CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION
EXPLORATION OF SENSITIVITY ANALYSES

NDA #:	204168
Drug Name:	FETZIMA (Levomilnacipran) extended-release capsules 20, 40, 80, and 120 mg
Indication:	Major Depressive Disorder
Applicant:	Forest Laboratories, Inc.
Date:	Submitted: 09/24/2012 PDUFA date: 07/25/2013
Review Priority:	Standard
Biometrics Division:	**Division of Biometrics I**
Statistical Reviewer:	Thomas Birkner, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., Team Leader H. M. James Hung, Ph.D., Division Director
Medical Division:	**Division of Psychiatry Products**
Clinical Team:	Kavneet Kohli-Chhabra, M.D., Medical Reviewer Ni Aye Khin, M.D., Medical Team Leader
Project Manager:	Juliette T. Toure, Pharm. D.

Keywords: sensitivity analyses, Pattern-Mixture Model

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1. Executive Summary

The sponsor used a Pattern-Mixture Model (PMM) approach in all three pivotal studies (LVM-MD-01, LVM-MD-10, and LVM-MD-03) to assess the robustness of the primary analysis (Mixed Model for Repeated Measures [MMRM]) to possible deviations from the missing at random (MAR) assumption. This reviewer replicated the sponsor's PMM results. A few issues with the approach and implementation were discovered, but none of those reached the level of serious doubt about the conclusion drawn by the sponsor, namely that the PMM analyses confirm the robustness of the MMRM analyses to potential deviations from the MAR assumption. The conclusion of the main review (sufficient statistical evidence of efficacy) remains unchanged.

2. Introduction

This add-on to the review of NDA 204,168 explores the Pattern-Mixture Model (PMM) which was applied as one of two sensitivity analysis in the three pivotal studies.

2.1 Overview

The following discontinuation rates were observed in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03: 29.0%, 21.5% and 22.8%. Analysis of Covariance last observation carried forward (ANCOVA LOCF) and PMM were used as sensitivity analyses for those studies. The PMM accommodates situations were the missingness mechanism is missing not at random (MNAR). Estimates of the mean or the mean difference at the final assessment (primary endpoint) from the PMM model can be compared to the estimates from the primary analysis model. Closeness of those estimates would indicate that the assumption of missing at random (MAR) needed for the primary efficacy analysis approach (MMRM) holds.

2.2 Data Sources

Study reports: \\Cdsesub1\evsprod\NDA204168\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\major-depressive-disorder\5351-stud-rep-contr

Data sets and SAS code: \\Cdsesub1\evsprod\NDA204168\0000\m5\datasets

3. Statistical Evaluation

3.1 Statistical Methodology

Pattern-Mixture Model with Non-Future Dependent Missing Assumption

The goal of the PMM was to assess the robustness of the primary MMRM results to the possible violation of the missing at random missingness assumption. The sponsor describes the pattern-mixture model based on the non-future dependent missing value restriction (Kenward et al. [2003]) in the MD-10 study report: "The non-future dependent missing value restriction states that the probability of drop-out at a specific visit can only depend on the observed value and the possibly missing value up to that visit, but not future values beyond that visit" (page 68).

"The pattern for the PMM was defined by the patient's last visit with observed value. The observed MADRS total score at a visit was assumed to have a linear relationship with the patient's prior measurement. The missing values were imputed under the assumption that the distribution of the missing observations differed from that of the observed only by a shift parameter value of Δ. The dataset with missing values was analyzed using the same model as the primary analysis for between-treatment group comparisons at Week 8. The imputation of missing values and the analysis were performed multiple times, and the inference of this sensitivity analysis was based on the combined estimates using the standard multiple imputation technique. The values for Δ were selected as 0 to 8 "(Study report MD-10 p. 68).

Details of the PMM model were provided as appendix 1 to the SAP and are included also in the appendix to this review.

Determination of the Shift Parameter Values

The common shift parameter Δ is the difference between the mean of y_{t+1} among those who drop out at Visit *t* and those who remain beyond Visit *t*. In a response (SN 0124) to a request for more information on the details of the PMM the sponsor reasons as follows regarding the choice of Δ between 0 and 8: (1) In the supportive study LP 202 the mean MADRS scores for dropouts were all above the mean MADRS scores for the non-dropouts at every visit, which suggest a positive Δ; (2) In a depression study with MADRS as primary measurement, the mean reduction of the MADRS total score from baseline at the end of treatment is likely within 20 points and a Δ value of 8 accounts for 40% of treatment efficacy.

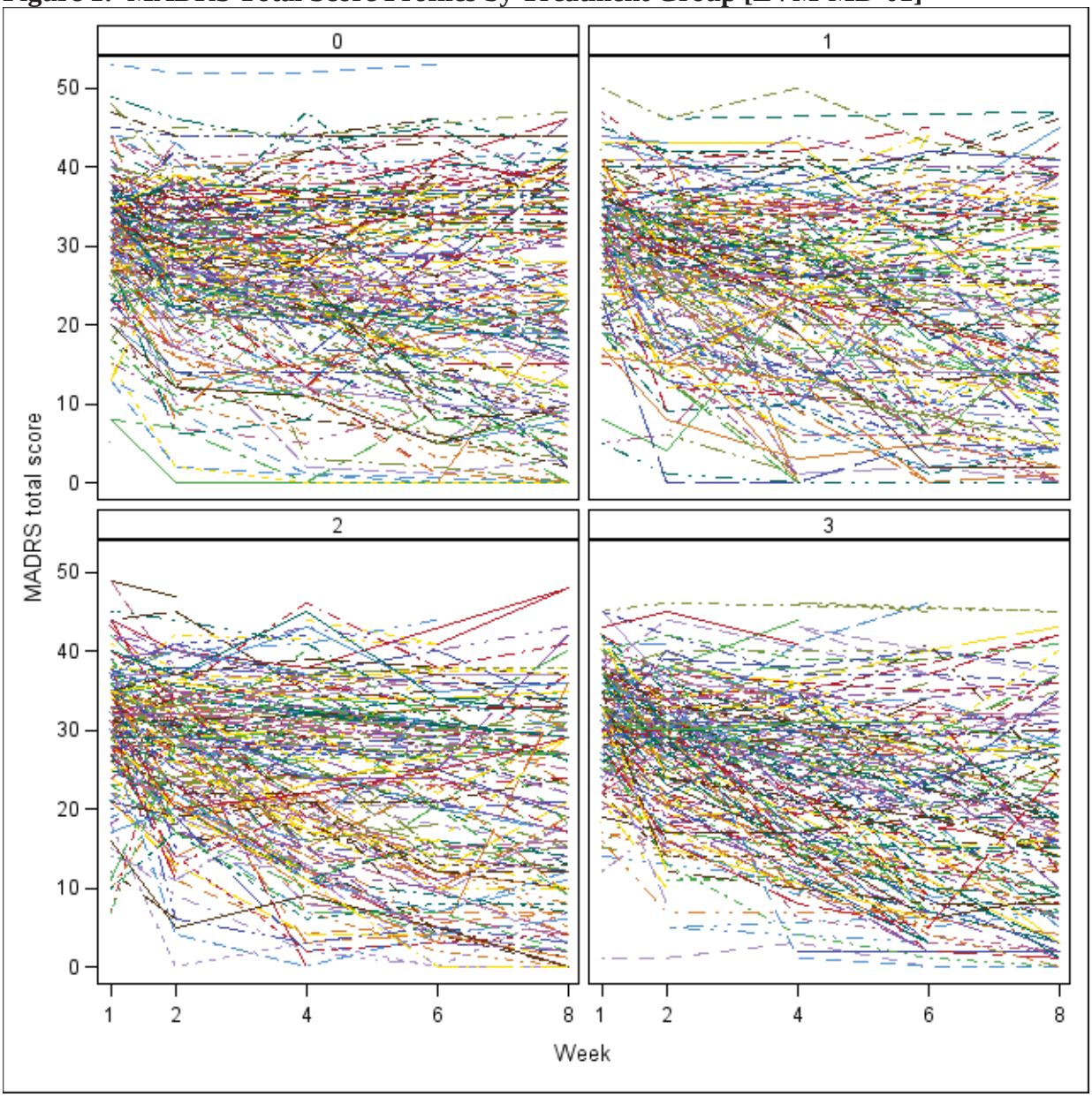
3.2 Results and Conclusions

3.2.1 LVM-MD-01

Sponsor's Results

The individual MADRS total score profiles from week 1 through week 8 by treatment arm are displayed in Figure 1.

Figure 1: MADRS Total Score Profiles by Treatment Group [LVM-MD-01]



(Source: Computed by reviewer; Treatment groups: Placebo (0), 40 mg (1), 80 mg (2), and 120 mg (3))

The estimates and 95% confidence intervals for the difference in change from baseline in MADRS total score for the primary analysis are given in Table 1; results of the sensitivity analyses are given in Table 2 and displayed graphically in Figure 2 for an easier comparison. The p-values over the range of the shift-parameter in the PMM are listed in Table 3.

Table 1: Primary Efficacy Analysis: Change from Baseline to Week 8 in the MADRS Total Score (MMRM) – ITT Population [LVM-MD-01]

	Placebo (N = 175)	*F2695 SR*		
		40 mg/d (N = 176)	*80 mg/d (N = 177)*	*120 mg/d (N = 176)*
Primary Analysis—MMRM				
Baseline, mean ± SEM	35.6 ± 0.3	36.0 ± 0.3	36.1 ± 0.3	36.0 ± 0.3
Change at Week 8, LS mean ± SE	–11.6 ± 0.97	–14.8 ± 0.99	–15.6 ± 1.00	–16.5 ± 1.02
LSMD vs placebo (95% CI)	—	–3.23 (–5.92, –0.54)	–3.99 (–6.69, –1.29)	–4.86 (–7.59, –2.12)
p-Value[a]	—	0.0186	0.0038	0.0005

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

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SR = sustained release.

(Source: Study report LVM-MD-01 p. 89)

Table 2: Sensitivity Analyses: Change from Baseline to Week 8 in the MADRS Total Score (LOCF and PMM) – ITT Population [LVM-MD-01]

	Placebo (N = 175)	*F2695 SR*		
		40 mg/d (N = 176)	*80 mg/d (N = 177)*	*120 mg/d (N = 176)*
LOCF				
Baseline, mean ± SEM	35.6 ± 0.3	36.0 ± 0.3	36.1 ± 0.3	36.0 ± 0.3
Change at Week 8, LS mean ± SE	–10.7 ± 0.93	–13.3 ± 0.92	–14.1 ± 0.92	–14.1 ± 0.92
LSMD vs placebo (95% CI)	—	–2.56 (–5.01, –0.11)	–3.45 (–5.90, –1.00)	–3.43 (–5.88, –0.97)
P-value[a]	—	0.0410	0.0058	0.0063
PMM[b]				
Shift parameter, LSMD vs placebo (95% CI):				
0	—	–3.16 (–5.77, –0.55)	–3.92 (–6.57, –1.28)	–4.90 (–7.70, –2.09)
2	—	–3.01 (–5.65, –0.36)	–3.87 (–6.54, –1.19)	–4.76 (–7.53, –1.99)
4	—	–3.05 (–5.74, –0.37)	–3.71 (–6.44, –0.97)	–4.58 (–7.35, –1.81)
6	—	–3.05 (–5.80, –0.29)	–3.51 (–6.33, –0.70)	–4.07 (–6.92, –1.21)
8	—	–2.93 (–5.75, –0.12)	–3.22 (–5.99, –0.44)	–3.62 (–6.54, –0.70)

a p-Value was obtained from an analysis-of-covariance model with treatment group and pooled study centers as factors and baseline MADRS-CR total score as covariate.

b For each shift parameter value, missing values are imputed multiple times using a PMM assuming non-future dependence. For each imputed dataset, MMRM analysis is performed.

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; n = number of patients in the ITT Population with available values at baseline and at a specific timepoint; PMM = pattern-mixture model; SR = sustained release.

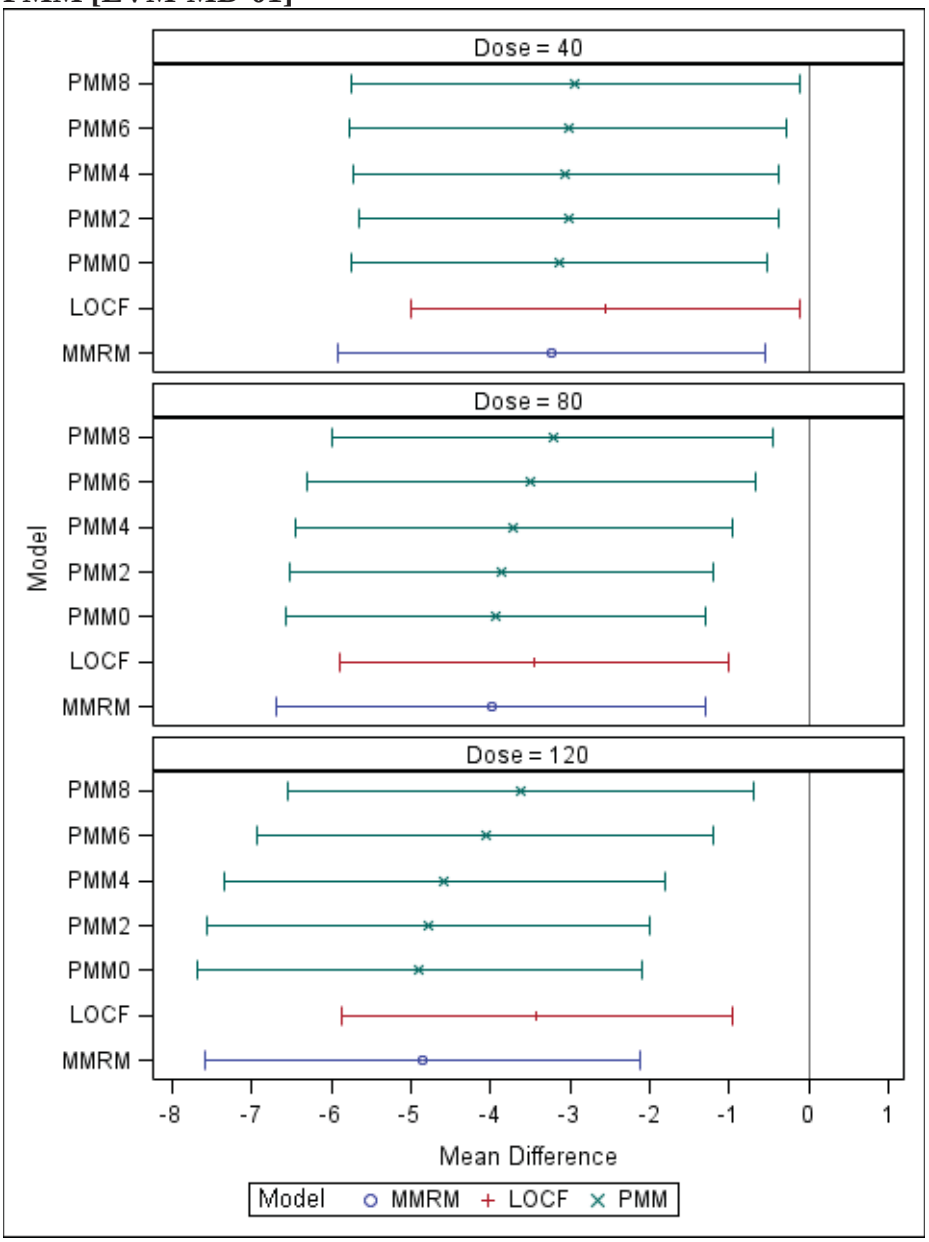
(Source: Study report LVM-MD-01 p. 91; this reviewer confirmed the estimates obtained from the PMM model in the table above within rounding error)

Table 3: Pattern-Mixture Model p-values [LVM-MD-01]

	Placebo (N=175)	**Levomilnacipran**		
		40 mg/day (N=176)	80 mg/day (N=177)	120 mg/day (N=175)
Shift parameter		p-value of LSMD vs. placebo		
0	--	0.0182	0.0036	0.0006
2	--	0.0254	0.0046	0.0008
4	--	0.0258	0.0079	0.0012
6	--	0.0313	0.0151	0.0055
8	--	0.0410	0.0230	0.0151

(Source: Values computed by this reviewer using SAS code provided by sponsor. The p-values in this and later PMM summary tables are provided in the context of exploratory sensitivity analyses only.)

