5). The titration schedule in the flexible dose studies was based on efficacy and tolerability.

Treatment margins (difference of levomilnacipran – placebo) for LSMD change from baseline to week 8 in MADRS, MMRM analysis were in the range of –3.10 to –4.86 for all four studies, demonstrating statistically significant results compared to placebo. The key secondary (SDS) and additional efficacy

parameters were supportive towards the positive efficacy profile observed of levomilnacipran for the treatment of MDD. See table below with the study results.

Study	Phase and design	Duration	# of subjects per arm	Study population	Primary and secondary efficacy results
LVM-MD-01	Phase 3, M,R,DB,PC, P, fixed dose	8 weeks	Placebo (175) LVM 40 mg (176) LVM 80 mg (177) LVM 120 mg (176)	Male and female patients (18 – 65 years) with MDD	<u>Δ MADRS LSMD</u> 40 mg vs. PBO = -3.23* 80 mg vs. PBO = -3.99** 120 mg vs. PBO = -4.86*** <u>Δ SDS LSMD</u> 40 mg vs. PBO = -1.41 80 mg vs. PBO = -2.51 * 120 mg vs. PBO = -2.57 *
LVM-MD-10	Phase 3, M,R,DB,PC, P, fixed dose	8 weeks	Placebo (185) LVM 40 mg (185) LVM 80 mg (187)	Male and female patients (18 – 75 years) with MDD	<u>Δ MADRS LSMD</u> 40 mg vs. PBO = -3.30** 80 mg vs. PBO = -3.14** <u>Δ SDS LSMD</u> 40 mg vs. PBO = -1.83 * 80 mg vs. PBO = -2.72 **
LVM-MD-03	Phase 3, M,R,DB,PC, P, flexible dose	8 weeks	Placebo (214) LVM 40-120 mg (174)	Male and female patients (18 – 80 years) with MDD	<u>Δ MADRS LSMD</u> LVM vs. PBO = -3.10** <u>Δ SDS LSMD</u> LVM vs. PBO = -2.6 **
F02695 LP 2 02	Phase 2, M,R,DB,PC, P, flexible dose	10 weeks	Placebo (277) LVM 75-100 mg (276)	Male and female patients (18 – 65 years) with MDD	<u>Δ MADRS LSMD</u> LVM vs. PBO = -4.2*** <u>Δ SDS LSMD</u> LVM vs. PBO = -3.4**

M-multicenter, R-randomized, DB-double-blind, PC-placebo-controlled, P-parallel, LVM- levomilnacipran

* p < 0.05, ** p < 0.01, *** p < 0.001

The sponsor states that the fixed-dose Study LVM-MD-01 was not powered to demonstrate differences between the different doses. However, there were numerical treatment differences observed with LSMD mean change at -3.23, -3.99 and -4.86 at the different doses of levomilnacipran 40, 80 and 120 mg/day. For the other fixed dose Study LVM-MD-10, the treatment differences observed with LSMD mean change were -3.30, -3.14 at the different doses of levomilnacipran 40 and 80mg/day, dose related efficacy response was not observed.

Levomilnacipran efficacy was not established beyond 8 weeks. There were no studies where doses lower than 40 mg/day of levomilnacipran efficacy tested in this program. Assessment of population subgroups (gender, age and race) did not reveal any clear evidence of differential response.

Based on the dosing regimen studied in the development program of levomilnacipran for MDD, 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 not less than 2 days. The recommended dose range for levomilnacipran is 40 to 120 mg once daily. The maximum recommended dose is 120 mg once daily.

6.1 Indication – Treatment of Major Depressive Disorder (MDD)

6.1.1 Rationale for Selection of Studies for Review

Levomilnacipran is developed for the treatment of MDD. The clinical development program was under IND 104,483. This clinical review will focus primarily on efficacy of levomilnacipran 40 to 120 mg administered once daily established through four short-term, double-blind, and placebo-controlled studies in adult patients with MDD.

Two of these studies are fixed dose studies (LVM-MD-01, and -10) and one is flexible dose study (LVM-MD-03). Study F02695 LP 2 02, was a non-US short-term, Phase 2, placebo-controlled, double-blind, randomized, parallel-group flexible dose study in adult patients with MDD. The sponsor has identified this study as “supportive study” to the other three pivotal positive efficacy trials (Studies LVM-MD-01, -03 and -10). They stated the doses studies in this study were different, though within the range of the doses used in US studies, therefore sponsor is presenting this as a supportive study. My efficacy review will focus on all four of these positive studies.

6.2 Study Summaries

Thomas Birkner, Ph.D. from the Division of Biometrics states in his review (dated 06/14/2013) that no major statistical issues were detected; and the statistical results provide an adequate evidence to support the efficacy claims proposed in the NDA.

6.2.1 Study LVM-MD-01

This multicenter trial was conducted in 38 US centers under 38 investigators.

The first subject was enrolled on September 14, 2009.
The last subject completed the study on May 09, 2011.
The study report was submitted on March 07, 2012.

Study Methods, Design and Statistical Analysis Plan

Study Title

Study LVM-MD-01 was entitled “A Double-blind, Placebo-Controlled, Fixed-Dose Study of F2695 SR in Patients with Major Depressive Disorder”.

Primary Objective

To evaluate the efficacy, safety, and tolerability of fixed doses of levomilnacipran compared with placebo in the treatment of adult patients with major depressive disorder.

Design

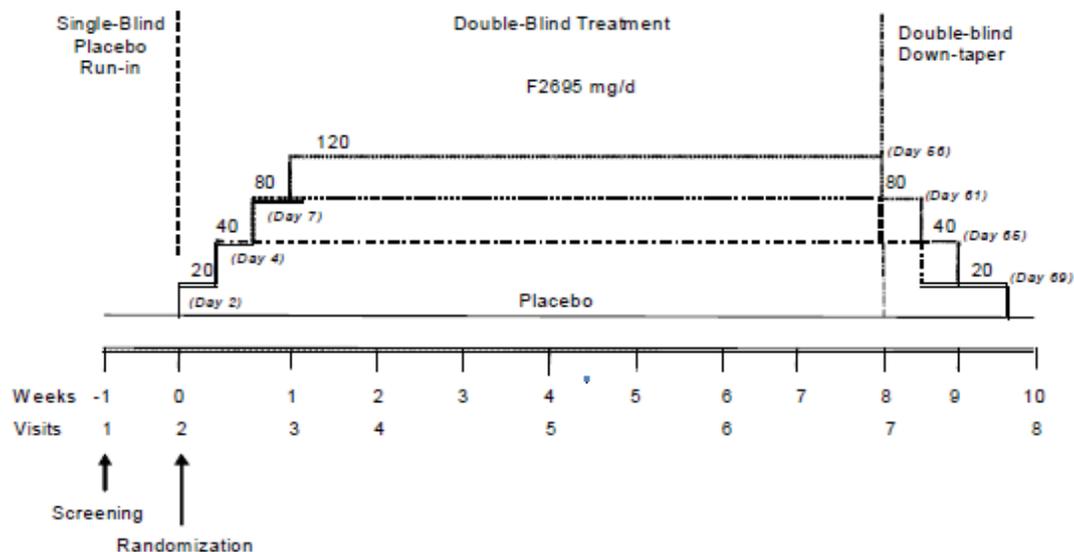
This was a Phase 3, multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group fixed dose study of levomilnacipran (levomilnacipran 40 mg, 80 mg, and 120 mg compared with placebo with an allocation ratio of 1:1:1:1) in adults aged 18-65 years with a diagnosis of MDD.

Patients who completed the 8-week double-blind treatment period or prematurely discontinued from the study were allowed to enter the 2-week double-blind down-taper period.

Duration

1-week of single-blind placebo run-in period, 8 weeks of double-blind treatment, followed by a 2-week, double-blind down-taper period. Total duration was 11 weeks.

Figure 1: Study design for Study LVM-MD-01



Source: Figure 9.1 in Section 9, page 32 of Clinical Study Report (CSR) (extracted from the sponsor's submission)

Titration

Patients were randomized into four different treatment groups including placebo treatment group. All treatment groups initiated the treatment with the 20 mg dose. The placebo treatment group was given the corresponding treatment.

Randomized dose group	Double-blind titration period			
	Days 1-2	Days 3-4	Days 5-7	Days 8-56
40 mg/day	20 mg	40 mg	40 mg	40 mg
80 mg/day	20 mg	40 mg	80 mg	80 mg
120 mg/day	20 mg	40 mg	80 mg	120 mg

The dosing could have been switched to the morning from evening dosing schedule if there were tolerability problems. Temporary dose reductions or discontinuation of levomilnacipran for reasons of tolerability, when deemed necessary by the investigator, were to be limited to no more than 2 days during the study, patients discontinued after that. The date and reason for any dose reduction was to be recorded on the appropriate page of the eCRF.

Key Inclusion Criteria

- Male and female outpatients who were 18 to 65 years of age
- Patients met Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for MDD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 8 weeks
- MADRS-CR score of ≥ 30 at screening and baseline and a MADRS-SR score of ≥ 26 at baseline
- Patients had a score of ≥ 4 on the CGI-S at screening and at baseline

- Patients with a body mass index (BMI) > 14 and < 40, normal physical examination, clinical laboratory test results, electrocardiogram (ECG) results, negative urine drug screen test, females with negative serum pregnancy test, and/or abnormal results that are judged not clinically significant by the investigator were included in this study.

Key Exclusion criteria

- DSM-IV-based diagnosis of an Axis I disorder other than MDD within 6 months before Visit 1 (secondary diagnoses of comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias were acceptable)
- Current serious suicidal or homicidal risk or a suicide attempt within past 1 year, score on ≥ 5 on Item 10 of the MADRS-CR, and/or significant risk judged by the investigator based on psychiatric interview or information collected in the C-SSRS
- Any cardiovascular disease that is clinically significant, unstable, or decompensated; atrial fibrillation (AF) or flutter with onset within 12 months or unknown, uncontrolled, symptomatic, or requiring anticoagulation, premature ventricular contraction (PVC) or second-degree or third-degree atrioventricular block, new myocardial infarction (MI) within 12 months or ischemic heart disease (IHD) within six months
- Additionally, the following specific conditions are exclusionary: QTc Fridericia ECG with QTc ≥ 450 msec for men or QTc ≥ 470 msec for women, heart rate on ECG of ≤ 50 bpm or ≥ 120 bpm, supine systolic BP > 140 mmHg or < 90 mmHg or diastolic BP > 90 mmHg or < 50 mmHg
- Electroconvulsive therapy (ECT) for current MDD; history of inadequate response to ECT, history of nonresponse to ≥ 2 or more antidepressants after adequate treatment trials (adequate treatment is defined as at least 8 weeks at an adequate dose(s) based on approved package insert recommendations).
- Patients with serious medical co-morbidity, patients with history of narrow angle glaucoma, and/or history of syndrome of inappropriate antidiuretic hormone secretion. History of seizure disorder, stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes toward risk for seizure. Male patients with history of obstructive voiding symptoms, including urinary retention. Hypothyroidism or hyperthyroidism (unless stable on medication without dose change within two months), history of serotonin syndrome or neuroleptic malignant syndrome; HIV or hepatitis B/C infections; liver transaminases over 1.5 times upper limit of normal; gastric bypass or any condition that affects drug absorption
- Women who are pregnant, lactating, or planning to become pregnant or during the study or within 30 days following the end of study participation. Women not currently using a medically acceptable method of contraception are excluded. Rhythm, withdrawal, single-barrier contraceptive methods, partner with vasectomy, and abstinence are not acceptable methods of contraception.
- Treatment with an levomilnacipran within (longer of) three months or five drug half-lives; history of intolerance or hypersensitivity to levomilnacipran or other chemically related agents; any condition that interferes with study conduct, confounds results, or affects subject safety

The inclusion and exclusion criteria were appropriate for this study. Overall, the population selected was reasonable to demonstrate the proposed objectives.

Concomitant Medication

No concomitant psychotropic medications or medications with psychotropic activity were permitted during the study. Psychotropic drugs were further described as anorexics, antidepressants, anticonvulsants, antipsychotics, anxiolytics, stimulants, sedatives, hypnotics, bupropion, herbal/dietary

products and supplements with potential psychoactive actions, including St. John's wort, kava, SAME, valerian root, DHEA, tyrosine, and 5-HTP. Patients were asked to limit their alcohol consumption to no more than 2 drinks a week during the study.

The following anti-insomnia agents were permitted up to 3 times a week: zolpidem (maximum: 10 mg/day), zolpidem extended-release (maximum: 12.5 mg/day), zaleplon (maximum: 10 mg/day), and/or eszopiclone (maximum: 3 mg/day).

Safety Assessments

Safety assessments of adverse event (AE), clinical laboratory evaluations (hematology, chemistry, and urinalysis), vital signs (including orthostatic blood pressure and body weight), ECGs, physical examination, and the C-SSR-S.

Primary Endpoint

The primary efficacy variable was the change from baseline to week 8 in Montgomery-Åsberg Depression Rating Scale (MADRS).

Secondary Endpoint

The pre-specified key secondary efficacy variable was the change from baseline to week 8 in Sheehan Disability Scale (SDS).

Additional exploratory efficacy measures

Response rate

- $\geq 50\%$ reduction from baseline in MADRS-CR at week 8
- $\geq 50\%$ reduction from baseline in HAMD-17 at week 8
- CGI-I score ≤ 2 at week 8

Remission rate

- MADRS-CR ≤ 10 at week 8
- HAMD-17 ≤ 7 at week 8

Change from baseline to week 8 in the following

- 17-item Hamilton Rating Scale for Depression (HAMD-17), HAMD-17 anxiety subscale, HAMD-17 depressed mood item, HAMD-17 psychomotor retardation subscale, HAMD-17 sleep disturbance subscale, HAMD-17 melancholia subscale, and CGI-I score at Week 8

Statistical Methods

The statistical analyses plan (SAP) was initially specified in the protocol and submitted for review on January 12, 2010 with amendment #1 and #2 submitted on May 18, 2011 and June 22, 2011, respectively. Site 008 enrolled fewer than 4 patients and was pooled with Site 036. The database was locked on 7/5/2011, and treatment codes were unblinded following the database lock.

Analysis populations were defined as:

- *Randomized Population* consisted of all patients in the Screened Population who were randomized to 1 of the 4 treatment groups in the study.
- *Safety Population* consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product (placebo; levomilnacipran 40, 80, or 120 mg).
- *Intent to Treat (ITT) population* defined as all patients in the Safety Population who had at least 1 postbaseline assessment of the MADRS-CR.

All statistical tests were 2-sided hypothesis tests performed at the 5% level of significance, all confidence intervals were 2-sided 95% confidence intervals, and to control the family-wise error rate, Hochberg multiple-comparison procedures were used.

The primary, secondary and additional efficacy parameters analysis was performed using the mixed-effects model for repeated measures (MMRM) approach with treatment group, pooled study center, each visit, and treatment group-by-visit interaction as factors and baseline value and baseline-by-visit interactions as covariates. Last-observation-carried forward (LOCF) and pattern-mixture model approaches were performed on the primary efficacy parameter as sensitivity analyses. The secondary efficacy analysis of SDS was carried out inferentially only if the results of the primary efficacy analyses were positive for comparisons of 3 doses of levomilnacipran with placebo at the 0.05 level.

Baseline Patient Characteristics

Demographics

There were no statistically significant differences among the treatment groups with respect to age, sex, race, ethnicity, or body mass index.

The overall mean weight was similar, the median (maximum) in placebo treatment group was slightly higher (142 kg) compared to the levomilnacipran 40 mg (129 kg), 80 mg (126 kg), and 120 mg (133 kg) treatment group. This resulted in a slight statistical significant difference ($p = 0.0475$) in baseline weight among the treatment groups.

The majority of patients enrolled were Caucasian (74%), females (63%) with a mean age of 41 years. Overall, the patient population in this trial is representative of the target patient population of patients treated for MDD. See table 8 below.

Table 8: Patient baseline demographic characteristics (Study LVM-MD-01)

Characteristic	LVM			Placebo (N= 176)	Total (N = 713)
	40 mg (N = 178)	80 mg (N = 179)	120 mg (N = 180)		
Age (years), Mean (SD)	42 (13)	41 (13)	40 (12)	41 (11)	41 (12)
Gender, n (%)					
Male	45 (48.9)	68 (38)	74 (41)	68 (39)	266 (37)
Female	47 (51.1)	111 (62)	106 (60)	108 (61)	447 (63)
Race, n (%)					
White	134 (76)	133 (75)	129 (72)	134 (76)	526 (74)
Black/African American	36 (20)	39 (22)	41 (23)	29 (17)	145 (20)
Other	6 (3)	4 (2)	4 (2)	3 (2)	17 (2)
Asian	3 (2)	5 (3)	3 (2)	8 (5)	4 (0.6)
American Indian/Alaska Native	0	2 (1)	1 (0.6)	1 (0.6)	19 (3)
Ethnic group, n (%)					
Not Hispanic or Latino	20 (11)	22 (12)	28 (16)	20 (11)	92 (13)
Hispanic or Latino	155 (87)	151 (84)	158 (88)	156 (89)	620 (87)
Weight (kg)					
Mean (SD)	84 (19)	80 (17)	83 (17)	84 (19)	83 (18)
Minimum; Maximum	47; 129	46; 126	48; 133	47; 142	46; 142
BMI (kg/m ²), Mean (SD)	29 (6)	28 (5)	29 (5)	29 (6)	29 (6)

Source: Table 14.2.2 of CSR, SD= Standard Deviation

Disease Characteristics

Baseline efficacy parameters (MADRS-CR, SDS, HAMD-17 and CGI-S) were fairly balanced between the treatment groups, see table 9 below.

Table 9: Patient baseline efficacy assessments (Study LVM-MD-01)

Baseline efficacy assessments	LVM			Placebo (N = 175)	P-value
	40 mg (N = 176)	80 mg (N=177)	120 mg (N=176)		
MADRS-CR, mean ± SD	36 ± 4	36.1 ± 4	36 ± 4	35.6 ± 5	0.6950
SDS, mean ± SD	21.1 ± 5	21.4 ± 5	21.3 ± 5	21.5 ± 5	0.9164
HAMD-17, mean ± SD	24.7 ± 4	24.7 ± 4	25 ± 4	24.6 ± 4	0.5660
CGI-S score, mean ± SD	4.1 ± 0.6	4.8 ± 0.6	4.9 ± 0.6	4.9 ± 0.6	-

Source: Table 14.2.8 of CSR

Incidence of common ($\geq 10\%$ Incidence) medical conditions among the treatment groups was evaluated, there were similar incidence of preexisting medical conditions among all treatment groups except for hypertension which was more commonly seen 12 %, 11% and 9% in the 40 mg, 80 mg and 120 mg levomilnacipran treatment groups, relatively compared to the 6% in the placebo treatment group.

MDD history was similar among the treatment groups. Most patients (71 to 83%) had a history of recurrent major depression and the mean duration of MDD was approximately 11 years with a mean onset at age 30. While most patients had recurrent depression, ~50% of all patients had ever received antidepressant therapy. Approximately ~25 of patients with previous antidepressant use had either a poor response or did not respond to therapy. At screening, no patients were considered to be suicide risks nor had any patients attempted suicide within the past year

Subject Disposition

Patient Population

The total number of patients screened was 1567, 843 patients were considered screen failures as they did not meet eligibility criteria and 724 subjects were randomized to receive double-blind treatment, and 506 subjects completed the study. See table 10 below.

Table 10: Patient populations (Study LVM-MD-01)

Screened patients = 1567, Screen failures = 843	LVM 40 mg	LVM 80 mg	LVM 120 mg	Placebo	Total
Randomized Population	181	181	183	179	724
Safety Population	178	179	180	176	713
ITT Population	176	177	176	175	704

Source: Table 14.1.1, Study report p. 82

Patient Disposition

Overall, in total 71% (n=506) patients completed the clinical study with 69% (n=492) patients entering the double-blind taper down period in the levomilnacipran treatment group. The most frequent reasons for discontinuation were listed as withdrawal of consent, AEs, and lost to follow-up. The number of adverse events was statistically significant and higher for all three levomilnacipran treatment groups compared to placebo. The 120 mg treatment group had a higher rate of informed consent withdrawal compared to the placebo treatment group. No randomization code was unblinded during the conduct of the study. See table 11 below.

Table 11: Patient disposition and reasons for discontinuations (Study LVM-MD-01)

Patient Status	LVM			Placebo (N =176) n (%)	Total (N =713) n (%)
	40 mg (N =178) n (%)	80 mg (N =179) n (%)	120 mg (N =180) n(%)		
Completed study ^a	130 (73)	121 (68)	117 (65)	138 (79)	506 (71)
Prematurely discontinued	48 (27)	58 (32) ^b	63 (35) ^b	38 (22)	207 (29)
Adverse event	13 (7)	26 (15) ^b	12 (7) ^b	3 (2)	54 (8)
Insufficient therapeutic response	4 (2)	1 (0.6) ^b	3 (2)	7 (4)	15 (2)
Protocol violation	5 (3)	9 (5)	10 (6)	9 (5)	33 (5)
Withdrawal of consent	12 (7)	11 (6)	23 (13) ^b	9 (5)	55 (8)
Lost to follow-up	14 (8)	8 (5)	15 (8)	10 (6)	47 (7)
Other ^c	0	3 (2) ^c	0	0	3 (0.4)
Entered down-taper ^d	123 (69)	122 (68)	117 (65)	130 (74)	492 (69)

Source: Tables 14.1.1, 14.1.2, 14.1.3, 14.1.4, and 14.1.5; Listing 16.2.2.1. of CSR

^a - Patients who completed the 8 week double-blind treatment period were considered completers

^b - Difference between placebo and levomilnacipran group was statistically significant (p-value <0.05) based on Fisher exact test

^c - Other reasons included discontinuation due to pregnancy (PID 0280110, 0300157, 0310118)

^d - Patients who were completers and patients who prematurely discontinued were eligible to enter the down-taper period

Concomitant Medication

On February 20, 2013 we requested the sponsor to identify specific concomitant medications used under the categories “psychoanaleptic” and “psycholeptics” for each of the treatment groups in the double-blind treatment period of the Studies LVM-MD-01, -03, -10, and F02695-lp202. We wanted them to present the information in the format of the Table modeled after Table 14.3.2.2A from their Clinical Study Reports.

On February 28, 2013, sponsor submitted the requested information which has been incorporated into the concomitant medication tables of each specific study.

Concomitant medications were used by 75%, 78 %, and 69% of the patients in the 40 mg, 80 mg and 120 mg levomilnacipran treatment groups compared to the 80% of the placebo treatment group. There were no substantial differences in concomitant medication use among treatment groups. It seems unlikely that the use of the concomitant medications would have significantly biased the results based on the pharmacology of the medications used and the equal distributions between the two treatment groups. These concomitant medications are likely to be used in the population for which this drug is intended. See table 12 below.

Table 12: Concomitant medications taken by > 10% of patients (Study LVM-MD-01)

Therapeutic Drug Class	LVM			Placebo (N = 176)
	40 mg (N = 178)	80 mg (N = 179)	120 mg (N =180)	
Any medication	133 (75)	140 (78)	124 (69)	141 (80)
Analgesics	62 (35)	63 (35)	48 (27)	67 (38)
Antihistamines (systemic use)	13 (7)	18 (10)	22 (12)	13 (7)
Anti-inflammatory and antirheumatic products	58 (32)	54 (30)	50 (28)	51 (29)
Psycholeptics	13 (7)	18 (10)	15 (8)	15 (8)
Eszopiclone	3 (2)	3 (2)	1 (0.6)	3 (2)
Zolpidem /Zolpidem Tartrate	8 (5)	11 (6)	10 (6)	12 (7)
Lorazepam	2 (1)	1 (0.6)	0	0
Alprazolam	0	1 (0.6)	1 (0.6)	0
Diazepam	0	1 (0.6)	0	0
Psychoanaleptics	3 (2)	1 (0.6)	0	4 (2)
Trazodone	1 (0.6)	0	0	0
Sertraline	0	1 (0.6)	0	0
Milnacipran	1 (0.6)	0	0	0
Escitalopram	1 (0.6)	0	0	1 (0.6)
Citalopram	1 (0.6)	0	0	2 (1)
Sex hormones and modulators of the genital system	20 (11)	21 (12)	14 (8)	19 (11)
Vitamins	31 (17)	33 (18)	36 (20)	35 (20)

Source: Table 14.3.2.2A of CSR and table 2 from module 1.11.3

Note: Only for Study LVM-MD-01 the sponsor in their analysis (seen in table above) of the concomitant medications included medications taken after the last dose of investigational product if the patient did not participate in the down-taper treatment period.

Protocol Deviations

Numbers of protocol deviations reported were comparable among the different treatment groups:

Levomilnacipran 40 mg: n=43/178 (24%)

Levomilnacipran 80 mg: n=48/179 (27%)

Levomilnacipran 120 mg: n=52/180 (29%)

Placebo group: n=40/176 (23%)

Numbers of patients that discontinued because of protocol deviations among different treatment groups:

Levomilnacipran 40 mg: n=5/178 (3%)

Levomilnacipran 80 mg: n=9/179 (5%)

Levomilnacipran 120 mg: n=10/180 (6%)

Placebo group: n=9/176 (5%)

Most common protocol deviation were related to the use of prohibited concomitant medications during the study, the incidences ranging from 8% to 12%, this rate was comparable among all the treatment

groups. Most common reasons listed for study discontinuations were positive Urine Drug Screen (UDS) results, noncompliance and taking prohibited concomitant medications. None of these deviations was considered to be major and these patients were not excluded from the efficacy or safety analyses.

Results

Primary efficacy variable

MADRS

The mean change from baseline at week 8 in MADRS-CR after adjustment for multiplicity were decreased 14.8, 15.6, and 16.5 points for levomilnacipran treatment group of 40 mg, 80 mg and 120 mg respectively compared to 11.6 point mean decrease in placebo treated patients, demonstrating levomilnacipran to be statistically significant at all three levomilnacipran dose groups. See table 13 below.

Table 13: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-01)

MADRS-CR	LVM			Placebo (N = 175)
	40 mg (N = 176)	80 mg (N = 177)	120 mg (N = 176)	
Baseline, mean ± SD	36.0 ± 4.1	36.1 ± 3.9	36.0 ± 3.9	35.6 ± 4.5
Endpoint, mean ± SEM	21.6 ± 1.1	19.9 ± 1.1	19.4 ± 1.1	22.9 ± 1.1
LS mean ± SE	-14.8 ± 0.99	-15.6 ± 1	-16.5 ± 1.02	-11.6 ± 0.97
LSMD versus placebo (95% CI)	-3.23 (-5.92, -0.54)	-3.99 (-6.69, -1.29)	-4.86 (-7.59, -2.12)	-
p-Value versus placebo	0.0186	0.0038	0.0005	-

Source: Table 14.4.3.1A.of CSR

SD = Standard deviation, SEM = Standard Error of Mean, SE = standard error, LSMD = difference in least squares mean

Key Secondary efficacy variable

SDS

The mean change from baseline at week 8 in SDS after adjustment for multiplicity were decreased 8.6, 9.7, and 9.7 points for levomilnacipran treatment group of 40 mg, 80 mg and 120 mg respectively compared to 7.2 point mean decrease in placebo treatment group, demonstrating levomilnacipran 80 mg and 120 mg as the only statistically significant doses and not the 40 mg levomilnacipran dose group. See table 14 below.

Table 14: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-01)

SDS	LVM			Placebo (N = 175)
	40 mg (N = 176)	80 mg (N = 177)	120 mg (N = 176)	
Baseline, mean ± SD	21.1 ± 4.8	21.4 ± 4.9	21.3 ± 5	21.5 ± 4.8
Endpoint, mean ± SEM	12.7 ± 0.8	11.3 ± 0.8	11.3 ± 0.9	13.8 ± 0.8
LS mean ± SE	-8.6 ± 0.75	-9.7 ± 0.77	-9.7 ± 0.78	-7.2 ± 0.74
LSMD versus placebo (95% CI)	-1.41 (-3.42, 0.60)	-2.51 (-4.54, -0.49)	-2.57 (-4.62, -0.52)	-
p-Value versus placebo	0.1687	0.0151	0.0141	-

Source: Table 14.4.2.1 of CSR

Additional efficacy variables

The result tables are listed in the Appendix 9.4.

6.2.2 Study LVM-MD-10

This multicenter trial was conducted in 47 centers in the US, 4 centers in Canada, and under 61 investigators.

The first subject was enrolled on June 13, 2011.
The last subject completed the study on March 01, 2012.
The study report was submitted on August 06, 2012.

Study Methods, Design and Statistical Analysis Plan

Study Title

Study LVM-MD-10 is “A Double-blind, Placebo-Controlled, Fixed-Dose Study of Levomilnacipran in Patients With Major Depressive Disorder”.

Primary Objective

The objective of this study was to evaluate the efficacy, safety, and tolerability of fixed doses of levomilnacipran compared with placebo in the treatment of adult patients with MDD.

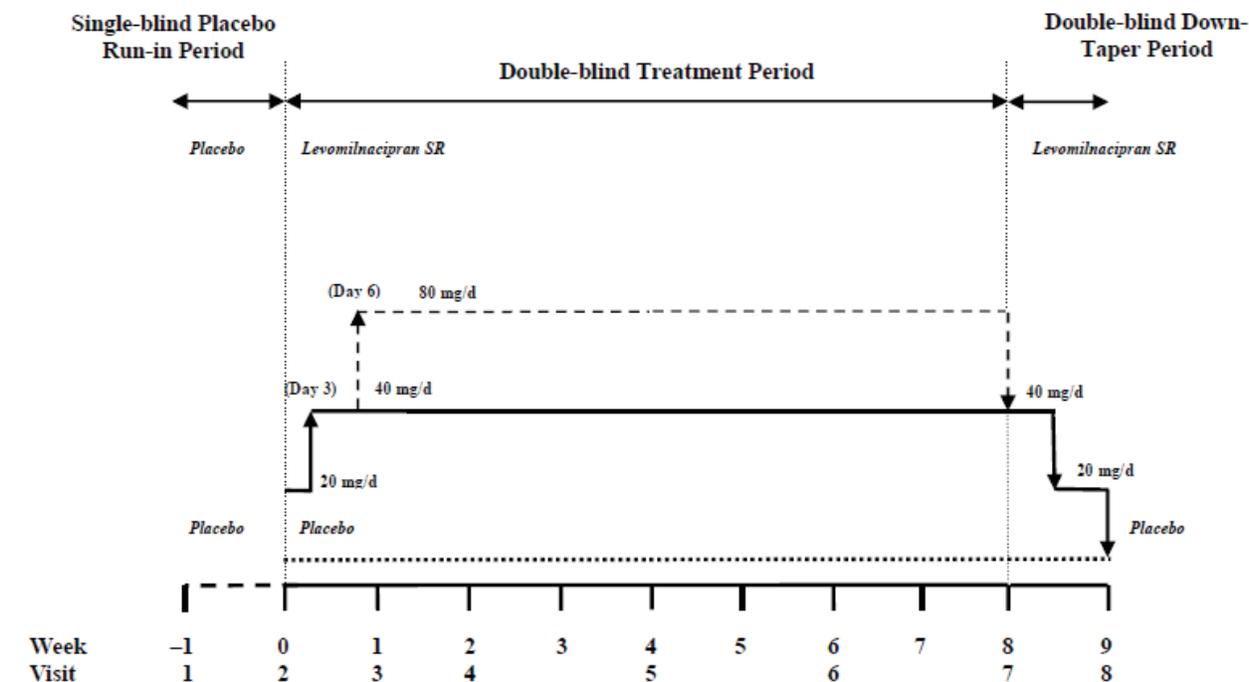
Design

This was a Phase 3, multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group fixed dose study of levomilnacipran (80 mg and 120 mg compared with placebo with an allocation ratio of 1:1:1) in adults aged 18-75 years with a diagnosis of MDD.

Duration

1-week of single-blind placebo run-in period, 8 weeks of double-blind treatment, followed by a 1-week, double-blind down-taper period. Total duration was 10 weeks.

Figure 2: Study design for Study LVM-MD-10



Source: Figure 9.1 in Section 9, page 32 of CSR (extracted from the sponsor's submission)

Titration

Patients were randomized into three different treatment groups including placebo treatment group. All treatment groups initiated the treatment with the 20 mg dose. The placebo treatment group was given the corresponding treatment.

Randomized dose group	Double-blind titration period			
	Days 1-2	Days 3-4	Days 5-7	Days 8-56
40 mg/day	20 mg	40 mg	40 mg	40 mg
80 mg/day	20 mg	40 mg	80 mg	80 mg

The dosing could have been switched to the morning from evening dosing schedule if there were tolerability problems. Temporary dose reductions or discontinuation of levomilnacipran for reasons of tolerability, when deemed necessary by the investigator, were to be limited to no more than 2 days during the study, patients discontinued after that. The date and reason for any dose reduction was to be recorded on the appropriate page of the eCRF.

Key Inclusion Criteria

- Male and female outpatients who were 18 to 75 years of age
- Patients met Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for MDD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 6 weeks. Patients had ≤ 5 major depressive episodes within the previous 5 years at Visit 1.
- MADRS-CR score of ≥ 26 at screening and baseline

- Patients had a score of ≥ 4 on the CGI-S at screening and at baseline
- Patients with a normal physical examination, clinical laboratory test results, electrocardiogram (ECG) results, negative urine drug screen test, females with negative serum pregnancy test, and/or abnormal results that are judged not clinically significant by the investigator were included in this study.

Key Exclusion criteria

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Concomitant Medication

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Safety Assessments

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Primary Endpoint

The primary efficacy variable was the change from baseline to week 8 in MADRS.

Secondary Endpoint

The pre-specified key secondary efficacy variable was the change from baseline to week 8 in SDS.

Additional exploratory efficacy measures

Response rate

- $\geq 50\%$ reduction from baseline in MADRS-CR at week 8
- $\geq 50\%$ reduction from baseline in HAMD-17 at week 8
- CGI-I score ≤ 2 at week 8

Remission rate

- MADRS-CR ≤ 10 at week 8
- HAMD-17 ≤ 7 at week 8

Change from baseline to week 8 in the following

- 17-item HAMD-17, HAMD-17 anxiety subscale, HAMD-17 depressed mood item, HAMD-17 psychomotor retardation subscale, HAMD-17 sleep disturbance subscale, HAMD-17 melancholia subscale, SDS work subscale, SDS social life subscale, SDS family life subscale, and CGI-S score at week 8

Statistical Methods

The SAP was submitted for review on October 06, 2011. The database was locked on 7/5/2011, and treatment codes were unblinded following the database lock. Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Baseline Patient Characteristics

Demographics

There were no statistically significant differences among the treatment groups with respect to age, sex, race, ethnicity, weight, or body mass index. The majority of patients enrolled were Caucasian (74%),

females (64%) with a mean age of 42.8 years. Overall, the patient population in this trial is representative of the target patient population of patients treated for MDD. See table 15 below.

Table 15: Patient baseline demographic characteristics (Study LVM-MD-10)

Characteristics	LVM 40 mg (N = 188)	LVM 80 mg (N = 188)	Placebo (N = 186)	Total (N = 562)
Age (years), Mean (SD)	43 (13)	43 (13)	42 (13)	43 (13)
Gender, n (%)				
Male	71 (38)	64 (34)	70 (38)	205 (37)
Female	117 (62)	124 (66)	116 (62)	357 (64)
Race, n (%)				
White	142 (76)	139 (74)	135 (73)	416 (74)
Black/African American	37 (20)	36 (20)	35 (19)	108 (19)
Other	5 (3)	5 (3)	10 (5)	20 (4)
Asian	4 (2)	3 (2)	7 (4)	4 (0.6)
American Indian/Alaska Native	0	0	3 (2)	3 (0.5)
Ethnic group, n (%)				
Not Hispanic or Latino	163 (88)	164 (87)	173 (92)	500 (89)
Hispanic or Latino	23 (12)	24 (13)	15 (8)	62 (11)
Weight (kg), Mean (SD), Median (Minimum, Maximum)	81 (17) 80 (49; 132)	81 (17) 81 (47; 128)	82 (18) 80 (49; 135)	82 (17) 81 (45; 135)
BMI (kg/m ²), Mean (SD)	28 (5)	29 (6)	29 (5)	29 (5)

Source: Table 14.2.1 of CSR

Disease Characteristics

Baseline efficacy parameters (MADRS-CR, SDS, HAMD-17 and CGI-S) were fairly balanced between the treatment groups. See table 16 below.

Table 16: Patient baseline efficacy assessments - ITT populations (Study LVM-MD-10)

Baseline efficacy assessments	LVM		Placebo (N = 185)	P-value
	40 mg (N = 185)	80 mg (N = 187)		
MADRS-CR, mean ± SD	31.0 ± 3	31.2 ± 4	31.0 ± 4	0.5305
SDS, mean ± SD	16.4 ± 7	17.6 ± 6	16.4 ± 6	0.2364
CGI-S score, mean ± SD	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.1524
HAMD-17, mean ± SD	21.7 ± 4	21.5 ± 4	21.7 ± 4	0.7789

Source: Tables 14.2.8 and 14.4.3.13A. of CSR

Incidence of common ($\geq 10\%$ Incidence) medical conditions among the treatment groups was evaluated; there were similar incidence of preexisting medical conditions among all treatment groups except for:

- Obesity was reported in a greater proportion of patients in the levomilnacipran 80 mg/day group (11%) than in the placebo treated group (5%) or levomilnacipran 40 mg/day group (3%)
- Insomnia was much lower in the levomilnacipran 40 mg/day group (5%) than in the placebo (11%) or levomilnacipran 80 mg/day group (9%)

MDD history was similar among the treatment groups. All patients had recurrent major depression with a mean onset at age 30. While most patients had recurrent depression, ~57% of all patients had ever received antidepressant therapy. Approximately ~25 of patients with previous antidepressant use had either a poor response or did not respond to therapy. At screening, no patients were considered to be suicide risks nor had any patients attempted suicide within the past year

Subject Disposition

Patient Population

A total number of patients screened were 959, 391 patients were considered screen failures as they did not meet eligibility criteria, 568 subjects were randomized to receive double-blind treatment, and a total of 441 subjects completed the study. See table 17 below.

Table 17: Patient populations (Study LVM-MD-10)

patients screened = 959, screen failures = 391	LVM 40 mg	LVM 80 mg	Placebo	Total
Randomized Population	190	189	189	568
Safety Population	188	188	186	562
ITT Population	185	187	185	557

Source: Table 14.1.1. of CSR

Patient Disposition

Overall 79% (n=441) patients completed the clinical study with 69% (n=492) patients entering the double-blind taper down period. The most frequent reasons for discontinuation were listed as AEs, and lost to follow-up. Statistically significant more patients discontinued due to adverse events in the levomilnacipran 40 mg (6%) and 80 mg (10%) treatment groups compared to the placebo treatment group (2%). No randomization code was unblinded during the conduct of the study. See table 18 below.

Table 18: Patient disposition and reasons for discontinuations (Study LVM-MD-10)

Patient disposition	LVM 40 mg (N =188) n (%)	LVM 80 mg (N =188) n (%)	Placebo (N =186) n (%)	Total (N =562) n (%)
Completed study ^a	145 (77)	142 (76)	154 (83)	441 (79)
Prematurely discontinued	32 (17)	46 (25)	38 (22)	121 (22)
Adverse event	12 (6) ^a	19 (10) ^a	3 (2)	34 (6)
Insufficient therapeutic response	3 (2)	3 (2)	3 (2)	15 (2)
Protocol violation	10 (5)	6 (3)	4 (2)	33 (5)
Withdrawal of consent	10 (5)	7 (4)	8 (4)	55 (8)
Lost to follow-up	8 (5)	11 (6)	14 (8)	47 (7)
Entered down-taper ^b	136 (72)	141 (75)	147 (79)	492 (69)

Source: Tables 14.1.3. of CSR

^a Statistically significant (p < 0.05) compared to placebo p-Values are based on the Fisher exact test.

^b Patients who completed the double-blind treatment period and patients who prematurely discontinued from the study were eligible to enter the double-blind down-taper period.

Concomitant Medication

The use of concomitant medication was 72% and 81% in the levomilnacipran 40 mg and 80 mg treatment group compared to 82% in placebo treatment group. The most commonly used psycholeptics were Zolpidem at a rate of 3 to 5 % among the treatment drug and placebo treatment group. There were no substantial differences in concomitant medication use among treatment groups. It seems unlikely that the use of the concomitant medications would have significantly biased the results based on the pharmacology of the medications used and the equal distributions between the two treatment groups. These concomitant medications are likely to be used in the population for which this drug is intended. See table 19 below.

Table 19: Concomitant medications taken by > 10% of patients (Study LVM-MD-10)

Therapeutic Drug Class	LVM 40 mg (N = 188)	LVM80 mg (N = 188)	Placebo (N = 186)
Any medication	135 (72)	152 (81)	152 (82)
Analgesics	39 (21)	44 (23)	52 (28)
Antihistamines (systemic use)	15 (8)	21 (11)	13 (7)
Anti-inflammatory and antirheumatic products	62 (33)	56 (30)	48 (26)
Psycholeptics	11 (6)	13 (7)	12 (7)
Zolpidem /Zolpidem Tartrate	6 (3)	10 (5)	8 (4)
Psychoanaleptics (Trazodone)	1 (0.5)	1 (0.5)	0
Sex hormones and modulators of the genital system	16 (9)	18 (10)	17 (9)
Drugs for acid-related disorders	19 (10)	20 (11)	19 (10)
Lipid-modifying agents	23 (12)	24 (13)	13 (7)
Vitamins	39 (21)	43 (23)	42 (23)

Source: Table 14.3.2.2A of CSR

Protocol Deviations

The overall total number of protocol violations reported in levomilnacipran and placebo treatment groups of this study were n=77/562 (14%). Most common protocol deviations were related to the use of prohibited concomitant medications during the study. Most common reasons listed for study discontinuations were positive Urine Drug Screen (UDS) results, noncompliance and taking prohibited concomitant medications.

There were 3 patients (PID #0011007, PID #0121006, and PID #371015) in the 40 mg treatment group and 1 patient (PID #0141002) in the 80 mg treatment group that had discontinued the study because they had enrolled in another levomilnacipran study. None of these deviations was considered to be major and these patients were not excluded from the efficacy or safety analyses.

Table 20: Summary of protocol deviations — safety population (Study LVM-MD-10)

Protocol deviations	LVM 40 mg (N=188)	LVM 80 mg (N=188)	Placebo (N=186)
Patients with any protocol deviation	33 (18)	23 (12)	21 (11)
Patients who discontinued because of a protocol violation	10 (5)	6 (3)	4 (2)

Source: Table 14.1.7 of CSR

Results

Primary efficacy variable

MADRS

The mean change from baseline at week 8 in MADRS after adjustment for multiplicity were decreased 14.6 and 14.4 points for levomilnacipran treatment groups of 40 mg and 80 mg respectively compared to 11.6 point mean decrease in placebo treated patients, demonstrating levomilnacipran to be statistically significant in both 40 and 80 mg treatment groups. See table 21 below.

Table 21: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-10)

MADRS	LVM 40 mg (N = 185)	LVM 80 mg (N = 187)	Placebo (N = 185)
Baseline, mean ± SD	30.8 ± 3.4	31.2 ± 3.5	31.0 ± 3.8
Endpoint, mean ± SEM	16 ± 0.9	17 ± 0.9	19 ± 0.8
LS mean ± SE	-14.6 ± 0.8	-14.4 ± 0.8	-11.3 ± 0.8
LSMD versus placebo (95% CI)	-3.3 (-5.4, -1.1)	-3.1 (-5.3, -0.9)	-
p-Value versus placebo	0.0027	0.0043	-

Source: Tables 14.2.8 and 14.4.1.1. of CSR

Key Secondary efficacy variable

SDS

The mean change from randomization at week 8 in SDS after adjustment for multiplicity were decreased 7.3 and 8.2 points for levomilnacipran treatment dose of 40 mg, and 80 mg respectively compared to 5.4 point mean decrease in placebo, demonstrating levomilnacipran 40 mg and 80 mg doses are statistically significant. See table 22 below.

Table 22: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-10)

SDS	LVM 40 mg (N = 185)	LVM 80 mg (N = 187)	Placebo (N = 185)
Baseline, mean ± SD	16.7 ± 7	17.6 ± 6	16.4 ± 6
Endpoint, mean ± SEM	8.9 ± 0.7	8.5 ± 0.8	10.7 ± 0.7
LS mean ± SE	-7.3 ± 0.68	-8.2 ± 0.66	-5.4 ± 0.66
LSMD versus placebo (95% CI)	-1.83 (-3.6, 0.03)	-2.72 (-4.5, -0.9)	-
p-Value versus placebo	0.0459	0.0028	-

Source: Tables 14.2.8 of CSR

Additional efficacy variables

The result tables are listed in the Appendix 9.4.

6.2.3 Study LVM-MD-03

This multicenter trial was conducted in 23 centers in the US, and under 23 investigators.

The first subject was enrolled on December 21, 2009.

The last subject completed the study on December 19, 2011.

The study report was submitted on July 23, 2012.

Study Methods, Design and Statistical Analysis Plan

Study Title

Study LVM-MD-03 is “A Double-blind, Placebo-Controlled, Flexible-Dose Study of F2695 SR in Patients With Major Depressive Disorder”.

Primary Objective

To evaluate the efficacy, safety, and tolerability of levomilnacipran versus that of placebo in the treatment of patients with MDD

Design

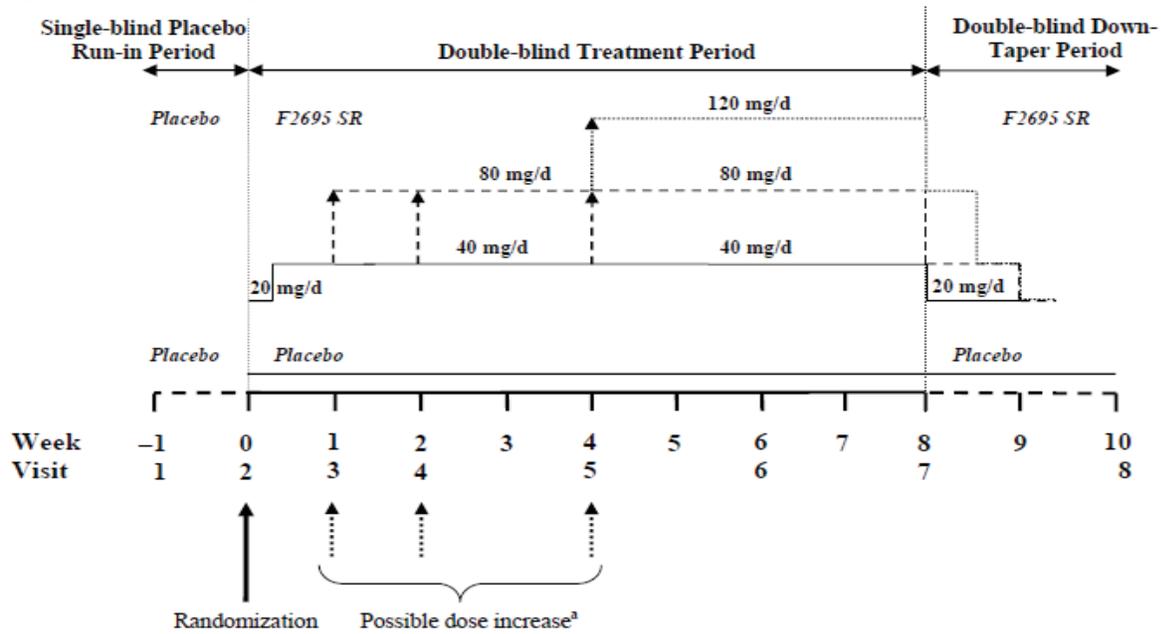
This was a Phase 3, multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group flexible dose study of levomilnacipran (levomilnacipran 20-120 mg) in adults aged 18-80 years with a diagnosis of MDD.

Patients who completed the 8-week double-blind treatment period or prematurely discontinued from the study were allowed to enter the 2-week double-blind down-taper period.

Duration

The study was a 1-week single-blind placebo run-in period, 8-weeks of double-blind treatment, followed by 2-weeks of double-blind down-taper period. Total duration was 11 weeks.

Figure 3: Study design for Study LVM-MD-03



^a If response is not adequate and there are no significant tolerability issues, the dosage may be increased at Visits 3 or 4 and again at Visit 5.

^a If response is not adequate and there are no significant tolerability issues, the dosage may be increased at Visits 3 or 4 and again at Visit 5.

Source: Study protocol (Appendix 16.1.1). Figure 9.1-1 in Section 9, Page 36 of 13268 of CSR (extracted from the sponsor's submission)

Titration

Patients were randomized into two levomilnacipran and placebo treatment groups (1:1). Treatment was initiated with the 20 mg dose X 1-2 days, 40 mg X 3-7 days, 80 mg X 8-28 days and 120 mg 29-56 days.

Dosage increase was based on efficacy and tolerability, efficacy measured as <50% improvement in the MADRS score from baseline (Visit 2) were eligible for a dosage increase if there were no dose-limiting AEs and were instructed to take 1 additional capsule daily. Patients with adequate response $\geq 50\%$ improvement in the MADRS score continued at their current dose. No dosage increase was permitted after week 4 (Visit 5).

The dosing could have been switched to the morning from evening dosing schedule if there were tolerability problems. Temporary dose reductions or discontinuation of levomilnacipran for reasons of tolerability, when deemed necessary by the investigator, were to be limited to no more than 2 days during the study, patients discontinued after that. The date and reason for any dose reduction was to be recorded on the appropriate page of the eCRF.

Main Inclusion Criteria

- Male and female outpatients who were 18 to 80 years of age
- Patients met Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for MDD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 4 weeks
- MADRS-CR score of ≥ 30 at screening and baseline and a MADRS-SR score of ≥ 26 at baseline
- Patients with a normal physical examination, clinical laboratory test results, electrocardiogram (ECG) results, negative urine drug screen test, females with negative serum pregnancy test, and/or abnormal results that are judged not clinically significant by the investigator were included in this study.

Exclusion criteria

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Concomitant Medication

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Safety Assessments

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Primary Endpoint

The sponsor's primary efficacy endpoint was the change from baseline to week 8 in MADRS.

Secondary Endpoint

The pre-specified key secondary efficacy variable was the change from baseline to week 8 in SDS.

Additional exploratory efficacy measures

Response rate

- $\geq 50\%$ reduction from baseline in MADRS-CR at week 8
- $\geq 50\%$ reduction from baseline in HAMD-17 at week 8
- CGI-I score ≤ 2 at week 8

Remission rate

- MADRS-CR ≤ 10 at week 8
- HAMD-17 ≤ 7 at week 8

Change from baseline to week 8 in the following

- 17-item HAMD-17, HAMD-17 anxiety subscale, HAMD-17 depressed mood item, HAMD-17 psychomotor retardation subscale, HAMD-17 sleep disturbance subscale, HAMD-17 melancholia subscale, SDS work subscale, SDS social life subscale, SDS family life subscale, and CGI-S score at week 8

Statistical Methods

The SAP was submitted for review on November 02, 2010. The treatment codes were unblinded following the database lock in this submission; I was unable to locate the date of the unblinding of these treatment codes. Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Baseline Patient Characteristics

Demographics

There were no statistically significant differences among the treatment groups with respect to age, sex, race, ethnicity, weight, or body mass index. The majority of patients enrolled were Caucasian (83%), females (65%) with a mean age of 44.8 years. See table 23 below.

Table 23: Patient baseline demographic characteristics (Study LVM-MD-03)

Characteristics	LVM 40-120 mg (N = 217)	Placebo (N = 217)	Total (N = 434)
Age (years), Mean (SD)	45 (13)	45 (14)	45 (14)
Gender, n (%)			
Male	77 (36)	74 (34)	151 (35)
Female	140 (65)	143 (66)	283 (65)
Race, n (%)			
White	177 (82)	182 (84)	359 (83)
Black/African American	33 (15)	28 (13)	61 (14)
Other	4 (2)	4 (2)	8 (2)
Asian	1 (0.9)	1 (0.9)	2 (0.9)
American Indian/Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
Ethnic group, n (%)			
Not Hispanic or Latino	196 (90)	200 (92)	396 (91)
Hispanic or Latino	21 (10)	17 (8)	38 (9)
Weight (kg), Mean (SD), Median (Minimum, Maximum)	85 (18) 83 (47; 143)	85 (18) 83 (47; 145)	85 (19) 83 (47; 145)
BMI (kg/m ²), Mean (SD)	29 (5)	30 (5)	29 (5)

Source: Table 14.2.1 of CSR

Disease Characteristics

Baseline efficacy parameters (MADRS-CR, SDS, HAMD-17, CGI-S and MEI-SF) were fairly balanced between the treatment groups. The Motivation and Energy Inventory–Short Form (MEI-SF) was assessed only in this study and at the time of baseline, Visit 5, 6 and 7. See table 24 below.

Table 24: Patient baseline efficacy assessments - ITT populations (Study LVM-MD-03)

Baseline efficacy assessments	LVM 4-120 mg (N = 215)	Placebo (N = 214)	P-value
MADRS-CR, mean ± SD	35.0 ± 4	35.2 ± 4	0.3508
SDS, mean ± SD	20.1 ± 5	19.7 ± 5	0.4274
HAMD-17, mean ± SD	23.3 ± 4	22.9 ± 4	0.2850
CGI-S score, mean ± SD	4.7 ± 0.7	4.8 ± 0.7	0.3820
MEI-SF, mean ± SD	29.3 ± 15	30.2 ± 16	0.5683

Source: Tables 14.2.8 and 14.4.3.15A of CSR

Incidence of common ($\geq 10\%$ Incidence) medical conditions among the treatment groups was evaluated; there were similar incidence of preexisting medical conditions among all treatment groups except for:

- Headache was reported in a greater proportion of patients in the placebo treated group (27%) than in the levomilnacipran 40-120 mg/day group (19%)
- Insomnia was reported in a greater proportion of patients in the placebo treated group (13%) than in the levomilnacipran 40-120 mg/day group (8%)

MDD history was similar among the treatment groups. Majority 82% patients had recurrent major depression with a mean onset at age 30, and mean count of 6 episodes. Mean duration of MDD was approximately 14 years, and the median duration of the current episode was approximately 7 months. While most patients had recurrent depression, ~50% of all patients had ever received antidepressant therapy. Approximately ~24 of patients with previous antidepressant use had either a poor response or did not respond to therapy. At screening, no patients were considered to be suicide risks nor had any patients attempted suicide within the past year

Subject Disposition

Patient Population

The total number of patients screened were 899, 457 patients were screen failures who did not meet eligibility criteria, 442 subjects were randomized to receive double-blind treatment, and 335 patients completed the study. See table 25 below.

Table 25: Patient populations (Study LVM-MD-03)

Total number of patients screened = 899, Screen failures = 457	LVM 40-120 mg	Placebo	Total
Randomized Population	222	220	442
Safety Population	217	217	434
ITT Population	215	214	429

Source: Table 14.1.1 of CSR

Patient Disposition

Overall, in total 75% (n=163) patients completed the clinical study with 79% (n=171) patients entering the double-blind taper down period in the levomilnacipran treatment group. The most frequent reasons for discontinuation were listed as withdrawal of consent, AEs, and lost to follow-up. No randomization code was unblinded during the conduct of the study. See table 26 below.

Table 26: Patient disposition and reasons for discontinuations (Study LVM-MD-03)

Patient disposition	LVM 40-120 mg (N=217) n (%)	Placebo (N=217) n (%)	Total (N=434) n (%)
Completed study ^a	163 (75)	172 (80)	335 (77)
Prematurely discontinued	54 (25)	45 (21)	99 (23)
Adverse event	17 (8)	7 (3)	24 (6)
Insufficient therapeutic response	4 (2)	4 (2)	8 (2)
Protocol violation	7 (3)	10 (5)	17 (4)
Withdrawal of consent	8 (4)	9 (4)	17 (4)
Lost to follow-up	16 (7)	14 (7)	30 (7)
Entered down-taper ^b	171 (79)	171 (79)	335 (77)

Source: Tables 14.1.3 of CSR

^a Patients who completed 8-week double-blind treatment period were considered completers.

^b Patients who were completers and patients who prematurely discontinued from the study were eligible to enter the down-taper period.

Concomitant Medication

The use of concomitant medication was 78% in the levomilnacipran 40-120 mg treatment group compared to 82% in placebo treatment group, no statistical differences in concomitant medication use among treatment groups. There was a slightly higher incidence of concomitant analgesic medication use being higher in the levomilnacipran treatment group (36%) than the placebo treatment group (30%). It seems unlikely that the use of the concomitant medications would have significantly biased the results based on the pharmacology of the medications used and the equal distributions between the two treatment groups. These concomitant medications are likely to be used in the population for which this drug is intended. See table 27 below.

Table 27: Concomitant medications taken by > 10% of patients (Study LVM-MD-03)

Therapeutic Drug Class	LVM 40-120 mg (N=217)	Placebo (N=217)
Any medication	170 (78)	177 (82)
Analgesics	77 (36)	66 (30)
Antihistamines (systemic use)	30 (14)	24 (11)
Anti-inflammatory and antirheumatic products	71 (33)	76 (35)
Psycholeptics	10 (5)	14 (7)
Zolpidem /Zolpidem Tartrate	6 (3)	10 (5)
Psychoanaleptics	1 (0.5)	1 (0.5)
Acetylcarnitine	1 (0.5)	0
Citalopram	0	1 (0.5)
Sex hormones and modulators of the genital system	16 (7)	16 (7)
Drugs for acid-related disorders	30 (14)	29 (13)
Lipid-modifying agents	27 (12)	24 (11)
Vitamins	46 (21)	40 (18)

Source: Table 14.3.2.2A of CSR

Protocol Deviations

The overall total number of protocol violations reported in this study were n=42/217 (19%) this was comparable to placebo n=46/217 (21%). Most common protocol deviations were related to the use of prohibited concomitant medications 8% in the levomilnacipran treatment group compared to 7% in placebo treatment group during the study. Most common reasons listed for study discontinuations were positive Urine Drug Screen (UDS) results, noncompliance and taking prohibited concomitant medications. None of these deviations was considered to be major and these patients were not excluded from the efficacy or safety analyses.

Table 28: Summary of protocol deviations — safety population (Study LVM-MD-03)

Protocol deviations	LVM 40-120 mg (N=217) n (%)	Placebo (N=217) n (%)
Patients with any protocol deviation	42 (19)	46 (21)
Patients who discontinued because of a protocol violation	7 (3)	10 (5)

Source: Table 14.1.7 of CSR for Study 03

Results

Primary efficacy variable

MADRS

The mean change from baseline at week 8 in MADRS-CR were decreased 15 points for levomilnacipran doses of 40-120 mg compared to 12 point mean decrease in placebo treatment group, demonstrating levomilnacipran to be statistically significant. See table 29 below.

Table 29: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-03)

MADRS-CR	LVM 40-120 mg (N=215)	Placebo (N=214)
Baseline, mean ± SD	35.0 ± 3.6	35.2 ± 3.8
Endpoint, mean ± SEM	19.7 ± 0.8	23.0 ± 0.9
LS mean ± SE	-15.3 ± 0.8	-12.2 ± 0.8
LSMD versus placebo (95% CI)	-3.1 (-5.3, -0.9)	-
p-Value versus placebo ^a	0.0051	-

Source: Tables 14.4.1.1, 14.4.3.1A, and 14.4.3.1B of CSR

Key Secondary efficacy variable

SDS

The mean change from baseline at week 8 in SDS were decreased 8 points for levomilnacipran treatment group of 40-120 mg compared to 5.4 point mean decrease in placebo treatment group, demonstrating levomilnacipran 40-120 mg dose group to be statistically significant. See table 30 below.

Table 30: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-03)

SDS	LVM 40-120 mg (N = 215)	Placebo (N = 214)
Baseline, mean ± SD	20.1 ± 5.0	19.7 ± 5.2
Endpoint, mean ± SEM	11.6 ± 0.6	14.4 ± 0.6
LS mean ± SE	-8.0 ± 0.6	- 5.4 ± 0.6
LSMD versus placebo (95% CI)	-2.6 (-4.2, -1.1)	-
p-Value versus placebo ^a	0.0010	-

Source: Tables 14.4.3.2A of CSR

Dose Exposure

Based on efficacy and tolerability, 21%, 34% and 44% patients were titrated to the final dose of 40 mg, 80 mg and 120 mg/day.

Additional efficacy variables

The result tables are listed in the Appendix 9.4.

6.2.4 Study F02695 LP 2 02

This was a Phase 2 study, flexible dose trial with positive efficacy results for the 75-100 mg levomilnacipran dose. The sponsor has identified this trial to be a supportive study to the 3 pivotal efficacy trials (LVM-MD-01,-03, AND -10).

This multicenter trial was conducted in 68 centers; there were 11 sites in France, 5 sites in Bulgaria, 5 sites in Czech Republic, 4 sites in Estonia, 7 sites in Finland, 7 sites in Germany, 8 sites in India, 2 sites in Latvia, 5 sites in Lithuania, 6 sites in Sweden and South Africa (8 centers). There were 66 investigators.

The first subject was enrolled on December 13, 2006.

The last subject completed the study on October 22, 2007.

The study report was submitted on September 25, 2009.

Study Methods, Design and Statistical Analysis Plan

Study Title

Study F02695 LP 2 02 is “A double-blind, multinational, multicenter, placebo-controlled, 10-week study assessing the efficacy and the safety of F2695 SR flexible dose (75-100 mg) in the treatment of patients with Major Depressive Disorder.”

Primary Objective

To study the clinical efficacy of levomilnacipran (dose 75 or 100 mg/day) compared to placebo in patients with MDD through the assessment of MADRS after 10 weeks of treatment

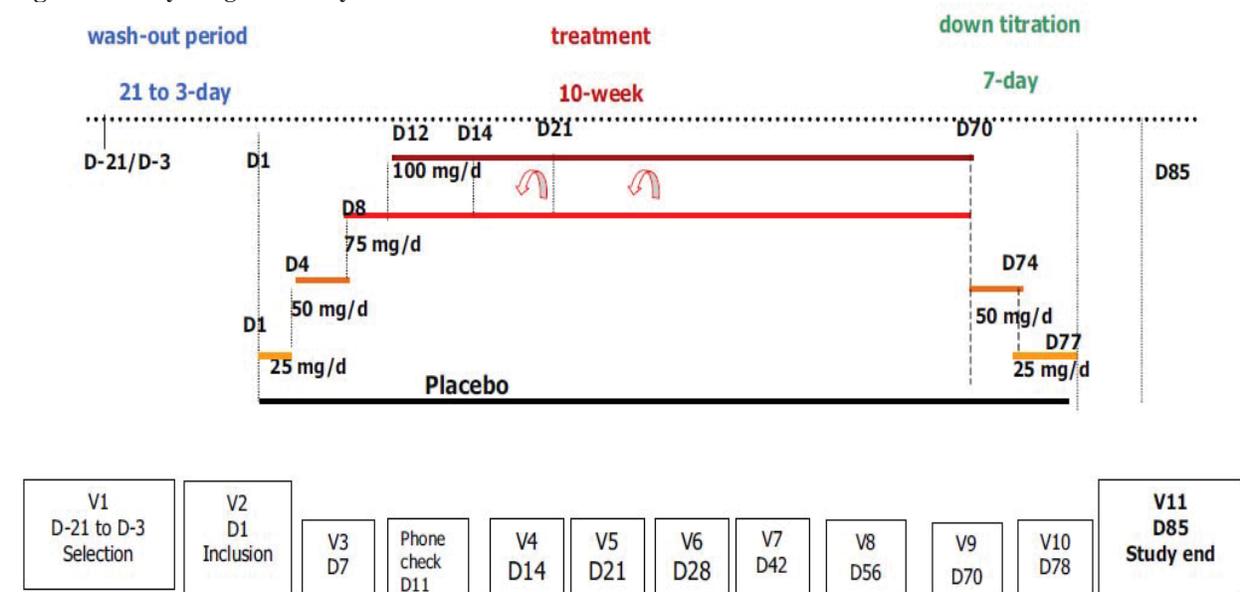
Design

This was an 10-week, Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group stratified study of the efficacy and safety of levomilnacipran (levomilnacipran 75 or 100 mg/day) treatment groups compared with placebo for the treatment of MDD in adults.

Duration

There were 2-weeks of titration, 10-weeks of double-blind treatment, followed by 1-week of double-blind down-taper period. Total duration was 13 weeks.

Figure 4: Study design for Study F02695 LP 2 02



Source: extracted from the sponsor's Figure 2, Page 53/364 of CSR (extracted from the sponsor's submission)

Stratification

At randomization, patients were stratified within each center according to the severity of the episode at inclusion, based on MADRS score at baseline. Two strata were defined

- 1st stratum: patients with a total MADRS score at inclusion <30
- 2nd stratum: patients with a total MADRS score at inclusion ≥ 30

Titration

- Day 1 to 3: 25 mg for 3 days
- Day 4 to 7: 50 mg for 4 days
- Day 8 to 11: 75 mg for 4 days
- On D12, based on evaluation of tolerance by investigator (assessed by phone on D11), the dose was either increased to 100 mg or maintained to 75 mg. The patient was withdrawn from the study in the case of intolerance with 75 mg dose. If the treatment had to be stopped from D21 to D70, the investigator performed a 1-week down titration.

Key Inclusion Criteria

- Male and female outpatients who were 18 to 70 years of age
- Patients met Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for MDD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 4 weeks
- MADRS-CR score of ≥ 30 at screening and baseline

- Stratum 1 corresponding to patients with a MADRS less than <30 at baseline and stratum 2 corresponding to patients with a MADRS of ≥ 30 and more at baseline
- HAM-D17 > 22 at selection and inclusion visits
- SDS ≥ 10 and with at least one score ≥ 6 on one of the subscales at selection and inclusion visits
- Patients with a normal physical examination, clinical laboratory test results, electrocardiogram (ECG) results, negative urine drug screen test, females with negative serum pregnancy test, and/or abnormal results that are judged not clinically significant by the investigator were included in this study.

Key Exclusion criteria

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Concomitant Medication

No concomitant psychotropic medications or medications with psychotropic activity were permitted during the study. The following rules had to be met regarding hypnotics and anxiolytics use.

1. For hypnotics and anxiolytics use: the chronic users of low doses of hypnotics/anxiolytics (10 mg of diazepam equivalent), can use their treatment if it had been initiated at least 3 months before inclusion visit, and it remained unchanged throughout the study
2. Restriction of use: from D1 to D14, and for a maximum of 3 days of treatment (consecutives or not) if needed:
 - Low doses of anxiolytics (≤ 10 mg of diazepam-equivalent) or
 - Hypnotics: zolpidem or zopiclone (1 capsule at the marketed dosage) or chloralhydrate (1g/d) or
 - Neuroleptics at low dose (levomepromazine at 25mg/d or chlorpromazine 50mg/d or alimemazine or equivalent at 50 mg/d)

Safety Assessments

Were similar to Study LVM-MD-01 and can be seen in section 6.2.1.

Primary Endpoint

The sponsor's primary efficacy endpoint was the change from baseline to D70 in MADRS.

Secondary Efficacy Analysis Parameters

The secondary efficacy variables were percentage of MADRS and HAM-D17 responders and remitted patients, change in HAM-D17 and "core symptoms" HAM-D17 factor from baseline to D70, CGI improvement score on D70, percentage of CGI responders, change in total score and subscores SDS from baseline to D70, change in VAS from baseline to D70, and COVI scale. Note that SDS was defined as one of several secondary parameters and not as the key secondary parameter unlike other pivotal studies of this program.

Note: None of the above endpoints were designated as key secondary.

Statistical Methods

The SAP was submitted for review on January 28, 2008. The treatment codes were unblinded following the database lock. The database was locked on January 30, 2008 and the database was unlocked on August 07, 2008.

The statistical analysis was conducted in the Full Analysis Set (FAS) with few other population subsets were identified and evaluated in this study and are described below:

- *Safety data set* included all randomized patients who received at least one dose of the study treatment minus #1108 center
- *The Full Analysis Set (FAS)* included all randomized patients who received at least one dose of the study treatment and with at least one post-baseline evaluation of the primary efficacy criterion (MADRS)
- *The Rebound Analysis Data Set*, was a subset of the FAS completers including all randomized FAS patients who completed the study until D85, excluding completers having received a rescue medication between D70 and D85
- *The Cardiovascular history data set* was a subset of the Safety Data Set including all randomized patients who received at least one dose of study drug and with cardiovascular history i.e.: patients with history of cardio-vascular disorder (including ECG abnormalities), patients with an history of arterial hypertension (treated or not), patients without history of arterial hypertension but with SBP >160 mmHg and DBP > 110 mmHg in supine position at selection and/or at inclusion.

I reviewed the sponsor's results of the Rebound data set and Cardiovascular History data set analysis and the summary of these results are in the Appendix listed under Study F02695 LP 2 02.

The primary analysis model used was MMRM, and for sensitivity analysis the LOCF model was utilized. Methods used in the statistical evaluation of the additional efficacy parameters are listed below:

- Response rates (MADRS-CR, HAMD-17, and CGI-I) and remission rates (MADRS-CR and HAMD-17) are analyzed using a logistic model with the treatment group and the corresponding baseline score (the baseline CGI-S score will be used for CGI-I), GEE (Generalized Estimating Equations) and Cochran-Mantel-Haenszel test stratified by center group on D70 for the LOCF approach only. For COVI: Descriptive statistics will be used. For the remainder of the additional efficacy parameters, analyses is performed using MMRM and LOCF approach similar to those used for the primary efficacy parameter.

Baseline Patient Characteristics

Demographics

There were no statistically significant differences among the treatment groups with respect to age, sex, race, ethnicity, weight, or body mass index. The majority of patients enrolled were Caucasian (91%), females (67%) with a mean age of 44.1 years. See table 31 below.