Figure 2: LSMD in MADRS Total Score at Week 8 and 95% CI from MMRM, LOCF and PMM [LVM-MD-01]



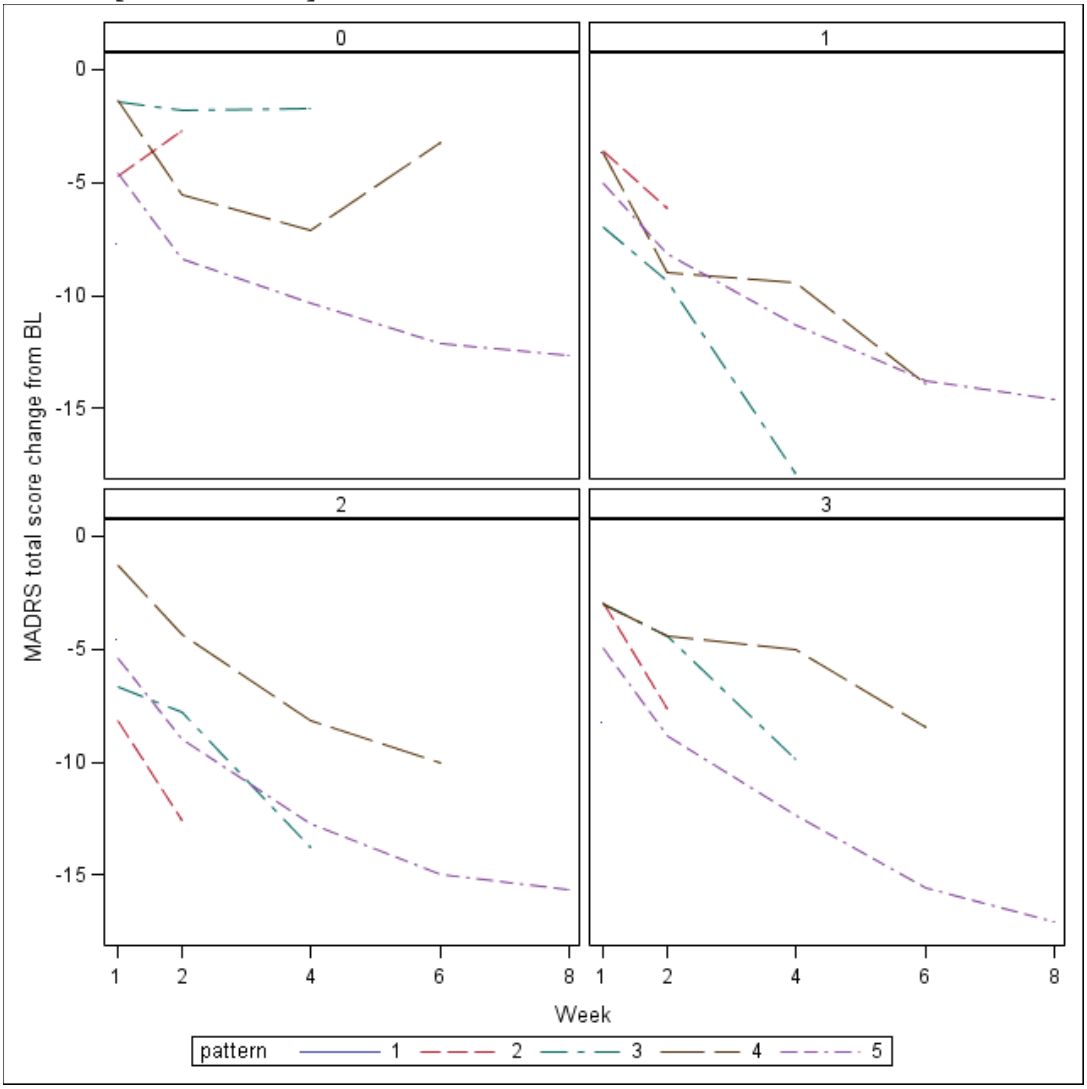
(Source: Graph created by reviewer; MMRM = Mixed Model Repeated Measures; LOCF = ANCOVA LOCF; PMM = Pattern-Mixture Model [The number attached to PMM along the y-axis indicates the value of the shift parameter.])

The sponsor concluded the following from the PMM results: "For all selected values of the shift parameter in the PMM analysis, the mean decrease in MADRS-CR total score from baseline remained greater and statistically significant in patients treated with F2695 SR compared with patients in the placebo group, indicating the result of primary efficacy analysis was robust" (Study report LVM-MD-01 p. 90).

This reviewer obtained the same PMM results as the sponsor (see Table 2) when using the SAS code submitted by the sponsor.

Figure 3 depicts the mean observed MADRS total score change by treatment and drop-out pattern. Here we do not see a mean increase (worsening) in the MADRS total score before the patients drop out in general. An upward slope before drop-out is only observed for patterns 2, 3 and 4 in the placebo arm. As evident from Table 5 below, the number of subjects in each drop out pattern is relatively small, expect for pattern 5. The trajectories for patterns 1 through 4 in Figure 3 are based on these small numbers and are therefore not very reliable.

Figure 3: Mean Observed MADRS Total Score Change by Treatment and Drop-out Pattern [LVM-MD-01]



(Source: Computed by reviewer; Treatment groups: Placebo (0), 40 mg (1), 80 mg (2), 120 mg (3); Pattern 1 appears only as one dot at week 1)

Potential Issues

A) Coding Problem

Table 4: Sample Size per Treatment Arm and Drop-out Pattern [LVM-MD-01]

Treatment Group	Pattern (Week of last visit)					
	1 (1)	2 (2)	3 (4)	4 (6)	5 (8)	Total
Placebo	5	8	10	8	138	169
Levo 40 mg	12	12	9	12	125	170
Levo 80 mg	6	18	14	15	120	173
Levo 120 mg	10	22	12	11	114	169
Total	33	60	45	46	497	**681**

(Source: Computed by reviewer)

Table 4 displays the number of subjects in each drop-out pattern by treatment arm as generated by the sponsor's SAS code. According to the study report there should be 704 ITT patients, but there are only 703 unique subject id's in the efficacy dataset.

Table 4 lists only 681 subjects, meaning that 22 patients were omitted. The issue appears to be the statement in SAS proc sql "where week = 1" with variable "week" created earlier taking values from 1 to 5 corresponding to analysis visits (1, 2, 4, 6, 8). This statement excludes the 22 subjects without a MADRS total score at week 1 (analysis visit 1), but who had at least one MADRS total score recorded at the later visits. Most of them (16) continued to the end of the study at week 8 (4 dropped out after week 2, 1 after week 4 and 1 after week 6) [see Table 5 and Figure 4]. The omission of the 22 subjects distorts the number of subjects in each pattern used in the calculations later (compare the incorrect frequencies in Table 4 with the correct ones in Table 5). However, the impact on the sensitivity analysis results was minimal (see Table A1 in appendix for corrected estimates, confidence intervals, and p-values). The omission of patients was limited to the segment of code where the number of subjects in each pattern was calculated, all 703 ITT subjects were used for the analysis in general.

Table 5: Sample Size per Treatment Arm and Drop-out Pattern – Corrected [LVM-MD-01]

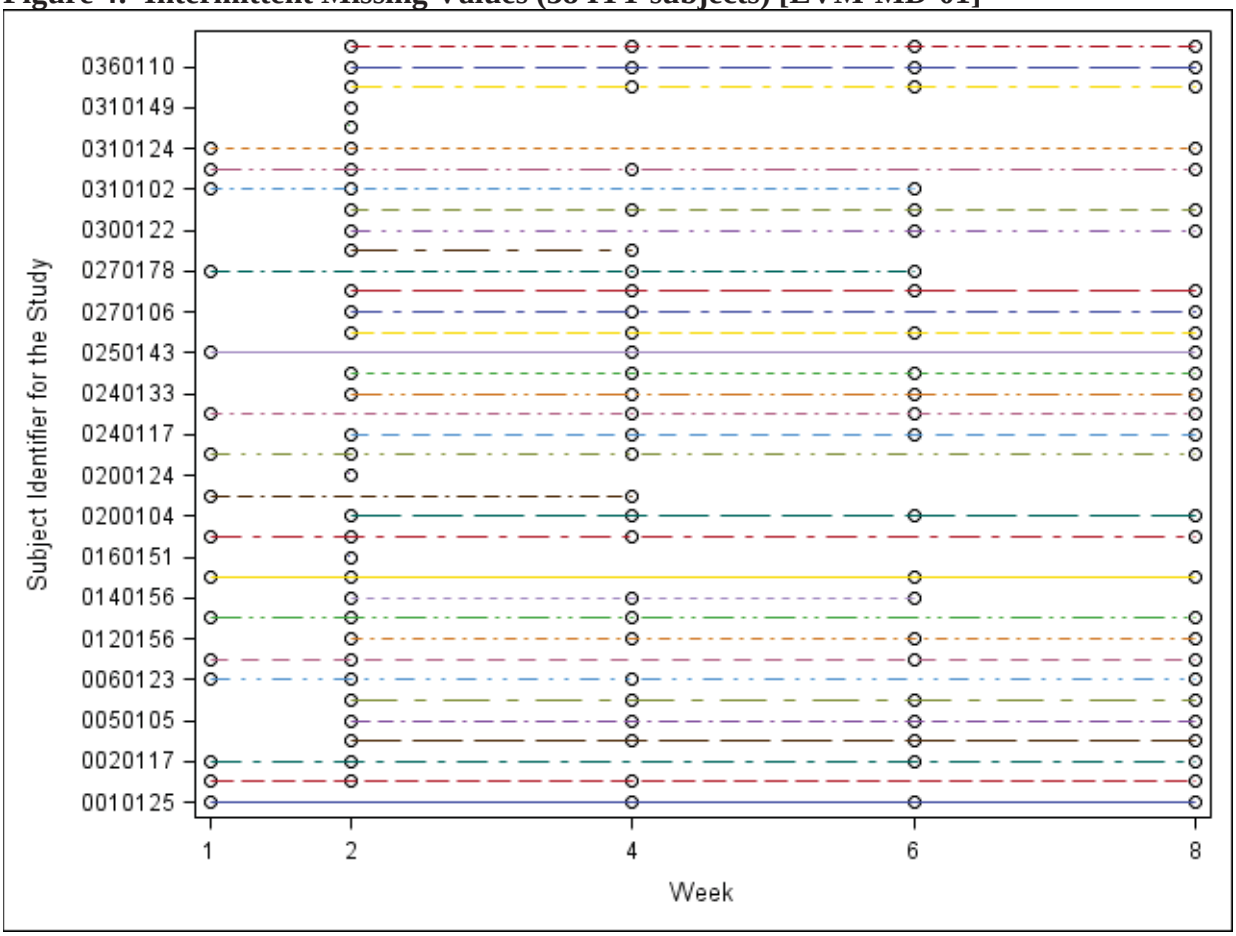
Treatment Group	Pattern (Week of last visit)					
	1 (1)	2 (2)	3 (4)	4 (6)	5 (8)	Total
Placebo	5	10	10	9	141	175
Levo 40 mg	12	12	10	12	130	176
Levo 80 mg	6	19	14	15	123	177
Levo 120 mg	10	23	12	11	119	175
Total	33	64	46	47	513	**703**

(Source: Computed by reviewer)

B) Intermittent Missing Values

There are 38 patients out of 703 with at least one intermittent missing value of the MADRS total score (22 subjects have no value for week 1, 5 for week 2, 10 for week 3, 15 for week 6). The sponsor used LOCF to fill in those intermittent missing values since the PMM assumes monotone missingness. The proportion of patients (approximately 5%) with intermittent missing values is small and the occurrence of intermittent missing values is likely random. The issue of intermittent missing values is (probably) unavoidable. However, the impact of the LOCF imputation (to "fix" the violation of the monotone missingness assumption) on the PMM results is unclear.

Figure 4: Intermittent Missing Values (38 ITT subjects) [LVM-MD-01]



(Source: Graph created by reviewer. A dot indicates that the MADRS total score value exists for this visit/week. Not all subject id's are shown along the y-axis due to space constraints.)

C) Range of Shift Parameter

Although the sponsor's choice for the range of the shift parameter (0, 2, …, 8) appears sensible on face this reviewer extended the range beyond the maximum value considered by the sponsor. The results are presented in **Table 6**.

Table 6: Pattern-Mixture Model – Shift Parameters: 10, 12, 14, 16, 18 [LVM-MD-01]

	Placebo (N=175)	**Levomilnacipran**		
		40 mg/day (N=176)	80 mg/day (N=177)	120 mg/day (N=175)
Shift parameter		LSMD (95% CI) p-value		
10	--	-2.859 (-5.731, 0.013) 0.0510	-3.127 (-6.059, -0.196) 0.0365	-3.350 (-6.273, -0.426) 0.0248
12	--	-2.796 (-5.788, 0.195) 0.0669	-2.905 (-5.976, 0.167) 0.0638	-3.016 (-6.039, 0.008) 0.0506
14	--	-2.590 (-5.721, 0.542) 0.1049	-2.665 (-5.851, 0.521) 0.1010	-2.745 (-5.876, 0.386) 0.0857
16	--	-2.664 (-5.871, 0.542) 0.1034	-2.519 (-5.802, 0.764) 0.1325	-2.408 (-5.732, 0.917) 0.1556
18	--	-2.530 (-5.804, 0.744) 0.1298	-2.204 (-5.503, 1.095) 0.1903	-1.836 (-5.204, 1.533) 0.2852

(Source: Computed by reviewer using modified sponsor code)

The results for the larger shift parameters are quite interesting, because starting with the 40 mg/day dose at a shift parameter of 10 and continuing with the 80 and 120 mg/day dose groups at a shift parameter of 12 all doses loose statistical significance at alpha = 0.05.

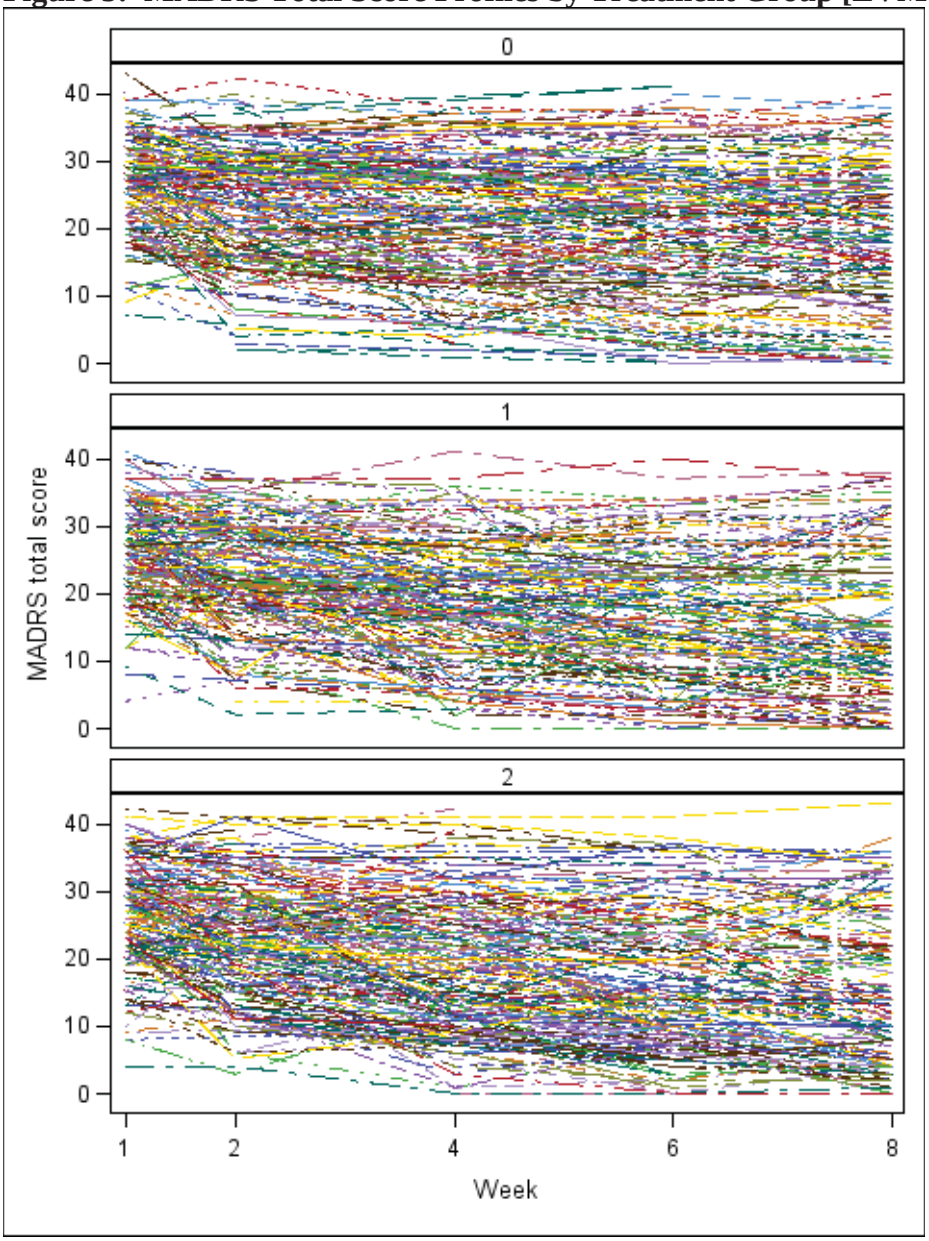
The "Tipping point" is reached one or two steps (2 to 4 MADRS total score units) above the greatest shift parameter used by the sponsor. The sponsor wrote that "the mean reduction of the MADRS total score from baseline at the end of treatment is likely within 20 points and a Δ value of 8 accounts for 40% of treatment efficacy" (SN 0124). *Is a Δ value of 10 accounting for 50% of treatment efficacy then completely unrealistic?* Another potential issue not further explored here is whether it is reasonable to assume the same shift parameter for the placebo and drug groups.

3.2.2 LVM-MD-10

Sponsor's Results

Figure 5 displays the individual MADRS total score from week 1 through week 8 of the double-blind treatment period of Study LVM-MD-10.

Figure 5: MADRS Total Score Profiles by Treatment Group [LVM-MD-10]



(Source: Computed by reviewer; Treatment groups: Placebo (0), 40 mg (1), and 80 mg (2))

The results of the primary as well as both sensitivity analyses are summarized by the sponsor in Table 7 below.

Table 7: Primary and Sensitivity Analyses: Change from Baseline to Week 8 in the MADRS Total Score (MMRM, LOCF and PMM) – ITT Population [LVM-MD-10]

			Placebo (N = 185)	*F2695 SR 40 mg/day (N = 185)*	*F2695 SR 80 mg/day (N = 187)*
Primary analysis—MMRM[a]					
Baseline, mean ± SD			31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5
Change at Week 8, LS mean (SE)			–11.3 (0.77)	–14.6 (0.79)	–14.4 (0.79)
LSMD vs placebo (95% CI)			—	–3.303 (–5.457, –1.148)	–3.141 (–5.293, –0.988)
p-Value			—	0.0027	0.0043
Sensitivity analysis—LOCF[b]					
Baseline, mean ± SD			31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5
Change at Week 8, LS mean (SE)			–10.7 (0.77)	–13.1 (0.79)	–13.1 (0.76)
LSMD vs placebo (95% CI)			—	–2.415 (–4.521, –0.309)	–2.380 (–4.451, –0.308)
p-Value			—	0.0247	0.0244
Sensitivity analysis—PMM[c]					
	Shift parameter				
Change at Week 8, LSMD vs Placebo (95% CI)	**0**		—	–3.342 (–5.453, –1.231)	–3.138 (–5.242, –1.034)
	2		—	–3.263 (–5.392, –1.134)	–3.073 (–5.242, –0.904)
	4		—	–3.267 (–5.371, –1.164)	–3.043 (–5.236, –0.850)
	6		—	–3.319 (–5.480, –1.157)	–2.936 (–5.136, –0.737)
	8		—	–3.318 (–5.624, –1.011)	–2.727 (–4.969, –0.485)

a p-Values are from a MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores.

b p-Value was obtained from an analysis-of-covariance model with treatment group and pooled study centers as factors and baseline MADRS total score as covariate.

c For each shift parameter value, missing values were imputed multiple times using a PMM assuming non-future dependence. For each imputed dataset, MMRM analysis was performed.

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; n = number of patients in the ITT population with available values at baseline and at a specific time point; PMM = pattern-mixture model; SD = standard deviation; SE = standard error; SR = sustained release.

(Source: Study report LVM-MD-10 p. 93; this reviewer confirmed the estimates obtained from the PMM model in the table above)

Table 8 contains the p-values of the PMM analysis given the shift parameter range from 0 to 8.

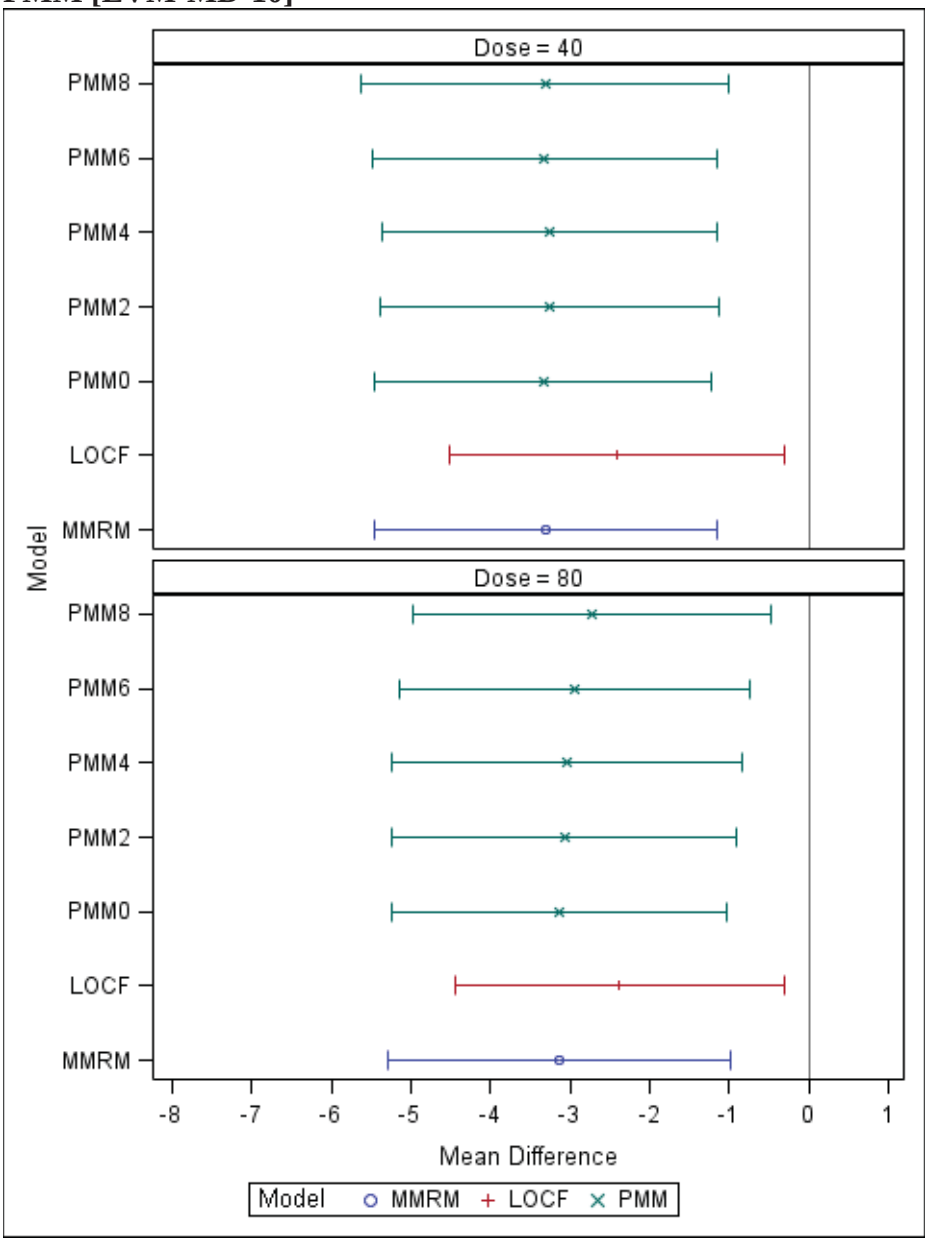
Table 8: Pattern-Mixture Model p-values [LVM-MD-10]

	Placebo (N=185)	**Levomilnacipran**	
		40 mg/day (N=185)	80 mg/day (N=187)
Shift parameter		p-value of LSMD vs. placebo	
0	--	0.0019	0.0035
2	--	0.0027	0.0055
4	--	0.0023	0.0066
6	--	0.0026	0.0089
8	--	0.0048	0.0172

(Source: Values computed by this reviewer using SAS code provided by sponsor)

Given the results from the PMM model in Study LVM-MD-10 (see Table 7 and Table 8) the sponsor came to the following conclusion: "A second sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions […] also confirmed the robustness of the results of the primary analysis with F2695 SR treatment groups demonstrating statistically significant improvement compared to placebo at each selected value of the shift parameter" (Study report LVM-MD-10 p. 92). Figure 6 below displays the results from Table 7 in a graphical way. Using the SAS code provided by the sponsor this reviewer obtained the same results as displayed in the sponsor generated Table 7.

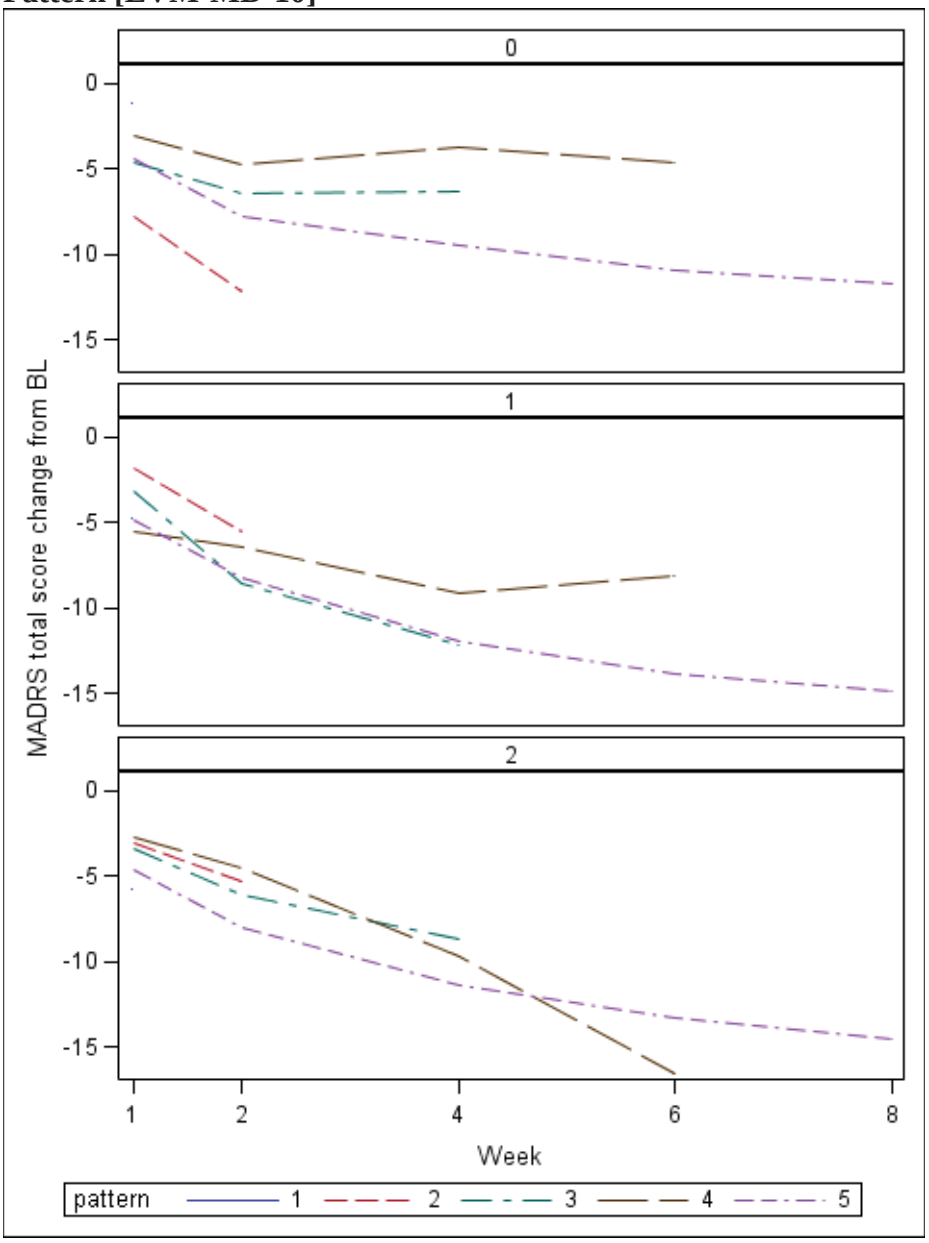
Figure 6: LSMD in MADRS Total Score at Week 8 and 95% CI from MMRM, LOCF and PMM [LVM-MD-10]



(Source: Graph created by reviewer; MMRM = Mixed Model Repeated Measures; LOCF = ANCOVA LOCF; PMM = Pattern-Mixture Model [The number attached to PMM indicates the value of the shift parameter.])

Figure 7 depicts the mean observed MADRS total score change by drop-out pattern within treatment group. The slopes of the curves, except for two, are negative (indicating improvement) even if the patients dropped out shortly after.

Figure 7: Mean Observed MADRS Total Score Change by Treatment Arm and Drop-out Pattern [LVM-MD-10]



(Source: Computed by reviewer; Treatment groups: Placebo (0), 40 mg (1), and 80 mg (2); Pattern 1 only shows as one dot at week 1)

Potential Issues

A) Coding Problem

A similar issue as in MD-01 also occurred in MD-10 - five subjects were omitted from the calculation of subjects per pattern (frequencies are based on 552 instead of 557 subjects). The discrepancies per pattern can be observed by comparing Table 9 and Table 10 below. These five subjects missed the first visit, but had later visits. Due to the small number of excluded subjects the impact should be minimal. A PMM re-analysis appears not warranted.