Table 31: Patient baseline demographic characteristics (Study F02695 LP 2 02)

Characteristics	LVM 75-100 mg (n= 277) n (%)	Placebo (n= 276) n (%)	Total (n= 553) n (%)
Age (years), Mean (SD)	44 (13)	45 (12)	44 (12)
Gender, n (%)			
Male	90 (33)	95 (34)	185 (34)
Female	186 (67)	182 (66)	368 (67)
Race, n (%)			
White	253 (92)	251 (91)	504 (91)
Black/African American	1 (0.4)	-	1 (0.2)
Other	5 (2)	5 (2)	10 (2)
Asian	17 (6)	21 (7)	38 (7)
American Indian/Alaska Native	-	-	-
Ethnic group, n (%)			
Not Hispanic or Latino	272 (98)	272 (98)	545 (99)
Hispanic or Latino	3 (1)	5 (2)	8 (1)
Weight (kg), Mean (SD), Median (Minimum, Maximum)	73 (18) 72 (36; 165)	73 (18) 72 (36; 165)	73 (17) 71 (36; 165)
BMI (kg/m ²), Mean (SD)	26 (6)	26 (6)	26 (5)

Source: Table 14.2.1 of CSR

Disease Characteristics

Baseline efficacy parameters (MADRS-CR, SDS, HAMD-17 and CGI-S) were fairly balanced between the treatment groups. See table 32 below.

The mean MADRS at inclusion was 30.7 for the levomilnacipran treatment group. Patients were stratified according to MADRS score, 219 patients had a score of <30 (mean score 27.1) and 334 patients had a score of ≥30 (mean score 33.1) in levomilnacipran treatment group, these scores were comparable to placebo scores. See table 33 below.

Table 32: Patient baseline efficacy assessments (Study F02695 LP 2 02)

Baseline efficacy assessments	LVM 75-100 mg (n=276)	Placebo (n=277)
MADRS-CR, mean ± SD	30.7 ± 4	30.5 ± 4
SDS, mean ± SD	26.2 ± 3	25.8 ± 3
HAMD-17, mean ± SD	21.3 ± 4	20.8 ± 4
CGI-Severity		
Moderately ill	106 (39 %)	113 (41 %)
Markedly ill	133 (49 %)	137 (50 %)
Severely ill	36 (13%)	27 (10 %)
COVI, mean ± SD	5.6 ± 2	5.4 ± 2

Source: Table 10, page 95/364

Table 33: MADRS at inclusion by strata [FAS] (Study F02695 LP 2 02)

	LVM 75-100 mg (n=276)		Placebo (n=277)	
	STRATUM 1 : MADRS score at inclusion	STRATUM 2 : MADRS score at inclusion	STRATUM 1 : MADRS score at inclusion	STRATUM 2 : MADRS score at inclusion
Criteria	< 30 n=116	≥30 n=161	<30 n=103	≥ 30 n=173
MADRS-CR, mean ± SD	26.9 ± 2	33.2 ± 3	27.2 ± 2	32.9 ± 3

Source: Table 11, page 96/364

No analysis regarding incidence of common ($\geq 10\%$ Incidence) medical conditions among the treatment groups was found in this submission.

MDD history was similar among the treatment groups. Majority 73% patients had recurrent major depression with a mean onset at age 36, and mean count of 2.6 episodes. Mean duration of MDD was approximately 14 years, and the median duration of the current episode was approximately 7 months. While most patients had recurrent depression, ~82% of all patients had ever received antidepressant therapy. Approximately ~24 of patients with previous antidepressant use had either a poor response or did not respond to therapy. At screening, no patients were considered to be suicide risks nor had any patients attempted suicide within the past year

Subject Disposition

Patient Population

The total number of patients screened was 659, 563 patients were included and randomized in this study, 282 in the levomilnacipran treatment group and 281 in the placebo treatment group. See table 34 below.

Six patients (2 patients in the placebo treatment group and 4 patients in the levomilnacipran treatment group) from one center (site #1108) in South Africa were excluded from all data sets because their data was invalidated with GCP concerns. The sponsor elaborated that this site did not have medical history collected at the time of screening, certain AE's were not reported at the study visits, and the expert independent reviewer of this site revealed that there were intra as well as inter inconsistencies within the various scales.

Approximately, 72% (n= 189) of the patients were on 100 mg dose of levomilnacipran and ~29% (n=75) were on 75 mg dose of levomilnacipran treatment.

Table 34: Patient populations (Study F02695 LP 2 02)

Patients screened = 659, Patients randomized = 563	LVM 75-100 mg	Placebo	Total
Safety Data Set	278 (99 %)	279 (99 %)	557 (99 %)
Full Analysis Set (FAS)	276 (98 %)	277 (99 %)	553 (98 %)
Rebound Analysis Data Set	221 (78%)	202 (72%)	423 (75 %)
Cardio-vascular history data set	37 (13 %)	34 (12 %)	71 (13%)

Source: Table 7, page 91/364

Patient Disposition

Overall, 25% of placebo patients withdrew from the study compared to 20% of patients in the placebo treatment group. There were 4% of patients in the levomilnacipran treatment group that were classified as withdrawing due to worsening of MDD compared to 6% in the placebo treatment group. The total percentage of withdrawal due to therapeutic failure was 14% in the placebo treatment group and 8% in the levomilnacipran treatment group. See table 35 below.

Table 35: Patient disposition and reasons for discontinuations - randomized patient set (Study F02695 LP 2 02)

Patient disposition	LVM 75-100 mg (n=276) n (%)	Placebo (n=277) n (%)	Total (n=553) n (%)
Number of withdrawn patients	57 (20%)	70 (25 %)	127 (23 %)
Significant Suicidal Risk	1 (0.4 %)	6 (2 %)	7 (1.2 %)
SAE/Non SAE	26 (9 %)	17 (6 %)	43 (7.6 %)
Therapeutic Failure	22 (8 %)	40 (14 %)	62 (11 %)
-Insufficient therapeutic response	16 (6 %)	33 (12 %)	49 (9 %)
-Worsening of MDD	11 (4 %)	17 (6 %)	28 (5 %)
Consent withdrawal	29 (10 %)	37 (13 %)	66 (12 %)
Lost to follow-up	1 (0.4 %)	-	1 (0.2 %)
Other reason	8 (3 %)	10 (4 %)	18 (3 %)

Source: Study report p. 85

Concomitant Medication

The concomitant medication use among levomilnacipran (32%, n=90/278) compared to placebo (30%, n=84/279) treatment groups were similar. The psycholeptics (Alprazolam, Diazepam, Clonazepam, Bromazepam and Chlordiazepoxide) and psychoanaleptics (Duloxetine and Piracetam) were all used at comparable rates ~10% and 0.4% between the two treatment groups, respectively. There were no substantial differences in concomitant medication use among treatment groups. It seems unlikely that the use of the concomitant medications would have significantly biased the results based on the pharmacology of the medications used and the equal distributions between the two treatment groups. These concomitant medications are likely to be used in the population for which this drug is intended.

Protocol Deviations

The overall total numbers of protocol violations reported in this study were 9 % (n=25/276) of patients in the levomilnacipran treatment group and 8% (n=23/277) of patients in the placebo treatment group. The major protocol deviation in this study was patients not receiving at least 18 days of study drug by D21, which occurred in 7% (n=20/276) of the levomilnacipran treatment group and in 7% (n=18/277) placebo treatment group. This major protocol deviation occurred in many countries, at different center sites and it was not explained as to why this occurred. Other reasons listed were noncompliance and taking prohibited concomitant medications.

Results

Primary efficacy variable

MADRS

The mean change from baseline at day70 in MADRS-CR were decreased 19 points for levomilnacipran doses of 75-100 mg/day compared to 15 point mean decrease in placebo treatment group, demonstrating levomilnacipran to be statistically significant. See table 36 below.

There was a Test for Visit Treatment effect analyzed and the results observed were statistically significant as well, with difference steadily increasing in the levomilnacipran treatment group with mean change in MADRS of -0.1 at day 7 and -4.2 at day 70.

Table 36: Primary efficacy analysis - change from baseline to day 70 (MMRM) - FAS - (Study F02695 LP 2 02)

MADRS-CR	LVM 75-100 mg (n=276)	Placebo (n=277)	LS Means (SE) difference between groups	p-Value versus placebo
MADRS	-18.7 (0.56)	-14.5 (0.56)	-4.2 (0.79)	<0.0001

Source: Table 16

Dose Exposure

Based on efficacy and tolerability, 28% received the 75 mg dose and 72% patients received the 100 mg/day dose.

Secondary efficacy variables

I reviewed the sponsor's results of all the secondary efficacy variables; some of these secondary efficacy variable results are noted in this table 37 below.

Table 37: Secondary efficacy analysis - change from baseline to day 70 (LOCF) – FAS - (Study F02695 LP 2 02)

Secondary efficacy analysis	LVM 75-100 mg (n=276)	Placebo (n=277)	LS Means (SE)	p-Value
CGI Improvement score	-2.0 (0.07)	-2.5 (0.07)	-0.4 (0.09)	<0.0001
SDS (SE)	-11.1 (0.43)	-7.7 (0.44)	-3.4 (0.61)	<0.0001
MADRS response (≥50% reduction from baseline, n/N1 (%))	59% (n=163)	42% (n=117)	-	<0.0001
MADRS remission (≤ 10 in MADRS, n/N1 (%))	46% (n=128)	26% (n=72)	-	<0.0001
HAM-D17 (SE)	-14.5 (0.45)	-11.5 (0.46)	-3.4 (0.64)	<0.0001
HAMD-17 response (≥ 50% reduction from baseline)	56% (n=155)	39% (n=107)	-	<0.0001
HAMD-17 remission (≤7)	33% (n=92)	21% (n=57)	-	<0.0001
CGI-I response (CGI-I score ≤ 2)	46% (n=126)	68% (n=187)	-	<0.0001

Source: 11.4.1.2. Secondary criterion of the CSR

6.2.5 Study LVM-MD-02

This multicenter trial was conducted in 24 centers in the US, and under 24 investigators.

The first subject was enrolled on September 14, 2009.

The last subject completed the study on October 29, 2010.

The study report was submitted on September 06, 2011.

Study Methods, Design and Statistical Analysis Plan

Study Title

Study LVM-MD-10 is “A Double-blind, Placebo-Controlled, Flexible-Dose Study of F2695 SR in Patients with Major Depressive Disorder”.

Primary Objectives

The objective of this study was to evaluate the efficacy, safety, and tolerability of levomilnacipran versus placebo in the treatment of patients with MDD.

Design

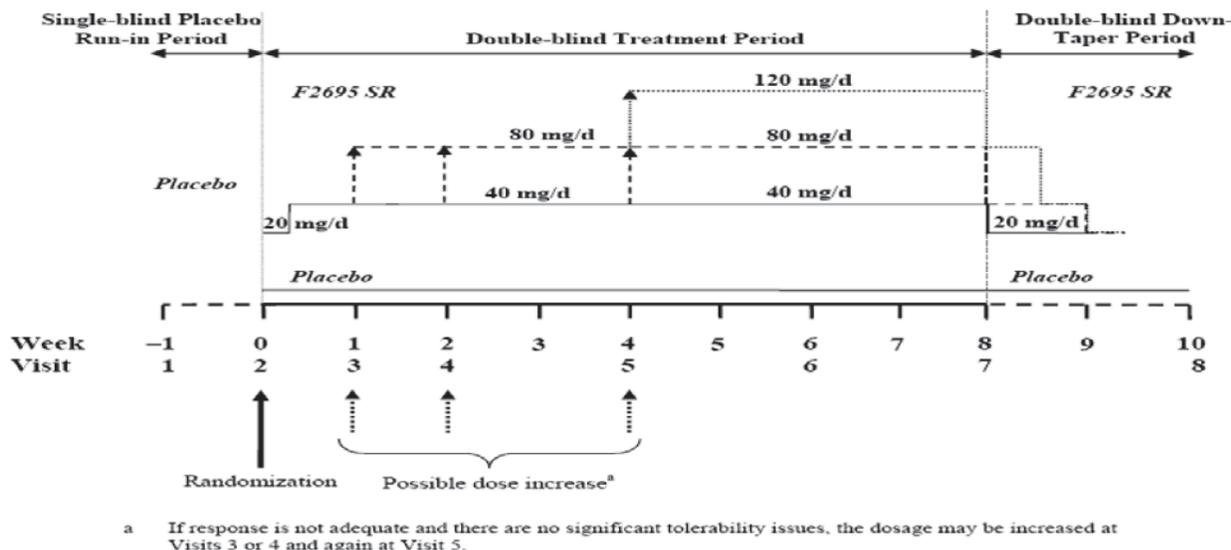
This was a Phase 3, multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group flexible dose study of levomilnacipran (levomilnacipran 40 mg -120 mg compared with placebo with an allocation ratio of 1:1) in adults with a diagnosis of MDD.

Patients who completed the 8-week double-blind treatment period or prematurely discontinued from the study were allowed to enter the 2-week double-blind down-taper period.

Duration

1-week of single-blind placebo run-in period, 8 weeks of double-blind treatment, followed by a 2-week, double-blind down-taper period. Total duration was 11 weeks.

Figure 5: Study Design of Study LVM-MD-02



Source: Appendix 16.1.1, Figure 9.1 in Section 9, page 34 of CSR (extracted from the sponsor's submission)

Titration

Patients were randomized into two treatment groups, placebo and levomilnacipran (1:1). The treatment was initiated with the 20 mg dose X 1-2 days, 40 mg dose X 3-7 days, 80 mg X 8-28 days and 120 mg for 29-56 days.

Dosage increase was based on efficacy and tolerability, efficacy measured as <50% improvement in the MADRS score from baseline (Visit 2) were eligible for a dosage increase if there were no dose-limiting AEs and were instructed to take 1 additional capsule daily. Patients with adequate response $\geq 50\%$ improvement in the MADRS score continued at their current dose. No dosage increase was permitted after week 4 (Visit 5).

The dosing could have been switched to the morning from evening dosing schedule if there were tolerability problems. Temporary dose reductions or discontinuation of levomilnacipran for reasons of tolerability, when deemed necessary by the investigator, were to be limited to no more than 2 days during

the study, patients discontinued after that. The date and reason for any dose reduction was to be recorded on the appropriate page of the eCRF.

Key Inclusive Criteria

- Male and female outpatients who were 18 to 80 years of age
- Patients met Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for MDD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 4 weeks
- MADRS-CR score of ≥ 30 at screening and baseline and a MADRS-SR score of ≥ 26 at baseline
- Patients with a normal physical examination, clinical laboratory test results, electrocardiogram (ECG) results, negative urine drug screen test, females with negative serum pregnancy test, and/or abnormal results that are judged not clinically significant by the investigator were included in this study.

Key Exclusion Criteria

Were similar to Study LVM-MD-01 and can be referred to section 6.2.1.

Concomitant Medication

Were similar to Study LVM-MD-01 and can be referred to section 6.2.1.

Safety Assessments

Were similar to Study LVM-MD-01 and can be referred to section 6.2.1. This was the only study that incorporated the Arizona Sexual Experiences (ASEX) scale for assessment of sexual dysfunction.

Primary Endpoint

The primary efficacy endpoint was the change from baseline to week 8 in MADRS.

Secondary Endpoint

The secondary efficacy variable was the change from baseline to week 8 in SDS.

Additional exploratory efficacy measures

Response rate

- $\geq 50\%$ reduction from baseline in MADRS-CR at week 8
- $\geq 50\%$ reduction from baseline in HAMD-17 at week 8
- CGI-I score ≤ 2 at week 8

Remission rate

- MADRS-CR ≤ 10 at week 8
- HAMD-17 ≤ 7 at week 8

Changes from baseline to week 8 in the following

- 17-item HAMD-17, HAMD-17 anxiety subscale, HAMD-17 depressed mood item, HAMD-17 psychomotor retardation subscale, HAMD-17 sleep disturbance subscale, HAMD-17 melancholia subscale, SDS work subscale, SDS social life subscale, SDS family life subscale, CGI-1 score, CGI-S scores, and Brief Pain Inventory scores

Statistical Methods

The SAP was submitted for review on December 04, 2009 and the amended version submitted on January 11, 2011. The database was locked on 01/12/2011, and treatment codes were unblinded following the database lock.

The SAP was similar to Study LVM-MD-01 and can be referred to section 6.2.1.

Baseline Patient Characteristics

Demographics

There were no statistically significant differences among the treatment groups with respect to age, sex, race, ethnicity, weight, or BMI. Most patients were Caucasian (79%), 43 years of age, and ~60% were females.

Efficacy Assessments

At baseline, the efficacy parameters (MADRS, HAMD-17, CGI-S, SDS-social and family life items) showed no statistical differences between the treatment groups in the ITT population. SDS-work item mean score was 6.9 for levomilnacipran treatment group and 6.4 for placebo treatment groups; I consider this treatment difference to be minor. I did not evaluate baseline disease characteristics (medical and depression history) data regarding this failed study.

Subject Disposition

Patient Population

The total number of patients screened was 659, 362 patients were included and randomized in this study, 174 in the levomilnacipran treatment group and 181 in the placebo treatment group, ITT population and a total of 284 patients completed the study. See table 38 below.

Table 38: Patient populations (Study LVM-MD-02)

Total number of patients screened = 793 Screen failures = 431	LVM 40-120 mg	Placebo	Total
Randomized Population	178	184	362
Safety Population	175	182	357
ITT Population	174	181	355

Source: Tables 14.1.1, 14.1.2, 14.1.3, and 14.1.5; Listing 16.2.2.1. of CSR

Patient Disposition

Statistically significant differences were seen in the discontinuations secondary to adverse event rate in the levomilnacipran treatment group (n=14/175, 8%) versus the placebo treatment group (n=4/182, 2%). I reviewed the narratives of these 14 AEs in the levomilnacipran treatment group and none of these stood out as a relapse of depression. In this study there was only one case as seen in the table below of insufficient therapeutic response. No randomization code was unblinded during the conduct of the study. See table 39 below.

Table 39: Patient disposition and reasons for discontinuations (Study LVM-MD-02)

Patient disposition	LVM 40-120 mg (N =175) n (%)	Placebo (N =182) n (%)	Total (N =357) n (%)
Completed study ^a	135 (77)	149 (82)	284 (80)
Prematurely discontinued	40 (23)	33 (18)	73 (20)
Adverse event	14 (8)	4 (2)	18 (5)
Insufficient therapeutic response	1 (0.6)	1 (0.5)	2 (0.6)
Protocol violation	12 (7)	9 (5)	21 (6)
Withdrawal of consent	9 (5)	13 (7)	22 (6)
Lost to follow-up	4 (2)	5 (3)	9 (3)
Other (pregnancy)	0	1 (0.5)	1 (0.3)
Entered down-taper ^b	137 (78)	149 (82)	286 (80)

Source: Tables 14.1.3 and 14.1.4; Listing 16.2.2.1.CSR

^a Patients who completed the 8-week double-blind treatment period were considered completers.

^b Patients who were completers and patients who prematurely discontinued from the study were eligible to enter the down-taper period.

Concomitant Medications

Most common concomitant medications utilized during the double-blind treatment period at a rate of >10% were analgesics and anti-inflammatory and antirheumatic products. There were no statistical differences regarding different concomitant medications use among levomilnacipran and placebo treatment groups.

Protocol deviations

Overall, protocol deviations occurred in a similar percentage of patients in each treatment group. The most common protocol deviation among patients in the levomilnacipran treatment group was positive urine drug screen result (n=16/175 patients, 9%).

Results

Primary efficacy variable

MADRS

The mean change from randomization at week 8 in MADRS were decreased (b) (4) points for levomilnacipran doses of 40 -120 mg compared to 14.2 point mean decrease in placebo treatment group. Though a slight numerically greater decrease in mean MADRS was observed in for the levomilnacipran treatment group, however the between treatment group difference was not statistically significant (p-value (b) (4)). See table 40 below.

The LSMD mean change response noted in the placebo treatment group of Studies LVM-MD-01,-10, -03 and F02695 LP 2 02 were -11.6, -11.3, -12.2, and -14.5, respectively. In my opinion, the placebo effect observed in this study was no different than placebo effect observed among other similar short term levomilnacipran studies. As this study had no active control, it is difficult to interpret assay sensitivity from these results.

The sponsor cited the reason for efficacy failure in this study was most likely secondary to the larger placebo response observed in this study.

Table 40: Primary efficacy analysis - change from baseline to week 8 in the MADRS (MMRM), ITT population (Study LVM-MD-02)

MADRS	LVM 40-120 mg N = ^(b) ⁽⁴⁾ (b)(4)	Placebo N = 153
Baseline, mean ± SEM		35.5 ± 0.3
Endpoint, mean		21.5
LS mean ± SE		-14.2 ± 0.9
LSMD versus placebo (95% CI)		-
p-Value versus placebo		-

Source: Tables 14.4.1.1, 14.4.3.1A, and 14.4.3.1B. of CSR.

Key Secondary efficacy variable

SDS

The mean change from randomization at week 8 in SDS were decreased ^(b)
⁽⁴⁾ points for levomilnacipran treatment group of 40-120 mg compared to 8.2 point mean decrease in placebo, demonstrating no statistical difference for levomilnacipran treatment group. See table 41 below.

Table 41: Secondary efficacy analysis - change from baseline to week 8 in the SDS (MMRM), ITT population (Study LVM-MD-02)

SDS	LVM 40-120 mg N = ^(b) ⁽⁴⁾ (b)(4)	Placebo N = 142
Baseline, mean ± SEM		20.8 ± 0.4
LS mean ± SE		-8.2 ± 0.67
LSMD versus placebo (95% CI)		-
p-Value versus placebo		-

Source: Tables 14.2.8, 14.4.3.2A, 14.4.3.2B, 14.4.3.21A, 14.4.3.22A, and 14.4.3.23A

Additional efficacy variables

The results tables are listed in the Appendix 9.4.

6.2.6 Study LVM-MD-05

This multicenter trial was conducted in 30 centers in the US, and 6 centers in Canada, and under 55 investigators.

The first subject was enrolled on March 11, 2010.
 The last subject completed the study on October 12, 2011.
 The study report was submitted on August 08, 2012.

Study Methods, Design and Statistical Analysis Plan

Study Title

Study LVM-MD-10 is “A Multicenter, Randomized, Double-blind, Placebo-Controlled, Relapse-Prevention Study with F2695 SR in Patients with Major Depressive Disorder”.

Objective

The objective of this study was to evaluate the safety and efficacy of levomilnacipran relative to placebo in the prevention of depression relapse in patients with major depressive disorder (MDD).

Study Design

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, relapse prevention study.

At the end of the screening period, patients who met the entry criteria were enrolled in the flexible-dose, 12-week, open-label treatment period and received levomilnacipran 40 -120 mg.

Titration schedule involved initially starting at 20 mg for 2 days, titrated up to 40 mg for days 3-7 it could have increased up to 80 mg and/or 120 mg based on the investigator's judgment of patient's response and tolerability. No further dosage increases were allowed after Visit 5 (end of week 4).

Sustained response criteria (to assess if patients were to remain in the open label Phase)

- MADRS ≤ 12 and CGI-I ≤ 2 at weeks 4, 6, and 8 (Visits 5, 6 or 7 respectively), and at all subsequent visits until randomization

Responder's criteria (to assess if patients were responders at end of open label Phase)

- defined same as the sustained response on weeks 10 and 12 (Visit 8 and Visit 9 respectively) at the end of open-label treatment period were randomized in a 2:1 ratio (levomilnacipran: placebo) to double-blind treatment for 24 weeks

Randomization criteria (to be met before entering the double-blind Phase)

- MADRS ≤ 12
- CGI-I score ≤ 2

The dose was fixed during the double-blind treatment period, and patients randomized to the levomilnacipran treatment group continued on the same dosage (40, 80, or 120 mg) that they were receiving at the end of the open-label treatment period. Patients randomized to the placebo treatment group were gradually tapered down during the first week after randomization and received the placebo capsules thereafter.

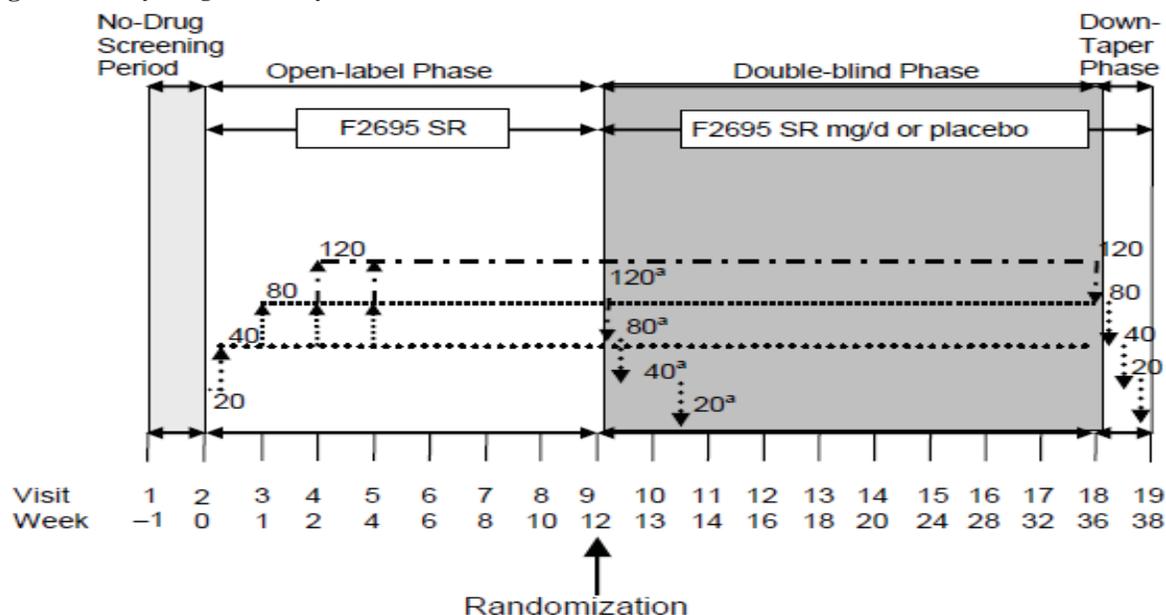
Patients who were not randomized to double-blind treatment or who prematurely discontinued from the study (open-label or the double-blind treatment period) entered a 2-week down-taper treatment period.

Patients who had not relapsed at the end of the double-blind treatment period and those who prematurely discontinued from the double-blind treatment period for reasons other than insufficient therapeutic response were censored in the analysis of the primary efficacy parameter.

Duration

Total study duration was 39 weeks: 1-week of screening, 12 weeks open-label treatment, 24 weeks double-blind treatment, followed by 2 weeks double-blind down-taper.

Figure 6: Study design for Study LVM-MD-05



^a Patients randomized to the placebo group will begin a down-taper of their investigational product at Visit 9.

Source: Figure 9.1-1 in Section 9, page 31 of CS (extracted from sponsor submission)

Key Inclusion Criteria

- Male and female outpatients who were 18 to 65 years of age
- Patients met Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for MDD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 4 weeks
- MADRS score of ≥ 22 at screening and baseline.
- Patients with a normal physical examination, clinical laboratory test results, electrocardiogram (ECG) results, negative urine drug screen test, females with negative serum pregnancy test, and/or abnormal results that are judged not clinically significant by the investigator were included in this study.

Key Exclusion Criteria

Were similar to Study LVM-MD-01 and can be referred to section 6.2.1.

Concomitant Medication

Were similar to Study LVM-MD-01 and can be referred to section 6.2.1.

Safety Assessments

Were similar to Study LVM-MD-01 and can be referred to section 6.2.1.

Primary efficacy endpoint

The primary efficacy endpoint was the time to relapse from randomization to the double-blind treatment. Time to relapse (days) was calculated as date of relapse - date of randomization + 1.

Cox proportional hazard-regression model with different treatment group and baseline MADRS scores as the explanatory variables based on the double-blind ITT population were used for the statistical analysis of the primary efficacy endpoint. Kaplan-Meier estimates and curves for cumulative rates of relapse were analyzed for the double-blind treatment period.

Relapse criteria were one or more of the following

- MADRS ≥ 22 at 2 consecutive visits
- ≥ 2 points increase in CGI-I score compared with the CGI-I score at Visit 9 at 2 consecutive visits
- Premature discontinuation due to insufficient therapeutic response
- MADRS item 10 score ≥ 4

Additional efficacy endpoints

- There was no key secondary efficacy endpoint identified. Additional efficacy measures included change from baseline to week 8 of MADRS, CGI-S, CGI-I and SDS.

Statistical Methods

The amended SAP was submitted for review on December 12, 2011. The database was locked on 01/16/2012, and treatment codes were unblinded following the database lock.

All efficacy analyses were based on the Intent to Treat (ITT) Population, all statistical tests were 2-sided hypothesis tests performed at the 5% level of significance, and all confidence intervals were 2-sided 95% confidence intervals. The statistical analysis plan for the primary efficacy review is mentioned in the Study design section above. For the additional efficacy analysis the LS mean change from baseline and p-value are based on MMRM analysis of all post-baseline observed data using a mixed model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as factors and baseline value and baseline value-by-visit interaction as covariates

Analysis populations were defined as:

- *The Open-label Safety Population* consisted of all patients in the Screened Population who took at least 1 dose of open-label levomilnacipran during the 12-week open-label treatment
- *Open-label Intent-to-Treat Population* consisted of all patients in the Open-label Safety Population who had at least 1 assessment of the MADRS during the 12-week open-label treatment
- *The Randomized Population* consisted of all patients in the Screened Population who were randomized to 1 of 2 double-blind treatment groups during the double-blind treatment
- *The Double-blind Safety Population* consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product
- *The Double-blind ITT Population* consisted of all patients in the Double-blind Safety Population who had at least 1 post randomization assessment of MADRS or CGI-I, or those who discontinued for an insufficient therapeutic response during the double-blind treatment period

Baseline Patient Characteristics

Demographics

There were no statistically significant differences among the treatment groups with respect to age, sex, race, ethnicity, weight, or body mass index between the two treatment groups for the double-blind safety population. The majority of patients enrolled were Caucasian (75%), females (58%) with a mean age of 43 years. See table 42 below.

Table 42: Patient baseline demographic characteristics - safety populations (Study LVM-MD-05)

Characteristics	Open-label LVM 40-120 mg (N = 734) n (%)	Double-blind		
		LVM 40-120 mg (N = 233) n (%)	Placebo (N = 112) n (%)	Total (N = 345) n (%)
Age (years), Mean (SD)	42 (12)	42 (12)	45 (13)	43 (12)
Gender, n (%)				
Male	309 (42)	94 (42)	51 (46)	145 (42)
Female	425 (58)	139 (60)	61 (55)	200 (58)
Race, n (%)				
White	519 (71)	176 (76)	83 (74)	259 (75)
Black/African American	162 (22)	42 (18)	22 (20)	64 (19)
Other	19 (3)	6 (3)	2 (2)	8 (2)
Asian	24 (3)	6 (3)	3 (3)	9 (3)
American Indian/Alaska Native	8 (1)	2 (1)	2 (2)	4 (1)
Ethnic group, n (%)				
Not Hispanic or Latino	640 (87)	204 (88)	99 (88)	303 (88)
Hispanic or Latino	94 (13)	29 (12)	13 (12)	42 (12)
Weight (kg), Mean (SD), Median (Minimum, Maximum)	83 (18) 82 (42; 141)	84 (19) 83 (49; 132)	84 (19) 83 (49; 141)	84 (19) 83 (42; 141)
BMI (kg/m ²), Mean (SD)	29 (5)	29 (6)	29 (6)	29 (6)

Source: Table 14.1.3A and B of CSR

Disease Characteristics

Baseline efficacy parameters (MADRS-CR, SDS, and CGI-S total) were fairly balanced between the treatment groups. See table 43 below.

Table 43: Patient baseline disease characteristics - ITT populations (Study LVM-MD-05)

Baseline efficacy assessments	Open-label LVM 40-120 mg (N = 724)	Double-blind		
		LVM 40-120 mg (N = 230)	Placebo (N = 112)	p-Value
MADRS, mean ± SD	30.7 ± 5	6 ± 4	6 ± 4	0.8409
SDS, mean ± SD	19.6 ± 5	5 ± 5	5 ± 6	0.9485
CGI-S score, n (%)				
Normal, not at all ill	0	104 (45)	45 (40)	0.9722
Borderline ill	0	99 (43)	60 (54)	-
Mildly ill	2 (0.3)	27 (12)	7 (6)	-
Moderately ill	425 (59)	0	0	-
Markedly ill	250 (35)	0	0	-
Severely ill	46 (6)	0	0	-
Among the most extremely ill	1 (0.1)	0	0	-

Source: Tables 14.2.8A and 14.2.8B; Listings 16.2.6.2, 16.2.6.3, and 16.2.6.4 of CSR

The incidence and type of common medical conditions ($\geq 10\%$) reported in the open-label and double-blind population period was similar.

Most patients (~75%) had a history of recurrent major depression. The mean duration was approximately 12 years in both treatment groups, and the mean onset age was slightly younger in the levomilnacipran treatment group (30 years) than in the placebo group (33 years).

Subject Disposition

Patient Population

The total number of patients screened was 1066, 332 patients were screen failures, 734 patients were included in the 12 week open-label Phase of this study, 494 patients completed the open label Phase, 348 patients were randomized into the 24 week double-blind Phase (n=235 levomilnacipran and n= 113 in the placebo treatment group) and 177 patients completed the double-blind Phase in the levomilnacipran treatment group and 92 patients completed it in the placebo treatment group. No randomization code was broken during the conduct of the study. See table 44 below.

Table 44: Patient populations (Study LVM-MD-05)

Total number of patients screened = 1066	Open-label	Double-blind LVM 40-120 mg	Double-blind placebo
Screened population	1066	-	-
Open label Safety Population	734	-	-
Open Label ITT Population	724	-	-
Randomized Population	348	235	113
Double-blind Safety Population	345	233	112
Double-blind ITT Population	342	230	112
Completed double-blind Phase	-	177	92

Source: Table 14.1.1; Listings 16.2.2.1A and 16.2.2.1B.

Note: the number of 348 patients in the randomized population is below the expected number of 360 from the sample size calculation by the sponsor.

Patient Disposition

At the end of 12 week open label Phase, those patients who had reached the endpoint of the study (relapsed - classified as patients with insufficient therapeutic response), did not enter into the 24-week randomization Phase.

During the double-blind treatment period, there was an overall higher incidence of discontinuations in the levomilnacipran treatment group (24%) than in the placebo treatment groups (18%), but it was not statistically significant. Withdrawal of consent was the most frequent reason for discontinuation during the double-blind treatment period of the levomilnacipran treatment group (9%) compared to the patients in the placebo treatment group (10%).

Table 45: Patient disposition - Safety populations (Study LVM-MD-05)

Patient disposition	Open-label LVM 40-120 mg (N = 734) n (%)	Double-blind		Total (N = 345) n (%)
		LVM 40-120 mg (N = 233) n (%)	Placebo (N = 112) n (%)	
Completed study ^a	494 (67)	177 (76)	92 (82)	269 (78)
Prematurely discontinued	240 (33)	56 (24)	20 (18)	76 (22)
Adverse event	80 (11)	8 (3)	3 (3)	11 (3)
Insufficient therapeutic response	26 (4)	-	-	-
Protocol violation	39 (5)	7 (3)	2 (2)	9 (3)
Withdrawal of consent	53 (7)	22 (9)	11 (10)	33 (10)
Lost to follow-up	42 (6)	17 (7)	4 (4)	17 (7)
Other ^b	0	2 (0.9)	0	2 (0.6)
Entered down-taper ^c	179 (24)	165 (71)	80 (71)	245 (71)

Source: Tables 14.1.3b of CSR

^a Patients who completed the 12-week open-label treatment period or the 24-week double-blind treatment period

^b Other reasons included positive serum pregnancy test result (PID 0060516 and PID 0290525)

^c Patients who were completers and prematurely discontinued from the study were eligible to enter the down-taper period

Concomitant Medication

The overall use of concomitant medication in the open-label group was 77%, and during the double-blind levomilnacipran and placebo treatment group was the same incidence rate of 81%. Most commonly used concomitant medications were analgesics, anti-inflammatory and antirheumatic products, and vitamins. See table 46 below.

Table 46: Concomitant medications taken by > 10% of patients — safety populations (Study LVM-MD-05)

Therapeutic drug class	Open label LVM 40-120 mg (N = 734) n (%)	Double-blind	
		LVM 40-120 mg (N = 233) n (%)	Placebo (N = 112) n (%)
Any medication	563 (77)	188 (81)	91 (81)
Agents acting on the renin angiotensin system	43 (6)	14 (6)	12 (11)
Analgesics	200 (27)	74 (32)	31 (28)
Antihistamines (systemic use)	77 (11)	31 (13)	20 (18)
Anti-inflammatory and antirheumatic products	201 (27)	80 (34)	38 (34)
Sex hormones and modulators of the genital system	87 (12)	31 (13)	10 (9)
Drugs for acid-related disorders	79 (11)	24 (10)	12 (11)
Lipid-modifying agents	64 (9)	27 (12)	16 (14)
Vitamins	170 (23)	60 (26)	31 (28)

Source: Tables 14.3.2.2A and 14.3.2.3; Listing 16.2.5.1. of CSR

Protocol Deviations

Protocol deviations occurred at a similar rate in the levomilnacipran (37%) and placebo (36%) treatment groups of the double-blind safety population. The most common protocol deviation in both treatment groups was use of a prohibited concomitant medication for more consecutive days than allowed was at the rate of 22%.

Table 47: Summary of protocol deviations — double-blind, randomized population (Study LVM-MD-05)

Protocol deviations	LVM 40-120 mg (N=235) n (%)	Placebo N=113 n (%)
Patients with any protocol deviation	85 (37)	41 (36)
Patients who discontinued because of a protocol violation*	7 (3)	2 (2)
Patients who failed to meet inclusion/exclusion criteria	5 (2)	0
Positive urine drug screen result	13 (6)	9 (8)
Patients who took prohibited concomitant antidepressant, anxiolytic, or antipsychotic medication at any time	4 (2) ^a	4 (3) ^b
Patients who took CM for more consecutive days than allowed	52 (22)	25 (22)
Patients who took < 90% of their assigned treatment	4 (2)	2 (2)
Patients who missed ≥ 3 consecutive doses of treatment	13 (6)	7 (6)
Patients who had a maximum dosage of > 3 capsules/day	18 (8)	6 (5)

Source: Table 14.1.6.of CSR; CM – concomitant medication

* Note there were six patients that either enrolled twice in this study or were concurrently enrolled in a different study. All available data for those six patients has been included (1 patient was part of the placebo treatment group, 5 out of 6 were discontinued early in the open-label Phase)

^a 1 patient took temazepam for insomnia, 2 patients took diazepam for back pain, and 1 patient took Xanax and Restoril for anxiety and insomnia.

^b 1 patient took alprazolam for anxiety, 1 took St. John’s wort for depression, 1 took melatonin for insomnia, and 1 took doxepin for hives

Results

Primary efficacy parameter

Time to relapse analysis

The rate of relapse observed at the end of the 24-week double-blind period in the levomilnacipran treatment group was (b) (4) compared to 21% (n=23/112) in the placebo treatment group. The total amounts of relapsed events observed were (b) (4). The number of patients who were censored from the primary efficacy endpoint analysis was (b) (4) in the levomilnacipran treatment group compared to 80% in the placebo treatment group. These rates of relapse were lower than the estimated probabilities set by the sponsor based on the sample size calculation of (b) (4) in the levomilnacipran treatment group and 38% in the placebo treatment group.

The expected population to enter randomization as per pre-specified number by the sponsor was 360, in this study however, only (b) (4) were admitted in to the randomization treatment period.

The estimated hazard ratio of (b) (4) indicated fewer patients than expected relapsed in the levomilnacipran and placebo treatment group, thus the treatment difference based on the hazard ratio was not statistically significant (p-value = (b) (4)). These results showed levomilnacipran did not prove efficacy in prevention of depression relapse, thus this was considered a failed study.

Table 48: Primary efficacy parameter: Time to relapses - double-blind ITT population (Study LVM-MD-05)

Time to relapse	LVM 40-120 mg (N = (b) (4))	Placebo (N = 112)
Number of patients relapsed, n (%)	(b) (4)	23 (21)
Number of patients censored, n (%)	(b) (4)	89 (80)
Hazard ratio (95% CI)	(b) (4)	
P-value	(b) (4)	

Source: Table 14.4.1.1; Listings 16.2.6.1.

The Kaplan-Meier curves, around 4-16 weeks, showed the relapse rates between the two treatment groups ran parallel and the difference was determined to be not statistically significant.

Figure 7: Kaplan-Meier estimates of rate of relapse during DB treatment period - Study LVM-MD-05

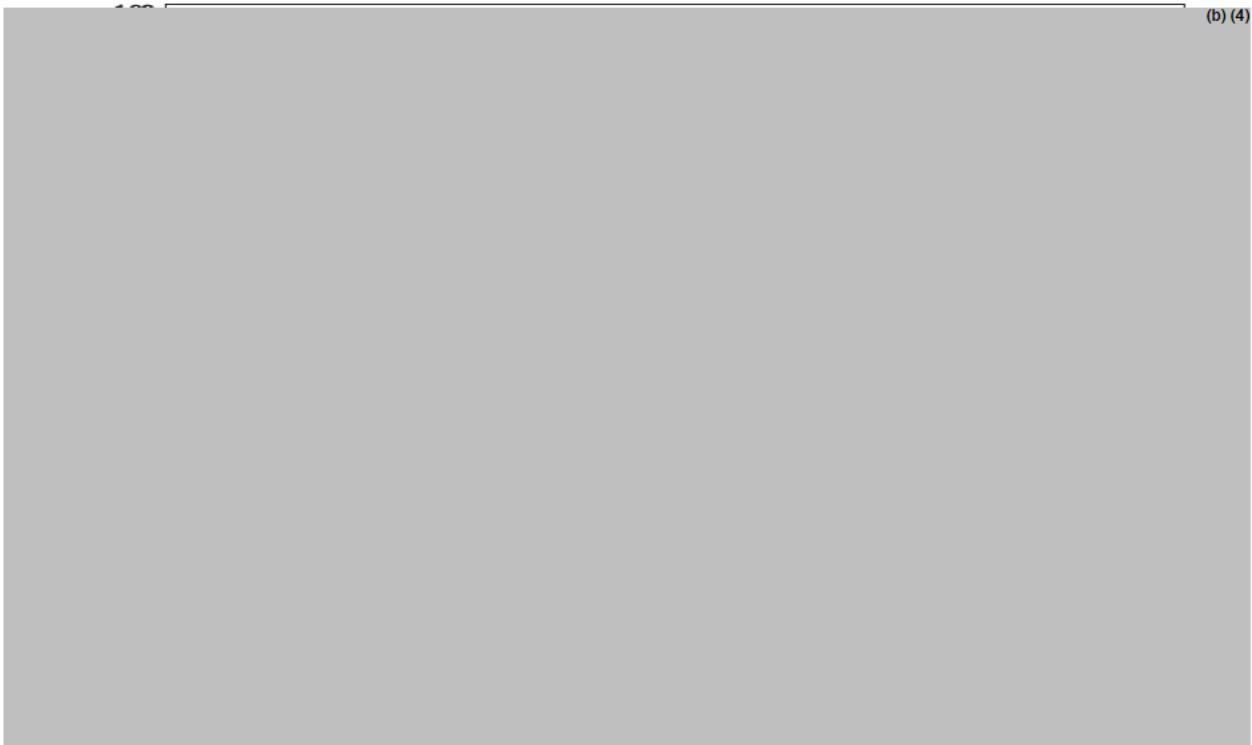


Table below summarizes the between treatment group differences for the rate of relapse in regards to treatment, dose, and relapse category during the double-blind treatment period. A (b) (4) (b) (4) of relapse was observed in the 120 mg higher dose of levomilnacipran. All ways to acquire and judge the relapse rates for various parameters were found to be comparable between the levomilnacipran and placebo treatment groups and considered not clinically significant. See table 49 below.

Table 49: Summary of relapse rates during the double-blind treatment, ITT population (Study LVM-MD-05)

	LVM (N = (b) (4)) n (%)				Placebo (N = 112) n (%)
	40 mg	80 mg	120 mg	Total	
Number of patients	(b) (4)				112
Any relapse ^a					23 (21)
MADRS ≥ 22 at 2 consecutive visits					6 (5)
Increase of ≥ 2 points in CGI-I score at 2 consecutive visits compared with CGI-I score at Visit 9 ^b					10 (9)
Premature discontinuation due to insufficient therapeutic response					12 (11)
MADRS item 10 score ≥ 4					0

Source: Table 14.4.1.2; Listings 16.2.6.1, 16.2.6.2, and 16.2.6.3.

^a Patients may have met more than one criterion of relapse, but are counted only once in the total

^b Baseline visit for the double-blind treatment period.

Exploratory analysis

On July 5, 2011 through an email communication, the Division asked the sponsor to measure responders criteria (defined as MADRS ≤12 and CGI-I ≤2 at Visit 8 and Visit 9) at all consecutive visits until randomization, sponsor should incorporate an overall longer stabilization period. The sponsor on August 31, 2011 responded that this study's enrollment from open label Phase to double-blind Phase is completed, and it is not feasible to incorporate the longer stabilization period. Through another email communication on October 4, 2011 the Division stated they then would like an additional analysis conducted to evaluate how many patients (or % of patients) met the stabilization criteria consecutively starting at week 4, week 6 or week 8. This analysis was to be performed on the double-blind ITT population using the same Cox proportional hazard-regression model as in the primary efficacy analysis, the hazard ratio was time to relapse in patients who had achieved sustained response at weeks 4, 6, or 8 (i.e., Visits 5, 6, or 7, of open label period, respectively). The sponsor conducted these analysis and results are as follows.

The results of this analysis indicated that (b) (4) of the patients in the levomilnacipran treatment group compared to the 35%, 51% and 73% of the patients in the placebo treatment group had achieved stabilization by week 4, 6 and 8, respectively. Though not clinically significant the larger difference evident at week 4 was ~35% of the patients in the placebo treatment group had obtained stabilization compared to (b) (4) patients in the levomilnacipran treatment group.

The rates of relapse for the patient groups stabilized at week 4, 6 or 8 were also analyzed as part of this exploratory analysis. The hazard ratio results did not markedly favor either placebo or levomilnacipran. See table 50 below.

Table 50: Analysis of time to relapse – exploratory analysis, double-blind ITT Population (Study LVM-MD-05)

Visit patient achieved sustained response	Placebo (n=112)		LVM (N= (b) (4))		Hazard Ratio [2]	
	n	%	n	%	Estimate (95% CI)	p-value
Week 4	8/39	21	(b) (4)			
Week 6	10/58	17				
Week 8	17/82	21				

Source: Study report p. 327, n = patients relapsed/patients who achieved s

Post-hoc analysis

Additionally, a post-hoc analysis using Cox proportional hazard model with treatment effect on different groups of patients indicated that the higher the MADRS (≥ 36) at the beginning of the study (baseline) or at open label baseline, the greater was the reduction of risk of relapse among the levomilnacipran treated patients. The table 51 below indicates the placebo and levomilnacipran populations were comparable based on the baseline efficacy characteristics.

Table 51: Post-hoc Analysis: Relapse rate by MADRS at Screening and Open-label Baseline (Study LVM-MD-05)

MADRS Score at Screening(V1) and at Open label Baseline (V2)	Placebo n1/ N1 (%)	LVM 40-120 mg/d, n1/ N1 (%)	Hazard Ratio	
			Estimate (95% CI)	p-value
≥ 26	16/82 (19.5)			(b) (4)
≥ 28	14/70 (20)			
≥ 30	13/53 (24.5)			
≥ 32	10/39 (25.6)			
≥ 34	6/25 (24.0)			
≥ 36	5/13 (38.5)			

n1 = number of patients who relapsed; N1 = number of patients with MADRS that met the criterion at Screening (V1) and at open-label baseline (V2)
 Source: Table 14.4.1.5.

Additional efficacy variable

The results tables are listed in the Appendix 9.4.

Reviewer’s comments

This study’s main objective was to assess the rates of depression relapse in patients with MDD. The primary efficacy parameter was the time to relapse from randomization to double-blind treatment period.

In my opinion the initial inclusion criteria and rating scale cut off scores (MADRS and CGI-I) utilized for the enrollment into the open label Phase, the responder/stability criteria, the randomization criteria, the relapse criteria, the 12-week open label design period, and the 24-week double blind randomized Phase all seemed appropriate and comparative with other relapse prevention study designs of the approved antidepressant drugs.

Based on the Kaplan-Meier estimates the relapse prevention study results showed that time to relapse (b) (4) in the levomilnacipran treatment group than in the placebo treatment group; however it was not large enough of a difference for it to be statistically significant.

The sponsor expected the randomized ITT analysis to include 360 patients, though only (b) (4) to were randomized, per Dr. Birkner’s review this decreased number of patients enrolled did not alter the statistical power of the study results.

There were a few limitations in this study that attributed to its failed study status. One of the possible shortcomings was that this study was not adequately statistically powered. The expected relapse rate set by the sponsor for the placebo treatment group was at 38% and for the levomilnacipran it was at (b) (4). The sample size was calculated based on an (b) (4) difference between levomilnacipran and placebo treatment groups. The results showed that 20.5% of patients relapsed in the placebo treatment group, which was not only a lot lower relapse rate than expected but was a much lowered observed relapse rate

when compared to other antidepressant drugs. In the levomilnacipran treatment group, (b) (4) patients relapsed, which is a comparable rate of relapse when compared to other antidepressant drugs. This study showed an overall observed treatment difference of (b) (4) and in my opinion the main reason for failure of this study had to be a lack of robust rate of relapse observed in the placebo treatment group.

Thus, we will be asking the sponsor as one of the Postmarketing Commitments in our letter of approval to conduct another relapse prevention study in order to establish a maintenance effect with levomilnacipran.

6.3 Cross-cutting issues

6.3.1 Subpopulations

The subgroup analyses evaluated the effect of the following variables on four the positive studies (Studies LVM-MD-01,-03,-10 and F02695 LP 2 02):

- Gender (males, females)
- age (< 55 years, ≥ 55 years)
- race (white, all other races)
- baseline disease severity (< 35, ≥ 35)

Gender

The change in MADRS was smaller in males than in females in the Studies LVM-MD-10 and -03. However, this difference was not statistically significant. See table 52 below.

Table 52: Change from baseline to EOT in MADRS by gender in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02

GENDER	LVM-MD-01				LVM-MD-10			LVM-MD-03		F02695 LP 2 02	
	Placebo	40mg	80mg	120mg	Placebo	40mg	80mg	Placebo	40-120mg	Placebo	75-100mg
Males (n)	68	56	68	72	70	69	64	73	75	95	90
Change, Mean ± SD	-10.6 ± 11.3	-12.8 ± 12	-15.0 ± 11.2	-14.9 ± 11.0	-9.7 ± 9.9	-15.1 ± 10	-14.8 ± 9.4	-11.8 ± 10.9	-13.3 ± 9.9	-12.4 ± 10.0	-16.4 ± 10.4
Difference	-	-2.2	-4.4	-4.3	-	-5.4	-5.1	-	-1.6	-	-4.0
Females (n)	107	120	109	104	115	116	123	141	140	182	186
Change, Mean ± SD	-11.0 ± 12.4	-13.7 ± 12	-13.9 ± 11.8	-13.7 ± 11.2	-11.3 ± 9.6	-12.2 ± 10	-12.4 ± 10.6	-11.2 ± 10.9	-14.0 ± 10.5	-13.0 ± 9.9	-17.3 ± 10.2
Difference	-	-2.7	-2.9	-2.7	-	-0.9	-1.1	-	-2.9	-	-4.3

Source: Table 1.1 in Appendix 13.2.

Analysis on ITT Population

EOT – End of Treatment

Age

The change in MADRS was smaller in ≥ 55 years old group in all the studies except one (Study LVM-MD-03) where the change in ≥ 55 years old group was -4.3 and -1.8 in < 55 years old group. However, this difference was not statistically significant as the sample size for ≥ 55 years old group was smaller. Inclusion age of 18-78 years old listed for Study LVM-MD-03 was the oldest, and the two oldest participants in all of these pivotal studies were both 76 year olds. See table 53 below

Table 53: Change from baseline to EOT in the MADRS by age in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02

AGE	LVM-MD-01				LVM-MD-10			LVM-MD-03		F02695 LP 2 02	
	Placebo	40mg	80mg	120mg	Placebo	40mg	80mg	Placebo	40-120mg	Placebo	75-100mg
< 55 years	152	139	142	154	148	150	148	163	158	215	210
Change, Mean \pm SD	-10.8 \pm 12	13.4 \pm 12	-14.4 \pm 12	-14.5 \pm 11	-10.4 \pm 10	-13.4 \pm 10	-13.1 \pm 10	-11.8 \pm 11	-13.6 \pm 10	-12.7 \pm 10	-17.1 \pm 10
Difference	-	-2.6	-3.6	-3.7	-	-3.0	-2.8	-	-1.8	-	-4.4
≥ 55 years	23	37	35	22	37	35	39	51	57	62	66
Change, Mean \pm SD	-11.3 \pm 13	13.5 \pm 10	-14.1 \pm 11	-12.0 \pm 13	-11.9 \pm 9	-13.0 \pm 10	-13.5 \pm 10	-10.1 \pm 10	-14.4 \pm 10	-13.2 \pm 9	-16.7 \pm 10
Difference	-	-2.2	-2.8	-0.7	-	-1.0	-1.5	-	-4.3	-	-3.5

Source: Table 1.2 in Appendix 13.2.

Analysis on ITT Population

Race

Overall, the mean reduction in MADRS was numerically higher in white patients, although the sample size in the 'all other races' was much smaller. See table 54 below.

Table 54: Change from baseline to EOT in MADRS by race in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02

RACE	LVM-MD-01				LVM-MD-10			LVM-MD-03		F02695 LP 2 02	
	Placebo	40mg	80mg	120mg	Placebo	40mg	80mg	Placebo	40-120mg	Placebo	75-100mg
White	133	131	128	128	134	141	139	180	176	251	253
Change, Mean \pm SD	-11.1 \pm 12	14.1 \pm 12	-15.1 \pm 12	-14.9 \pm 11	-10.3 \pm 10	-13.9 \pm 10	-13.3 \pm 10	-11.1 \pm 11	-14.3 \pm 10	-12.8 \pm 10	-17.5 \pm 10
Difference	-	-3.1	-4.0	-3.8	-	-3.6	-3.0	-	-3.2	-	-4.6
Other Races	41	45	49	48	51	44	48	24	29	26	23
Change, Mean \pm SD	-9.9 \pm 13	11.3 \pm 12	-12.3 \pm 10	-12.4 \pm 11	-11.7 \pm 9	-11.5 \pm 11	-12.9 \pm 11	-12.7 \pm 11	-11.3 \pm 10	-12.3 \pm 12	-11.9 \pm 15
Difference	-	-1.4	-2.3	-2.5	-	0.3	-1.1	-	1.4	-	0.4

Source: Table 1.3 in Appendix 13.2.

Analysis on ITT Population

MADRS

Overall, the mean reduction in MADRS was numerically higher in patients with more severe depression (MADRS \geq 35).

Table 55: Change from baseline to EOT in MADRS by baseline MADRS in Studies LVM-MD-01, -03,-10 and Study F02695 LP 2 02

MADRS	LVM-MD-01				LVM-MD-10			LVM-MD-03		F02695 LP 2 02	
	Placebo	40mg	80mg	120mg	Placebo	40mg	80mg	Placebo	40-120mg	Placebo	75-100mg
Baseline MADRS < 35	83	73	64	64	151	161	153	100	115	241	232
Change, Mean \pm SD	-11.7 \pm 12	-13.9 \pm 12	-15.2 \pm 10	-12.9 \pm 10	-10.3 \pm 10	-12.9 \pm 10	-13.1 \pm 10	-10.7 \pm 10	-13.2 \pm 10	-12.3 \pm 10	-15.9 \pm 10
Difference	-	-2.2	-3.5	-1.2	-	-2.6	-2.8	-	-2.5	-	-3.6
Baseline MADRS \geq 35	92	103	113	112	34	24	34	114	100	36	44
Change, Mean \pm SD	-10.1 \pm 12	-13.1 \pm 12	-13.8 \pm 12	-15.0 \pm 12	-12.5 \pm 11	-15.9 \pm 13	-13.6 \pm 11	-12.0 \pm 11	-14.5 \pm 11	-15.7 \pm 12	-22.7 \pm 12
Difference	-	-3.0	-3.8	-4.9	-	-3.4	-1.1	-	-2.5	-	-7.0

Source: Table 1.4 in Appendix 13.2.
Analysis on ITT Population, (LOCF)

An analysis by geographic region is not warranted since all studies, besides the supportive Phase 2 study, were conducted in the US and Canada regions. Overall, it appears that a greater sample size yields a more favorable levomilnacipran outcome.

6.3.2 Analysis of Clinical Information Relevant to Dosing Recommendations

In the pivotal trials, the sponsor evaluated the efficacy of 40-120 mg dose range of levomilnacipran. The recommended dosing range for levomilnacipran is 40-120 mg. Titration should be initiated at 20 mg once a day for 2 days, and based on efficacy and tolerability; levomilnacipran may then be increased in increments of 40 mg every 2 days. The maximum recommended dose is 120 mg once daily. This recommended dosing titration is based on how the drug was doses in the clinical trials.

The sponsor states that the fixed-dose Study LVM-MD-01 was not powered to demonstrate differences between the different doses. However, there were numerical treatment differences observed with LSMD mean change at -3.23, -3.99 and -4.86 at the different doses of levomilnacipran 40, 80 and 120 mg, establishing a dose-dependent efficacy. For the other fixed dose Study LVM-MD-10, the treatment differences observed with LSMD mean change were -3.30 and -3.14 at the levomilnacipran 40 and 80 mg, respectively with no clear dose dependency observed.

In Study LVM-MD-03, based on efficacy and tolerability, 21%, 34% and 44% patients were titrated to the final dose of 40 mg, 80 mg and 120 mg/day.

In Study F02695 LP 2 02, based on efficacy and tolerability, 28% received the 75 mg dose and 72% patients received the 100 mg/day dose.

Table 56: Efficacy results from three pivotal (Studies LVM-MD-01, -10, and -03) and 1 supportive study (Study F02695 LP 2 02)

Study	Levomilnacipran, mg/day			
	40	80	120	Flexible dose
LVM-MD-01	-3.23*	-3.99**	-4.86***	-
LVM-MD-10	-3.30**	-3.14**	-	-
LVM-MD-03 (Dose 40-120 mg/day)	-	-	-	-3.10**
F02695 LP 2 02 (Dose 75-100 mg/day)	-	-	-	-4.2***

* p < 0.05, ** p < 0.01, *** p < 0.001

6.3.3 Discussion of Persistence of Efficacy and/or Tolerance Effects

The three pivotal Studies LVM-MD 01, -03, and -10 were of 8 week’s duration and in my opinion, were not designed to assess the persistence of efficacy and/or tolerance effects.

Study LVM-MD-05, a randomized withdrawal study was conducted to evaluate the safety and efficacy of levomilnacipran relative to placebo in the prevention of depression relapse in adult patients with MDD; however, this study failed. The estimated hazard ratio indicated a reduced risk of relapsing for the levomilnacipran group, and the treatment difference based on the hazard ratio was not statistically significant.

There is data from the supportive Study F02695 LP 2 02 that supports efficacy, safety and tolerability of Levomilnacipran 75-100 mg/day for up to 10 weeks suggestive of additional benefit with slightly longer term treatment.

In conclusion, the efficacy of levomilnacipran has not been demonstrated beyond 8 weeks.

6.3.4 Additional Efficacy Issues/Analyses

In Study F02695 LP 2 02 sponsor had conducted a Rebound Data and Cardiovascular History Data subset analysis, results of these analysis are in the Appendix under Study F02695 LP 2 02 section.

It is not apparent from the trials conducted for MDD by the sponsor, that the lowest effective dose has been identified. I was unable to locate any data from PET receptor studies in this submission – you need to say why that is important or what you were looking for. As some adverse events are dose-related, we would request the sponsor to further characterize the efficacy and safety of levomilnacipran in the treatment of adults with MDD with 20 mg levomilnacipran dose compared to placebo in an adequate well controlled trial.

As stated in the Study LVM-MD-05 reviewer’s comments section above, the Division would be asking the sponsor to conduct another randomized withdrawal design study to gain insight into longer term efficacy data and maintenance potential of levomilnacipran.

7 Review of Safety

The primary reviewer, Kavneet Kohli-Chhabra M.D., was unable to complete the entire clinical review. On June 4, 2013, Tiffany Farchione, M.D. was assigned to complete certain sections of this NDA review. Sections 7, 9.1, and 9.2 below reflect Dr. Farchione's extensive edits and additions, both in content and format, to Dr. Kohli-Chhabra's initial review draft.

Safety Summary

This safety review focuses primarily on findings of five short term, placebo-controlled, Phase 3 studies. Four of these studies were conducted in the United States and Canada (LVM-MD-01, LVM-MD-02, LVM-MD-03, LVM-MD-10); an additional study was conducted in Europe, South Africa, and India (F02695 LP 2 02).

The sponsor has also submitted data from a long-term, open-label study (LVM-MD-04) and a relapse-prevention study (LVM-MD-05); these subjects are included in the overall safety population. In addition, the sponsor submitted data from several early Phase clinical pharmacology and biopharmaceutic studies in healthy subjects. For the purposes of this review, information regarding adverse events at the more serious end of the spectrum (deaths, non-fatal serious adverse events, and adverse events that led to dropout) from the Phase I, long-term, and relapse prevention studies was examined.

A total of 2655 subjects were exposed to levomilnacipran in the clinical development program for the treatment of Major Depressive Disorder. In the controlled, short-term trials 1583 patients were exposed to levomilnacipran. The total levomilnacipran exposure in clinical studies was 899.5 patient-years. Six hundred ninety-one patients were exposed for at least 24 weeks, with 324 patients exposed for at least 48 weeks.

Short-term treatment with levomilnacipran appears to have been reasonably safe in the MDD population studied, with an adverse event profile generally similar to those seen in other SNRIs.

Deaths

Two deaths were reported, both outside the treatment periods. One occurred prior to the patient receiving any study drug. The other did not appear to be related to levomilnacipran.

Non-Fatal Serious Adverse Events

In short-term trials, there were 35 non-fatal serious adverse events (SAEs) affecting a total of 25 individual patients. Approximately 0.07% of the patients receiving levomilnacipran in short-term studies experienced a non-fatal serious adverse event, compared to 1.3% of patients receiving placebo. Of the 11 patients on active drug who experienced SAEs in the double-blind period, four experienced events that were deemed drug-related by the sponsor. SAEs considered levomilnacipran-related included aggression, suicidal ideation, seminal vesiculitis, prostatitis, hypertension, non-cardiac chest pain, premature baby, and small for dates baby. Six of these 11 patients were discontinued from the study; and additional two temporarily discontinued treatment.

Discontinuations/Dropouts due to Adverse Events

In short term trials, approximately 9% of levomilnacipran treated patients discontinued secondary to adverse events (AEs) compared with 3% of patients in the placebo treatment group. In the two fixed-dose

trials, no dose-relatedness in discontinuations was observed for AEs. The treatment emergent adverse events (TEAEs) leading to discontinuation were predominantly gastrointestinal events, with most frequent being nausea (1.5%) and vomiting (0.8%). There were 17 patients who discontinued in the levomilnacipran treatment group secondary to combined urinary disorders. Six patients (0.4%) discontinued in the levomilnacipran treatment group secondary to rash, two of these patients had a history of hypersensitivity. Most of the rashes were considered mild or moderate, and no cases of Stevens - Johnson syndrome or angioedema were reported.

Common Adverse Events

The most common adverse events ($\geq 5\%$ and 2x placebo) in short term studies of levomilnacipran were: nausea (17.1% in levomilnacipran vs. 4.1% in placebo), constipation (8.5% vs. 3.0%), hyperhidrosis (8.5% vs. 1.1%), erectile dysfunction (5.7% vs. 2.2%), heart rate increased (5.7% vs. 0.8%), tachycardia (4.9% vs. 1.7%), vomiting (4.8% vs. 0.6%), and palpitations (4.7% vs. 0.8%).

Examining dose-relatedness of adverse events, urinary hesitation and erectile dysfunction were reported with increasing frequency at higher doses. In addition to these findings, it appears there may be some dose dependency for potentially clinically significant weight gain.

Laboratory Analysis

In the short term studies, no patients met Hy's law criteria for potential drug-induced liver injury or had ALT or AST $\geq 3 \times$ upper limit of normal (UNL) and total bilirubin ≥ 1.5 UNL. A higher incidence of potentially clinically significant (PCS) values was noted for some liver function parameters. These increases were rarely sustained and returned to baseline levels while the patient continued on levomilnacipran treatment. The mean increases in ALT, AST, and alkaline phosphatase were slightly higher in the levomilnacipran-treated patients relative to those observed in placebo treated patients. Based on data from the fixed-dose studies, the increase does not appear to be dose-dependent. One patient was prematurely discontinued from the study due to abnormal liver function tests.

In short term trials, changes in the levomilnacipran-treated patients were similar to that in the placebo group for both glucose and total cholesterol. In addition, there was no dose-dependent change in post-baseline fasting glucose status among levomilnacipran-treated patients. One patient was discontinued from the long term open-label trial (LVM-MD-04) due to elevated blood glucose.

No clinically meaningful trends were observed in serum potassium levels. Two patients experienced TEAEs associated with PCS increases in potassium; one of these patients was discontinued from LVM-MD-03 for other adverse events occurring at the same time as the hyperkalemia; elevated potassium was not cited as a reason for discontinuation.

No other clinically meaningful trends were observed in clinical laboratory results over time in short term trials.

Vital Signs

As expected for an SNRI, the mean change from baseline to the end of treatment for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate showed an increase mean change for levomilnacipran compared to placebo. No dose-dependent relationship to blood pressure changes was observed in the fixed-dose studies. Six levomilnacipran-treated patients were discontinued for BP increase or hypertension.

In the fixed-dose studies, a greater mean increase in heart rate was observed in the levomilnacipran 120-mg dose group (9.1 bpm) relative to lower-dose levomilnacipran groups (7.2 bpm increase in both treatment arms). The sponsor concluded that no consistent pattern was observed, suggesting that these changes are not dose-responsive. However, a more conservative interpretation suggests that these changes may reflect a positive dose-response relationship. No dose-response relationship in heart rate increase was observed in the thorough QT study. Nine patients in the levomilnacipran group were prematurely discontinued for TEAEs of tachycardia or heart rate increase.

The mean change from baseline to study endpoint in body weight was a decrease of 0.59 kg for levomilnacipran-treated patients and an increase of 0.02 kg for placebo-treated patients. In short term studies, PCS changes in weight (> 7% increase or decrease) were similar between the 2 treatment groups. In the fixed-dose studies, more patients in the levomilnacipran 120 mg/day group met PCS criteria for weight increase: 0.3% in 40 mg/day group, 0.5% in 80 mg/day group, and 1.7% in 120 mg/day group. No discontinuations due to weight changes are described in the Integrated Summary of Safety.

Electrocardiogram

The sponsor conducted a thorough QT study, which was reviewed by the Interdisciplinary Review Team (IRT) for QT Studies. Overall, the IRT team concluded that a significant, but modest, QTc prolongation effect was detected. In contrast to the IRT review, the sponsor concluded that levomilnacipran did not appear to have a clinically significant impact on the QTc interval. The differences in these conclusions appear to be based on the type of QTc corrections used.

Drug-Demographic Interactions

Female patients experienced nausea (20.9%) at approximately twice the rate of male patients (10.6%). The incidence for palpitation was higher in the < 55 years population, while the incidence for hyperhidrosis was higher in ≥ 55 years.

Drug-Disease Interactions

Moderate and severe renal impairment increased exposure (AUC) of levomilnacipran by 92% and 180%, respectively when compared with subjects with normal renal function. 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.

Drug-Drug Interactions

Co-administration with ketoconazole caused statistically significant increases in C_{max} (39%) and AUC_{0-∞} (57%), delayed the T_{max} for 2 hours, and had no effect on the T_{1/2} of levomilnacipran. Levomilnacipran dose should not exceed 80 mg when co-administered with ketoconazole or other strong inhibitors of CYP3A4.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review is focused on the safety of levomilnacipran 40 to 120 mg/day for the treatment of adult patients with major depressive disorder as derived from five short term, placebo-controlled studies. Four of these studies were conducted in the United States and Canada (LVM-MD-01, LVM-MD-02, LVM-MD-03, LVM-MD-10); an additional study was conducted in Europe, South Africa, and India (F02695 LP 2 02). For purposes of this review, the phrase “short term studies” (or variations thereof) will refer to these five studies. A total of 1583 patients received levomilnacipran in these five short term studies.

The sponsor has also submitted data from a long-term, open-label study (LVM-MD-04) and a relapse-prevention study (LVM-MD-05); these subjects are included in the overall safety population. In addition, the sponsor submitted data from several early Phase clinical pharmacology and biopharmaceutical studies in healthy subjects. For the purposes of this review, information regarding adverse events at the more serious end of the spectrum (deaths, non-fatal serious adverse events, and adverse events that led to dropout) from the Phase I, long-term, and relapse prevention studies was examined.

The data cut-off date for the Integrated Summary of Safety (ISS) was April 30, 2012. In the ISS, the sponsor grouped studies; they referred to them throughout by the assigned group number (i.e., Group 1, Group 1A, etc.). A table summarizing these groupings is included in the Appendix of this review.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. The JMP file for adverse events was reviewed with emphasis on the verbatim to preferred term coding. In general, it appeared that verbatim terms were appropriately coded to preferred terms.

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

See Section 7.1.1.

7.2 Adequacy of Safety Assessments

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

In short-term studies, for the levomilnacipran group, most patients were white (78%), female (64%), and the average patient age was approximately 43 years. Across all studies, 74-85% patients had recurrent depression by history.

Overall, 2655 patients were exposed to 40-120 mg/day dose of levomilnacipran for a total of 899.5 patient-years. Six hundred ninety-one patients were exposed for at least 24 weeks, with 324 patients exposed for at least 48 weeks. Using ICH E1 exposure guidelines, the overall exposure is considered adequate.

7.2.2 Explorations for Dose Response

Explorations for dose-response focused on data from fixed-dose trials. Two of the three pivotal clinical trials included fixed dose designs evaluating two or more doses of levomilnacipran compared to placebo:

LVM-MD-01: 40, 80, or 120 mg/day levomilnacipran, or placebo (1:1:1:1)

LVM-MD-10: 40 or 80 mg/day levomilnacipran, or placebo (1:1:1)

Throughout the clinical development program, more AEs and discontinuations were reported with higher doses of levomilnacipran. Two AEs showed dose-relatedness—the incidence of urinary hesitancy and erectile dysfunction were higher as the dose increased.