Table 9: Sample Size per Treatment Arm and Drop-Out Pattern [LVM-MD-10]

Treatment Group	**Pattern (Week of last visit)**					
	1 (1)	2 (2)	3 (4)	4 (6)	5 (8)	Total
Placebo	7	7	6	12	151	183
Levo 40 mg	7	14	8	8	147	184
Levo 80 mg	9	12	12	11	141	185
Total	23	33	26	31	439	**552**

(Source: Computed by reviewer)

Table 10: Sample Size per Treatment Arm and Drop-Out Pattern – Corrected [LVM-MD-10]

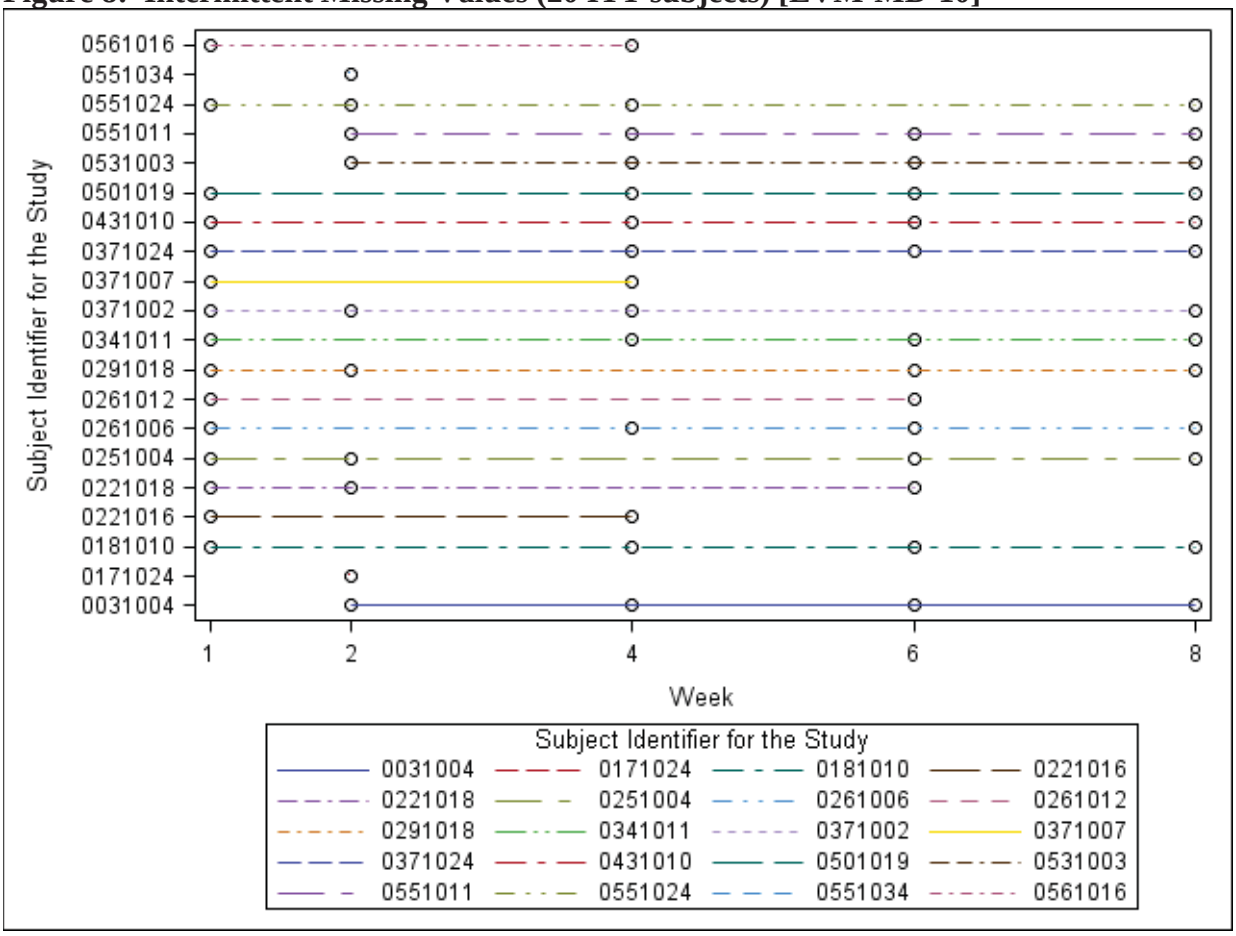
Treatment Group	**Pattern (Week of last visit)**					
	1 (1)	2 (2)	3 (4)	4 (6)	5 (8)	Total
Placebo	7	7	6	12	153	185
Levo 40 mg	7	15	8	8	147	185
Levo 80 mg	9	13	12	11	142	187
Total	23	35	26	31	442	**557**

(Source: Computed by reviewer)

B) Intermittent Missing Values

There are 20 ITT subjects with intermittent missing values in Study MD-10. A graphical description is provided in Figure 8. The intermittent missing values were imputed by LOCF with unknown impact on the results of the PMM analysis, which assumes monotone missingness.

Figure 8: Intermittent Missing Values (20 ITT subjects) [LVM-MD-10]



(Source: Computed by reviewer. A dot indicates that the MADRS total score value exists for this visit/week.)

C) Range of Shift Parameter

The range of the shift parameter was expanded beyond the maximum shift considered by the sponsor. The 40 mg dose remains statistically significant at alpha = 0.05 at any of the larger shift parameters. The 80 mg dose looses statistical significance at the shift parameter of 12. The results of the PMM model with the shift parameter ranging from 10 to 18 are given in Table 11.

Table 11: Pattern-Mixture Model – Shift parameters: 10, 12, 14, 16, 18 [LVM-MD-10]

	Placebo (N=185)	**Levomilnacipran**	
		40 mg/day (N=185)	80 mg/day (N=187)
Shift parameter		LSMD (95% CI) p-value	
10	--	-3.320 (-5.717, -0.924) 0.0067	-2.586 (-4.886, -0.286) 0.0276
12	--	-3.224 (-5.652, -0.795) 0.0093	-2.368 (-4.773, 0.038) 0.0537
14	--	-3.299 (-5.861, -0.737) 0.0116	-2.160 (-4.687, 0.368) 0.0940
16	--	-3.407 (-6.016, -0.798) 0.0105	-1.871 (-4.494, 0.752) 0.1620
18	--	-3.330 (-6.041, -0.620) 0.0161	-1.463 (-4.189, 1.263) 0.2927

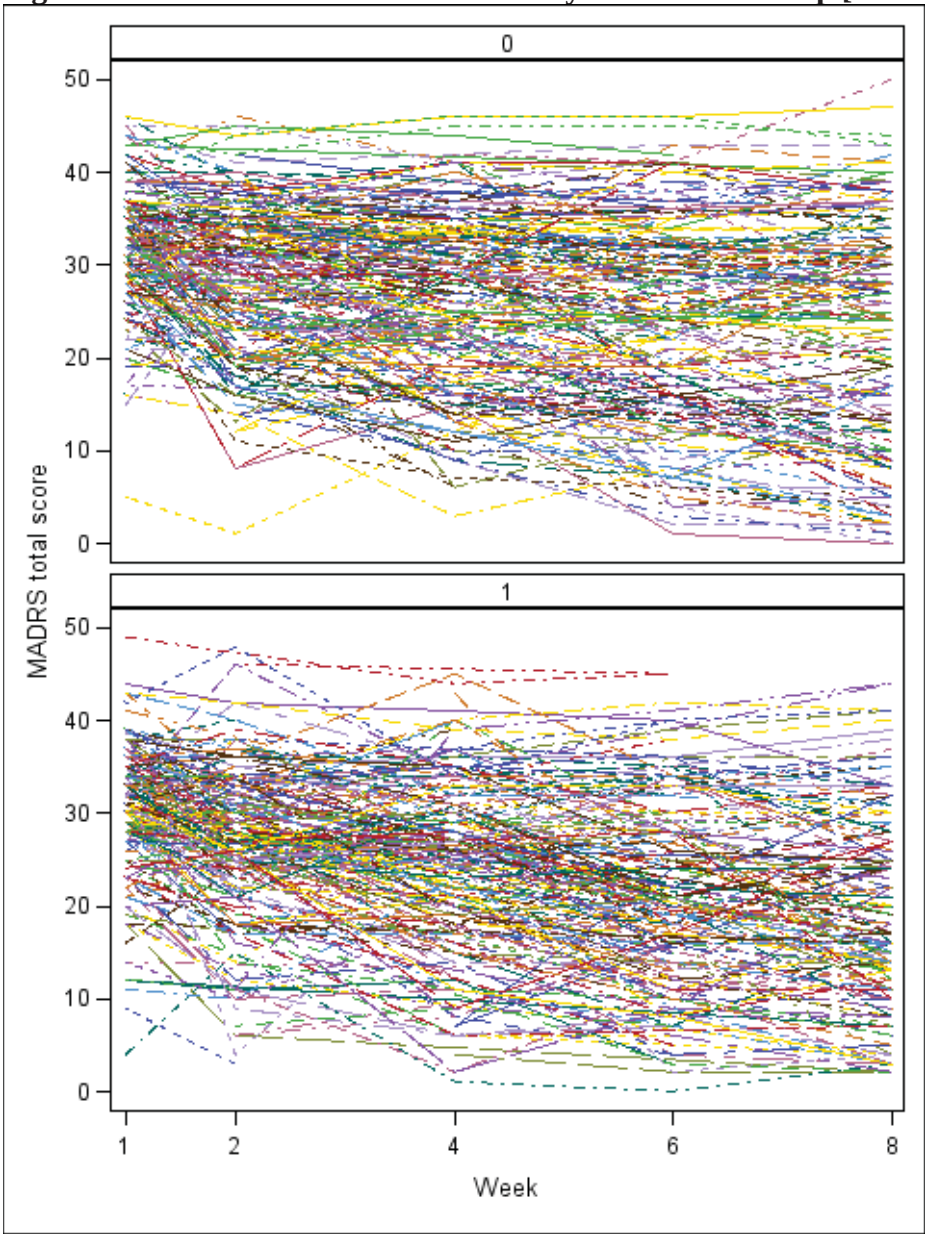
(Source: Computed by reviewer using modified sponsor code)

3.2.3 LVM-MD-03

Sponsor's Results

The individual MADRS total score profiles between week 1 and week 8 of the double-blind treatment period are displayed in Figure 9.

Figure 9: MADRS Total Score Profiles by Treatment Group [LVM-MD-03]



(Source: Computed by reviewer; Treatment groups: Placebo (0), and 40-120 mg (1))

Results of the primary and of both sensitivity analyses are summarized in Table 12. The p-values of the PMM analysis given different shift parameters are provided in Table 13.

Table 12: Primary and Sensitivity Analyses: Change from Baseline to Week 8 in the MADRS Total Score (MMRM, LOCF and PMM) – ITT Population [LVM-MD-03]

		Placebo (N = 214)	*F2695 SR 40-120 mg/day (N = 215)*
Primary analysis—MMRM[a]			
Baseline, mean ± SD		35.2 ± 3.8	35.0 ± 3.6
Change at Week 8, LS mean (SE)		–12.2 (0.78)	–15.3 (0.79)
LSMD (95% CI)		—	–3.095 (–5.256, –0.935)
p-Value		—	0.0051[a]
Sensitivity analysis—LOCF[b]			
Baseline, mean ± SD		35.2 ± 3.8	35.0 ± 3.6
Change at Week 8, LS mean (SE)		–11.4 (0.76)	–13.9 (0.75)
LSMD (95% CI)		—	–2.553 (–4.557, –0.549)
p-Value		—	0.0127[b]
Sensitivity analysis—PMM[c]			
LSMD (95% CI)	Shift parameter		
	0	—	–3.135 (–5.255, –1.016)
	2	—	–3.015 (–5.128, –0.902)
	4	—	–2.925 (–5.051, –0.800)
	6	—	–2.870 (–5.087, –0.652)
	8	—	–2.792 (–5.057, –0.526)

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

b p-Value was obtained from an analysis-of-covariance model with treatment group and pooled study centers as factors and baseline MADRS–CR total score as covariate.

c For each shift parameter value, missing values were imputed multiple times using a PMM assuming non-future dependence. For each imputed dataset, MMRM analysis was performed.

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS–CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT population; n = number of patients in the ITT Population with available values at baseline and at a specific time point; PMM = pattern-mixture model; SD = standard deviation; SE = standard error; SR = sustained release.

(Source: Study report LVM-MD-03 p. 97-98; this reviewer confirmed the estimates obtained from the PMM model in the table above)

Table 13: Pattern-Mixture Model p-values [LVM-MD-03]

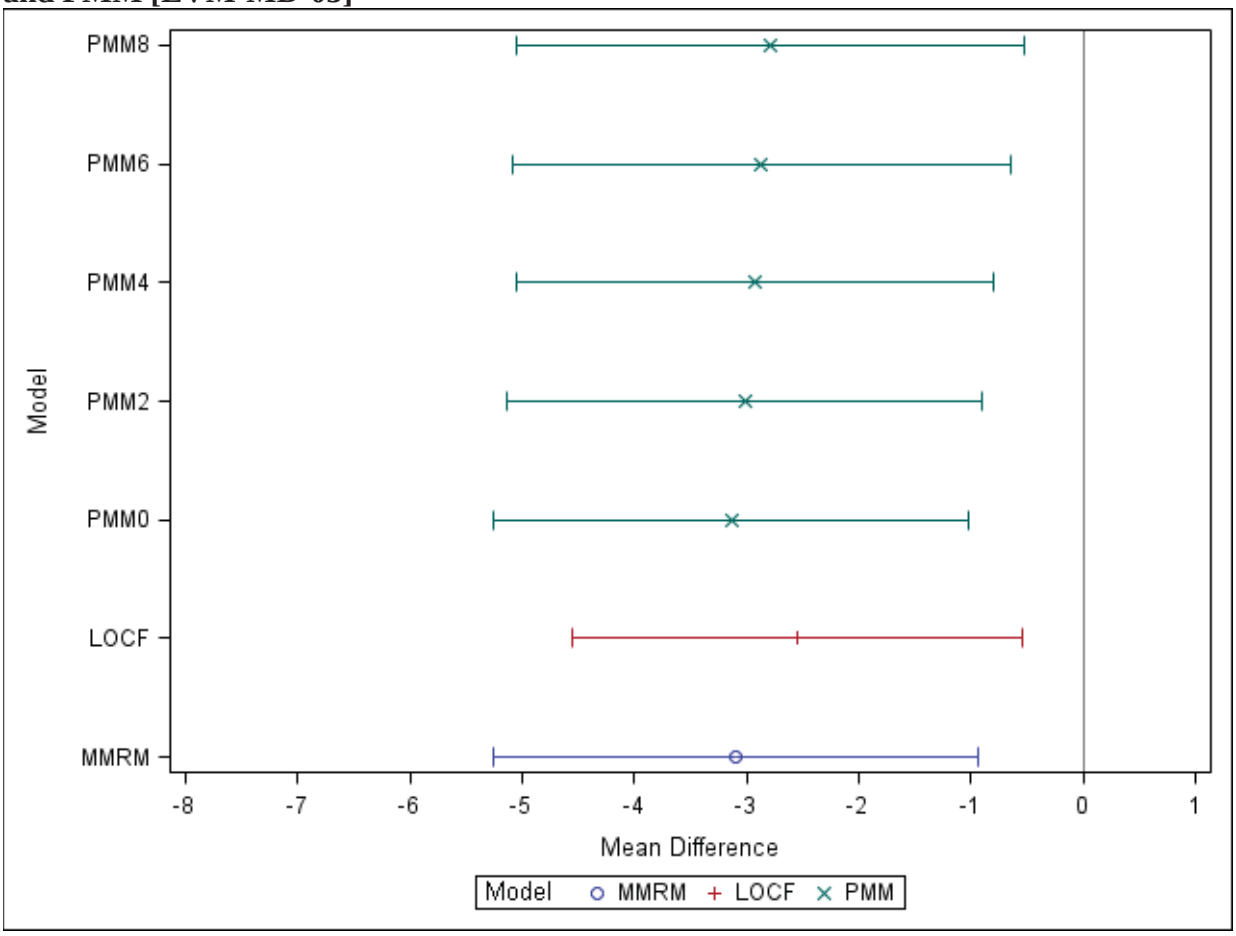
	Placebo (N=214)	**Levomilnacipran** 40-120 mg/day (N=215)
Shift parameter	p-value of LSMD vs. placebo	
0	--	0.0038
2	--	0.0052
4	--	0.0070
6	--	0.0112
8	--	0.0158

(Source: Values computed by this reviewer using SAS code provided by sponsor)

The sponsor summarizes the results of the sensitivity analyses for Study LVM-MD-03 as follows: “Statistically significant improvement was also seen in the LOCF analysis (p = 0.0127) and the PMM analysis at each selected value of the shift parameter, confirming the robustness of the primary efficacy analysis” (Study report LVM-MD-03 p. 97). The results of the PMM model generated by the sponsor and shown in Table 12 were replicated by this reviewer using the sponsor provided SAS code.