For additional details, see the corresponding safety sections of this review.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The clinical trials program included usual routine safety assessments at screening, baseline, at various time points during studies and at the end of study. Safety assessments comprised adverse event (AE) recording, clinical laboratory evaluations (see Table 57 below. Source: LVM-MD-01 Clinical Study Report, page 55, Table 9.5.1.4.6-1). Identical tables are found in the study reports from LVM-MD-02 and LVM-MD-03), vital signs (including orthostatic blood pressure and body weight), ECG, physical examination, and the Columbia–Suicide Severity Rating Scale. One of the short-term clinical studies (LVM-MD-02) also included assessment of sexual dysfunction using the Arizona Sexual Experiences (ASEX) scale.

The clinical laboratory evaluations in studies LVM-MD-10 and F02695-LP2-02 differed slightly from those in the other short-term studies. In addition to the evaluations in Table 58, LVM-MD-10 also included gGTP, magnesium, and HIV screening in the clinical laboratory evaluation. F02695-LP2-02 included the hematology studies listed below, but did not include urinalysis. Chemistry included AST, ALT, alkaline phosphatase, gGTP, cholesterol, triglycerides, sodium, potassium, creatinine, and glucose. Other labs included only serum pregnancy and urine drug screen.

Table 57: Clinical laboratory tests

<i>Hematology</i>	<i>Chemistry</i>	<i>Urinalysis</i>	<i>Other</i>
Hematocrit	Albumin	Blood	Hepatitis screen ^b
Hemoglobin	Alkaline phosphatase	Glucose	Pregnancy test ^c
Platelet count	ALT	Ketones	Thyroid-stimulating hormone, T3, free T4 levels ^d
RBC count/indices ^a	AST	pH	Urine drug screen ^e
WBC count/differential	Bilirubin, total	Protein	
	BUN	Specific gravity	
	Calcium		
	Chloride		
	Cholesterol		
	Creatinine		
	Glucose		
	Potassium		
	Total protein		
	Sodium		

- a Included mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- b Included hepatitis–C virus antibody, hepatitis–B surface antigen, and hepatitis–B core antibody total at Visit 1 (Screening). Reflex hepatitis–B core antibody IgM was measured for all hepatitis–B core antibody total positive or reactive results. Positive test results were sent for confirmation testing.
- c A serum human chorionic gonadotropin pregnancy test was conducted in women of childbearing potential at Visit 1 (Screening), Visit 5, and Visit 7. Positive results on the pregnancy test at Visit 1 excluded patients from participating in the study. Positive results at Visit 5 resulted in patient termination from the study.
- d Performed at Screening (Visit 1) only.
- e Urine drug screening was scheduled at Visit 1 (Screening), Visit 5, and Visit 7/ET. A negative urine drug screen for prohibited substances was required before Visit 2 (Baseline) and at Visit 5 for the patient to continue in the study.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell

In addition to the standard 12-lead ECG performed for all patients, a separate thorough QT study was also conducted (LVM-PK-07).

7.2.5 Metabolic, Clearance, and Interaction Workup

The key findings of the Clinical Pharmacology review are summarized below:

- For patients with moderate renal impairment (Clcr: 30-59ml/min), the dose of levomilnacipran should not exceed 60 mg daily.
- For patients with severe renal impairment (Clcr: <30ml/min), the dose of levomilnacipran should not exceed 40 mg daily.
- Levomilnacipran exposure increased by about 30% in patients with severe hepatic impairment compared to subjects with normal hepatic function.
- Dose adjustment is not recommended for patients with hepatic impairment, but caution should be used when dosing in patients with severe hepatic impairment (Child Pugh C: 10 - 15).
- Levomilnacipran dose should not exceed 80 mg when levomilnacipran is co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole).

- Levomilnacipran can be taken with or without food.
- Marginal increase in QTc interval (approximately 10 ms) at both therapeutic and supratherapeutic doses was identified in a thorough QT study.

See the Clinical Pharmacology review by Kofi Kumi, Ph.D. (6/17/ 2013) for additional details. A review of key findings from the thorough QT study is presented in 7.4.5 below.

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

Some of the relevant safety issues for the class of antidepressants and, in particular, SNRIs include clinical worsening and suicide risk, activation of mania, serotonin syndrome, elevated blood pressure and heart rate, abnormal bleeding, discontinuation syndrome, hyponatremia, and mydriasis. The clinical trials included appropriate assessments for these adverse events.

Sexual dysfunction is also a relevant class safety issue for antidepressants. In four of the five short-term clinical studies, the incidence of sexual dysfunction was assessed via spontaneous reporting of adverse events. In LVM-MD-02, the sponsor included the Arizona Sexual Experiences Scale (ASEX), a five-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. However, no positive control (i.e., an SSRI known to cause sexual dysfunction) was included. In addition, the sponsor's ASEX result analysis was based on mean change from baseline in ASEX; however, the ASEX is designed to be analyzed in a categorical, not continuous, fashion. An information request was sent to the sponsor on June 25, 2013 asking the sponsor to analyze the ASEX data from LVM-MD-02 using continuous rather than categorical variables.

7.3 Major Safety Results

7.3.1 Deaths

Two deaths were reported, both outside the treatment periods. These cases are summarized below.

1. Subject 001S069, 40yo female: Patient enrolled in LVM-PK-10. She signed consent but died from accidental drowning during the study screening period prior to receiving the investigational product.
2. Subject 0160222, 54yo female: Patient was enrolled in LVM-MD-04. She received levomilnacipran for 224 days in an open label study (Study LVM-MD-04) before she discontinued secondary to SAE of gastric adenocarcinoma. Prior to enrolling in this open label study, the patient had completed Study LVM-MD-02, in which she had received placebo. Her relevant medical history included uterine leiomyoma (2003, resolved) and hypertension. She died 42 days after discontinuation from the study; the cause of death listed was gastric cancer Stage IV. This event was considered serious in nature, and not related to levomilnacipran treatment.

7.3.2 Nonfatal Serious Adverse Events

Short Term Trials

In short-term trials, there were 35 non-fatal serious adverse events affecting a total of 25 individual patients. These events are summarized in Table 58 below (adapted from Integrated Summary of Safety, Vol 1, page 83-84—Table 8.4.1-1).

Table 58: Incidence of serious adverse events in short-term clinical trials of levomilnacipran - safety population

System Organ Class, Preferred Term	Placebo (N=1040), n (%)	LVM 40-120 mg (N=1583), n (%)
Patients with any SAE	14 (1.3)	11 (0.7)
Gastrointestinal disorders		
Intussusception	0	1 (0.1)
General disorders and administration site conditions		
Chest pain	1 (0.1)	1 (0.1)
Non-cardiac chest pain	1 (0.1)	1 (0.1)
Infections and infestations		
Cytomegalovirus and mononucleosis	0	1 (0.1)
Injury, poisoning and procedural complications		
Road traffic accident	2 (0.2)	1 (0.1)
Scratch	0	1 (0.1)
Facial bones fracture	1 (0.1)	0
Head injury	1 (0.1)	0
Open fracture	1 (0.1)	0
Traumatic liver injury	1 (0.1)	0
Investigations		
Blood pressure increased	1 (0.1)	0
Musculoskeletal and connective tissue disorders		
Back pain	0	1 (0.1)
Intervertebral disc protrusion	0	1 (0.1)
Psychiatric disorders		
Suicidal ideation	2 (0.2)	1 (0.1)
Aggression	0	1 (0.1)
Suicide attempt through an intentional overdose	0	1 (0.1)
Depression	2 (0.2)	0
Major depression	2 (0.2)	0
Depressive symptom	1 (0.1)	0
Stress	1 (0.1)	0
Reproductive system and breast disorders		
Prostatitis	0	1 (0.1)
Seminal vesiculitis	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders		
Asthma	1 (0.1)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.1)	0
Vascular disorders		
Deep vein thrombosis	0	1 (0.1)

Table 59 below (source: Integrated Summary of Safety, Vol 1, pages 85-88, Table 8.4.1-2) provides additional details for all SAEs, and includes patients on active treatment and placebo. Of note, this table

contains more SAEs than listed in the previous table. The additional SAEs occurred either prior to dosing or during the down-taper period.

Table 59: List of patients with SAEs in short-term clinical trials of levomilnacipran - safety population

<i>PID No. (Age/Sex)</i>	<i>Treatment Group</i>	<i>Treatment Duration (Days)^a</i>	<i>SAE Start/ Stop Day^b</i>	<i>Preferred Term/ Investigator Term</i>	<i>Intensity/ Relationship</i>	<i>Action Taken</i>
Post-randomization period (No investigational product taken)						
<i>LVM-MD-01</i>						
0130127 (62/M) ^c	LVM 80 mg/day	0	UNK	Coronary arterial stent insertion / cardiac stent procedure	Severe/N	Discontinued
Double-blind treatment period						
<i>LVM-MD-01</i>						
0230119 (50/F)	LVM 40 mg/day	60	50/92	Chest pain / chest pain	Severe/N	IP temporarily stopped
			50/53	Deep vein thrombosis / Deep vein thrombosis	Severe/N	IP temporarily stopped
0300175 (26/M)	LVM 40 mg/day	14	11/11	Aggression / violent outburst	Severe/Y	Discontinued
0380101 (25/F)	LVM 80 mg/day	56	53/55	Cytomegalovirus mononucleosis / cytomegalovirus/ mononucleosis	Severe/N	None
<i>LVM-MD-02</i>						
0120207 (51/F)	Placebo	55	34/36	Blood pressure increased/ Elevated blood pressure	Moderate/N	None
			34/34	Chest pain/ Atypical chest pain	Moderate/N	None
<i>LVM-MD-03</i>						
0520311 (39/F)	Placebo	39	42/54	Non-cardiac chest pain / "Chest and torso pain" was non cardiac in nature	Severe/N	Discontinued
0550326 (39/F)	Placebo	29	30/Ongoing	Head injury/ Head injury	Severe/N	Discontinued
				Road traffic accident/ 4-Wheeler accident	Severe/N	Discontinued
				Traumatic liver injury/ Liver laceration	Severe/N	Discontinued
0720332 (54/F)	Placebo	21	14/14	Asthma/Asthma flare	Severe/N	Discontinued
				Chronic obstructive pulmonary disease/COPD flare	Severe/N	None

Table 59: List of patients with SAEs in short-term clinical trials of levomilnacipran - safety population (con't.)

<i>PID No. (Age/Sex)</i>	<i>Treatment Group</i>	<i>Treatment Duration (Days)^a</i>	<i>SAE Start/ Stop Day^b</i>	<i>Preferred Term/ Investigator Term</i>	<i>Intensity/ Relationship</i>	<i>Action Taken</i>
0670303 (32/F)	LVM 40-120 mg/day	8	9/9	Intentional overdose/ Intentional overdose	Severe/N	Discontinued
			9/9	Suicide attempt/Suicide attempt	Severe/N	Discontinued
0660324 (22/M)	LVM 40-120 mg/day	39	51/ Ongoing	Back pain/Back pain	Moderate/N	None
			51/54	Road traffic accident/ Motor vehicle accident	Severe/N	None
			51/ Ongoing	Scratch/Scratches	Moderate/N	None
LVM-MD-10						
0261001 (23/M)	Placebo	54	19/38	Facial bones fracture/Left-sided facial/orbital fractures	Moderate/N	None
			19/19	Road traffic accident/traumatic bicycle accident	Moderate/N	None
0281002 (67/M)	LVM 40 mg/day	55	4/4	Non-cardiac chest pain/chest pain syndrome (non-cardiac)	Severe/N	Study drug stopped temporarily
0551024 (48/F)	LVM 40 mg/day	30	27/31	Intussusception/ intussuception	Severe/N	Discontinued from study
0601023 (60/F)	LVM 40 mg/day	13	13/ongoing	Asthma/episodic asthma	Moderate/N	Discontinued from study
F02695 LP 2 02						
010808 (49/F)	Placebo	15	17/ongoing	Suicidal ideation/worsening with suicidal ideas	Severe/Y	Discontinued from study
011107 (40/F)	Placebo	31	23/ongoing	Depression/worsening depression	Severe/Y	Discontinued from study
030111 (44/F)	Placebo	15	17/58	Depressive symptom/exacerbation on the depressive symptom	Severe/Y	None
040402 (60/F)	Placebo	13	12/ongoing	Depression/severe worsening of depression	Severe/Y	Discontinued from study
050409 (53/F)	Placebo	8	8/ongoing	Major depression/depression severe without psychotic features	Severe/Y	Discontinued from study

Table 59: List of patients with SAEs in short-term clinical trials of levomilnacipran - safety population (con't.)

<i>PID No. (Age/Sex)</i>	<i>Treatment Group</i>	<i>Treatment Duration (Days)^a</i>	<i>SAE Start/ Stop Day^b</i>	<i>Preferred Term/ Investigator Term</i>	<i>Intensity/ Relationship</i>	<i>Action Taken</i>
070406 (66/M)	Placebo	52	53/67	Suicidal ideation/suicidal tendency	Severe/Y	Discontinued from study
090305 (59/F)	Placebo	70	71/ongoing	Major depression/major depressive episode	Severe/N	Discontinued from study
100209 (54/F)	Placebo	62	62/ongoing	Stress/stress	Severe/N	Discontinued from study
110201 (30/F)	Placebo	71	26/ongoing	Open fracture/open fracture of tibia	Moderate/N	None
080501 (58/F)	LVM 75-100 mg/day	14	14/ongoing	Suicidal ideation/suicidal ideation	Severe/Y	Discontinued from study
080703 (41/M)	LVM 75-100 mg/day	57	54/unlk	Prostatitis/prostatitis	Moderate/Y	None
			54/unlk	Seminal vesiculitis/seminal vesiculitis	Moderate/Y	None
110104 (43/F)	LVM 75-100 mg/day	49	50/53	Intervertebral disc protrusion/prolapsed disc L5/L6 intervertebral disc protrusion	Severe/N	Discontinued from study
Down-taper treatment period						
LVM-MD-01						
0090114 (35/F)	Placebo	55	75/132	Pneumonia / Pneumonia	Severe/N	None
0270152 (29/F)	LVM 40-mg	57	67/67	Suicide attempt / Aborted suicide attempt	Severe/N	None
LVM-MD-03						
0640304 (53/M)	LVM 40-120 mg	56	71/72	Hypertension/ Hypertension	Severe/Y	None
			70/72	Non-cardiac chest pain/ Non cardiac chest pain	Severe/Y	None
0660308 (24/F)	LVM 40-120 mg	55	78/80	Suicidal ideation/Suicidal ideations	Moderate/N	None

Table 59: List of patients with SAEs in short-term clinical trials of levomilnacipran - safety population (con't.)

<i>PID No. (Age/Sex)</i>	<i>Treatment Group</i>	<i>Treatment Duration (Days)^a</i>	<i>SAE Start/ Stop Day^b</i>	<i>Preferred Term/ Investigator Term</i>	<i>Intensity/ Relationship</i>	<i>Action Taken</i>
<i>Post-study</i>						
0120167 (25/F) ^d	LVM 120-mg	59	—	Premature baby / Premature baby	—/Y	None
				Small for dates baby / Premature birth weight	—/Y	
0310118 (35/F)	LVM 80-mg	31	184/283	Pre-eclampsia / Pre-eclampsia	Moderate/N	None

a Treatment duration = date of last dose of double-blind IP – date of first dose of double-blind IP + 1.

b AE start (stop) day = start (stop) date of AE – date of first dose of double-blind IP + 1.

c Patient was randomized but did not take double-blind investigational product.

d PID 0120167 was prematurely discontinued due to pregnancy. After discontinuation, AEs of drug exposure during pregnancy and premature delivery were reported. After database lock, she prematurely delivered a baby boy who remained hospitalized due to SAEs of premature baby and small for dates baby. Intensity category for these SAEs was not assessed.

AE = adverse event; F = female; IP = investigational product; LVM = levomilnacipran; M = male; N = the relationship to IP is unlikely or nonexistent; NA = not applicable; PID = patient identification; SAE = serious adverse event; UNK = unknown; Y = there is possible or probable relationship to IP.

Approximately 0.07% of the patients receiving levomilnacipran in short-term studies experienced a non-fatal serious adverse event, compared to 1.3% of patients receiving placebo. Of the 11 patients on active drug who experienced SAEs in the double-blind period, four experienced events that were deemed drug-related by the sponsor. Six of these 11 patients were discontinued from the study; and additional two temporarily discontinued treatment.

SAEs considered levomilnacipran-related included aggression, suicidal ideation, seminal vesiculitis, prostatitis, hypertension, non-cardiac chest pain, premature baby, and small for dates baby. Cases of depression and an additional case of suicidal ideation were considered placebo-related. A more detailed review of suicidal ideation and behavior data is presented in 7.7.1.

Among the additional six patients who experienced SAEs outside the double-blind period, two experienced events that were deemed drug-related by the sponsor (hypertension/non-cardiac chest pain, and premature baby/small-for-dates baby). Three of these six patients were discontinued from the study.

Table 60 below summarizes Dr. Kohli-Chhabra’s review of the case narratives of these SAEs, focusing solely on patients who received the active drug.

Table 60: Dr. Kohli-Chhabra’s review of the case narratives of the SAEs of patients who received the drug

Study/ ID/ Age/Sex	Treatment Group	Preferred Term	Comments
SAEs Occurring During the Double-Blind Treatment Period			
LVM-MD-01/ 0230119/50/F	LVM 40 mg	Chest pain Deep vein thrombosis	Pt underwent phlebotomy, got DVT, hospitalized, two days later DVT resolved
LVM-MD-01/ 0300175/26/M	LVM 40 mg	Aggression	H/O of anger outbursts
LVM-MD-01/ 0380101/25/F	LVM 80 mg	Cytomegalovirus mononucleosis	Pre-CM infection, pt had influenza virus
LVM-MD-03/ 0670303/32/F	LVM 40-120 mg	Intentional overdose / Suicide attempt	H/o of prior suicidal attempts, she took 15-20 capsules of 500 mg acetaminophen/25 mg diphenhydramine
LVM-MD-03/ 0660324/22/M	LVM 40-120 mg	Back pain /Road traffic accident/ Scratch	Pt car was hit by a drunk driver; lost to follow up.
LVM-MD-10/ 0281002/67/M	LVM 40 mg	Non-cardiac chest pain	H/o of HTN and long standing cardiac h/o. Pain resolved once pt got to the hospital. cardiac workup was negative
LVM-MD-10/ 0551024/48/F	LVM 40 mg	Intussusception	Multiple abdominal surgery and adhesion history
LVM-MD-10/ 0601023/60/F	LVM 40 mg	Asthma	Pt had a URI led to asthma and hospitalization. Pt fully recovered
F02695 LP 2 02/ 080501/58/F	LVM 75-100 mg	Suicidal ideation	Hospitalized, only ideation had no plan
F02695 LP 2 02/ 080703/41/M	LVM 75-100 mg	Seminal vesiculitis/ Prostatitis	Pt was hospitalized and TX with IV antibiotics
F02695 LP 2 02/ 110104/43/F	LVM 75-100 mg	Intervertebral disc protrusion	Pt had surgery discectomy and cervical spine fusion
AEs Occurring Outside the Double-Blind Treatment Period			
Study/ ID/ Age/sex	Treatment Group	Preferred Term	Comments
LVM-MD-01/ Screening period/ 0130127/62/M	Randomized to LVM 80 mg	Coronary arterial stent insertion	No cardiac H/O. On placebo x 7 days. All lab work normal
LVM-MD-01/ Down taper/ 0270152/29/F	LVM 40 mg	Suicide attempt	2 prior suicide attempts, was going to overdose on Tylenol, Nyquil and alcohol, therapist intervened and she was hospitalized
LVM-MD-03/ Down taper/ 0640304/53/M	LVM 40-120 mg	Hypertension Non-cardiac chest pain	H/o of chest pain and HTN. Chest pain started at end of down taper. BP was 190/90 mmHg (supine) and 188/88 mmHg (standing).Hospitalized and tx. SAE resolved
LVM-MD-03/ Down taper/ 0660308/24/F	LVM 40-120 mg	Suicidal ideation	After fight with boyfriend, thought of overdosing on Vicodin and muscle relaxants, but she stopped herself, hospitalized
LVM-MD-01/ Post study/ 0120167/25/F	LVM 120 mg	Premature baby Small for dates baby	H/o of 2 full term pregnancies and 2 spontaneous abortions. Pt at down taper time was + for pregnancy so d/c down taper. Baby stayed in hospital for 1 month
LVM-MD-01/ Post study/ 0310118/35/F	LVM 80 mg	Pre-eclampsia	H/o of 3 pregnancies with HTN. At visit 5 preg test + Pre-eclampsia occurred 150 days after d/c tx. Labor was induced baby girl with no complications

Long Term Open-Label Trial

In the long term, open-label study (LVM-MD-04), 35 patients reported a total of 51 SAEs during the 48-week treatment period (see Table 61 below; adapted from Integrated Summary of Safety, Vol 1, pages 89-91, Table 8.4.2-1). Due to the open label design, it is difficult to draw conclusions from the safety data generated by this study. However, the adverse events reported during this study are similar to those seen in the double-blind short term trials. SAEs deemed related to study drug include mania (1 patient); chest pain (1 patient); hypertension (2 patients); angina pectoris and heart rate increased (1 patient); convulsion and encephalopathy (1 patient); supraventricular extrasystoles, tachycardia, and ventricular extrasystoles (1 patient). The majority of patients experiencing SAEs in this study were discontinued.

Table 61: Incidence of SAEs in LVM-MD-04 - safety population

Preferred Term	LVM 40-120 mg/day (N=779) n (%)
Patients with any SAE	35 (4.5)
Cardiac disorders	
Ventricular extrasystoles	2 (0.3)
Angina pectoris	1 (0.1)
Coronary artery disease	1 (0.1)
Supraventricular extrasystoles	1 (0.1)
Tachycardia	1 (0.1)
Gastrointestinal disorders	
Abdominal pain	1 (0.1)
Colitis	1 (0.1)
Inguinal hernia	1 (0.1)
General disorders and administration site conditions	
Chest pain	3 (0.4)
Pyrexia	1 (0.1)
Infections and infestations	
Appendicitis	2 (0.3)
Cellulitis pharyngeal	1 (0.1)
External ear cellulitis Mastoiditis	1 (0.1)
Otitis media acute	1 (0.1)
Pneumonia	1 (0.1)
Urinary tract infection	1 (0.1)
Injury, poisoning and procedural complications	
Overdose	2 (0.3)
Fall	1 (0.1)
Forearm fracture	1 (0.1)
Lower limb fracture	1 (0.1)
Road traffic accident	1 (0.1)
Tibia fracture	1 (0.1)
Investigations	
Heart rate increased	1 (0.1)
Metabolism and nutrition disorders	
Hypokalemia	1 (0.1)
Neoplasms benign, malignant and unspecified	
Gastric cancer stage IV	1 (0.1)
Nervous system disorders	
Convulsion	1 (0.1)
Dizziness	1 (0.1)
Encephalopathy	1 (0.1)
Hypoaesthesia	1 (0.1)
Presyncope	1 (0.1)
Psychiatric disorders	
Depression	2 (0.3)
Suicidal ideation	2 (0.3)
Suicide attempt	2 (0.3)
Aggression	1 (0.1)
Anxiety	1 (0.1)
Major depression	1 (0.1)
Mania	1 (0.1)
Suicidal behavior	1 (0.1)
Reproductive system and breast disorders	
Ovarian cyst	1 (0.1)
Respiratory, thoracic and mediastinal disorders	
Pulmonary mass	1 (0.1)
Vascular disorders	
Hypertension	2 (0.3)

Select SAEs are reviewed below, with a focus on psychiatric adverse events and those events likely related to drug.

- Subject 0110119, 21yo female: Medical history was significant for laceration and hypothyroidism. Concomitant medication at the time of study entry was levothyroxine sodium. Patient had previously been enrolled in LVM-MD-01, and received placebo. On Study Day 38 (12 Mar 2010), the patient had an SAE of mania (Investigator term: manic episode). The patient was discontinued from the study because of the event, which was considered to be severe in intensity and related to investigational product.
- Subject 0120124, 50yo female: Relevant medical history included hypercholesterolemia, hysterectomy, asthma, and gastroesophageal reflux disease. The patient also had a history of borderline hypertension since January 2010. At the time of study entry, relevant concomitant medications included albuterol, seretide, and omeprazole. Patient had previously been enrolled in LVM-MD-01, and received placebo. In study LVM-MD-04, the patient received active drug for 336 days (25 Mar 2010 to 23 Feb 2011) and open-label down-taper treatment from 24 Feb 2011 to 17 Mar 2011. On Study Day (b) (6) the patient had an SAE of chest pain (Investigator term: atypical chest pain). The event was considered to be moderate in intensity and related to investigational product. On Study Day (b) (6), the patient had an adverse event of hypertension. The event was moderate in intensity and related to investigational product.
- Subject 0350110, 40yo male: Relevant medical history included spinal and knee (bilateral) osteoarthritis and hypertriglyceridemia. Family history was positive for coronary artery disease. At study entry, the only concomitant medication was naproxen as needed for arthritis. Patient had previously been enrolled in study LVM-MD-01 in which he received placebo. Following several non-serious AEs of hypertension and one of non-cardiac chest pain during the course of the study, on Study Day (b) (6) the patient had an SAE of hypertension, which was moderate in intensity and related to investigational product. The patient presented to the emergency room with back pain; in addition, he was experiencing intermittent chest pain, headaches, and high blood pressure for the past several weeks. After evaluation and treatment, the chest pain was deemed non-cardiac. The AE of non-cardiac chest pain resolved on Study Day (b) (6). The SAE of hypertension was considered ongoing.
- Subject 0120175, 39yo female: Relevant medical history included headache, hematuria, and tubal ligation. Family history included diabetes and hypertension. At the time of study entry, relevant concomitant medications included ibuprofen and naproxen sodium. Patient had previously been enrolled in Study LVM-MD-01 in which she received active drug, 40 mg/day. On 22 Dec 2010 the patient's blood pressure was 122/72 mmHg; dosage of study drug was increased to 120 mg/day on that day. On (b) (6), the patient experienced dizziness, weakness, nausea, and blurred vision. She came to the emergency room and was admitted to the hospital. Clinical impression was uncontrolled hypertension (new onset). Primary discharge diagnoses were uncontrolled hypertension and dizziness. The dizziness resolved on 24 Dec 2010, the nausea resolved on 25 Dec 2010, and the SAE of hypertension resolved on (b) (6). Following hospital discharge, blood pressures were normal. On Study Day (b) (6) the patient had another AE of hypertension (moderate) and was discontinued from the study at that time.

- Subject 0140155, 40yo male: Relevant medical history included insomnia. The patient was not taking any relevant concomitant medications at study entry. Patient had previously been enrolled in Study LVM-MD-01 in which he received active drug, 40mg/day. Prior to the SAE and during the course of the study, this patient had experienced suicidal ideation but no behavior. On Study Day (b) (6) (b) (6) approximately 2 weeks after that last dose of investigational product, the patient had SAEs of overdose and suicide attempt. Both events were considered to be severe in intensity and not related to investigational product. The patient was discontinued from the study because of these 2 SAEs.
- Subject 0070109, 41yo female: Relevant medical history included hypertension, diabetes mellitus, and blood cholesterol increased. Concomitant medications included lisinopril, metformin, and rosuvastatin. Patient had previously been enrolled in Study LVM-MD-01 in which she received active drug, 120mg/day. On Study Day 226 (18 Nov 2010), approximately 1 month after the last dose of investigational product, the patient had an SAE of depression (Investigator term: exacerbation of depression), which was considered to be moderate in intensity and not related to investigational product. The patient was discontinued from the study because of the event.
- Subject 0180101, 51yo male: Patient had a history of violent behavior and suicidal ideation. The patient was not taking any concomitant medications. Patient had previously been enrolled in LVM-MD-01 in which he received active drug, 120mg/day. The patient experienced dysuria and testicular pain, and was ultimately discontinued due to dysuria. On Study Day 26 (06 Feb 2010), 6 days after the last dose of levomilnacipran, the patient had SAEs of aggression and suicidal ideation. Both SAEs were considered to be severe in intensity and not related to investigational product.
- Subject 0610309, 60yo female: Relevant medical history included hysterectomy, hot flush, insomnia, arthritis, hypertension, and fibromyalgia. Patient's medical history also included a hospitalization when she was 16 for drinking rat poison after a fight with her mom. At the time of study entry, relevant concomitant medications included estradiol and metoprolol, naproxen, and celecoxib. Patient had previously been enrolled in LVM-MD-03 in which she received placebo. During open-label treatment, the most severe C-SSRS assessment for suicidal ideation was 'wish to be dead'. On Study Day (b) (6) (b) (6) the patient had an SAE of suicidal behavior. Patient was admitted to the hospital. She later cited multiple psychosocial stressors and denied suicidal intent. The event was considered to be severe in intensity and not related to investigational product. The patient was discontinued from the study because of this event.
- Subject 0620336, 50yo female: Relevant medical history included hysterectomy, migraines, cholecystectomy, thyroidectomy, and bradycardia. At study entry, relevant concomitant medications included ibuprofen. Patient was previously enrolled in LVM-MD-03 and received placebo. On Study Day (b) (6) (b) (6) the patient had SAEs of angina pectoris and heart rate increased. At the time, the patient was taking 120mg/day of study drug. Both events were considered to be severe in intensity and related to investigational product. The patient was discontinued from the study because of these 2 events, and the last dose of study drug was on 18 Nov 2010.

- Subject 0670318, 23yo female: Patient had no significant medical history, and was not taking any relevant concomitant medications. Patient was previously enrolled in LVM-MD-03 and received placebo. During both LVM-MD-03 and LVM-MD-04, patient reported ongoing thoughts of suicide by overdose, with varying frequency, without a plan. From Study LVM-MD-04 Visit 2 (11 May 2011) through Visit 13 (17 Jan 2011; the last visit before her suicide attempt), she reported no suicidal ideation. On Study Day [REDACTED] (b) (6) the patient had SAEs of overdose and suicide attempt (Investigator judged the events to be life-threatening). Both events were considered to be severe in intensity and not related to investigational product. The patient was discontinued from the study because of the events.
- Subject 0710310, 76yo female: Relevant medical history included type 2 diabetes mellitus, hypercholesterolemia, and hypertension. At study entry, relevant concomitant medications included acetylsalicylic acid and metformin. Patient was previously enrolled in LVM-MD-03 and received placebo. On Study Day [REDACTED] (b) (6) the patient had SAEs of convulsion and encephalopathy. The patient had no prior history of seizures or seizure risk factors. No other explanation for the event was found. Both events were considered to be severe in intensity and related to investigational product. The patient was discontinued from the study because of these events.
- Subject 0550313, 27yo male: Patient had no relevant medical history and was on no concomitant medications. Patient was previously enrolled in LVM-MD-03 and received active drug (dose not listed in narrative). In Study LVM-MD-04, the patient received study drug for 172 days from 09 Sep 2010 to 27 Feb 2011. Dosage was titrated to 80 mg/day on 23 Sep 2010 and to 120 mg/day on 26 Feb 2011. On Study Day 173 (28 Feb 2011), the patient had SAEs of depression and suicidal ideation. Both events were considered to be severe in intensity and not related to investigational product. The patient was discontinued from the study because of these events.
- Subject 0670312, 73yo male: Relevant medical history included aortic dilatation (congenital), rheumatoid arthritis, ankylosing spondylitis, prostate cancer/radiotherapy to prostate, transurethral prostatectomy, benign right kidney cortical cysts, and, per MedWatch, hematuria, palpitations, and hypertension. Concomitant medications included methotrexate for ankylosing spondylitis/rheumatoid arthritis, folic acid, and azathioprine for rheumatoid arthritis. Patient was previously enrolled in LVM-MD-03 and received active drug, 40-120mg daily. There were no relevant AEs or ECG changes during the lead in study. In study LVM-MD-04, the patient received active drug for 20 days. On Study Day [REDACTED] (b) (6) the patient had SAEs of supraventricular extrasystoles, tachycardia, and ventricular extrasystoles. All 3 SAEs were considered to be severe in intensity and related to investigational product. The patient was discontinued from the study because of these 3 SAEs.

Relapse Prevention Study

In Study LVM-MD-05, the overall rate of SAEs in the open-label treatment group was 0.8% and none of the events occurred in more than 1 patient. In the double-blind treatment period the overall rate in the placebo arm was higher (3.6%) than the levomilnacipran arm (0.9%) and none of the events occurred in more than 1 patient (see Table 62 below. Source: Integrated Summary of Safety, Vol 1, page 95, Table 8.4.3-1). No SAEs were reported in patients in either treatment group during the double-blind down-taper period.

Table 62: Incidence of SAEs during the open-label and double-blind treatment periods of Study LVM-MD-05 - safety populations

	<i>Open-label Treatment Period</i>	<i>Double-blind Treatment Period</i>	
	<i>Levomilnacipran (40-120 mg/d) (N = 734)</i>	<i>Placebo (N = 112)</i>	<i>Levomilnacipran (40-120 mg/d) (N = 233)</i>
Patients with at least 1 SAE	6 (0.8)	4 (3.6)	2 (0.9)
Ankle fracture	1 (0.1)	0	0
Blood creatine phosphokinase MB increased	1 (0.1)	0	0
Blood pressure increased	0	1 (0.9)	0
Cellulitis	0	1 (0.9)	0
Chest pain	1 (0.1)	0	0
Cholelithiasis	1 (0.1)	0	0
Deep vein thrombosis	0	1 (0.9)	0
Drug abuse	1 (0.1)	0	0
Drug hypersensitivity	0	1 (0.9)	0
Fall	1 (0.1)	0	0
Hypertension	1 (0.1)	0	0
Intentional self-injury	1 (0.1)	0	0
Intestinal ischaemia	0	0	1 (0.4)
Non-cardiac chest pain	0	0	1 (0.4)
Pancreatitis acute	1 (0.1)	0	0
Pneumonia	0	1 (0.9)	0
Suicidal behaviour	1 (0.1)	0	0
Suicide attempt	1 (0.1)	0	0
Troponin I increased	1 (0.1)	0	0

In study LVM-MD-05, only patients who tolerated the drug in the open-label Phase were randomized into the double-blind withdrawal Phase; thus, it is difficult to draw conclusions from the safety data generated by this study. However, the adverse events reported during this study are similar to those seen in the double-blind short term trials. Select SAEs from the open-label period are reviewed below, with a focus on psychiatric adverse events and those events likely related to drug.

- Subject 0030512, 60yo female: This patient's only significant medical history was major depressive disorder. She had no history of hypertension. At the time of study entry, the patient was taking unspecified "vitamin supplements" and no other medications. Patient's blood pressure was first reported as abnormal at Visit 5 (11 May 2010), at which time BP was 136/94 mmHg. ECG and pulse were normal. BP was again elevated at Visits 6 (25 May 2010) and 7 (08 Jun 2010), and at an unscheduled visit on 18 Jun 2010. On Day 76 (28 Jun 2010), AEs of epistaxis and hypertension (SAE) were reported. Both events were considered severe in intensity and related to investigational product. The SAE of hypertension led to discontinuation from the study. On 29 Jun 2010 (end-of-study visit), ECG was abnormal. After discontinuation, the patient's BP remained elevated. On Day (b)(6) the AE of diastolic hypertension resolved and an AE of hypertension was reported. The AE is considered ongoing and on 31 Jul 2010, the patient was started on lisinopril for the hypertension. No other BP assessments were reported following the start of lisinopril treatment.
- Subject 0110526, 41yo female: Patient's medical history included esophageal spasm, for which she was taking hyoscyamine. At Visits 2 through 5, from 03 Nov 2010 to 07 Dec 2010, MADRS total scores ranged from 21-24 and item 10 (suicidal thoughts) ranged from 0-1. At each of these visits, the C-SSRS assessment was negative for suicidal ideation and suicidal behavior. On Day (b)(6) an SAE of suicidal behavior (investigator term: suicidal gesture/took several Ambien) was reported. The event was considered moderate in intensity and not related to investigational product. The event resolved on the same day and investigational product was discontinued.
- Subject 0160515, 28yo male: This patient's only significant medical history was major depressive disorder. He was not taking concomitant medications. Between screening and Visit 5 (02 Dec 2010), the patient's C-SSRS score was negative for suicidal ideation / behavior. MADRS total scores ranged from 22-24, and item 10 scores (suicidal thoughts) ranged from 0-2. On Day (b)(6) the patient had serious adverse events (SAEs) of intentional self-injury (investigator term: scratched left wrist with broken ashtray) and suicide attempt. The intentional self-injury was severe and the suicide attempt was moderate in intensity, and both were considered not related to investigational product. Both of these events led to discontinuation from the study.

Phase I Trials

Two patients experienced SAEs during the Phase I trials. These events are summarized below.

- Subject 0901018, 37yo male, Study LVM-PK-03: Patient had a medical history significant only for recurrent bronchitis. Patient received a single dose of levomilnacipran 60 mg. He subsequently experienced an SAE of appendicitis, and was hospitalized ten days after dosing. This was considered severe in intensity and not considered to be related to the study drug.
- Subject 0010018, 39yo male, Study LVM-PK-093: Patient had no relevant medical history and was on no concomitant medications. He experienced an SAE of atrial fibrillation on levomilnacipran 120 mg. The investigator rated the severity of the SAE atrial fibrillation as

moderate, and related to the investigational product. The patient prematurely discontinued from the study.

7.3.3 Dropouts and/or Discontinuations

Short Term Trials

Approximately 9% of levomilnacipran treated patients discontinued secondary to AEs compared with 3% of patients in the placebo treatment group. In the two fixed-dose trials, no dose-relatedness in discontinuations was observed for AEs. Adverse events that occurred in two or more patients in either treatment group are summarized in Table 63 below (adapted from Integrated Summary of Safety, Vol 1, pages 100-101, Table 8.5.1-1).

Table 63: Incidence of discontinuation due to AEs in short-term trials - safety population

Preferred Term	Placebo (N = 1040), n (%)	LVM 40-120 mg (N = 1583), n (%)
Overall discontinuation	33 (3.2)	139 (8.8)
Cardiac disorders		
Tachycardia	1 (0.1)	6 (0.4)
Palpitations	0	5 (0.3)
Gastrointestinal disorders		
Nausea	4 (0.4)	24 (1.5)
Vomiting	0	12 (0.8)
Constipation	0	8 (0.5)
Diarrhea	2 (0.2)	5 (0.3)
Abdominal pain upper	1 (0.1)	4 (0.3)
Abdominal pain	0	5 (0.3)
Abdominal discomfort	0	2 (0.1)
Investigations		
Blood pressure increased	2 (0.2)	3 (0.2)
Heart rate increased	0	3 (0.2)
Musculoskeletal and connective tissue disorders		
Groin pain	0	2 (0.1)
Back pain	2 (0.2)	0
Nervous system disorders		
Dizziness	1 (0.1)	7 (0.4)
Headache	1 (0.1)	6 (0.4)
Tremor	2 (0.2)	1 (0.1)
Psychiatric disorders		
Anxiety	0	7 (0.4)
Insomnia	4 (0.4)	5 (0.3)
Suicidal ideation	4 (0.4)	4 (0.3)
Agitation	1 (0.1)	4 (0.3)
Depression	2 (0.2)	3 (0.2)
Panic attack	0	2 (0.1)
Renal and urinary disorders		
Urinary hesitation	0	6 (0.4)
Urinary retention	0	6 (0.4)
Dysuria	0	5 (0.3)
Reproductive system and breast disorders		
Testicular pain	0	5 (0.9)
Erectile dysfunction	0	4 (0.7)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2 (0.2)	6 (0.4)
Rash	0	6 (0.4)
Rash generalized	0	3 (0.2)
Urticaria	0	3 (0.2)

Vascular disorders		
Hot flush	0	4 (0.3)
Hypertension	0	3 (0.2)

The treatment emergent adverse events (TEAEs) leading to discontinuation were predominantly gastrointestinal events, with most frequent being nausea (1.5%) and vomiting (0.8%). There were 17 patients who discontinued in the levomilnacipran treatment group secondary to combined urinary disorders. Urinary disorders are reviewed in detail in 7.3.5. Six patients (0.4%) discontinued in the levomilnacipran treatment group secondary to rash, two of these patients had a history of hypersensitivity. Most of the rashes were considered mild or moderate, and no cases of Stevens - Johnson syndrome or angioedema were reported. Select cases of either events associated with other symptoms of hypersensitivity, or those for which no resolution date was cited are described below.

- Subject 0391013, 43yo female: Patient was enrolled in LVM-MD-10. On Day 41 of levomilnacipran 40mg, patient experienced an adverse event of mild hot flush, and moderate arthralgia and generalized rash. All 3 events were considered related to investigational product. The patient was discontinued from the study, and these adverse events resolved on Study Day 46.
- Subject 0270123, 18yo female: Patient was enrolled in LVM-MD-01. On Day 13 of levomilnacipran 80mg, the patient had an adverse event of rash (investigator term: rash on neck) which was mild in intensity and considered related to investigational product. The rash was treated with topical hydrocortisone and resolved on Day 43 (16 Feb 2010) while the patient continued investigational product. On Day 44, the patient had a second episode of rash (investigator term: rash recurrence/limbs) which was moderate in intensity and considered related to investigational product. The rash is ongoing and led to discontinuation from the study. On Day 45, the patient had an adverse event of dyspnea (investigator term: shortness of breath at night) that was ongoing at study discontinuation. The event was mild in intensity and considered related to investigational product. No additional details were provided in the case narrative, and it is unclear when these events ultimately resolved.
- Subject 0310144, 25yo female: Patient was enrolled in LVM-MD-01. On Day 11 (10 Feb 2011), the patient had an adverse event of mild rash (investigator term: rash on trunk, abdomen and arms) one day after the last dose of investigational product. The event was considered related to investigational product, was treated with loratidine, and resolved on Day 12. On Day 12 (11 Feb 2011), the patient had an adverse event of mild urticaria (investigator term: hives generalized) that was also considered related to investigational product. Although this event occurred three days after the last dose of study drug, the sponsor lists this as an adverse event leading to study medication discontinuation. The urticaria resolved on Day 14 (13 Feb 2011).

Long Term Open-Label Trial

In LVM-MD-04, approximately 14% of patients discontinued due to AEs. Nausea was most frequently reported TEAE leading to discontinuation. Other TEAEs leading to discontinuation in at least 3 patients included tachycardia (7 patients); hyperhidrosis (8 patients); hypertension (6 patients); headache (5 patients); depression, suicide attempt, and urinary hesitation (4 patients each); and urinary retention and blood pressure increased (3 patients each). The incidence and pattern of AEs that led a patient to discontinue in the long-term study were similar to that of the short-term studies.

Relapse Prevention Study

During the open-label period of LVM-MD-05, approximately 11% of patients prematurely discontinued because of TEAEs. TEAEs that led to the discontinuation of more than 3 patients included nausea (11 patients); headache (7 patients); urinary hesitation (5 patients); dysuria, heart rate increased, and rash (4 patients each); and constipation, ejaculation disorder, hypertension, insomnia, and urinary retention (3 patients each).

During the double-blind treatment period, the incidence of TEAEs leading to premature discontinuation was similar in both the placebo (2.7%) and levomilnacipran (3.4%) treatment groups. The majority of TEAEs that led to discontinuation started at least 3 weeks after the initiation of double-blind investigational product. No TEAE leading to discontinuation was reported by more than 1 patient in either treatment group. In the levomilnacipran group, TEAEs that led to discontinuation included dizziness, epididymitis, headache, heart rate increased, hyperhidrosis, lethargy, neutropenia, and palpitations. None of these TEAEs were SAEs.

Phase I Trials

Discontinuations secondary to AEs were seen in 28 patients (n=28/637, 4.4%). Events resulting in discontinuation were similar to those listed above, and included cardiovascular and urinary abnormalities, rash, and testicular pain.

7.3.4 Significant Adverse Events

Except as noted above, no other clinically significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

A number of safety issues are common concerns across antidepressants in general. Others are specific to the serotonin-norepinephrine reuptake inhibitors (SNRIs) more specifically. The items below reflect an examination of issues.

Suicidal Thoughts and Behaviors

The reported TEAEs associated with suicidal thoughts and behaviors were similar in both treatment groups. For 11 of the 15 patients (6 placebo, 5 levomilnacipran), the event was either reported as a SAE and/or contributed to premature discontinuation from the study (reviewed above). For additional details, see section 7.7.1.

Serotonin Syndrome and Neuroleptic Malignant Syndrome

Serotonin syndrome and neuroleptic malignant syndrome are potential class effects of SSRI and SNRI drugs. Per Dr. Kohli-Chhabra, the levomilnacipran safety database was searched for preferred terms that might indicate serotonin syndrome. When the terms were identified, Hunter's serotonin toxicity criteria (spontaneous clonus, or inducible clonus plus agitation or diaphoresis, or ocular clonus plus agitation or diaphoresis, or tremor plus hyperreflexia, or hypertonus plus temperature > 38 °C/100 °F plus ocular clonus or inducible clonus) were applied to identify patients with possible serotonin toxicity. The JMP

line listings were reviewed for preferred terms that might indicate serotonin syndrome. This was done to confirm the sponsor's assessment of no reports of serotonin syndrome; no cases of serotonin syndrome were identified.

Increased Blood Pressure and Heart Rate

As expected for an SNRI, the mean change from baseline to the end of treatment for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate showed an increase mean change for levomilnacipran compared to placebo. In the short-term controlled studies, the change from baseline to endpoint in levomilnacipran-treated patients was associated with mean increases of 3.0 mmHg in SBP and 3.2 mmHg in DBP compared to a mean decrease (0.4 mmHg) in SBP and no change in DBP in placebo-treated patients. The mean increase in heart rate at endpoint in levomilnacipran-treated patients was 7.4 bpm compared to a mean decrease of 0.3 bpm among placebo patients. In the fixed-dose studies, a greater mean increase in heart rate was observed in the levomilnacipran 120-mg dose group (9.1 bpm) relative to lower-dose levomilnacipran groups (7.2 bpm increase in both 40- and 80-mg treatment arms). A detailed review is presented in 7.4.3. Additionally, the thorough QT study (LVM-PK-07) is reviewed in 7.4.4.

Activation of Mania or Hypomania

In short-term studies, incidence rates of AEs related to hypomania were low and comparable in both the levomilnacipran (0.2%) and placebo (0.2%) groups. The single SAE of mania in the long term, open label trial is reviewed in 7.3.2.

Urinary Hesitation and Retention

Due to increased levels of NE, SNRI drugs in general have the potential of causing urinary obstruction; however, not all SNRIs carry a labeled warning for these adverse events.

Rates of obstructive uropathies in the short-term studies were higher in the levomilnacipran arm (7.9%) compared to the placebo arm (0.9%). In fixed-dose trials, dose dependent increases were seen for the TEAE of urinary hesitation (3.6% in 40 mg/day; 4.9% in 80 mg/day; 6.1% in 120 mg/day). Almost all events of dysuria and urinary hesitation had occurred in male patients. A total of 6/63 (9.5%) patients with TEAE of urinary hesitation and 5/24 (20.8%) patients with TEAEs of dysuria were prematurely discontinued from the study. None of the events were reported as SAEs.

Abnormal Bleeding

Incidence rates of TEAEs related to abnormal bleeding during the short term studies were comparable between the levomilnacipran group (1.9%) and placebo group (1.6%). Rates of hematuria were higher in the levomilnacipran group (0.6%) compared to the placebo group (0.3%); all of the events were considered mild in severity and none resulted in discontinuation of levomilnacipran. There was also a slightly higher rate of patients with a history of hematuria in the levomilnacipran group (0.5%) compared to the placebo group (0.1%). Incidence rates of all other terms were low and comparable in both treatment groups. Incidence rates of TEAEs related to abnormal bleeding did not suggest dose dependent effects.

Convulsion and Seizure Disorders

No seizures occurred in short term trials. One seizure occurred in the long term, open label trial; that event is reviewed in 7.3.2.

Discontinuation Syndrome

The sponsor evaluated discontinuation syndrome in 2 ways: Newly Emergent Adverse Events (NEAEs) during the down-taper period and Standardized MedDRA Queries (SMQ) search for TEAEs associated with discontinuation syndrome (see Table 64 below for SMQ terms). NEAEs was defined by if the AE was not present before the start of the down-taper treatment period, or it was present before the start of the down-taper treatment period and increased in severity during the down-taper treatment period. The SMQ terms are provided in Table below.

Table 64: SMQ preferred terms for discontinuation syndrome query

Discontinuation Syndrome (both broad and narrow terms in Drug Withdrawal SMQ)	MedDRA Code
Drug withdrawal convulsions	10013752
Drug withdrawal headache	10013753
Drug withdrawal maintenance therapy	10052970
Drug withdrawal syndrome	10013754
Drug withdrawal syndrome neonatal	10013756
Drug rehabilitation	10064773
Rebound effect	10038001
Steroid withdrawal syndrome	10042028
Withdrawal arrhythmia	10047997
Withdrawal syndrome	10048010

In short term trials, the most frequently reported NEAE during the double-blind, down-taper period was headache for both the levomilnacipran group (1.4%) and the placebo group (1.3%). Incidences for all NEAEs reported in the down-taper period were similar for levomilnacipran-treated patients and placebo-treated patients; rates were all less than 0.5%.

Based on the sponsor's SMQ search, no patients experienced discontinuation syndrome in short term studies.

Hyponatremia

No TEAEs of hyponatremia were reported in the short-term, placebo-controlled studies.

Narrow-angle glaucoma and mydriasis

Treatment with SNRIs could give rise to mydriasis and potentially lead to narrow angle glaucoma due to the increase in NE levels. Within this class of antidepressants, the level of warning language in product labels varies in regard to this issue.

The overall rates of TEAEs related to mydriasis in the levomilnacipran-treated patients were low in short term studies (0.9%). The fixed dose studies did not suggest any dose dependency. None of the events were reported as SAEs and no levomilnacipran-treated patients were discontinued from the study for

TEAEs related to mydriasis. All TEAEs related to mydriasis were considered either mild or moderate in severity. None of levomilnacipran-treated patients developed narrow angle glaucoma. Of note, patients with a history of narrow angle glaucoma were excluded from all short term trials.

Sexual Dysfunction

In short term trials, a higher percentage of levomilnacipran-treated male patients experienced TEAEs associated with sexual dysfunction compared with placebo-treated male patients. The most frequently reported TEAEs in levomilnacipran-treated male patients were erectile dysfunction (grouped terms), ejaculation disorder (grouped terms), and testicular pain (grouped terms) (5.9%, 4.7%, and 3.8% respectively). In fixed-dose trials, the incidence of erectile dysfunction was found to be dose-dependent (5.5% of male patients in the 40 mg group, 8.3% in the 80 mg group, 9.5% in the 120 mg group, and 2.2% in the placebo group).

In one short term trial (LVM-MD-02), the sponsor included the Arizona Sexual Experiences Scale (ASEX), a five-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. A major limitation of interpreting the ASEX data is that there was no positive control (i.e., an SSRI known to cause sexual dysfunction). In addition, the sponsor's ASEX result analysis was based on mean change from baseline in ASEX; however, the ASEX is designed to be analyzed in a categorical, not continuous, fashion. The sponsor did not report ASEX results in the Integrated Summary of Safety, nor has it been cited in the proposed product labeling.

An information request was sent to the sponsor on June 25, 2013 asking the sponsor to analyze the ASEX data from LVM-MD-02 using continuous rather than categorical variables. Because the data are from a single flexible-dose study, it is unlikely that these results will alter the overall safety assessment or label language.

Hepatotoxicity

Hepatotoxicity is not a class warning for antidepressants generally or SNRIs specifically. However, labeling for milnacipran, the racemic parent compound of levomilnacipran, contains language warning of rare fulminant hepatitis. Physicians are advised to avoid prescribing milnacipran to patients with substantial alcohol use or chronic liver disease. A detailed review of hepatic findings is presented in 7.4.2.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported AEs ($\geq 5\%$ and 2x placebo) at the preferred term level in short term studies of levomilnacipran were: nausea (17.1% in levomilnacipran vs. 4.1% in placebo), constipation (8.5% vs. 3.0%), hyperhidrosis (8.5% vs. 1.1%), erectile dysfunction (5.7% vs. 2.2%), heart rate increased (5.7% vs. 0.8%), tachycardia (4.9% vs. 1.7%), vomiting (4.8% vs. 0.6%), and palpitations (4.7% vs. 0.8%).

A list of all common ($\geq 2\%$) is presented in Table 65 below (source: Integrated Summary of Safety, Vol 1, page 72, Table 8.2.1-1). Relatedness is as determined by the sponsor.

Table 65: TEAEs reported in $\geq 2\%$ of levomilnacipran-treated patients and at a greater rate than placebo in short term trials -- safety population

<i>System Organ Class Preferred Term^a</i>	<i>Placebo (N = 1040) n (%)</i>		<i>Levomilnacipran 40-120 mg/d (N = 1583) n (%)</i>	
	<i>Total</i>	<i>Related</i>	<i>Total</i>	<i>Related</i>
Patients with any TEAE	639 (61.4)	424 (40.8)	1222 (77.2)	1009 (63.7)
Cardiac disorders				
Tachycardia	15 (1.4)	15 (1.4)	78 (4.9)	70 (4.4)
Tachycardia (grouped terms)	18 (1.7)	—	93 (5.9)	—
Palpitations	14 (1.3)	11 (1.1)	74 (4.7)	64 (4.0)
Gastrointestinal disorders				
Nausea	58 (5.6)	45 (4.3)	271 (17.1)	234 (14.8)
Dry mouth	73 (7.0)	68 (6.5)	160 (10.1)	153 (9.7)
Constipation	26 (2.5)	20 (1.9)	134 (8.5)	118 (7.5)
Vomiting	8 (0.8)	5 (0.5)	76 (4.8)	55 (3.5)
Diarrhea	41 (3.9)	30 (2.9)	70 (4.4)	52 (3.3)
Diarrhea (grouped terms)	43 (4.1)	—	70 (4.4)	—
General disorders and administration site conditions				
Fatigue	20 (1.9)	18 (1.7)	31 (2.0)	24 (1.5)
Infections and infestations				
Upper respiratory tract infection	43 (4.1)	1 (0.1)	66 (4.2)	1 (0.1)
Upper respiratory tract infection (grouped terms)	46 (4.4)	—	71 (4.5)	—
Nasopharyngitis	33 (3.2)	1 (0.1)	61 (3.9)	5 (0.3)

Investigations				
Heart rate increased	9 (0.9)	8 (0.8)	90 (5.7)	83 (5.2)
Heart rate increased (grouped terms)	10 (1.0)	—	90 (5.7)	—
Blood pressure increased	11 (1.1)	9 (0.9)	37 (2.3)	34 (2.1)
Blood pressure increased (grouped terms)	12 (1.2)	—	45 (2.8)	—
Metabolism and nutrition disorders				
Decreased appetite	8 (0.8)	6 (0.6)	40 (2.5)	34 (2.1)
Nervous system disorders				
Headache	132 (12.7)	87 (8.4)	262 (16.6)	200 (12.6)
Headache (grouped terms)	142 (13.7)	—	275 (17.4)	—
Dizziness	50 (4.8)	43 (4.1)	129 (8.1)	108 (6.8)
Somnolence	18 (1.7)	18 (1.7)	36 (2.3)	34 (2.1)
Psychiatric disorders				
Insomnia	45 (4.3)	30 (2.9)	80 (5.1)	63 (4.0)
Insomnia (grouped terms)	45 (4.3)	—	88 (5.6)	—
Anxiety	11 (1.1)	8 (0.8)	31 (2.0)	24 (1.5)
Renal and urinary disorders				
Urinary hesitation	0	0	63 (4.0)	62 (3.9)
Reproductive system and breast disorders				
Erectile dysfunction ^a	5 (1.3)	5 (1.3)	33 (5.7)	30 (5.2)
Testicular pain ^a	1 (0.3)	1 (0.3)	18 (3.1)	15 (2.6)
Ejaculation disorder ^a	0	0	18 (3.1)	16 (2.8)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	20 (1.9)	20 (1.9)	135 (8.5)	122 (7.7)
Vascular disorders				
Hot flush	7 (0.7)	7 (0.7)	45 (2.8)	40 (2.5)
Hypertension	11 (1.1)	8 (0.8)	38 (2.4)	31 (2.0)
Hypertension (grouped terms)	11 (1.1)	—	39 (2.5)	—

Note: **tachycardia (grouped terms)**: tachycardia, sinus tachycardia, and postural orthostatic tachycardia syndrome; **diarrhea (grouped terms)**: diarrhea and frequent bowel movements; **upper respiratory tract infection (grouped terms)**: upper respiratory tract infection and viral upper respiratory tract infection; **heart rate increased (grouped terms)**: heart rate increased and orthostatic heart rate response increased; **blood pressure increased (grouped terms)**: blood pressure increased, blood pressure systolic increased, blood pressure diastolic increased, and blood pressure orthostatic increased; **headache (grouped terms)**: headache, tension headache, sinus headache, and head discomfort; **insomnia (grouped terms)**: insomnia, initial insomnia, terminal insomnia, insomnia related to another mental condition; **hypertension (grouped terms)**: hypertension and labile hypertension (see Table 1 in Appendix III for grouped terms).

a Sex-specific TEAE. Percentage is relative to the number of patients in the associated demographic sex category.

N = number of patients in the Safety Population; n = number of patients with the specified event;
TEAE = treatment-emergent adverse event.

7.4.2 Laboratory Findings

Liver Function Tests

In the short term studies, no patients met Hy's law criteria for potential drug-induced liver injury or had ALT or AST $\geq 3 \times$ upper limit of normal (UNL) and total bilirubin ≥ 1.5 UNL. A higher incidence of potentially clinically significant (PCS) values was noted for some liver function parameters (see Table 66 below. Source: Integrated Summary of Safety, Vol 1, page 122, Table 9.2.1-2). These increases were rarely sustained and returned to baseline levels while the patient continued on levomilnacipran treatment.

Table 66: Number (%) of patients with potentially clinically significant liver function test result in short term trials (US and Canada) - safety population

<i>Parameter</i>	<i>Placebo (N = 761) n/N1 (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1305) n/N1 (%)</i>
ALT		
$\geq 3 \times$ UNL	0	7/1211 (0.6)
$\geq 5 \times$ UNL	0	2/1211 (0.2)
AST		
$\geq 3 \times$ UNL	1/721 (0.1)	8/1211 (0.7)
$\geq 5 \times$ UNL	0	3/1211 (0.2)
ALT or AST		
$\geq 3 \times$ UNL	1/721 (0.1)	9/1211 (0.7)
$\geq 5 \times$ UNL	0	5/1211 (0.4)
Total bilirubin		
$> 1.5 \times$ UNL	1/719 (0.1)	3/1208 (0.2)
$\geq 2 \times$ UNL	0	2/1211 (0.2)
Alkaline phosphatase		
$\geq 1.5 \times$ UNL	0	4/1211 (0.3)
$\geq 3 \times$ UNL	0	0
Total protein, g/L		
$> 1.1 \times$ UNL	0	1/1208 (0.1)
$< 0.9 \times$ LNL	1/718 (0.1)	0
Albumin, g/L		
$> 1.1 \times$ UNL	0	1/1210 (0.1)
Concurrent Elevations		
AT $\geq 3 \times$ UNL and total bilirubin $\geq 1.5 \times$ UNL	0	0
AT $\geq 3 \times$ UNL and total bilirubin $\geq 2 \times$ UNL	0	0
AT $\geq 3 \times$ UNL and total bilirubin $\geq 2 \times$ UNL and alkaline phosphatase $< 2 \times$ UNL	0	0

Note: No patient met ALT or AST levels $\geq 10 \times$ UNL.

ALT = alanine aminotransferase; AT = aminotransferase (ALT or AST); AST = aspartate aminotransferase;
LNL = lower normal limit; N = number of patients in the Safety Population; n = number of patients who met the
criterion at least once postbaseline; N1 = number of patients with available baseline value and at least
one postbaseline assessment; UNL = upper normal limit.

The mean increases in ALT, AST, and alkaline phosphatase were slightly higher in the levomilnacipran-treated patients relative to those observed in placebo treated patients. Based on data from the fixed-dose studies, the increase does not appear to be dose-dependent. Changes in liver function parameters from baseline to the end of the treatment period are presented in Table 67 (source: Integrated Summary of Safety, Vol 1, page 121, Table 9.2.1-1).

Table 67: Changes from baseline to end of treatment period in liver function parameters in short term studies (US and Canada) - safety population

<i>Parameter, Unit</i>	<i>Placebo (N = 761)</i>		<i>Levomilnacipran 40-120 mg/d (N = 1305)</i>	
	<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>
Alanine aminotransferase, U/L				
Baseline	721	23.2 ± 11.9	1211	24.0 ± 12.7
Change at end of treatment period	721	0.5 ± 9.5	1211	2.6 ± 17.7
Aspartate aminotransferase, U/L				
Baseline	721	22.2 ± 6.8	1211	22.8 ± 7.3
Change at end of treatment period	721	0.2 ± 6.4	1211	2.3 ± 17.9
Alkaline phosphatase, U/L				
Baseline	721	74.7 ± 22.4	1211	74.3 ± 21.5
Change at end of treatment period	721	-1.3 ± 9.2	1211	3.6 ± 12.2
Gamma glutamyl transferase U/L^a				
Baseline	176	26.6 ± 25.9	356	23.9 ± 21.3
Change at end of treatment period	176	-0.5 ± 9.4	356	1.3 ± 12.1
Bilirubin, total, µmol/L				
Baseline	721	9.1 ± 4.8	1211	9.0 ± 4.9
Change at end of treatment period	721	-0.36 ± 3.3	1211	-0.53 ± 3.6
Albumin, g/L				
Baseline	721	45.5 ± 2.7	1211	45.8 ± 2.8
Change at end of treatment period	721	-1.1 ± 2.4	1211	-0.6 ± 2.6
Total protein, g/L				
Baseline	721	73.5 ± 4.7	1211	74.0 ± 4.7
Change at end of treatment period	721	-1.8 ± 4.1	1211	-0.7 ± 4.2

a Gamma glutamyl transferase assessed only in Study LVM-MD-10.

One patient was prematurely discontinued from the study due to abnormal liver function tests.

- Subject 0090211, 33yo male: Patient was enrolled in LVM-MD-02, had no relevant medical history, and received levomilnacipran for 32 days. Baseline ALT and AST values were 65 U/L and 41 U/L (reference ranges were 0-55 U/L and 0-45 U/L, respectively). On Day 27 (24 Nov 2009), ALT = 133 U/L and AST = 73 U/L. After discontinuing double-blind treatment, repeat assessment a week later showed decreased but continued elevation of ALT (71 U/L); AST decreased to 37 U/L. At the final study assessment, the ALT remained slightly elevated at 61 U/L while AST decreased to 33 U/L. Alkaline phosphatase and total bilirubin values were within normal limits throughout the study. The patient had negative urine drug tests for alcohol during

the 8-week double-blind treatment Phase. The TEAE was reported as mild in intensity and related to investigational product.

Metabolic Parameters

In short term trials, changes in the levomilnacipran-treated patients were similar to that in the placebo group for both glucose and total cholesterol. In addition, there was no dose-dependent change in post-baseline fasting glucose status among levomilnacipran-treated patients.

One patient was discontinued from the long term open-label trial (LVM-MD-04) due to elevated blood glucose.

- Subject 0700301, 52yo male: Patient had a baseline BMI of 36.9 kg/m², but no reported medical history or current medication. He received placebo in LVM-MD-03 prior to open-label treatment with levomilnacipran (20 to 40 mg/day) for 185 days. The patient had high glucose at screening and remained high or clinically high for the entire duration of the lead-in study and the open-label extension study. An AE of increased blood glucose was reported on Day 178 and the event was considered by the Investigator to be severe in intensity and related to investigational product. The patient was discontinued from the study on Day 190. A follow-up lab approximately 2 weeks later (Day 204) indicated a lower value but still PCS high value; no further information is available.

Other Chemistry Parameters

No clinically meaningful trends were observed in serum potassium levels. Two patients experienced TEAEs associated with PCS increases in potassium; one of these patients was discontinued from LVM-MD-03 for other adverse events occurring at the same time as the hyperkalemia; elevated potassium was not cited as a reason for discontinuation.

- Subject 0690309, 57yo female: Patient had no relevant medical history. She met the PCS-high criterion for potassium on Day 44 (potassium = 8.4 mmol/L; normal range 3.5-5.3 mmol/L) and a TEAE of blood potassium increased was reported (Days 44 to 142). The patient discontinued on Day 44 for 4 other TEAEs (anxiety, irritability, tachycardia, and constipation). A follow-up laboratory assessment performed on Day 142 indicated the potassium level normalized (4.2 mmol/L).

No other clinically meaningful trends were observed in clinical laboratory results over time in short term trials.

7.4.3 Vital Signs

Blood Pressure

As expected for an SNRI, the mean change from baseline to the end of treatment for systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed an increase mean change for levomilnacipran compared to placebo. In the short-term controlled studies, the change from baseline to endpoint in levomilnacipran-treated patients was associated with mean increases of 3.0 mmHg in SBP and 3.2 mmHg

in DBP compared to a mean decrease (0.4 mmHg) in SBP and no change in DBP in placebo-treated patients.

No dose-dependent relationship to blood pressure changes was observed among patients in the levomilnacipran 40 mg, 80 mg, and 120 mg groups in the fixed-dose studies (see Table 68 below. Source: Integrated Summary of Safety, Vol 2, page 61, Table 6.1.1.1-2). 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.

As an additional proxy measure of hypertension, the sponsor also investigated the number of patients initiating new antihypertensive treatment during the treatment period. The percentage of patients initiating new antihypertensive medications while receiving levomilnacipran in short term trials was 1.2% compared with 1.5% in the placebo group.

Six levomilnacipran-treated patients were discontinued for BP increase or hypertension. In the placebo group, two patients were prematurely discontinued for BP increased (one SAE).

Table 68: Changes from baseline to end of double-blind treatment in SBP and DBP in fixed-dose studies - safety population

Study Timepoint	Placebo (N = 362)		Levomilnacipran					
			40 mg/d (N = 366)		80 mg/d (N = 367)		120 mg/d (N = 180)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Supine systolic blood pressure, mm Hg								
Baseline	360	116.7 ± 10.8	363	117.0 ± 10.8	367	116.6 ± 10.9	177	117.1 ± 10.4
Change at end of treatment period	360	0.5 ± 10.2	363	3.3 ± 10.0	367	3.8 ± 9.8	177	2.7 ± 8.9
Supine diastolic blood pressure, mm Hg								
Baseline	360	74.3 ± 8.0	363	73.7 ± 8.0	367	74.1 ± 8.1	177	74.3 ± 7.5
Change at end of treatment period	360	0.1 ± 7.8	363	3.5 ± 7.5	367	3.8 ± 7.4	177	2.6 ± 7.1

In the short-term studies, the number of patients satisfying the sustained hypertension criterion (defined, by the relatively broader criterion, of SBP ≥ 140 mmHg AND increase ≥ 15 mmHg OR DBP ≥ 90 mmHg AND increase ≥ 10 mmHg for at least 3 visits) was greater with levomilnacipran (1.8%) than with placebo (1.2%). In the fixed-dose studies, the incidence of sustained hypertension among levomilnacipran-treated patients did not suggest any dose relationship.

The incidence of patients who met orthostatic hypotension criteria (reduction in SBP of ≥ 20 mmHg or reduction in DBP of ≥ 10 mmHg while changing from the supine to standing position) was higher in the levomilnacipran arm (11.6%) relative to placebo (9.7%). The incidences of patients who met either the SBP or DBP criterion for orthostatic hypotension were higher in all levomilnacipran dose-levels

compared to placebo. For the fixed dose studies, the percentage of patients with orthostatic hypotension was higher in all three levomilnacipran dose groups relative to placebo. Overall, there was no clear trend suggesting a dose-dependent increase (see Table 69 below. Source: Integrated Summary of Safety, Vol 1, page 158, Table 10.2.1.3-1).

Table 69: Number and percentage of patients with orthostatic hypotension in short term trials (US and Canada) - safety population

<i>Orthostatic Hypotension Criterion</i>	<i>Group 1A</i>		<i>Fixed Dose Studies</i>			
	<i>Placebo (N = 761) n/N1 (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1305) n/N1 (%)</i>	<i>Placebo (N = 362) n/N1 (%)</i>	<i>Levomilnacipran</i>		
				<i>40 mg/d (N = 366) n/N1 (%)</i>	<i>80 mg/d (N = 367) n/N1 (%)</i>	<i>120 mg/d (N = 180) n/N1 (%)</i>
Reduction in SBP of ≥ 20 mm Hg or reduction in DBP of ≥ 10 mm Hg while changing from the supine to standing position	73/755 (9.7)	150/1294 (11.6)	30/360 (8.3)	43/363 (11.8)	36/366 (9.8)	21/177 (11.9)
Reduction of ≥ 20 mm Hg in SBP while changing from the supine to standing position	27/750 (3.6)	86/1290 (6.7)	11/360 (3.1)	28/363 (7.7)	21/364 (5.8)	12/177 (6.8)
Reduction of ≥ 10 mm Hg in DBP while changing from the supine to standing position	55/744 (7.4)	92/1275 (7.2)	22/356 (6.2)	21/359 (5.8)	22/360 (6.1)	17/173 (9.8)

DBP = diastolic blood pressure; N = number of patients in the Safety Population; n = number of patients who met the criterion at least once during the double-blind treatment period; N1 = number of patients with baseline and at least 1 postbaseline assessment of vital signs; SBP = systolic blood pressure.

Group 1A = Short term trials at US and Canada sites only (excludes F02695-LP2-02).

Heart Rate

As expected for an SNRI, the mean change from baseline to the end of treatment for heart rate showed an increase mean change for levomilnacipran compared to placebo. In the short term controlled studies, the mean increase in heart rate at endpoint in levomilnacipran-treated patients was 7.4 bpm compared to a mean decrease of 0.3 bpm among placebo patients. The mean increase in heart rate at endpoint in levomilnacipran-treated patients was 7.4 bpm compared to a mean decrease of 0.3 bpm among placebo patients.