The MADRS mean difference estimates at week 8 provided in Table 12 by analysis method are presented graphically in Figure 10.

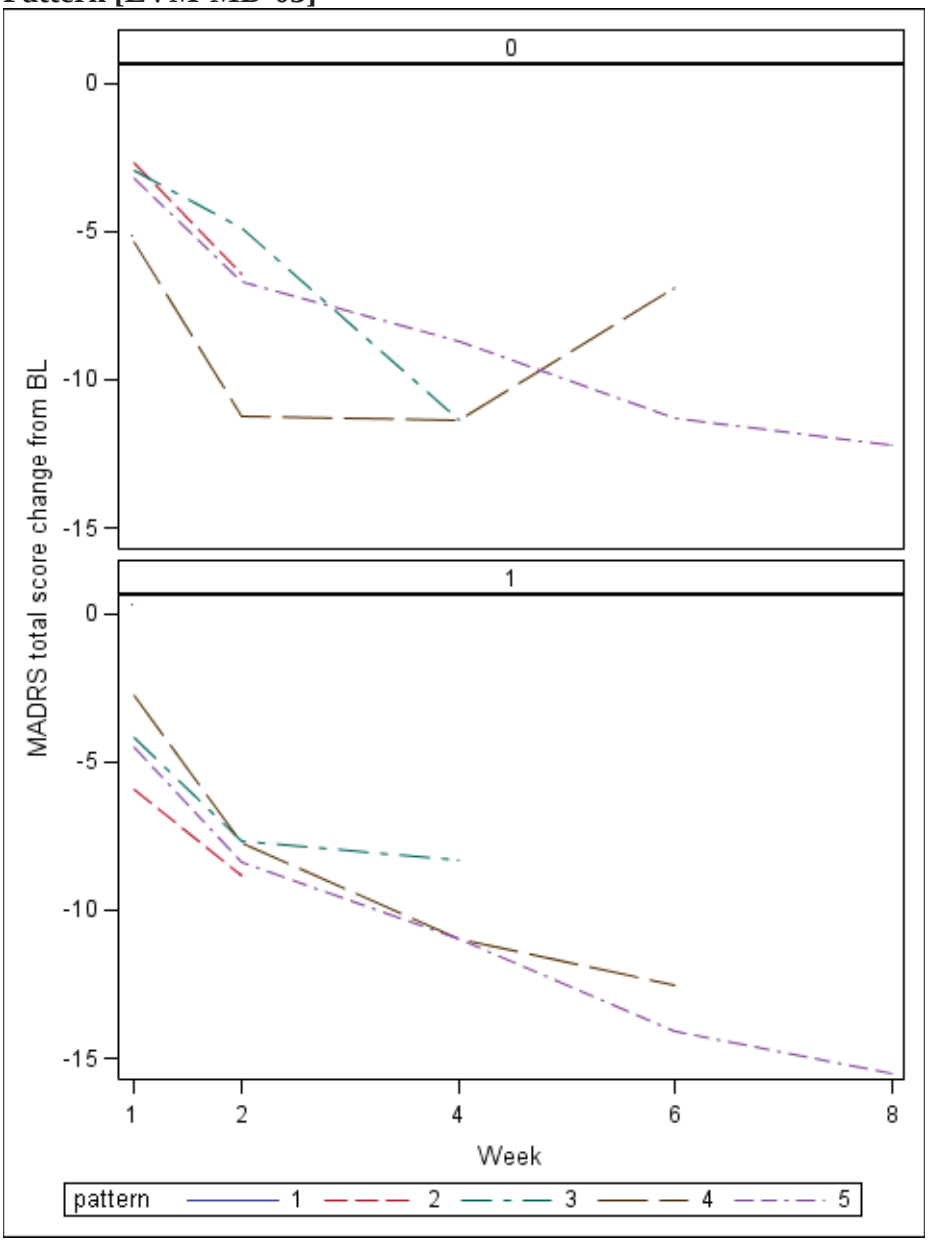
Figure 10: LSMD in MADRS Total Score at Week 8 and 95% CI from MMRM, LOCF and PMM [LVM-MD-03]



(Source: Graph created by reviewer; MMRM = Mixed Model Repeated Measures; LOCF = ANCOVA LOCF; PMM = Pattern-Mixture Model [The number attached to PMM indicates the value of the shift parameter.])

Figure 11 displays the mean observed MADRS total score change by drop-out pattern for the placebo as well as for the active treatment group. Almost all slopes are negative indicating some improvement on the MADRS scale regardless of subsequent drop-out or continuation in the trial.

Figure 11: Mean Observed MADRS Total Score Change by Treatment and Drop-out Pattern [LVM-MD-03]



(Source: Computed by reviewer; Treatment groups: Placebo (0), and 40-120 mg (1); Pattern 1 only shows as one dot at week 1.)

Potential Issues

A) Coding Problem

Table 14: Sample Size per Treatment Arm and Drop-out Pattern [LVM-MD-03]

Treatment Group	**Pattern (Week of last visit)**					
	1 (1)	2 (2)	3 (4)	4 (6)	5 (8)	Total
Placebo	9	9	10	9	173	210
Levomilnacipran 40-120 mg	8	16	11	14	163	212
Total	17	25	21	23	336	**422**

(Source: Computed by reviewer)

The same oversight in the coding as before excludes seven subjects from the pattern frequencies, with minimal impact on the final PMM results (compare Table 14 and Table 15 to see the small discrepancies in frequencies).

Table 15: Sample Size per Treatment Arm and Drop-out Pattern - Corrected [LVM-MD-03]

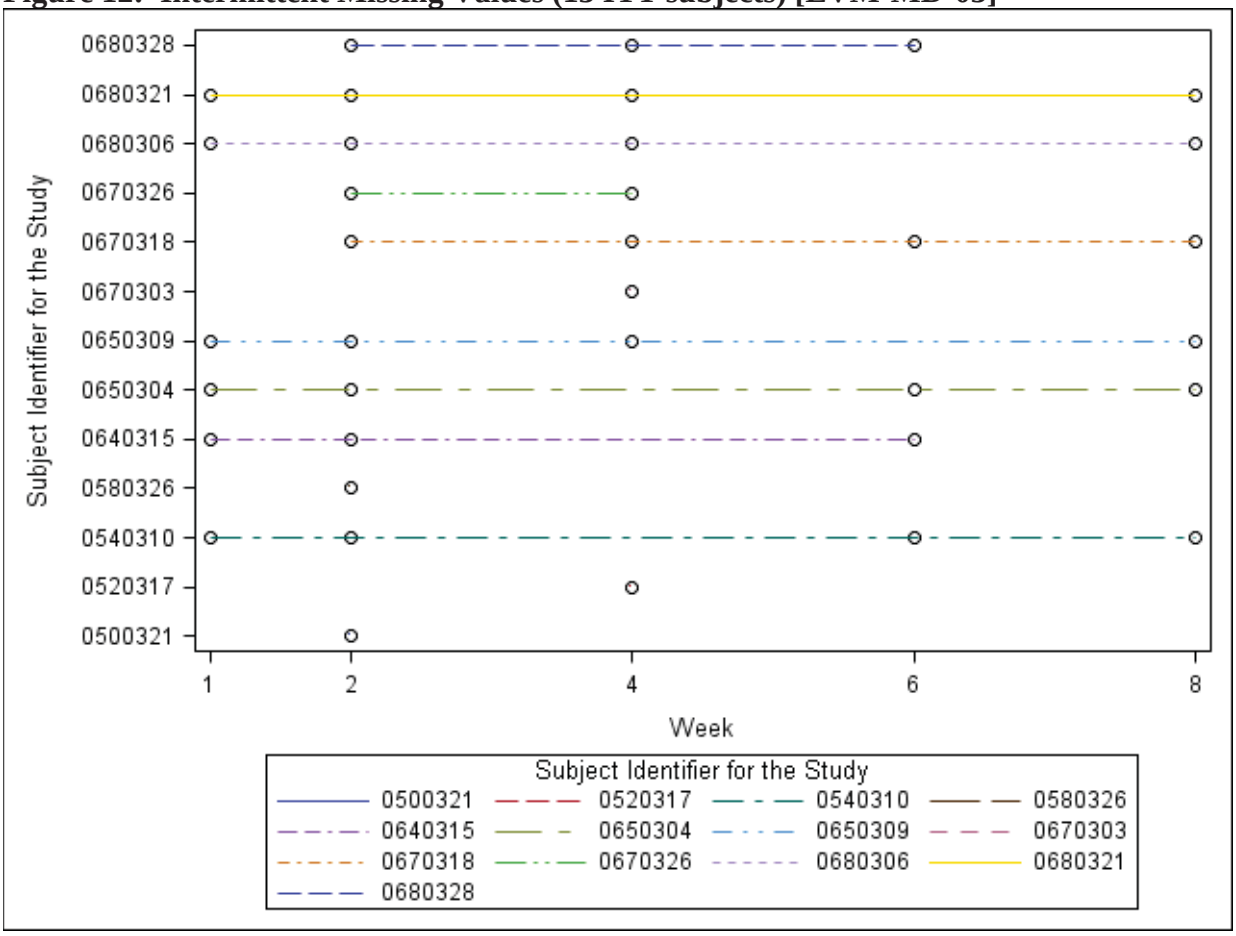
Treatment Group	**Pattern (Week of last visit)**					
	1 (1)	2 (2)	3 (4)	4 (6)	5 (8)	Total
Placebo	9	11	11	9	174	214
Levomilnacipran 40-120 mg	8	16	13	15	163	215
Total	17	27	24	24	337	**429**

(Source: Computed by reviewer)

B) Intermittent Missing Values

Intermittent missing values occurred for 13 ITT subjects (see Figure 12). Those missing values were imputed by LOCF to achieve monotone missingness – an assumption of the PMM approach. Although the effect of the LOCF imputation is not clear, it is unlikely to have had any major impact given that the approach was used for only 13 out of 429 ITT subjects.

Figure 12: Intermittent Missing Values (13 ITT subjects) [LVM-MD-03]



(Source: Computed by reviewer. A dot indicates that the MADRS total score value exists for this visit/week.)

C) Range of Shift Parameter

A "tipping point" analysis was conducted by increasing the shift parameter beyond the maximum value of 8 considered by the sponsor. The mean difference in MADRS change scores between drug and placebo would loose statistical significance at alpha = 0.05 at a shift parameter of 16 (see Table 16). The value of 16 appears to be rather large and unlikely to be a realistic mean difference at y_{t+1} between patients that drop-out after the t^{th} visit and patients that continue. The PMM model results are consistent with the primary MMRM model results at the more realistic values of the shift parameter (i.e., 2, 4, …, 14).

Table 16: Pattern-Mixture Model – Shift Parameters: 10, 12, 14, 16, 18 [LVM-MD-03]

	Placebo (N=214)	**Levomilnacipran** 40-120 mg/day (N=215)
Shift parameter	LSMD (95% CI) p-value	
10	--	-2.719 (-4.994, -0.444) 0.0192
12	--	-2.573 (-4.926, -0.219) 0.0321
14	--	-2.534 (-5.000, -0.067) 0.0441
16	--	-2.507 (-5.051, 0.036) 0.0533
18	--	-2.467 (-5.058, 0.124) 0.0620

(Source: Computed by reviewer using modified sponsor code)

4. Summary and Conclusions

4.1 Statistical Issues

The assumption of monotone missingness for the PMM necessitates the imputation of intermittent missing values. The sponsor decided to use LOCF to accomplish this task. Those imputed values are treated as observed values in the subsequent analysis. How much bias the approach introduces is unknown, but it certainly depends on the proportion of patients with intermittent missing values and how many visits were missed before the final recorded visit.

The sponsor chose values of 0, 2, 4, 6, and 8 as reasonable values for the shift parameter. An increase of the shift parameter by one or two increments (from 8 to 10 or 12) in Study MD-01, the first study conducted, would render all three tested doses as not statistical significant at alpha = 0.05. It seems that the sponsor would be hard pressed to explain why a shift parameter of 8 appears “reasonable” but values of 10 or 12 are out of the question. Study MD-10 reaches the “tipping point” at a shift parameter of 12 for the 80 mg dose and Study MD-03 reaches the “tipping point” at a shift parameter of 16.

4.2 Conclusions and Recommendations

Although some issues regarding the set-up and conduct of the Pattern-Mixture model were detected in this exploration they do not amount to enough critical mass to reject the PMM approach taken by the sponsor. The PMM results based on a reasonable range of the shift parameter are mostly consistent with the primary analysis results. No change to the main review’s conclusion of substantial evidence of efficacy is warranted.

Appendices

Table A1: Pattern-Mixture Model – Numbers of Subjects in Each Pattern Corrected [LVM-MD-01]

	Placebo (N=175)	**Levomilnacipran**		
		40 mg/day (N=176)	80 mg/day (N=177)	120 mg/day (N=175)
Shift parameter		LSMD (95% CI) p-value		
0	--	-3.146 (-5.755, -0.536) 0.0182	-3.928 (-6.568, -1.289) 0.0036	-4.892 (-7.687, -2.097) 0.0006
2	--	-3.014 (-5.650, -0.378) 0.0250	-3.866 (-6.537, -1.194) 0.0046	-4.767 (-7.575, -1.960) 0.0009
4	--	-3.026 (-5.713, -0.339) 0.0273	-3.692 (-6.442, -0.941) 0.0086	-4.558 (-7.323, -1.793) 0.0013
6	--	-3.003 (-5.748, -0.259) 0.0320	-3.520 (-6.326, -0.715) 0.0140	-4.050 (-6.933, -1.167) 0.0060
8	--	-2.957 (-5.798, -0.116) 0.0414	-3.253 (-6.016, -0.491) 0.0210	-3.643 (-6.566, -0.720) 0.0146

(Source: Computed by reviewer)

Pattern-Mixture Model Details
(Source: SAP for LVM-MD-10, Amendment #1 from March 27, 2012, pages 39-48)

For repeated measures under monotone missing, the pattern-mixture model with non-future dependent missing assumption proposed by Kenward et al (2003) provides a feasible solution to accommodate certain missing not at random (MNAR) mechanism. The methodology relies on constructing unidentifiable conditional densities using identifiable densities and borrows techniques from standard multiple imputation.

1. Non-Future Dependent Missing Assumption

(b) (4)

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4. SAS Implementation

Suppose that there is one placebo and one treatment group and there is a baseline and five postbaseline measurements. The sample code can be easily adapted to accommodate more than one treatment group and a different number of postbaseline measurements. The primary interest is the treatment difference in mean change from baseline at the last time point.

Sample SAS code is provided below to

(I) estimate mean vector and covariance matrix to be used to estimate the density functions for each pattern,

(II) calculate the weight delta in formula (5),

(III) perform the missing data imputations as outlined in section 2.

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Reference

Kenward, M.G., Molenberghs, G., and Thijs, H. (2003), Pattern-mixture models with proper time dependence. *Biometrika*, Vol. 90(1): 53-71.

Panel on Handling Missing Data in Clinical Trial (2010), *The Prevention and Treatment of Missing Data in Clinical Trials*. National Research Council. Available: http://www.nap.edu/catalog/12955.html

Rubin, D.B. (1987), *Multiple Imputation for Nonresponse in Surveys*. New York: Wiley.

SAS Institute Inc. (2004), *SAS/STAT User's Guide,* Version 9.1, Cary, NC: SAS Institute Inc.

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/s/

THOMAS BIRKNER
07/23/2013

PEILING YANG
07/23/2013
The purpose of this review is to explore sensitivity analyses to the potential deviation of the missing data assumption. This should not affect the conclusions in Dr. Birkner's primary review signed off on 6/14/2013.