In the fixed-dose studies, a greater mean increase in heart rate was observed in the levomilnacipran 120-mg dose group (9.1 bpm) relative to lower-dose levomilnacipran groups (7.2 bpm increase in both treatment arms) (see Table 70 below. Source: Integrated Summary of Safety, Vol 2, page 75, Table 6.2.1.1-2). The sponsor concludes that no consistent pattern was observed, suggesting that these changes are not dose-responsive. However, a more conservative interpretation suggests that these changes may reflect a positive dose-response relationship. (No dose-response relationship in heart rate increase was observed in the thorough QT study. See 7.4.5 below.) Nine patients in the levomilnacipran group were prematurely discontinued for TEAEs of tachycardia or heart rate increase. In the placebo group, one patient was prematurely discontinued for tachycardia.

Table 70: Changes from baseline to end of double-blind treatment in heart rate in fixed-dose studies - safety population

Study Timepoint	Placebo (N = 362)		Levomilnacipran					
			40 mg/d (N = 366)		80 mg/d (N = 367)		120 mg/d (N = 180)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Baseline	360	69.5 ± 9.6	363	69.7 ± 9.4	367	69.9 ± 9.3	177	68.5 ± 8.7
Change at end of treatment period	360	-0.0 ± 9.0	363	7.2 ± 10.2	367	7.2 ± 11.5	177	9.1 ± 10.6

N = number of patients in the Safety Population; n = number of patients with an available value at both baseline and a specific timepoint.

Weight

The mean change from baseline to study endpoint in body weight was a decrease of 0.59 kg for levomilnacipran- treated patients and an increase of 0.02 kg for placebo-treated patients. In short term studies, PCS changes in weight (> 7% increase or decrease) were similar between the 2 treatment groups. In the fixed-dose studies, more patients in the levomilnacipran 120 mg/day group met PCS criteria for weight increase: 0.3% in 40 mg/day group, 0.5% in 80 mg/day group, and 1.7% in 120 mg/day group. No discontinuations due to weight changes are described in the Integrated Summary of Safety.

7.4.4 Electrocardiograms (ECGs)

A thorough QT study (LVM-PK-07) was conducted as part of this development program. Results of that study are reviewed in 7.4.5 below.

In short term studies (US and Canada only, excludes F02695-LP2-02), a greater mean increase in ventricular heart rate was observed in the levomilnacipran treatment group relative to the placebo group (12.5 vs 1.6 bpm). In addition, a greater increase in mean QTcB interval was observed in the levomilnacipran group relative to the placebo group (9.5 vs. 0.1 msec). The sponsor asserts that this was likely consistent with the increased heart rate observed. Details are presented in Table 71 below (source: Integrated Summary of Safety, Vol 1, page 171, Table 11.2.1-1).

Table 71: Change from baseline to endpoint in ECG parameters (Short Term Trials, US and Canada) - safety population

<i>Parameter, Unit</i>	<i>Placebo (N = 761)</i>		<i>Levomilnacipran 40-120 mg/d (N = 1305)</i>	
	<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>
Ventricular heart rate, bpm				
Baseline	737	66.1 ± 10.2	1234	65.4 ± 9.6
Change from baseline to end of treatment period	737	1.6 ± 9.6	1234	12.5 ± 11.6
PR interval, msec				
Baseline	737	158.6 ± 21.0	1234	159.4 ± 21.2
Change from baseline to end of treatment period	737	0.4 ± 12.2	1234	-6.5 ± 13.6
QRS interval, msec				
Baseline	737	90.3 ± 7.6	1234	90.6 ± 7.8
Change from baseline to end of treatment period	737	- 0.0 ± 6.7	1234	-1.0 ± 6.9
QT interval, msec				
Baseline	737	397.5 ± 27.2	1234	398.4 ± 27.0
Change from baseline to end of treatment period	737	- 4.2 ± 23.2	1234	-24.5 ± 25.6
QTcB interval, msec				
Baseline	737	414.6 ± 22.3	1234	413.6 ± 22.4
Change from baseline to end of treatment period	737	0.1 ± 19.2	1234	9.5 ± 20.7
QTcF interval, msec				
Baseline	737	408.6 ± 19.3	1234	408.2 ± 19.7
Change from baseline to end of treatment period	737	- 1.4 ± 16.0	1234	-2.5 ± 16.8

bpm = beats per minute; N = number of patients in the Safety Population; n = number of patients with an available baseline and at least 1 postbaseline assessment; QTcB = QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$); QTcF = QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$).

In short term trials, the incidence of patients with PCS ECG values was low and similar between the 2 treatment groups (see Table 72 below. Source: Integrated Summary of Safety, Vol 1, page 172, Table 11.2.2-1). No TEAEs associated with ECG changes were reported for levomilnacipran-treated patients who met the PCS criterion for QRS interval. A PCS increase in QTcB interval was reported in one levomilnacipran-treated patient.

Subject 0140127, 6yo female: Enrolled in LVM-MD-01, randomized to the 40-mg group. This patient had baseline QTcB and QTcF intervals of 485 msec and 468 msec, respectively. On Day 15, a TEAE of heart rate increased was reported. On Day 29, ECG results showed QTcB = 513 msec (QTcF = 479 msec) and a TEAE of electrocardiogram. QT prolonged was reported. The patient's pulse rate remained elevated during the double-blind treatment and down-taper periods, ranging from 80 bpm to 102 bpm. The TEAE of heart rate increased was ongoing when the patient completed the study; the TEAE of electrocardiogram QT prolonged resolved on Day 29.

Table 72: Summary of potentially clinically significant ECG values in short term trials (US and Canada) - safety population

<i>Criterion, msec</i>	<i>Placebo (N = 761) n/N1 (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1305) n/N1 (%)</i>
Postbaseline Values		
PR Interval \geq 250	1/737 (0.1)	0
QRS Interval \geq 150	1/736 (0.1)	1/1234 (0.1)
QTcB Interval > 500	0	1/1234 (0.1)
QTcF Interval > 500	0	0

N = number of patients in the Safety Population; n = number of patients with an available value; QTcB = QT interval corrected for heart rate using the Bazett formula; QTcF = QT interval corrected for heart rate in the Fridericia formula.

The number (percentage) of patients with post baseline increase in QTc intervals is summarized in Table 73 (source: Integrated Summary of Safety, Vol 1, page 173, Table 11.2.2–2). Post baseline QTcF high values (> 450 msec in males, > 470 msec in females) or increase \geq 60 msec increase were reported in 6 levomilnacipran-treated patients; 1 female and 5 males. In all cases in which the high values were not recorded at the last assessment, the elevations were transient.

Table 73: Summary of postbaseline QTc values ≥ 30 msec or > 450 msec in short term trials (US and Canada) - safety population

<i>QTc Change Criteria</i>	<i>Placebo (N = 761) n/N1 (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1305) n/N1 (%)</i>
Post baseline QT interval increase from baseline		
QTcB increase ≥ 30 but < 60 msec	93/737 (12.6)	288/1234 (23.3)
QTcB increase ≥ 60 msec	0	23/1234 (1.9)
QTcF increase ≥ 30 but < 60 msec	34/737 (4.6)	51/1234 (4.1)
QTcF increase ≥ 60 msec	1/737 (0.1)	1/1234 (0.1)
Post baseline QT interval		
QT ≥ 480	1/ 737 (0.1)	1/1234 (0.1)
QTcB > 470 or increase ≥ 60 (female)	4/ 463 (0.9)	42/ 780 (5.4)
QTcB > 450 or increase ≥ 60 (male)	8/ 274 (2.9)	41/ 454 (9.0)
QTcF > 470 or increase ≥ 60 (female)	2/ 463 (0.4)	1/ 780 (0.1)
QTcF > 450 or increase ≥ 60 (male)	3/ 274 (1.1)	5/ 454 (1.1)

N = number of patients in the Safety Population; n = number of patients with an available value; QTcB = QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{1/2}$); QTcF = QT interval corrected for heart rate in the Fridericia formula ($QTcF = QT/[RR]^{1/3}$).

7.4.5 Special Safety Studies/Clinical Trials

Study LVM-PK-07

A thorough QT (TQT) study was conducted to assess the effects of the investigated maximum therapeutic dose (120 mg/d) and a suprathreshold dose (300 mg/d) of levomilnacipran on cardiac repolarization as determined by manual measurement of QTc on repeated digitally recorded 12-lead electrocardiograms (ECGs). This was a Phase 1, multicenter, randomized (stratified by sex), double-blind, placebo- and positive-controlled, parallel-group, escalating multiple-dose study in 170 healthy male and female subjects aged 18 through 45 years; 149 subjects completed the study.

Subjects were randomized to receive one of the following three treatment regimens under fed conditions:

- Group 1:** Placebo on Day -2 and Day -1; escalating once-daily doses of levomilnacipran on Day 1 to Day 24, as follows: 20 mg on Day 1; 40 mg once a day for 3 days (Days 2-4); 80 mg once a day for 3 days (Days 5-7); 120 mg once a day for 4 days (Days 8-11); 160 mg once a day for 3 days (Days 12-14); 200 mg once a day for 3 days (Days 15-17); 260 mg once a day for 3 days (Days 18-20); 300 mg once a day for 4 days (Days 21-24); and placebo on Day 25
- Group 2:** Placebo on Day -2 and Day -1; moxifloxacin 400 mg on Day 1; placebo on Day 2 to Day 24; placebo on Day 25
- Group 3:** Placebo on Day -2 and Day -1; placebo on Day 1 to Day 24; moxifloxacin 400 mg on Day 25

The TQT study was reviewed by the Interdisciplinary Review Team (IRT) for QT Studies (Primary reviewer: Janice Brodsky, Ph.D.; review dated April 11, 2013). The IRT review noted that a modest increase in QTc (~ 7 ms) was detected in this thorough QT study. The increase was not considered dose-

or concentration-dependent. The suprathreshold dose in this study (300 mg) provided exposure (C_{max} and AUC) of 2.8-fold those values at the maximum therapeutic dose and covered a worst-case exposure scenario in patients. The team observed that the increase in QTc in this study was similar to the increase reported in the label for milnacipran (8 ms).

In addition, the IRT review noted that an increase in heart rate (~ 20 bpm) was also detected in this study at both doses. The effect was not dose- or concentration dependent. It also noted that an increase in blood pressure was observed in this study. The placebo-adjusted change from baseline in systolic and diastolic blood pressure was approximately 7 mmHg and 12 mmHg, respectively.

Overall, the IRT team concluded that a significant QTc prolongation effect of 120 mg and 300 mg levomilnacipran HCl 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 contrast to the IRT review, the sponsor concluded that levomilnacipran did not appear to have a clinically significant impact on the QTc interval at either the maximum therapeutic dose of 120 mg/day or the suprathreshold dose of 300 mg/day. The sponsor acknowledges that, for both the 120 mg and 300 mg groups, the upper limit of the two-sided 90% CI of the largest time-matched $\Delta\Delta QTcNi$ were higher than the upper boundary threshold of 10 msec. The sponsor suggests that this is consistent with the lack of significant QTc findings in other clinical and pharmacokinetic studies, where the only QT findings were QTcB increases that were consistent with heart rate increases.

In addition to mean change from baseline in QT, the number and percentage of subjects with extreme values for individually corrected QTc interval also examined. Extreme values were defined as individually corrected QTc interval greater than 450, 480, or 500 msec; or individually corrected QTc interval change from time-matched baseline on Day -2 of greater than 30 or 60 msec. Table 74 lists the number of subjects as well as the number of observations whose QTcI values are \leq 450 ms or between 450 ms and 480 ms (source: IRT team review, Table 10). No subject's QTcI was above 480 ms.

Table 74: Categorical Analysis for QTcI

	N	Value <= 450 ms	450 ms < Value <= 480 ms
Treatment Group			
Levomilnacipran 120 mg	86	80 (93.0%)	6 (7.0%)
Placebo	74	70 (94.6%)	4 (5.4%)
Treatment Group			
Levomilnacipran 300 mg	78	72 (92.3%)	6 (7.7%)
Placebo	72	69 (95.8%)	3 (4.2%)
Treatment Group			
Moxifloxacin 400 mg	72	63 (87.5%)	9 (12.5%)
Placebo	74	69 (93.2%)	5 (6.8%)

Table 75 lists the categorical analysis results for Δ QTcI (source: IRT team review, Table 11). There is 1 (1.2%) subject who experienced QTcI greater than 60 ms in levomilnacipran 120 mg.

Table 75: Categorical Analysis for Δ QTcI

	N	Value <= 30 ms	30 ms < Value <= 60 ms	Value > 60 ms
Treatment Group				
Levomilnacipran 120 mg	86	79 (91.9%)	6 (7.0%)	1 (1.2%)
Placebo	74	72 (97.3%)	2 (2.7%)	0 (0.0%)
Treatment Group				
Levomilnacipran 300 mg	78	72 (92.3%)	6 (7.7%)	0 (0.0%)
Placebo	72	72 (100%)	0 (0.0%)	0 (0.0%)
Treatment Group				
Moxifloxacin 400 mg	72	71 (98.6%)	1 (1.4%)	0 (0.0%)
Placebo	74	73 (98.6%)	1 (1.4%)	0 (0.0%)

7.4.6 Immunogenicity

No specific evaluations of immunogenicity were reported under this NDA. In short term trials, 220 patients (13.9%) receiving any dose of levomilnacipran experienced AEs in the skin and subcutaneous tissue disorders SOC compared to 55 (5.3%) in the placebo group; the most common preferred term for both groups was hyperhidrosis. No SAEs in this SOC were reported in short term studies. Eighteen patients discontinued levomilnacipran in short term studies due to skin and subcutaneous tissue disorder AE, compared to two patients who discontinued placebo. Selected discontinuations were reviewed in 7.3.3.

Two patients (0.1%) experienced AEs of hypersensitivity on levomilnacipran compared to one (0.1%) on placebo.

No cases of Stevens - Johnson syndrome or angioedema were reported. In LVM-MD-01, there was a single case of facial swelling. No narrative is available for review. The information below was culled from the AE dataset and Table 10.6.1 in Appendix VI of the Integrated Summary of Safety (Vol 2, page 12736).

- Subject 090149, 56yo female: Patient experienced moderate swelling face (Investigator term: right lower facial swelling) and moderate hypoesthesia (Investigator term: right lower facial numbness) beginning on Study Day 8, ending Study Day 9. The patient later experienced moderate swelling face (Investigator term: left lower facial swelling) and moderate hypoesthesia (Investigator term: left lower facial numbness) beginning on Study Day 11, ending Study Day 12. All events were considered related to the investigational product. The patient went on to complete both the short term trial in which the AE occurred as well as the long term open-label study.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Data from short term, placebo controlled, fixed-dose studies was examined to explore for any potential dose dependency of adverse events. Several TEAEs occurred more commonly in levomilnacipran-treated patients, but most of these did not appear to demonstrate a dose-dependent relationship for incidence with the exception of urinary hesitation and erectile dysfunction. Urinary hesitation was reported by 3.6% of patients in the 40 mg group, 4.9% of patients in the 80 mg group, 6.1% of patients in the 120 mg group, and no patients in the placebo group. Erectile dysfunction was reported by 5.5% of male patients in the 40 mg group, 8.3% in the 80 mg group, 9.5% in the 120 mg group, and 2.2% in the placebo group. A few events had higher incidences for the 80 mg dose group than the other two dose groups (e.g., tachycardia and hyperhidrosis); no clear explanation for these reported incidence differences were found (see Table 76 below. Source: Integrated Summary of Safety, Vol 1, page 76, Table 8.2.2-2).

In addition to these findings, it appears there may be some dose dependency for potentially clinically significant weight gain. Although overall PCS changes in weight (> 7% increase or decrease) were similar between the 2 treatment groups, in the fixed-dose studies, more patients in the levomilnacipran 120 mg/day group met PCS criteria for weight increase: 0.3% in 40 mg/day group, 0.5% in 80 mg/day group, and 1.7% in 120 mg/day group.

Table 76: Common TEAEs ($\geq 2\%$ in any levomilnacipran group and at a greater rate than in the placebo group) in short term, fixed-dose studies - safety population

<i>System Organ Class Preferred Term^a</i>	<i>Placebo (N = 362) n (%)</i>	<i>Levomilnacipran</i>		
		<i>40 mg/d (N = 366) n (%)</i>	<i>80 mg/d (N = 367) n (%)</i>	<i>120 mg/d (N = 180) n (%)</i>
Cardiac disorders				
Palpitations	3 (0.8)	15 (4.1)	18 (4.9)	8 (4.4)
Tachycardia	6 (1.7)	8 (2.2)	26 (7.1)	3 (1.7)
Gastrointestinal disorders				
Nausea	15 (4.1)	46 (12.6)	68 (18.5)	23 (12.8)
Dry mouth	24 (6.6)	39 (10.7)	30 (8.2)	27 (15.0)
Constipation	11 (3.0)	32 (8.7)	30 (8.2)	23 (12.8)
Vomiting	2 (0.6)	15 (4.1)	19 (5.2)	6 (3.3)
Diarrhea	13 (3.6)	15 (4.1)	14 (3.8)	7 (3.9)
General disorders and administration site conditions				
Fatigue	4 (1.1)	3 (0.8)	8 (2.2)	5 (2.8)
Infections and infestations				
Upper respiratory tract infection	21 (5.8)	24 (6.6)	19 (5.2)	4 (2.2)
Nasopharyngitis	16 (4.4)	20 (5.5)	16 (4.4)	7 (3.9)
Investigations				
Heart rate increased	3 (0.8)	31 (8.5)	22 (6.0)	17 (9.4)
Blood pressure increased	4 (1.1)	9 (2.5)	10 (2.7)	4 (2.2)
Metabolism and nutrition disorders				
Decreased appetite	4 (1.1)	8 (2.2)	10 (2.7)	6 (3.3)
Nervous system disorders				
Headache	36 (9.9)	51 (13.9)	61 (16.6)	27 (15.0)
Dizziness	9 (2.5)	17 (4.6)	29 (7.9)	14 (7.8)
Somnolence	4 (1.1)	4 (1.1)	12 (3.3)	1 (0.6)
Psychiatric disorders				

Table 76: Common TEAEs ($\geq 2\%$ in any levomilnacipran group and at a greater rate than in the placebo group) in short term, fixed-dose studies - safety population (con't.)

<i>System Organ Class Preferred Term^a</i>	<i>Placebo (N = 362) n (%)</i>	<i>Levomilnacipran</i>		
		<i>40 mg/d (N = 366) n (%)</i>	<i>80 mg/d (N = 367) n (%)</i>	<i>120 mg/d (N = 180) n (%)</i>
Insomnia	12 (3.3)	13 (3.6)	20 (5.4)	7 (3.9)
Anxiety	2 (0.6)	5 (1.4)	5 (1.4)	5 (2.8)
Renal and urinary disorders				
Urinary hesitation	0	13 (3.6)	18 (4.9)	11 (6.1)
Reproductive system and breast disorders				
Erectile dysfunction ^a	3 (2.2)	7 (5.5)	11 (8.3)	7 (9.5)
Testicular pain ^a	0	5 (3.9)	5 (3.8)	2 (2.7)
Ejaculation disorder ^a	0	2 (1.6)	1 (0.8)	2 (2.7)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	4 (1.1)	16 (4.4)	42 (11.4)	10 (5.6)
Vascular disorders				
Hot flush	3 (0.8)	6 (1.6)	13 (3.5)	4 (2.2)

Note: Group 1A fixed-dose studies include LVM-MD-01 and LVM-MD-10. Only TEAEs reported in at least 2 percent of levomilnacipran treated patients (total) and greater than placebo are included.

a Sex-specific TEAE. Percentage is relative to the number of patients of the appropriate sex.

7.5.2 Time Dependency for Adverse Events

The sponsor did not specifically examine time dependency for adverse events in the short term trials. To explore this, a subset of the AE database containing only adverse events that occurred from Days 1 through 56 was created to encompass the 8-week double-blind treatment period of the short term studies. Only time-dependency in the active treatment arms was examined. Using this dataset, it appears that the majority of AEs occurred in the first two weeks of treatment: 35.0% in Days 1-7, 23.0% in Days 7-14, 11.8% in Days 15-21, 8.6% in Days 22-28, 7.6% in Days 29-35, 4.7% in Days 36-42, 4.5% in Days 43-49, and 4.8% in Days 50-56. While these calculations provide a general overview of AEs, they do not take into account whether AEs were newly emergent or ongoing, they do not explore time-dependency of any specific AE, and they do not take drop-outs into consideration.

The sponsor did evaluate time dependency of adverse events in the long term open-label trial (LVM-MD-04). The sponsor's analyses suggest that TEAEs by time of onset generally did not reveal new TEAEs reported with longer term treatment (> 24 weeks). The majority of the common TEAEs ($\geq 5\%$) in LVM-MD-04 were reported during first eight weeks of initiation of open-label treatment. Of these, nausea was reported more frequently in patients who received placebo compared to levomilnacipran during the lead-in study. Among patients with any TEAE, 73.8% experienced an AE in the first eight weeks of open-label treatment.

7.5.3 Drug-Demographic Interactions

Sex

In the short term studies, levomilnacipran-treated female patients experienced nausea (20.9%) at approximately twice the rate of male patients (10.6%). The incidences of tachycardia, palpitations, constipation, vomiting, heart rate increased, and hyperhidrosis were not appreciably different in the two sexes in levomilnacipran-treated patients. Table 77 below presents TEAEs that were reported in at least 5% of levomilnacipran-treated patients and at twice the rate of placebo by sex (source: Integrated Summary of Safety, Vol 1, page 195, Table 13.1.1-1).

Table 77: TEAEs reported in ≥5% of patients in the levomilnacipran treatment group and at twice the rate of the placebo group in either sex category in short term trials - safety population

	<i>Male Patients</i>		<i>Female Patients</i>	
	<i>Placebo (N = 374) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 577) n (%)</i>	<i>Placebo (N = 666) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1006) n (%)</i>
Patients with any TEAE	221 (59.1)	448 (77.6)	418 (62.8)	774 (76.9)
Cardiac disorders				
Tachycardia	6 (1.6)	30 (5.2)	9 (1.4)	48 (4.8)
Palpitations	5 (1.3)	22 (3.8)	9 (1.4)	52 (5.2)
Gastrointestinal Disorders				
Nausea	16 (4.3)	61 (10.6)	42 (6.3)	210 (20.9)
Constipation	9 (2.4)	43 (7.5)	17 (2.6)	91 (9.0)
Vomiting	1 (0.3)	21 (3.6)	7 (1.1)	55 (5.5)
Investigations				
Heart rate increased	3 (0.8)	35 (6.1)	6 (0.9)	55 (5.5)
Reproductive system and breast disorders				
Erectile dysfunction ^a	5 (1.3)	33 (5.7)	—	—
Skin and subcutaneous tissue disorders				
Hyperhidrosis	7 (1.9)	48 (8.3)	13 (2.0)	87 (8.6)

^a Sex-specific TEAE. Percentage is relative to the number of patients in the associated demographic sex category.
n = number of patients with the specified event; N = number of patients in the Safety Population in the designated subgroup; TEAE = treatment-emergent adverse event

Age

In short term trials, based on the drug-placebo difference (DPD), the incidence for palpitation was higher in the < 55 years population (DPD = 4.3% in < 55yo; 0.5% in > 55yo). The incidence for hyperhidrosis was higher in ≥ 55 years (DPD = 5.8% in < 55yo; 9.4% in > 55yo). The incidences of tachycardia, heart rate increased, vomiting, constipation, dizziness, and erectile dysfunction were not appreciably different between the two age groups (see Table 78 below. Source: Integrated Summary of Safety, Vol 1, page 196, Table 13.1.1-2).

Table 78: TEAEs reported in $\geq 5\%$ of patients in the levomilnacipran treatment group and at twice the rate of the placebo group in either age category in short term trials - safety population

	<i>Patients < 55 Years</i>		<i>Patients ≥ 55 Years</i>	
	<i>Placebo (N = 822) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1259) n (%)</i>	<i>Placebo (N = 218) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 324) n (%)</i>
Patients with any TEAE	518 (63.0)	967 (76.8)	121 (55.5)	255 (78.7)
Cardiac disorders				
Tachycardia	11 (1.3)	60 (4.8)	4 (1.8)	18 (5.6)
Palpitations	9 (1.1)	65 (5.2)	5 (2.3)	9 (2.8)
Gastrointestinal Disorders				
Nausea	51 (6.2)	217 (17.2)	7 (3.2)	54 (16.7)
Constipation	18 (2.2)	93 (7.4)	8 (3.7)	41 (12.7)
Vomiting	8 (1.0)	65 (5.2)	0	11 (3.4)
Investigations				
Heart rate increased	8 (1.0)	76 (6.0)	1 (0.5)	14 (4.3)
Nervous system disorders				
Dizziness	42 (5.1)	105 (8.3)	8 (3.7)	25 (7.4)
Reproductive system and breast disorders				
Erectile dysfunction ^a	4 (1.3)	27 (5.7)	1 (1.4)	6 (5.6)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	17 (2.1)	100 (7.9)	3 (1.4)	35 (10.8)

a Sex-specific TEAE. Percentage is relative to the number of patients in the associated demographic sex category. n = number of patients with the specified event; N = number of patients in the Safety Population in the designated subgroup; TEAE = treatment-emergent adverse event

Race

The incidences of tachycardia, palpitations, heart rate increased, nausea, constipation, hyperhidrosis, and erectile dysfunction were not appreciably different between the two race groups (see Table 79 below. Source: Integrated Summary of Safety, Vol 1, page 197, Table 13.1.1-3).

Table 79: TEAEs reported in $\geq 5\%$ of patients in the levomilnacipran treatment group and at twice the rate of the placebo group in either race category in short term trials - safety population

	<i>White</i>		<i>All Other Races</i>	
	<i>Placebo (N = 851) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1237) n (%)</i>	<i>Placebo (N = 188) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 346) n (%)</i>
Patients with any TEAE	527 (61.9)	981 (79.3)	111 (59.0)	241 (69.7)
Cardiac disorders				
Tachycardia	14 (1.6)	65 (5.3)	1 (0.5)	13 (3.8)
Palpitations	13 (1.5)	63 (5.1)	1 (0.5)	11 (3.2)
Gastrointestinal Disorders				
Nausea	47 (5.5)	220 (17.8)	11 (5.9)	51 (14.7)
Constipation	20 (2.4)	106 (8.6)	6 (3.2)	28 (8.1)
Investigations				
Heart rate increased	7 (0.8)	67 (5.4)	2 (1.1)	23 (6.6)
Reproductive system and breast disorders				
Erectile dysfunction ^a	5 (1.7)	24 (5.5)	0	9 (6.4)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	19 (2.2)	121 (9.8)	1 (0.5)	14 (4.0)

^a Sex-specific TEAE. Percentage is relative to the number of patients in the associated demographic sex category. n = number of patients with the specified event; N = number of patients in the Safety Population in the designated subgroup; TEAE = treatment-emergent adverse event

7.5.4 Drug-Disease Interactions

Drug-disease interactions were examined in two pharmacokinetic trials—impaired renal function in LVM-PK-02 and hepatic impairment in LVM-PK-05.

Impaired Renal Function

Study LVM-PK-02 was intended to evaluate the PK characteristics and safety profile of levomilnacipran and its non-active metabolite F17400 after a single oral dose of 40-mg levomilnacipran in male and female patients with various degrees of impaired renal function compared with healthy subjects with normal renal function. This study was a single-dose, open-label, parallel-group study. A total of 32 volunteers consisting of 8 subjects with normal renal function, 8 patients with mildly impaired renal function, 8 patients with moderately impaired renal function, and 8 patients with severely impaired renal function, were enrolled and all patients/subjects completed the study as planned.

Categorization of renal impairment was based on the creatinine renal clearance (CL_{cr}) value determined on Day-1 based on the Cockcroft-Gault equation:

- Normal renal function = CL_{cr} \geq 80 mL/min
- Mild renal impairment = CL_{cr} \geq 50 and $<$ 80 mL/min
- Moderate renal impairment = CL_{cr} \geq 30 and $<$ 50 mL/min

- Severe renal impairment = CL_{cr} > 5 and < 30 mL/min

A single dose of levomilnacipran 40mg was administered and PK profiles of drug and metabolite were obtained. Pharmacokinetic parameters were evaluated based on plasma and urine concentration versus time data collected for 96 hours after the dose.

The sponsor concluded that patients with severe renal impairment did exhibit more pronounced changes during the study in systolic BP (increased), higher incidence of a few PCS laboratory values and more shifts to abnormal ECG. Further, based on the observation that renal impairment is associated with increased levomilnacipran exposure and prolonged T_{1/2}, dosing adjustment is recommended in patients with moderate or severe renal impairment.

In his Clinical Pharmacology review (6/17/2013), Kofi Kumi, Ph.D. also notes that mild renal impairment did not significantly affect levomilnacipran exposure. However, moderate and severe renal impairment increased exposure (AUC) of levomilnacipran by 92% and 180%, respectively when compared with subjects with normal renal function. He recommends dose adjustment 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.

Hepatic Impairment

Study LVM-PK-05 was intended to evaluate the PK characteristics and safety profile of levomilnacipran and its non-active metabolite F17400 after a single oral dose of 40 mg levomilnacipran in male and female patients with varying degrees of impaired hepatic function compared with healthy subjects with normal hepatic function. This study was a single-dose, open-label, parallel-group study conducted in 24 male and female patients with hepatic impairment (8 each of mild, moderate and severe hepatic impairment) and 8 healthy male and female subjects, aged 33-66 years.

Classification of hepatic impairment was based on the Child-Pugh Classification. Patients with Child-Pugh scores greater than 13 were not enrolled in this study.

The sponsor concluded that a single dose of levomilnacipran 40 mg was generally well tolerated by healthy subjects as well as by patients with mild, moderate and severe hepatic impairment. Exposure of the metabolite F17400 was lower in patients with severe hepatic impairment by about 85% compared to healthy subjects. F17400 being an inactive metabolite, this difference is not clinically significant both in terms of efficacy or safety. In severe hepatic impairment the exposure to levomilnacipran was approximately 32% higher compared with subjects with normal hepatic function. The sponsor stated that dose adjustment may not be necessary in mild, moderate and severe hepatic impairment.

In his Clinical Pharmacology review (6/17/2013), Kofi Kumi, Ph.D. agreed that dose adjustment was not necessary in hepatic impairment.

7.5.5 Drug-Drug Interactions

There were three pharmacokinetic studies that examined extrinsic factors: LVM-PK-08 (ketoconazole interaction), LVM-PK-09 (carbamazepine interaction), and LVM-PK-010 (alprazolam interaction).

Ketoconazole Interaction

Study LVM-PK-08 was intended to assess the effects of ketoconazole at steady state on the pharmacokinetics of a single dose of levomilnacipran. This was a single-center, randomized, open-label, 2 x 2-crossover, drug-drug interaction study in 34 healthy subjects aged 18 through 45 years. Subjects received 2 treatments in a randomized order, separated by at least a 6-day washout period.

The sponsor concluded that co-administration with ketoconazole caused statistically significant increases in C_{max} (39%) and AUC_{0-∞} (57%), delayed the T_{max} for 2 hours, and had no effect on the T_{1/2} of levomilnacipran. (b) (4)

In his Clinical Pharmacology review (6/17/2013), Kofi Kumi, Ph.D. disagreed with the sponsor's recommendation. He recommended that levomilnacipran dose should not exceed 80 mg when co-administered with ketoconazole or other strong inhibitors of CYP3A4.

Carbamazepine Interaction

Study LVM-PK-09 was intended to assess the effects of carbamazepine XR on the pharmacokinetics of a single dose of levomilnacipran. This study was a single-center, open-label, fixed-sequence, multiple-dose, 4-period study in 34 healthy male and female subjects, aged 19 through 42 years. Subjects received treatments A (levomilnacipran), B (carbamazepine XR), C (concomitant levomilnacipran and carbamazepine XR), and D (carbamazepine XR) in a fixed order. Treatments A and B were separated by a 7-day washout period, and there were no washout periods between treatments B, C or D.

The sponsor concluded that there was a statistically significant decrease in the exposure of levomilnacipran (<29%) by the treatment with carbamazepine XR. No effect of levomilnacipran treatment on the exposure of carbamazepine was observed and the effect on the formation of carbamazepine-10,11-epoxide was inconclusive. Although there was a trend of increase in AEs when levomilnacipran and carbamazepine were co-administered compared to the incidence of AEs when each drug was administered alone, the sponsor concluded that the increase was small and most likely not clinically significant. Based on the PK results and safety measurements, the sponsor stated there was not a clinically significant difference when F2695 and carbamazepine were co-administered under steady-state conditions.

In his Clinical Pharmacology review (6/17/2013), Kofi Kumi, Ph.D. agreed that dose adjustment was not necessary due to carbamazepine.

Alprazolam Interaction

Study LVM-PK-010 was intended to assess the effects levomilnacipran at steady state on the pharmacokinetics of alprazolam following a single-dose administration of an alprazolam XR tablet. This study was a single-center, randomized, open-label, 2 × 2-crossover, drug-drug interaction study in 30 healthy male and female subjects aged 18 through 45 years. Subjects were randomized to 1 of the 2 treatment sequences, separated by a 9-day washout period between treatments for Sequence I and a 7-day washout period between treatments for Sequence II.

The sponsor concluded that steady state levomilnacipran had no clinically relevant effect on the single-dose pharmacokinetics of alprazolam, single-dose alprazolam had no clinically relevant effect on the steady state pharmacokinetics of levomilnacipran, and the use of alprazolam in combination with levomilnacipran is not likely to alter the safety profile of either drug in patients with major depressive disorder.

In his Clinical Pharmacology review (6/17/2013), Kofi Kumi, Ph.D. agreed that dose adjustment was not necessary due to alprazolam.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The overall incidence of adverse events in the SOC “Neoplasms benign, malignant and unspecified” was reviewed to determine whether there may be a potential signal of human carcinogenicity in the levomilnacipran development program. Two cases were identified in the levomilnacipran group, two in placebo. Each group had one case of melanocytic nevus. There was one skin papilloma in the levomilnacipran group, and one basal cell carcinoma in the placebo group. One death related to neoplasm (Subject 0160222) was reported in LVM-MD-04, the long term, open label study; this case was reviewed in 7.3.1, and was likely unrelated to levomilnacipran.

7.6.2 Human Reproduction and Pregnancy Data

No studies examining the effect of levomilnacipran on human reproduction were reported under this NDA. Fifteen pregnancies were reported while patients were on treatment. Of these, two patients experienced SAEs related to their pregnancies.

- Subject 0310118, 35yo female: Patient was enrolled in LVM-MD-01, and received 80mg levomilnacipran. Relevant medical history included hypertension in three prior pregnancies. At Visit 5 (27 Jan 2010), pregnancy testing was positive and investigational product was discontinued. Bupropion hydrochloride was started on 01 June 2010 for treatment of major depressive disorder. An SAE of moderate pre-eclampsia was reported on 30 June 2010, approximately 150 days after stopping investigational product. The SAE was considered not related to investigational product. The patient delivered a healthy girl and the patient reported that blood pressure returned to normal approximately 6 weeks after hospital discharge.

- Subject 0120167, 25yo female: Patient was enrolled in LVM-MD-01, and received 120mg levomilnacipran. Relevant medical history included four previous pregnancies, two full-term and two spontaneous abortions, with hypertension during her first pregnancy. The patient completed the study after 59 days of treatment with active drug, and down-taper treatment for seven days. Pregnancy testing was negative at screening and Visit 5 (6 Oct 2010). On 08 Nov 2010, upon completion of the study, pregnancy test result was positive, and patient discontinued down-taper therapy on 14 Nov 2010. Based on last menstrual period date, the sponsor estimated that the patient became pregnant 30 days after starting study medication. She prematurely delivered a baby boy who remained hospitalized for 3-4 weeks due to SAEs of premature baby and small-for-dates baby.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies were reported under this application, and no data on the exposure of children and adolescents to levomilnacipran are available. The sponsor is seeking a waiver for children under 7 years of age and a deferral for children 7 to 17 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Overdose was defined in two ways: any patient who took ≥ 180 mg/day of levomilnacipran or any patient for whom an AE of overdose was reported during the study. In short term studies, overdose was reported as a TEAE in 3 patients: 1 suicide attempt (Study LVM-MD-03, Subject 0670303) and 2 accidental overdoses (Study F02695 LP 2 02, Subjects 110403 and 110404). Subject 0670303 attempted suicide by taking 15-20 capsules of 500 mg acetaminophen / 25 mg diphenhydramine. Subjects 110403 and 110404 took 2 capsules (200 mg) levomilnacipran instead of 1 capsule (100 mg).

The maximum daily dose ingested in the clinical studies occurred in LVM-MD-04. One patient (Subject 0350121) misunderstood instructions and took nine capsules of 40 mg (360 mg) daily for seven days instead of the prescribed dosage of three capsules (120 mg) daily. This overdose was not reported as a TEAE, and the patient completed the study.

Drug Abuse Potential

No human studies examining drug abuse potential were conducted with levomilnacipran.

Withdrawal and Rebound

See discussion of Discontinuation Syndrome under 7.3.5.

7.7 Additional Submissions / Safety Issues

7.7.1 Suicidality and Other Psychiatric Adverse Events

The reported TEAEs associated with suicidal thoughts and behaviors were similar in both treatment groups. For 11 of the 15 patients (6 placebo, 5 levomilnacipran), the event was either reported as a SAE and/or contributed to premature discontinuation from the study (reviewed above). See Table 80 below for additional details (source: Integrated Summary of Safety, Vol 1, page 108, Table 8.7.1-1).

Table 80: Incidence of TEAEs associated with suicidal thoughts and behaviors in short term trials - safety population

	<i>Placebo (N = 1040) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1583) n (%)</i>
Patients with at least one suicidality TEAE	7 (0.7)	8 (0.5)
Completed suicide	0	0
Suicide attempt	0	1 (0.1)
Suicidal ideation	6 (0.6)	6 (0.4)
Suicidal behavior	1 (0.1)	1 (0.1)
Intentional overdose	0	1 (0.1)

TEAE = treatment-emergent adverse event.

Table 81 below (source: Integrated Summary of Safety, Vol 1, page 109, Table 8.7.1-2) presents the lifetime incidence of suicidal ideation and behavior, as well as the incidence of most severe suicidal ideation and most severe suicidal behavior reported in short term trials (US and Canada; does not include F02695-LP2-02), based on Investigators' evaluations of patient responses to the C-SSRS. During the double-blind treatment period, suicidal behavior was reported in 5 levomilnacipran-treated patients (0.4%) compared with 1 patient (0.1%) in the placebo group. The percentage of patients with C-SSRS reports of suicidal ideation was similar for the two treatment groups.

Table 81: Number (percentage) of patients with most severe suicidal ideation and most severe suicidal behavior as reported in the C-SSRS (short term trials) - safety populations

<i>Parameter</i>	<i>Placebo (N = 761) n (%)</i>	<i>Levomilnacipran 40-120 mg/d (N = 1305) n (%)</i>
Lifetime History		
Suicidal Ideation	378 (49.7)	661 (50.7)
Suicidal Behavior	150 (19.7)	246 (18.9)
Double-blind Treatment Period		
N1	754	1294
No suicidal ideation	585 (77.6)	982 (75.9)
Suicidal Ideation	169 (22.4)	312 (24.1)
Most severe suicidal ideation		
Active suicidal ideation with specific plan and intent	2 (0.3)	4 (0.3)
Active suicidal ideation with some intent to act, without specific plan	5 (0.7)	7 (0.5)
Active suicidal ideation with any methods (not plan) without intent to act	25 (3.3)	49 (3.8)
Non-specific active suicidal thoughts	24 (3.2)	41 (3.2)
Wish to be dead	113 (15.0)	211 (16.3)
No suicidal behavior	753 (99.9)	1289 (99.6)
Suicidal behavior	1 (0.1)	5 (0.4)
Most severe suicidal behavior		
Completed suicide	0	0
Actual attempt	0	3 (0.2)
Interrupted attempt	0	0
Aborted attempt	0	1 (0.1)
Preparatory acts or behavior	1 (0.1)	1 (0.1)

Note: Patients are counted once for each suicidal ideation and each suicidal behavior. Only the most severe ideation type and the most severe suicidal behavior across all visits during the double-blind treatment period are counted for each patient.

C-SSRS = Columbia-Suicide Severity Rating Scale; N = number of patients in the Safety Population; n = number of patients within a specific category; N1 = number of patients with assessment available for analysis at a specific time point; SR = sustained release.

7.7.2 Sedative events

By AE preferred term, somnolence was considered a common AE (2.3% of levomilnacipran-treated patients vs. 1.7% placebo) for all patients who have received levomilnacipran in short term trials. It did not, however, reach the “most common” threshold of $\geq 5\%$ and 2x placebo. Sedation was not a common AE.

7.7.3 120-Day Safety Update

The sponsor submitted the 120-day Safety Update Report for levomilnacipran on January 16, 2013. The data cut-off date for the Safety Update was September 24, 2012. The Safety Update included additional safety information for LVM-MD-04, the open-label extension study.

The Safety Update included data for 46 additional patients who were active at the ISS data cut-off date. Key safety findings in these additional levomilnacipran-treated patients include:

- 43 patients completed the study; 3 were prematurely discontinued, one due to a protocol violation and two lost to follow-up.

- One SAE of non-cardiac chest pain
 - Subject 0640347, 50yo female: The patient's pertinent medical history included gastroesophageal reflux disease. Concomitant medications included calcium 600 mg BID, omeprazole 20 mg/day, and naproxen.

The data from the additional 46 patients did not change the overall conclusions for laboratory values, vital signs, or electrocardiograms (ECGs). No clinically meaningful adverse events of special interest were observed. No additional patients reported TEAEs associated with suicidality.

8 Postmarketing Experience

Levomilnacipran is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

The sponsor conducted a literature search on December 10, 2012 for levomilnacipran utilizing the major electronic databases MEDLINE, EMBASE and BIOSIS by using the key words "F2695", "F()2695" "LEVOMILNACIPRAN" or "RN=175131-60-9". The search retrieved 144 unique records of publications, including reviews, clinical research articles, and meeting abstracts. Of these, nine publications were considered relevant to levomilnacipran SR capsules. A summary of the nine publications was submitted to FDA on February 28, 2013. The nine cited abstracts and posters address findings from three of the completed studies for which results were submitted in the NDA: F02695 LP 2 02 (Phase II, supportive study), LVM-MD-01 (fixed dose Phase III positive study) and LVM-MD-02 (flexible dose Phase III, negative study). The efficacy and safety results of these studies are reported in much greater detail in the ISE and ISS (and clinical study reports).

9.2 Labeling Recommendations

Complete labeling recommendations will be provided in a separate Word document using track changes. A summary of major labeling recommendations is presented below. In general, other labeling proposed by the sponsor is deemed acceptable.

Complete labeling recommendations will be provided in a separate Word document using track changes. A summary of major labeling recommendations is presented below.

Overarching Comments to Sponsor

- Update the product nomenclature ("extended-release" (b) (4) and remove the word (b) (4) as related to medication class throughout the label.
- Update full prescribing information (FPI) *Warnings and Precautions* headings to match (by name and order) those listed in *Highlights*.
- Remove (b) (4) throughout the label.

Highlights

- The boxed warning and other labeling related to suicidal ideation and behavior have been updated in content and format to match current class labeling.

Indications and Usage

- [REDACTED] (b) (4)
- To meet requirements of the single enantiomer exclusivity, a limitation was added noting that efficacy and safety of this product in fibromyalgia have not been established.

Dosage and Administration

- Under *Special Populations [2.2]*, subsections for pregnant women and nursing mothers were deleted because there are no specific recommendations. Language was moved to relevant subsections of *Use in Specific Populations*.
- Under *Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant [2.5]*, the recommendation to allow (b) (4) days after stopping this product before starting an MAOI was changed to 7 days [REDACTED] (b) (4)
- Dosing recommendations for concomitant use with strong inhibitors of CYP3A4 were added.

Warnings & Precautions

- Subsections were reordered to reflect decreasing order of clinical concern.
- The boxed warning and other labeling related to suicidal ideation and behavior have been updated in content and format to match current class labeling.
- Language under *Serotonin Syndrome [5.2]* was modified, reducing the number of examples of other serotonergic drugs.
- Data relating to mean increases in SBP and DBP, and to orthostatic hypotension was added to *Elevated Blood Pressure [5.3]*.

Adverse Reactions

- The list of common adverse reactions was reordered to reflect decreasing incidence.
- The sponsor was asked to group similar event terms for 1) palpitation, heart rate increased, and tachycardia; 2) increased blood pressure and hypertension. The sponsor was asked to recalculate the percent of patients experiencing these events for Table 3, and to insert a footnote which terms were combined.
- The sponsor was asked to delete any events occurring in < 2% of patients from Table 4.
- Under the “Other adverse reactions observed in clinical studies” heading, the sponsor was asked to remove any items already mentioned elsewhere in the label.
- Language related to the thorough QT study was modified to reflect our view that QTc prolongation was observed.
- Any information regarding vital signs data already discussed in *Warnings & Precautions* was removed.
- Laboratory data that did involve clinically significant results was removed.

- Language related to weight change was modified to more accurately reflect the findings related to PCS changes from the fixed dose studies.

Drug Interactions

- Recommendations regarding dose adjustment when this product is co-administered with inhibitors of CYP3A4 were added, and the rest of *Potential for Other Drugs to Affect TRADENAME [now 7.4]* was expanded and reformatted.
- The sponsor was asked to modify the forest plot presented in Figure 1 to reflect the revised dosing recommendations.
- *Potential for TRADENAME to Affect Other Drugs [now 7.5]* was similarly expanded and reformatted.
- The sponsor was asked to include an additional forest plots to describe the study results based on alprazolam or carbamazepine.
- *Central Nervous System (CNS)-Active Agents [now 7.6]* was combined with *Alcohol [previously 7.9]*.
- *Triptans* (b) (4) was deleted. This information is included in *Warnings & Precautions*.

Use in Specific Populations

- This section was updated to be more consistent in content and format with other SNRIs.
- (b) (4)
- The sponsor was asked to include recommended dose adjustments under *Renal Impairment [8.7]*.
- The sponsor was asked to change the term (b) (4) to “Gender” in heading of 8.8, as well as in the forest plot in this section (currently Figure 2). “Gender” is the current preferred term based on the most recent version of the Labeling Review Tool.

Clinical Pharmacology

- *Mechanism of Action [12.1]* was updated with current class language.
- QT information with revised language was moved to *Pharmacodynamics [12.2]*.

Clinical Studies

- Information presented in the primary efficacy table was removed from the text.
- (b) (4)
- (b) (4)

How Supplied/Storage and Handling

- Titration pack information was removed.

Patient Counseling Information

- The sponsor was asked to update this section, noting that references should be consistent with relevant sections of the label, and that the order of listed warnings should be consistent with those under *Warnings & Precautions*.
- The sponsor was advised that providing information about what to do if one misses a dose is a requirement for medication guides according to the CFR.

- The sponsor was further advised that the information must also be in the FPI in order to be in the Medication Guide.

Some additional editorial changes were made to the sponsor’s proposed label to reflect current labeling format guidelines. In general, other labeling proposed by the sponsor is deemed acceptable.

9.3 Advisory Committee Meeting

It was decided that this NDA would not be presented to an Advisory Committee since there are several previously approved agents in the SNRI antidepressant class of drugs, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the design and results of the efficacy trials did not pose particular concerns.

9.4 Additional Efficacy Results and Tables

Study LVM-MD-01

Additional efficacy parameter results

Table 82: Change from baseline to week 8 in additional efficacy parameters (MMRM), ITT population (Study LVM-MD-01)

Additional efficacy parameters	LVM			Placebo (N = 175)
	40 mg (N = 176)	80 mg (N = 177)	120 mg (N = 176)	
HAMD-17				
Baseline, mean ± SEM	24.7 ± 0.3	24.9 ± 0.3	25.0 ± 0.3	24.6 ± 0.3
Change at week 8, LS mean ± SE	-9.4 ± 0.7	-10.5 ± 0.8	--11.1 ± 0.7	-8.7 ± 0.7
p-Value	0.1994	0.0289	0.0155	-
CGI-I score				
Baseline, mean ± SEM	3.6 ± 0.1	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0
Value at week 8, LS mean ± SE	2.7 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.8 ± 0.1
p-Value	0.2946	0.0131	0.0206	-
CGI-S score				
Baseline, mean ± SEM	4.9 ± 0	4.8 ± 0	4.9 ± 0	4.9 ± 0
Change at week 8, LS mean ± SE	-1.5 ± 0.1	-1.7 ± 0.1	-1.7 ± 0.1	-1.3 ± 0.1
p-Value	0.0615	0.0084	0.0335	-

Source: Tables 14.4.3.3A, 14.4.3.6A, 14.4.3.9A, 14.4.3.10A, 14.4.3.11A, 14.4.3.12A, 14.4.3.13A, and 14.4.3.15A.

Table 83: Response rates for MADRS-CR at week 8 (LOCF), ITT population

Response rates for MADRS-CR	LVM			Placebo (N =175)
	40 mg (N = 176)	80 mg (N = 177)	120 mg (N = 176)	
MADRS-CR response, $\geq 50\%$ reduction from baseline, n/N1 (%)	64 (36)	66 (37)	73 (42)	51 (29)
p-Value	0.1129	0.0742	0.0107	-
MADRS remission (≤ 10 in MADRS, n/N1 (%))	38 (22)	37 (21)	36 (21)	34 (19)
p-Value	0.4988	0.5845	0.6795	-
HAMD-17 response rate - Responder, n/N1 (%)	63 (36)	62 (35)	65 (37)	51 (29)
p-Value	1.363	1.325	1.444	-
HAMD-17 remission rate - Remitters, n/N1 (%)	34 (19)	39 (22)	35 (20)	36 (21)
p-Value	0.946	1.140	1.010	-
CGI-I Response (CGI-I score ≤ 2), n/N1 (%)	72 (41)	82 (46)	78 (44)	66 (38)
p-Value	1.122	1.418	1.313	-

Source: Tables 14.4.3.4, 14.4.3.5, 14.4.3.7, 14.4.3.8, 14.4.3.1

Study LVM-MD-10

Additional efficacy parameter results

Table 84: Change from baseline to week 8 in additional efficacy parameters Study LVM-MD-10 (MMRM), ITT population

Additional efficacy parameters	LVM 40 mg (N = 185)	LVM 80 mg (N = 187)	Placebo (N = 185)
HAMD-17			
Baseline, mean \pm SEM	21.5 \pm 3.9	21.8 \pm 4.1	21.7 \pm 4.1
Change at week 8, LS mean \pm SE	-9 \pm 0.6	-8.6 \pm 0.6	-7 \pm 0.6
p-Value	0.0068	0.0428	-
CGI-S score			
Baseline, mean \pm SEM	4.4 \pm 0.5	4.4 \pm 0.5	4.4 \pm 0.5
Change at week 8, LS mean \pm SE	-1.5 \pm 0.09	-1.5 \pm 0.09	-1.2 \pm 0.09
p-Value	0.0200	0.0148	-

Source: Tables 14.4.3.5A, 14.4.3.8A, 14.4.3.9A, 14.4.3.10A, 14.4.3.11A, 14.4.3.12A, and 14.4.3.13A.

Table 85: Response and remission rates for additional efficacy parameters at week 8 Study LVM-MD-10 (LOCF), ITT population

Response and remission rates	LVM		Placebo (N =175)
	40 mg (N = 176)	80 mg (N = 177)	
MADRS response ($\geq 50\%$ reduction from baseline, n/N1 (%))	90/185 (48.6)	87/187 (46.5)	62/185 (33.5)
p-Value	0.0035	0.0095	-
MADRS remission (≤ 10 in MADRS, n/N1 (%))	55/185 (29.7)	59/187 (31.6)	34/185 (18.4)
p-Value	0.0117	0.0020	-
HAMD-17 response rate - Responder, n/N1 (%)	77/172 (44.8)	70/178 (39.3)	54/174 (31.0)
p-Value	0.0088	0.1010	-
HAMD-17 remission rate - Remitters, n/N1 (%)	52/172 (30.2)	54/178 (30.3)	35/174 (20.1)
p-Value	0.0280	0.0225	-

Source: Tables 14.4.3.3, 14.4.3.4, 14.4.3.6, and 14.4.3.7.

Study LVM-MD-03

Additional efficacy parameters results

Table 86: Change from baseline to week 8 in additional efficacy parameters (MMRM), ITT population (Study LVM-MD-03)

Additional efficacy measures	LVM 40-120 mg (N = 215)	Placebo (N = 214)
HAMD-17		
Baseline, mean ± SD	23.3 ± 4.1	22.9 ± 4.1
Change at week 8, LS mean ± SE	-9.6 ± 0.5	-7.5 ± 0.5
p-Value	0.0038	-
CGI-I score		
Baseline, mean ± SEM	3.5 ± 0.0	3.6 ± 0.1
Change at week 8, LS mean ± SE	2.6 ± 0.1	2.9 ± 0.1
p-Value	0.0881	-
CGI-S score		
Baseline, mean ± SEM	4.7 ± 0.1	4.8 ± 0
Change at week 8, LS mean ± SE	-1.5 ± 0.1	-1.2 ± 0.1
p-Value	0.0083	-
MEI-SF total score		
Baseline, mean ± SD	29.25 ± 15.61	30.19 ± 15.14
Change at week 8, LS mean ± SE	23.4 ± 1.7	18.3 ± 1.7
p-Value	0.0382	-

Source: Tables 14.2.8, 14.4.3.3A, 14.4.3.6A, 14.4.3.9A, 14.4.3.10A, 14.4.3.11A, 14.4.3.12A, 14.4.3.13A, 14.4.3.15A, 14.4.3.19A, 14.4.3.20A, and 14.4.3.21A.

Table 87: Response and remission rates at week 8 (LOCF), ITT population (Study LVM-MD-03)

Response and remission rates	LVM 40-120 mg (N = 215)	Placebo (N =175)
MADRS response (≥50% reduction from baseline, n/N1 (%))	90 (42)	63 (29)
p-Value	0.0083	-
MADRS remission (≤ 10 in MADRS, n/N1 (%))	37 (17)	39 (18)
p-Value	0.7255	-
HAMD-17 response (≥ 50% reduction from baseline)	83 (39)	60 (28)
p-Value	0.0198	-
HAMD-17 remission (≤ 7)	36 (17)	38 (18)
p-Value	0.9185	-
CGI-I response (CGI-I score ≤ 2)	96 (45)	70 (33)
p-Value	0.0124	-

Source: Tables 14.4.3.4, 14.4.3.5, 14.4.3.7, 14.4.3.8, and 14.4.3.14.

Study F02695 LP 2 02

The cardiovascular history data subset safety results

The cardiovascular history data was a subset of the safety data and was compromised of 71 patients in total, relatively small number of patients when compared to the study total of 557. There were no deaths or SAEs reported in this cardiovascular history data set.

TEAEs

About 74% (25/34) of the patients in the placebo treatment group reported a total of 75 TEAEs and 84% (31/37) of patients in the levomilnacipran treatment group reported a total of 112 TEAEs. The most common TEAEs (>10%) in this data set were headache, dry mouth, dizziness, hyperhidrosis, insomnia, tachycardia, and fatigue; these TEAE findings were similar to the TEAE results of the other studies.

Mean changes

The mean change in SBP at baseline to day 70 in the levomilnacipran treatment group was 4.3 mmHg compared to -0.1 in the placebo treatment group. The mean change in DBP at baseline to day 70 in the levomilnacipran treatment group was 2.2 mmHg compared to 0.4 in the placebo treatment group. The mean change in HR at baseline to day 7.4 in the levomilnacipran treatment group was 4.3 mmHg compared to -1.4 in the placebo treatment group. There were no patients with QTc Fridericia rate ≥ 450 msec in the levomilnacipran treatment group.

Changes in vital sign measurements

- PID 030101 had SBP increase of 20 mmHg (baseline value of 140 mmHg to highest value observed was 160 mmHg) and DBP increase of 17 mmHg (baseline value of 90 mmHg to highest value observed was 107 mmHg) on day 70
- PID 060505 had SBP increase of 26 mmHg (baseline value of 154 mmHg to highest value observed was 180 mmHg) on day 21
- PID 010608 had HR increases of 21 bpm (102 bpm at baseline to 120 bpm) on day 21

Overall, the sponsor noted that there were no new cardiovascular findings observed in this foreign study through evaluation of cardiovascular history dataset that have not been observed in other studies.

The rebound analysis data set results

Potential rebound was assessed through MADRS and HAM-D17 during the down titration day 70 to day 85. This analysis was performed on the Rebound Analysis Data Set. The Rebound Analysis Data Set, was a subset of the Full Analysis Set completers including all randomized FAS patients who completed the study until D85, excluding completers who received a rescue medication between D70 and D85.

A total of 467 patients underwent down-titration: 85% (n=235/276) patients in the levomilnacipran treatment group compared to 84% (n=232/277) in the placebo treatment group. A total of 423 patients were included in this Rebound Analysis Data set: 202 (78%) patients in the placebo treatment group and 221 (72%) patients in the levomilnacipran treatment group.

MADRS mean change from day 70 to day 85 was (b) (4) in the levomilnacipran treatment group compared to 0.1 mean change in the placebo treatment group. HAM-D17 mean change from day 70 to day 85 was -

(b) (4)

Study LVM-MD-02

Additional efficacy parameter results

Table 88: Change from baseline to week 8 in additional efficacy parameters (MMRM), ITT population (Study LVM-MD-02)

Additional efficacy parameters	LVM 40-120 mg	Placebo
HAMD-17	(b) (4)	N=152
Baseline, mean ± SEM		24.4 ± 0.3
Change at week 8, LS mean ± SE		-9.2 ± 0.6
LSMD versus placebo (95% CI)		-
p-Value		-
CGI-I score		N=152
Change at week 8, LS mean ± SE		2.7 ± 0.09
LSMD versus placebo (95% CI)		-
p-Value		-

Source: Tables 14.2.8, 14.4.3.3A, 14.4.3.6A, 14.4.3.9A, 14.4.3.10A, 14.4.3.11A, 14.4.3.12A, 14.4.3.13A, 14.4.3.15A, 14.4.3.16A, 14.4.3.17A, 14.4.3.18A, 14.4.3.19A, and 14.4.3.20A.

Table 89: Response and remission rates at week 8 (LOCF), ITT Population (Study LVM-MD-02)

Response and remission rates	LVM 40-120 mg (N ^{(b)(4)}) n (%)	Placebo (N=181) n (%)
MADRS response (≥50% reduction from baseline, n/N1 (%))	(b) (4)	63 (35)
p-Value		-
MADRS remission (≤ 10 in MADRS, n/N1 (%))		43 (24)
p-Value		-
HAMD-17 Response (≥ 50% reduction from baseline)		62 (34)
p-Value		-
HAMD-17 Remission (≤ 7)		33 (18)
p-Value		-
CGI-I Response (CGI-I score ≤ 2)		70 (39)
p-Value		-

Source: Tables 14.4.3.4, 14.4.3.5, 14.4.3.7, 14.4.3.8, 14.4.3.14

Study LVM-MD-05

Additional efficacy parameters results

Table 90: Change from baseline to end of open-label and double-blind treatment periods for additional efficacy parameters - ITT populations (Study LVM-MD-05)

Additional efficacy parameters	Open-label LVM 40-120 mg	Double-blind	
		LVM 40-120 mg (b) (4)	Placebo
HAMD-17			N=112
Baseline, mean ± SEM			5.9 ± 3.8
Change at week 8, LS mean ± SE			2.3 ± 0.8
LSMD versus placebo (95% CI)			-
p-Value			-
CGI-I			N=112
Baseline, mean ± SEM			1.7 ± 0.6
Change at week 8, LS mean ± SE			0.3 ± 0.1
LSMD versus placebo (95% CI)			-
p-Value			-
CGI-S			N=103
Baseline, mean ± SEM			1.6 ± 0.8
Change at week 8, LS mean ± SE			1.7 ± 0.1
LSMD versus placebo (95% CI)			-
p-Value			-
SDS			N=103
Baseline, mean ± SEM			4.9 ± 5.6
Change at week 8, LS mean ± SE			-0.2 ± 0.6
LSMD versus placebo (95% CI)			-
p-Value			-

Source: Tables 14.4.3.1, 14.4.3.2, 14.4.3.3, 14.4.3.4, 14.4.3.5A, 14.4.3.6A, 14.4.3.7A, and 14.4.3.8A; Listings 16.2.6.2, 16.2.6.3, and 16.2.6.4.

9.5 Additional Safety Results and Tables

Sponsor - Assigned Grouping of Studies

Table 91 (source: Integrated Summary of Safety, Vol 1, page 27, Table 4.3.1-2) presents the list of clinical studies along with the treatment duration for the seven clinical studies; six completed and one ongoing. Completed studies are defined as those studies that achieved database lock and treatment code unblinding by the ISS clinical cut-off date of April 30, 2012. The ongoing study is a long-term, open-label extension study (LVM-MD-04), which included patients completing one of the 3 lead-in studies (LVM-MD-01, -02, and -03). For the purposes of this NDA, the sponsor included in the ISS all safety data for patients who either completed the long-term, open-label study or prematurely discontinued from this study as of February 15, 2012.

Table 91: Levomilnacipran clinical studies

<i>Group 1: Short-term, Placebo-Controlled Studies</i>	
<i>Group 1A: US Short-term, Placebo-Controlled Studies</i>	<i>Group 1B: Non-US Short-term, Placebo-Controlled Study</i>
Fixed-dose Studies: LVM-MD-01 LVM-MD-10 ^a Flexible-dose Studies: LVM-MD-02 LVM-MD-03	Flexible-Dose Study: F02695 LP 2 02 ^b
<i>Group 2: Long-term, Open-label Study</i>	
LVM-MD-04	
<i>Group 3: Relapse-Prevention Study</i>	
LVM-MD-05 ^a	
<i>Group 4: Clinical Pharmacology and Biopharmaceutic Studies in Healthy Subjects</i>	
<i>BA/BE Studies</i>	
F02695 GE 1 02	LVM-PK-14
F02695 LP 1 01	LVM-PK-16
LVM-PK-06	LVM-PK-19
LVM-PK-12	
<i>PK Studies</i>	
F02695 GE 1 01	LVM-PK-03 ^c
F02695 LP 1 02	LVM-PK-01
	LVM-PK-15
<i>Intrinsic Factors</i>	
LVM-PK-02	LVM-PK-05
LVM-PK-04	
<i>Extrinsic Factors</i>	
LVM-PK-08	LVM-PK-10
LVM-PK-09	
<i>PK/PD Study</i>	
LVM-PK-07	
<i>Group 5: Studies in Other Indications</i>	
(b) (4) ^d	LVM-MD-06

- a Study also conducted at sites in Canada.
- b Studies conducted worldwide.
- c Study also known as F02695 PO 1 01.
- d Study was prematurely terminated by the sponsor due to administrative reasons.

Pregnancies

A total of 15 pregnancies were reported while patients were on treatment. Table 92 (source: Integrated Summary of Safety, Vol 1, pages 200-202) summarizes these cases.

Table 92: List of pregnancies in the levomilnacipran development program

<i>Study</i>	<i>Patient (age in years)</i>	<i>Treatment (dose)</i>	<i>Treatment Duration (days)</i>	<i>SAE (Y/N)</i>	<i>ADO (Y/N)</i>	<i>Outcome</i>
F02695 LP 2 02	040207 (51)	Not randomized ^a	Withdrawn prior to randomization	N	Y Withdrawn from study prior to randomization	No further information available
LVM-MD-01	0120167 (25)	levomilnacipran 120 mg/day	59	Y SAEs of premature baby and small for dates baby reported.	N Patient reported positive pregnancy testing during down taper (30 days after starting IP)	Live birth (premature) with no complications. Baby hospitalized for 3-4 weeks, subsequently discharged with no further complications reported.
LVM-MD-01	0280110 (26)	levomilnacipran 80 mg/day	13	N	Y (Patient was discontinued after reporting a home pregnancy test [date unknown] was positive and did not enter down taper)	False pregnancy - study site confirmed from another physician that patient was never pregnant
LVM-MD-01	0300157 (24)	levomilnacipran 80 mg/day	32	N	Y (Patient discontinued from study after Visit 8 pregnancy testing was positive; did not enter down taper)	Live birth with no complications
LVM-MD-01	0310118 (35)	levomilnacipran 80 mg/day	31	Y (pre-eclampsia reported 150 days after discontinuing IP)	Y (Visit 5 pregnancy lab test was positive - patient discontinued and did not enter down taper)	Labor induced early due to pre-eclampsia. Live birth with no complications
LVM-MD-02	0180209 (24)	Placebo	15	N	Y (On Day 15, patient discontinued from the study due to pregnancy and did not enter down taper)	Elective abortion with no complications approximately 16 days after discontinuation from the study on Day 15
LVM-MD-02	0230211 (32)	Placebo	58	N	Y (Completed DB treatment but discontinued after 4 days on down taper treatment due to positive pregnancy test)	Elective abortion with no complications
LVM-MD-03	0690337 (23)	Placebo	28	N	Y (Patient withdrew consent after 28 days of DB treatment with PBO - notified site she was pregnant after discontinuation (date unknown))	Lost to follow up
LVM-MD-04	0090218 (30)	levomilnacipran	330	N	N (Visit 16 pregnancy test was positive)	Live birth with no complications
LVM-MD-04	0250141 (33)	levomilnacipran	173	N	N (On Study Day 160 [06 Sept 2011], the patient's scheduled pregnancy test was positive)	Live birth via Cesarean section with no complications

Table 93: List of pregnancies in the levomilnacipran development program (con't.)

<i>Study</i>	<i>Patient (age in years)</i>	<i>Treatment (dose)</i>	<i>Treatment Duration (days)</i>	<i>SAE (Y/N)</i>	<i>ADO (Y/N)</i>	<i>Outcome</i>
LVM-MD-04	0310131 (29)	levomilnacipran	131	N	N (On Study Day 142 [12 Apr 2011], the patient's scheduled pregnancy test was positive)	Live birth via Cesarean section with no complications
LVM-MD-05	0130505 (31)	Placebo	168	N	N (Pregnancy test was positive at last DB visit)	Elective abortion with no complications
LVM-MD-05	0180519 (35)	Not randomized into DB	67 days with OL treatment only	N	Y (Patient withdrew consent prior to DB phase - on early termination visit, pregnancy test was positive)	Lost to follow up
LVM-MD-05	0290525 (25)	levomilnacipran	39	N	Y (home pregnancy test positive approx 1 month after Visit 10 visit - patient discontinued at that time)	Lost to follow up
LVM-MD-10	0271011 (27)	levomilnacipran 80 mg/day	62	N	Y (Positive pregnancy test at Visit 7 on Day 62 - patient discontinued)	Lost to follow up

Source: Individual narratives from CSRs LVM-MD-01, LVM-MD-02, LVM-MD-03, LVM-MD-04, LVM-MD-05, LVM-MD-10 based on project database and Medwatch forms, and F02695 LP 2 02 CSR.

a The patient reported the pregnancy prior to randomization and was withdrawn from the study without receiving treatment with IP.

ADO = adverse event leading to dropout; DB = double blind; IP = investigational product; OL = open label; PBO = placebo; SAE = serious adverse event.

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

/s/

KAVNEET KOHLI-CHHABRA
07/02/2013

TIFFANY R FARCHIONE
07/02/2013

NI A KHIN
07/02/2013
See CDTL memo for additional comments.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204168

Applicant: Forest

Stamp Date: 09/25/2012

**Drug Name: levomilnacipran
HCI sustained-release (LVM)**

**NDA/BLA Type: original
505b(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			electronic CTD Global Review Submit: \\CDSESUB1\EVSPR OD\NDA204168\204168.enx
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			Quality, nonclinical, clinical
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			2.7.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			2.7.4
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Section 6.0 page 47 in 2.5 Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: LVM-MD-01 Study Title: "A Double-blind, Placebo-Controlled, <i>Fixed-Dose</i> Study of F2695 SR in Patients With Major Depressive Disorder." Sample Size and Arms: Placebo (175), LVM 80 mg/d (177), LVM 120 mg/d (176) Study Site: USA	x			F2695 was the earlier nomenclature for levomilnacipran. Among the 3 well-controlled pivotal efficacy studies submitted, 2 are fixed dose studies (Studies LVM-MD-01 and -10) and 1 (Study LVM-MD-03) is a flexible

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Study Number: LVM-MD-03 Study Title: “A Double-blind, Placebo-Controlled, <i>Flexible-Dose</i> Study of F2695 SR in Patients With Major Depressive Disorder.” Sample Size and Arms: Placebo (214), LVM 40-120 mg/d (215) Study Site: USA</p> <p>Study Number: LVM-MD-10 Study Title: “A Double-Blind, Placebo-Controlled, <i>Fixed-Dose</i> Study Of Levomilnacipran SR In Patients With Major Depressive Disorder.” Sample Size and Arms: Placebo (185), LVM 40 mg/d (185), LVM 80 mg/d (187) Study Site: USA and Canada</p>				dose study. Location in submission for all three studies is module 2 and 5
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			Module 2.7.3 For details of the 3 well-controlled pivotal efficacy studies, see question #13.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			Section 13.1 in IES
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			Section 13.1 in IES
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			The Division has routinely accepted foreign data for this indication. The Sponsor has included 3 pivotal efficacy studies conducted in US/Canada and 1 nonpivotal study that was conducted in nonUS sites.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	Not marketed or submitted for approval anywhere else in the

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					world
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			4.4.1 in ISS
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			The sponsor adequately monitored vital signs, including HR and ECGs. They also had conducted a thorough QTc study.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Module 1.9.1 +1.9.2. Ages 0 to 6: A partial waiver for pediatric studies is requested. Ages 7 to17: A deferral for pediatric studies is requested.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			Same answer as question #17
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			Module 5.3.5.3.24
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			Module 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

1. If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

No filing issues were identified on the 45-day filing meeting held on Monday, November 05, 2012. The filing date for this application is November 24, 2012.

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

Clinical comment for the sponsor:

Please provide a comprehensive literature review pertaining to the levomilnacipran (LVM) Sustained Release Capsules. Please include search methodology (search terms, databases, etc.), summary of findings, comments on the relevance of these findings to the safety or pharmacology of the drug, and overall conclusion.

Kavneet Kohli-Chhabra M.D.

November 07, 2012

Reviewing Medical Officer

Date

Ni Khin, M.D.

November 7, 2012

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

KAVNEET KOHLI-CHHABRA
11/07/2012

NI A KHIN
11/07/2012