HSIEN MING J HUNG
07/23/2013

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	204168
Drug Name:	FETZIMA (Levomilnacipran) extended-release capsules 20, 40, 80, and 120 mg
Indication:	Major Depressive Disorder
Applicant:	Forest Laboratories, Inc.
Date:	Submitted: 09/24/2012
	PDUFA date: 07/25/2013
Review Priority:	Standard
Biometrics Division:	**Division of Biometrics I**
Statistical Reviewer:	Thomas Birkner, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., Team Leader
	H. M. James Hung, Ph.D., Division Director
Medical Division:	**Division of Psychiatry Products**
Clinical Team:	Kavneet Kohli-Chhabra, M.D., Medical Reviewer
	Ni Aye Khin, M.D., Medical Team Leader
Project Manager:	Juliette T. Toure, Pharm. D.

Keywords: clinical studies, mixed models, sensitivity analyses, subgroup analyses

Table of Contents

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1 EXECUTIVE SUMMARY

The sponsor, Forest Laboratories, submitted three Phase 3 studies (two fixed dose, one flexible dose) and one supportive Phase 2 study (flexible dose) to support a claim that levomilnacipran extended-release capsules are efficacious in the treatment of major depressive disorder.

The Phase 3 studies were all conducted in the US and Canada. The Phase 2 study enrolled patients internationally. Two other Phase 3 studies (one short-term flexible dose and one maintenance trial) completed in the same program were negative (for details on those see section 3.2.4.6).

The primary endpoint for all acute studies was the change from baseline in the Montgomery-Asberg Depression Rating Scale total score (MADRS) at week 8 (week 10 for the Phase 2 study). The key secondary outcome measure was the Sheehan Disability Scale (SDS). The difference between placebo and any evaluated dose of levomilnacipran ER (40, 80, 120 mg or flexible 40-120 mg or flexible 75-100 mg) for the primary endpoint achieved statistical significance in all three Phase 3 studies and also in the supportive Phase 2 study at alpha = 0.05. The point estimates of the LS Mean Difference for the primary endpoint were estimated to be in the range from -3.10 (Study MD-03) to -4.86 (120 mg group in Study MD-01). The results for the key secondary outcome SDS were statistically significant for the 80 mg (Studies MD-01 and MD-10) and 120 mg (Study MD-01) dose groups and also in the flexible dose studies MD-03 and LP 2 02. The point estimates of the LS Mean Difference for the key secondary endpoint were estimated to be in the range from -1.41 (40 mg group in Study MD-01) to -2.63 (Study MD-03). The 40 mg dose group's change in SDS scores was not statistically significant different from placebo in Study MD-01. The results from the primary and supportive analyses for SDS in the 40 mg group from Study MD-10 are inconsistent with a p-value either barely below the 0.05 threshold (primary analysis) or slightly above (supportive analysis). Associated with the borderline statistical significance of the 40 mg dose for the key secondary endpoint in Study MD-10 is the finding that 27% percent of SDS baseline scores for the ITT population are missing in this study (see section 3.2.4.2). The overall mean daily dose in the flexible dose study MD-03 was 73 mg and 46 (21%) of all patients on active treatment had a final daily dose of 40 mg.

The sample size was increased from 360 to 440 in Study MD-03 after results from another flexible dose study indicated a smaller effect size than previously assumed. However, results from analysis including only the 360 initially randomized patients are consistent with the final analysis based on the larger sample size (see section 3.2.4.3).

A summary of the primary and key secondary outcome measure results is provided in Tables 38 and 39 in section 3.2.4.5. No major statistical issues were detected. The strength of statistical evidence supports the claim of the sponsor except for the 40 mg dose at the key secondary outcome measure.

2 INTRODUCTION

2.1 Overview

Levomilnacipran ER is a selective serotonin and norepinephrine reuptake inhibitor developed for the treatment of major depressive disorder (MDD) by Forest Research Institute, Inc., and Pierre Fabre Medicament. The sponsor is basing the claim for an indication in MDD for adults 18 years of age and older on three pivotal studies (LVM-MD-01, LVM-MD-10, and LVM-MD-03) conducted in the United States and Canada, and on one supportive study (F02695 LP 2 02) conducted internationally by Pierre Fabre Medicament. All four studies were placebo-controlled. Two of the studies tested fixed doses while the other two used a flexible dose. The studies enrolled male and female patients who met the criteria for MDD. A Montgomery-Asberg Depression Rating Scale total score ≥ 30 was one of the entry criteria for studies MD-01 and MD-03. To be eligible for Study MD-10 the MADRS total score had to be ≥ 26. One of the inclusion criteria for Study LP 2 02 was a HAMD-17 score > 22.

Table 1: List of Studies Selected for Full Review

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
LVM-MD-01	Phase 3, parallel, 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
LVM-MD-10	Phase 3, parallel, fixed dose	8 weeks	Placebo (185) LVM 40 mg (185) LVM 80 mg (187)	Male and female patients (18 – 75 years) with MDD
LVM-MD-03	Phase 3, parallel, flexible dose	8 weeks	Placebo (214) LVM 40-120 mg (174)	Male and female patients (18 – 80 years) with MDD

The importance of a single site for the overall statistical significance of each of the Phase 3 studies was assessed by removing one site at a time from the primary analysis for the primary endpoint. A few sites were found to be of particular importance for the overall success of the studies (see figures A1-A3 in appendix). Site inspections were conducted: Only minor deficiencies unlikely to affect the study outcome were detected.

Table 2: Placebo-Controlled Efficacy Studies in Forest's Levomilnacipran MDD Program

Protocol Number/ Countries	*Study Design*	*Double-Blind Treatment Duration*	*Efficacy Parameters*		*Treatment Groups (N)*[a]
			Primary	*Secondary*	
Pivotal Studies					
LVM-MD-01 US	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study	8 weeks	MADRS	SDS	Placebo (175) LVM 40 mg/d (176) LVM 80 mg/d (177) LVM 120 mg/d (176)
LVM-MD-10 US and Canada	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study	8 weeks	MADRS	SDS	Placebo (185) LVM 40 mg/d (185) LVM 80 mg/d (187)
LVM-MD-03 US	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study	8 weeks	MADRS	SDS	Placebo (214) LVM 40-120 mg/d (215)
Supportive Study					
F02695 LP 2 02 ex-US	Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study	10 weeks	MADRS	SDS[b]	Placebo (277) LVM 75-100 mg/d (276)
Other MDD Studies					
LVM-MD-02 US	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study	8 weeks	MADRS	SDS	Placebo (181) LVM 40-120 mg/d (174)
LVM-MD-05 US and Canada	Phase 3, multicenter, randomized, double-blind, placebo-controlled, relapse-prevention study	24 weeks	Time to relapse	NA	<u>Open-label period</u> LVM 40-120 mg/d (724) <u>Double-Blind treatment period</u> Placebo (112) LVM 40-120 mg/d (230)

a Number of patients who received at least 1 dose of double-blind investigational product and had at least 1 postbaseline assessment of the MADRS total score (ITT Population).

b Additional efficacy parameters were listed as secondary in Section 11.4.1.2 of the F02695 LP 2 02 CSR.

ITT = intent to treat; LVM = levomilnacipran; MADRS = Montgomery-Åsberg Depression Rating Scale; NA = not applicable; SDS = Sheehan Disability Scale.

(Source: Summary of Clinical Effectiveness p. 20-21)

Studies LVM-MD-02 and LVM-MD-05 included in Table 2 above are negative studies.

2.2 Data Sources

Study reports: \\Cdsesub1\evsprod\NDA204168\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\major-depressive-disorder\5351-stud-rep-contr
Summary of Clinical Effectiveness: \\Cdsesub1\evsprod\NDA204168\0000\m2\27-clin-sum
Data sets and SAS code: \\Cdsesub1\evsprod\NDA204168\0000\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

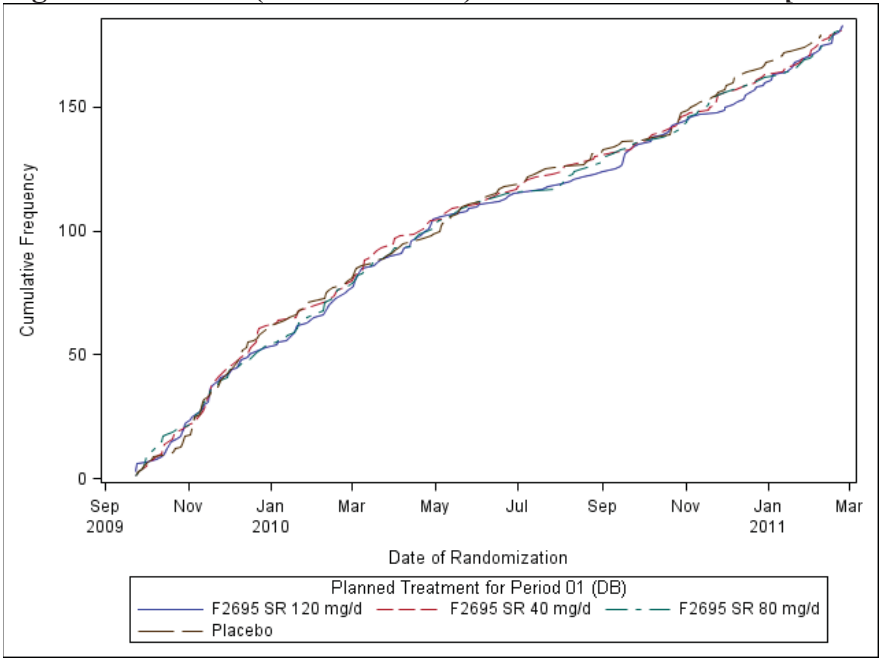
Quality control and assurance procedures were very similar for the three Phase 3 studies and are documented in the study reports. A short summary is provided here: The sponsor held investigator meetings for the personnel of all study sites before the initiation of the study for training purposes. All study personnel who were to perform efficacy assessments were required to receive training on the rating scales from (b) (4) (MD-01) or (b) (4) (MD-03) or meet the training requirements and qualification criteria set forth by the rater training vendor (MD-10). Site visits were conducted by the Regional Site Manager (RSM) to monitor the progress of the study after study initiation. "The Investigator and his/her staff were responsible for reviewing eCRFs, resolving data queries generated by the RSM via the system, providing missing or corrected data, approving all changes performed on his/her data, and endorsing the patient data within the EDC system" (Study reports MD-01 p. 50, MD-03 p. 67). This review revealed that approximately 27% of ITT subjects in Study MD-10 did not have a SDS baseline score record (for details see section 3.2.4.2 of this review).

A short documentation of blinding/unblinding procedures is provided in the Study Reports (MD-01 p. 44, MD-03 p. 51, MD-10 p. 51). Statistical analysis plans were submitted prior to completion of the studies.

The effort needed to process the data was minimal. Data from Study F02695 LP 2 02 was submitted in a legacy format, but the necessary adjustments to work with the data and code for this study were acceptable.

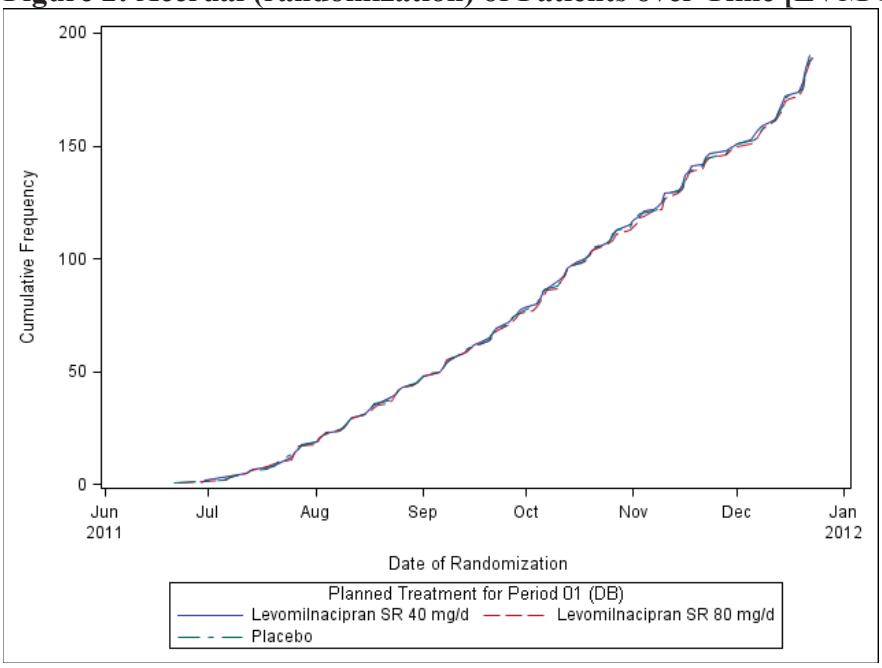
In order to evaluate the randomization process this reviewer plotted the cumulative frequencies of randomized patients in each treatment group versus the randomization dates. The plots are provided below and do not reveal any issues.

Figure 1: Accrual (randomization) of Patients over Time [LVM-MD-01]



(Source: Computed by reviewer)

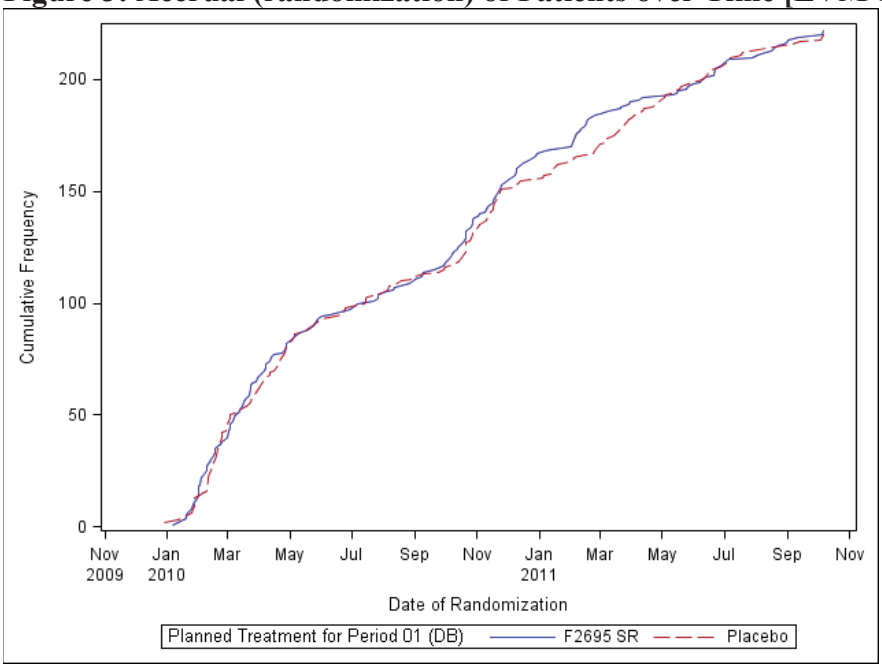
Figure 2: Accrual (randomization) of Patients over Time [LVM-MD-10]



(Source: Computed by reviewer)

The time needed to recruit and randomize patients in Study MD-10 was relatively short (approximately 6 months).

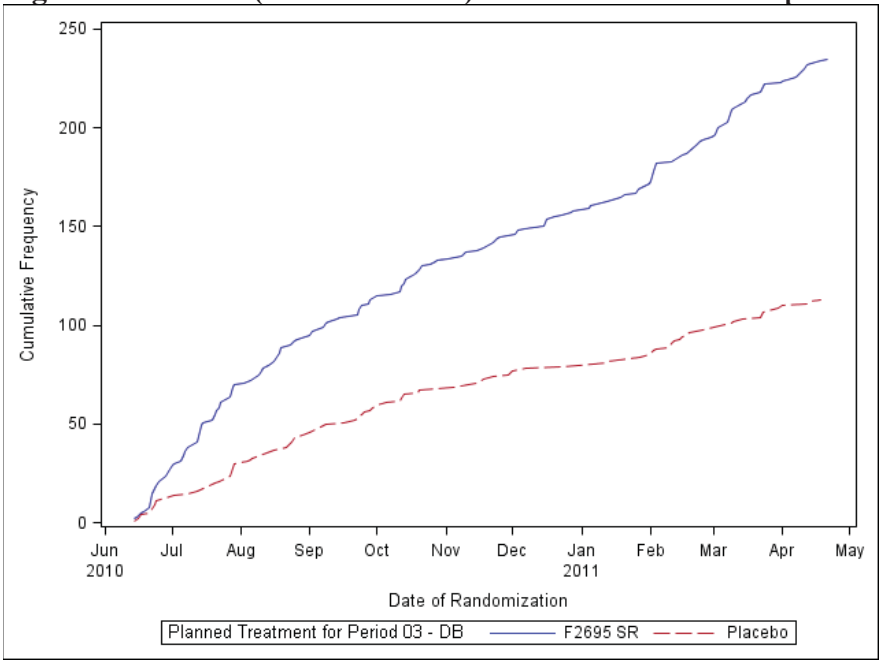
Figure 3: Accrual (randomization) of Patients over Time [LVM-MD-03]



(Source: Computed by reviewer)

Note that 17 patients were randomized on Saturday (10) and Sunday (7) in Study MD-03. All of them enrolled at site 56 (US). A total of 20 patients were randomized at this site.

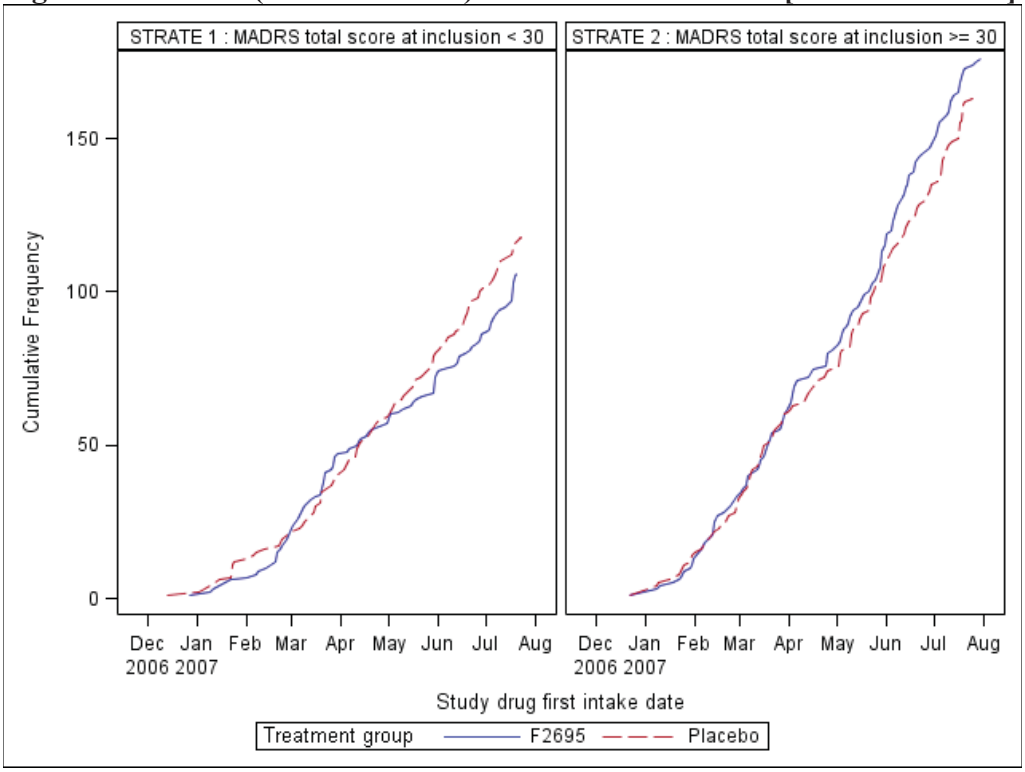
Figure 4: Accrual (randomization) of Patients over Time [LVM-MD-05]



(Source: Computed by reviewer)

A total of 348 patients were randomized in a 1:2 ratio (placebo:levomilnacipran) in Study MD-05.

Figure 5: Accrual (randomization) of Patients over Time [F02695 LP 2 02]



(Source: Computed by reviewer)

In Study F02695 LP 2 02 randomization occurred within stratum. The two strata were formed based on the MADRS total score at inclusion (< 30 vs. ≥ 30).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

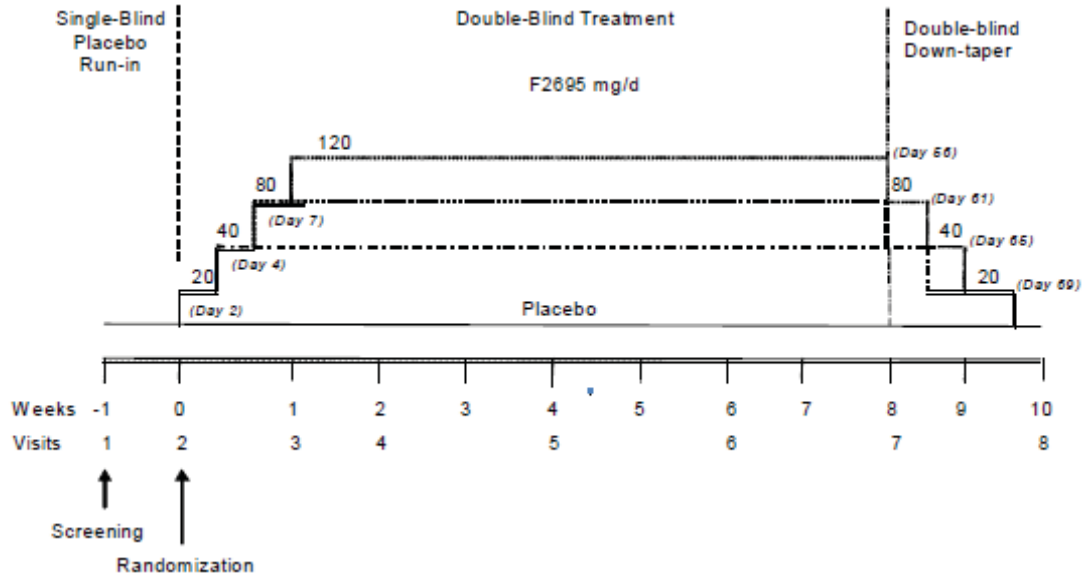
The primary efficacy assessment for all short-term studies reviewed from this submission is the Montgomery-Asberg Depression Rating Scale – Clinician Rated (MADRS). Likewise, the key secondary efficacy assessment is the Sheehan Disability Scale (SDS).

3.2.1.1 LVM-MD-01

Study LVM-MD-01 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in outpatients with MDD. A total of 724 patients with a primary diagnosis of MDD were randomized (1:1:1:1) to one of four parallel treatment groups: placebo, levomilnacipran ER 40, 80, or 120 mg/day. The study included eight scheduled visits over an 11-

week period: a 1-week, single-blind placebo run-in period; an 8-week double-blind treatment period; and a 2-week, double-blind down-taper period. The first visit of the first patient occurred in September 2009 and the last visit of the last patient in May 2011. The starting dose for patients randomized to the levomilnacipran ER groups was 20 mg/day. Patients were fixed-dose titrated to the target doses of 40, 80, or 120 mg/day over a 7-day period. Figure 6 provides a schematic diagram of the study design.

Figure 6: Study Design [LVM-MD-01]



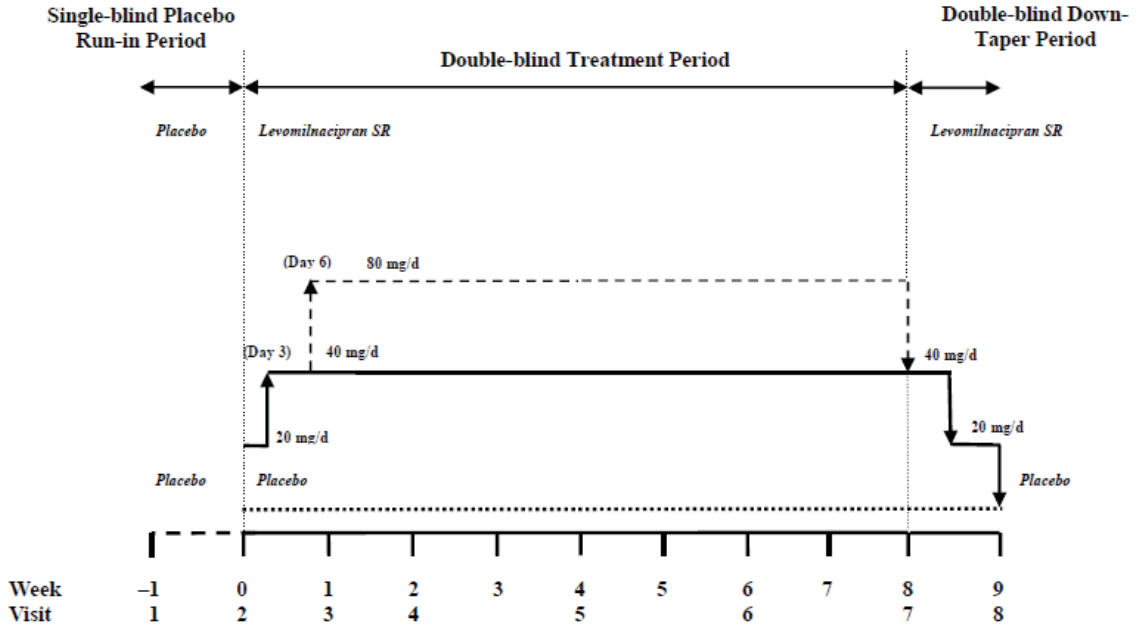
(Source: Study protocol p. 26)

3.2.1.2 LVM-MD-10

Study LVM-MD-10 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in outpatients with MDD. Patients were enrolled at 47 centers in the United States and 4 centers in Canada. The LVM-MD-10 study was conducted after the LVM-MD-01 study. The first visit for the first patient occurred in June 2011 and the last visit of the last patient in March 2012. The study duration was 10 weeks and included 8 scheduled study visits; a 1-week single-blind placebo run-in period; 8 weeks of double-blind treatment, followed by a 1-week, double-blind down-taper period. At Visit 2, 568 eligible patients were randomly assigned (1:1:1) to one of three parallel treatment groups: placebo, levomilnacipran ER 40

mg/day or levomilnacipran ER 80 mg/day. The starting dose for patients on levomilnacipran was 20 mg/day. Patients were fixed-dose titrated to the target doses of 40 or 80 mg/day over a 7-day period. Figure 7 provides a schematic diagram of the study design.

Figure 7: Study Design [LVM-MD-10]



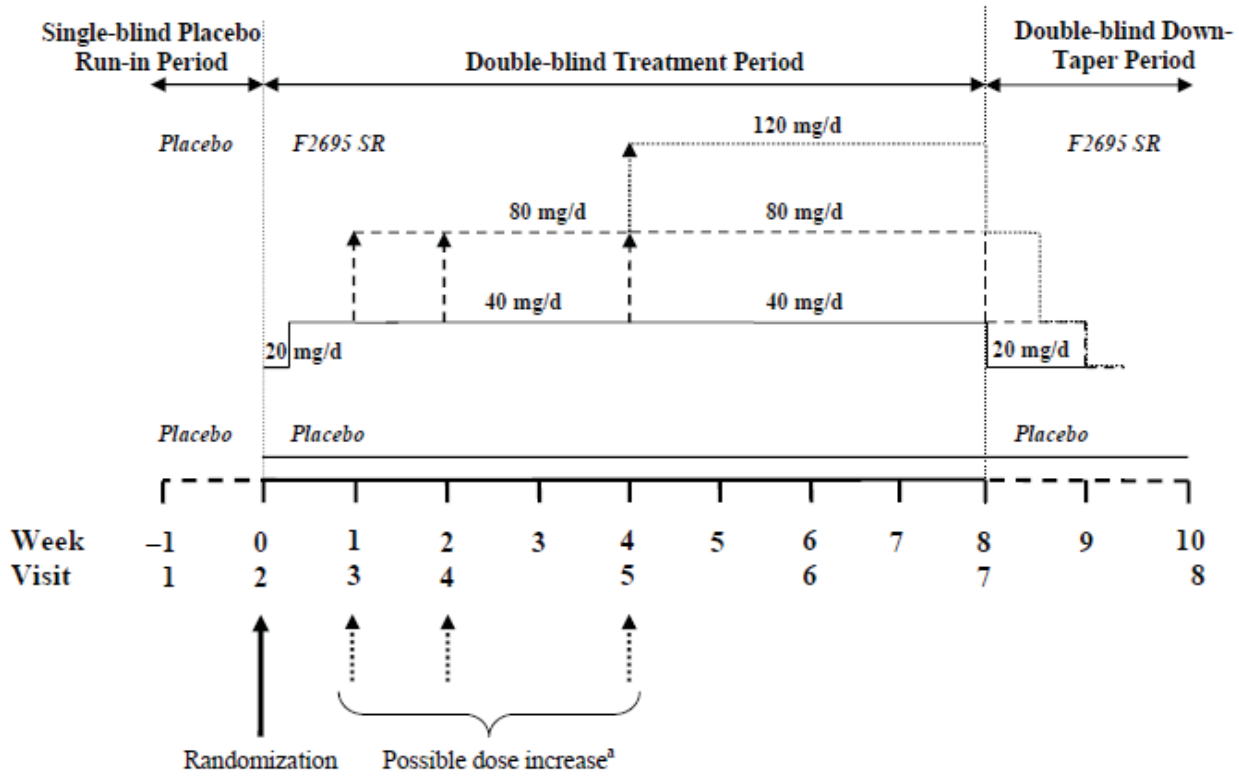
(Source: Study protocol p. 24)

3.2.1.3 LVM-MD-03

Study LVM-MD-03 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study comparing levomilnacipran ER with placebo in outpatients with MDD. The first visit of the first patient occurred in December 2009 and the last patient's last visit was in December 2011. The study consists of a single-blind 1-week placebo run-in period followed by 8 weeks of double-blind treatment and a 2-week double-blind down-taper period.

At the end of the screening period, eligible patients were randomized (1:1) to placebo or levomilnacipran. Patients assigned to active drug treatment received 20 mg/day for days 1 to 2 and 40 mg/day starting on day 3. A dosage increase from 40 to 80 mg/day was allowed at visit 3 or 4. At visit 5, the dosage could be increased again either from 40 to 80 mg/day or from 80 to 120 mg/day, based on patient response and tolerability. No dosage increase was permitted after visit 5. Figure 8 provides a schematic diagram of the study design.

Figure 8: Study Design [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.

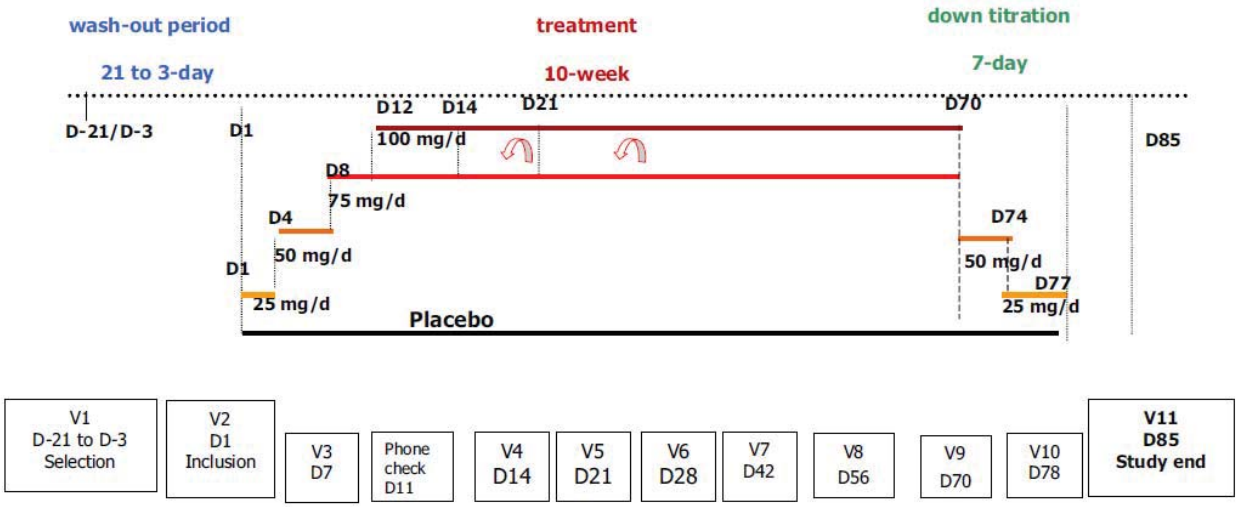
(Source: Study protocol p. 26)

3.2.1.4 F02695 LP 2 02 (Phase 2)

Study LP 2 02 is a 10-week, international, multicenter, double-blind, placebo-controlled, parallel group, randomized, flexible-dose Phase 2 trial involving 563 patients diagnosed with MDD. Two dose levels of levomilnacipran ER were assessed (75 and 100 mg/day). At randomization, patients were stratified within each center according to the severity of the episode at inclusion, based on the MADRS total score at baseline. Two strata were defined within each center with a MADRS score of 30 being the threshold value. After a wash-out period if necessary, patients began a 10-week treatment period, including a forced titration over the first 2 weeks for all randomized patients, and followed by a one week down titration. Under the forced titration scheme patients started on 25 mg, then took 50 mg for days 4 to 7 and then 75 mg from day 8 to 11. At day 12, based on an evaluation of tolerance by the investigator on day 11, the dosage was

either increased to 100 mg or remained unchanged at 75 mg. The dose for patients continuing on 75 mg at day 12 was fixed to the end of the study. The dose of patients moving to the 100 mg dose at day 12 could be reduced to 75 mg due to tolerability issues later on. The study design is illustrated in Figure 9.

Figure 9: Study Design [F02695 LP 2 02]



(Source: Study report p. 53)

The primary outcome measure in Study LP 2 02 was the comparison with placebo on the MADRS total score after 10 weeks of treatment. The Sheehan Disability Scale was one among several secondary outcome measures in this study.

3.2.1.5 LVM-MD-05 (Maintenance study)

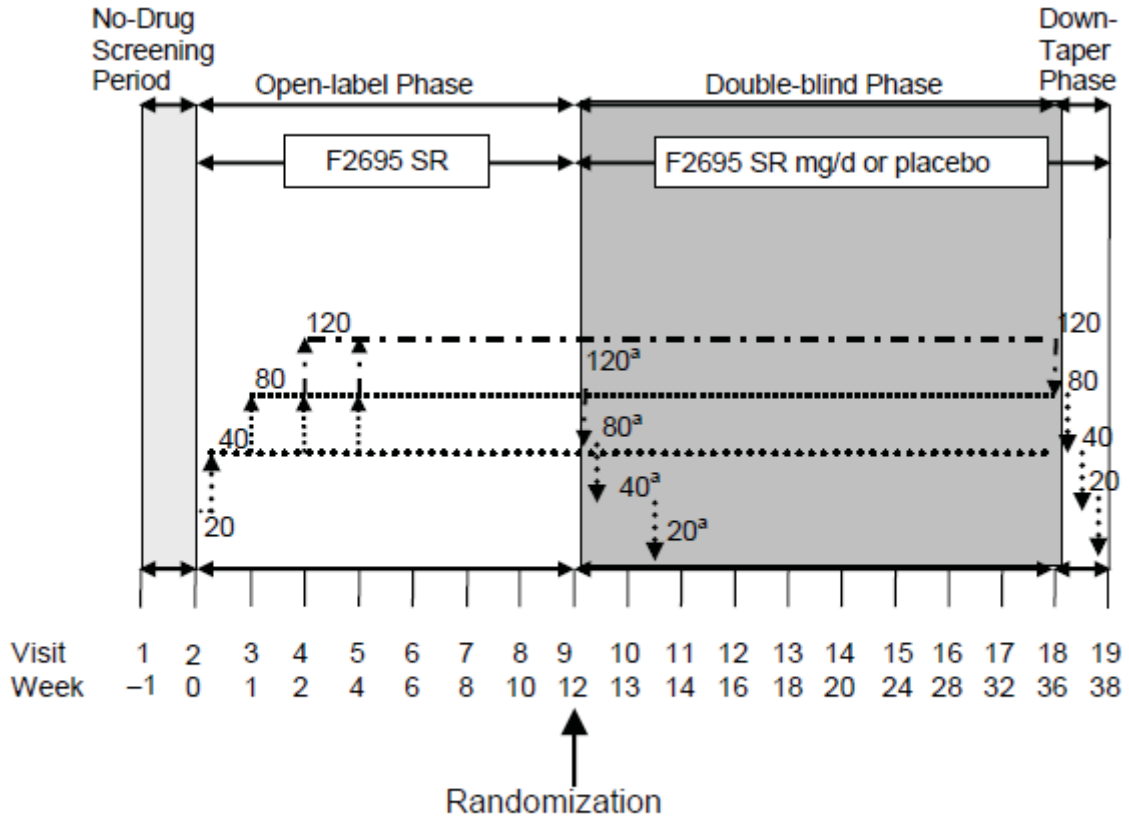
This section describes the design of the failed/negative maintenance study. Study LVM-MD-05 is a multicenter, randomized, double-blind, placebo-controlled study in patients with MDD. The study's duration was up to 39 weeks: consisting of a 1-week no-drug screening phase, a 12-week open-label treatment phase (levomilnacipran ER 40-120 mg/day), a 24-week double-blind treatment phase (40, 80, or 120 mg/day levomilnacipran ER or placebo), and a 2-week double-blind down-taper treatment phase. A total of 734 patients were enrolled in the open-label treatment phase of this study, and 348 patients were randomized to the double-blind treatment

phase. The first visit of the first patient occurred in March 2010 and last visit of the last patient in October 2011.

At the end of the screening phase, patients meeting the entry criteria were enrolled in the flexible-dose, 12-week, open-label treatment phase and received levomilnacipran ER starting at 20 mg/day. After 2 days, the levomilnacipran ER dose was increased to 40 mg/day and could be further increased at the end of Week 2 to 80 mg/day and/or 120 mg/day based on the investigator's judgment of patient's response and tolerability. By Day 15, patients were to remain on a stable dose of the maximum effective and tolerated dose for the remaining open-label treatment phase.

At the end of the open-label treatment phase, patients meeting responder criteria (defined as MADRS total score $\leq$ 12 and Clinical Global Impressions-Improvement (CGI-I) score $\leq$ 2 at both Visits 8 and 9) were randomly assigned in a 2:1 ratio (levomilnacipran:placebo) to double-blind treatment for 24 weeks. The dose was fixed during the double-blind treatment phase, and patients randomized to the levomilnacipran ER treatment group continued on the same dosage (40, 80, or 120 mg/day) that they were receiving at the end of the open-label treatment phase. Patients randomized to the placebo group were gradually tapered down during the first week after randomization and received the placebo capsules thereafter. Figure 10 provides a schematic diagram of the study design.

Figure 10: Study Design [LVM-MD-05]



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

(Source: Study protocol p. 25)

The primary efficacy parameter in Study MD-05 is the time to relapse during the double-blind treatment phase, defined as the number of days from the randomization date to the relapse date. Relapse is defined as one or more of the following:

1. MADRS total score ≥ 22 at 2 consecutive visits
2. Increase of 2 or more points in CGI-I score compared with the CGI-I score at Visit 9 at 2 consecutive visits
3. Premature discontinuation due to insufficient therapeutic response
4. MADRS item 10 score ≥ 4

All patients not randomized to double-blind treatment or who prematurely discontinued from the study (open-label or the double-blind treatment phase) were eligible to enter a 2-week down-taper treatment phase.

Note that with Amendment #2 to the protocol (submitted while the study was already ongoing) the total patient population in the open-label period was increased from 600 to 700. The sponsor decreased the expected response rate used in the sample size calculation from 60% to 52% with this amendment but did not provide an explanation for this change.

The electronic location of the amendment is: \\Cdsesub1\evsprod\IND104483\0109\m5\53-clin-stud-rep\535-rep-effic-safety-stud\major-depressive-disorder\5351-stud-rep-contr\lvm-md-05.

The statistical reviewer for this IND at the time indicated to the sponsor in an email on July 5 2011 that this increase is acceptable since it would not change the set sample size of 360 *randomized* patients.

3.2.2 Statistical Methodologies

3.2.2.1 LVM-MD-01

The efficacy analyses were performed on the Intent-To-Treat (ITT) Population. The change from baseline to week 8 in MADRS total score was used as the primary efficacy parameter. The primary efficacy analysis was performed using a Mixed Model Repeated Measures (MMRM) model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects and the baseline and baseline-by-visit interaction as the covariates.

The MMRM analysis model is shown here:

Δ MADRS total score = μ + MADRS total score baseline + pooled center + treatment + visit + patient + visit*treatment + baseline*visit + error.

Patient and error were considered as random effects. Baseline was defined as the last non-missing efficacy assessment prior to the first dosing of double-blind investigational product. Small centers, defined as having fewer than 4 patients in the ITT population, were pooled to form a pseudo-center. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation was employed to estimate denominator degrees of freedom.

The primary treatment comparisons were the contrasts between each of the three levomilnacipran ER groups and the placebo group at week 8. The Hochberg multiple-comparison procedure was used to control the family-wise error rate (for details see study report p. 64-65).

Two sensitivity analyses were conducted on the primary efficacy parameter: LOCF ANCOVA and a pattern-mixture model (PMM). For the LOCF approach, the between treatment group comparisons were performed by means of an analysis-of-covariance model with treatment group and pooled study center as factors and baseline MADRS total score as the covariate. Missing post-baseline values were imputed, provided at least one post-baseline assessment was available.

For the PMM approach, a pattern-mixture model based on non-future dependent missing value restrictions was utilized to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random missingness assumption. The non-future dependent missing value restriction states that the probability of drop-out at a specific visit can only depend on the observed value and the possibly missing value(s) up to that visit, but not future values beyond that visit. Details of this sensitivity analyses are described on page 16 of the SAP. There the sponsor states that the range of values (i.e., 0 to 8) for the shift parameter was selected based on experience with historical data.

The key secondary efficacy parameter, change from baseline to week 8 in Sheehan Disability Scale (SDS) total score, was analyzed similarly to the primary efficacy parameter and was tested using the Hochberg multiple-comparison procedure. The analysis of the key secondary efficacy parameter was carried out inferentially only if the results for the primary efficacy parameter (3 dose comparisons with placebo) were positive at the 0.05 level.

3.2.2.2 LVM-MD-10

The analysis methods were identical to study LVM-MD-01. Small centers, defined as centers with less than 3 patients in the ITT population, were pooled to form pseudo-centers. The SAP (p. 39-48) provides details on the pattern-mixture model.

3.2.2.3 LVM-MD-03

The statistical methods used to analyze the data obtained in this trial were the same as in studies LVM-MD-01 and LVM-MD-10. All the small centers (centers with fewer than 4 patients) were pooled to form a pseudo center.

3.2.2.4 F02695 LP 2 02 (Phase 2)

The primary efficacy criterion was the MADRS total score change from baseline (D1) to D70. The primary efficacy analysis used a Mixed-effects Model for Repeated Measures (MMRM) on MADRS total score changes from baseline and was performed on the ITT population. The model included Treatment, Center and Visit as main effects, MADRS total score at baseline as covariate, and treatment-by-visit and baseline-by-visit interactions. Appropriate contrasts on treatment factor and treatment-by-visit interaction were used to test the null hypothesis that MADRS total score changes from baseline to D70 for placebo and levomilnacipran ER flexible dose (75 or 100 mg/day) were equal conditional on baseline value versus the alternative that there was a difference. The main analysis was re-performed on the per protocol patient set as supportive analysis. Additional analyses were conducted using an analysis of covariance model with treatment and center as main effects and baseline MADRS total score as covariate. Centers which included less than 8 ITT population patients were pooled according to rules defined by the Validation Committee, prior to breaking the blind.

3.2.2.5 LVM-MD-05 (Maintenance Study)

The primary efficacy parameter was the time to relapse during the double-blind treatment period. The primary efficacy analysis compared the time from randomization to relapse between placebo and levomilnacipran ER groups, using the Cox proportional hazard-regression model with treatment group and baseline MADRS score as the explanatory variables based on the double-blind ITT population. Kaplan-Meier estimates and curves for cumulative rates of relapse are also presented for the double-blind treatment period. For efficacy analyses in which study center was a factor, all small centers (centers with fewer than 3 patients in the Double-blind ITT population) were pooled to form a pseudo-center.

3.2.2.6 Summary of Statistical Methodologies

Table 3: Endpoints and Analysis Methods

	Pivotal Studies			*Supportive Study*	*Other Study*
	LVM-MD-01	*LVM-MD-10*	*LVM-MD-03*	*F02695 LP 2 02*	*LVM-MD-02*
Primary Endpoint	Change from baseline MADRS at Week 8	Change from baseline MADRS at Week 8	Change from baseline MADRS at Week 8	Change from baseline MADRS at Week 10	Change from baseline MADRS at Week 8
Secondary Endpoint	Change from baseline SDS at Week 8	Change from baseline SDS at Week 8	Change from baseline SDS at Week 8	Change from baseline SDS at Week 10[a]	Change from baseline SDS at Week 8
Primary Analysis Model	MMRM	MMRM	MMRM	MMRM	MMRM
Sensitivity Analysis Model	LOCF PMM	LOCF PMM	LOCF PMM	LOCF	LOCF PMM

a Additional efficacy parameters were listed as secondary in Section 13.7.2 of the F02695 LP 2 02 protocol.
LOCF = last observation carried forward; MMRM = mixed-effects model for repeated measures; MADRS = Montgomery-Åsberg Depression Rating Scale; PMM = pattern-mixture model; SDS = Sheehan Disability Scale.

(Source: Summary of Clinical Effectiveness p. 26)

Studies LVM-MD-01, LVM-MD-10 and LVM-MD-03 are very much alike as far as endpoints and analysis methods are concerned. The Phase 2 Study F022695 LP 2 02 is similar to those, but assessed the change from baseline at week 10 instead of week 8. Additionally SDS was defined as one of several secondary parameters and not as the key secondary parameter. Recall that Study LVM-MD-02 included in the table above had negative results.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 LVM-MD-01

A total of 724 patients were randomized to receive double-blind treatment. Of the 713 patients who received at least one dose of double-blind treatment, 704 also had at least one post-baseline MADRS-CR assessment (ITT Population), and 506 subjects completed the study (see Tables 4 and 5).

Table 4: Patient Populations [LVM-MD-01]

Population	*Placebo*	*F2695 SR*			*Total*
		40 mg/d	*80 mg/d*	*120 mg/d*	
Randomized Population	179	181	181	183	724
Safety Population	176	178	179	180	713
ITT Population	175	176	177	176	704

ITT = intent to treat; SR = sustained release.
(Source: Study report p. 82)

The reasons for discontinuation are presented in Table 5. The proportion of patients that prematurely discontinued appears associated with the dose of levomilnacipran administered. Discontinuation rates are statistically significantly different between placebo and the 80 and 120 mg/day dose groups. The most frequent reasons for discontinuation were withdrawal of consent, adverse events and lost to follow-up. The number of adverse events was statistically significant higher for all three active treatment groups compared to placebo at nominal alpha = 0.05. The 120 mg group had a higher rate of informed consent withdrawal compared to the placebo group.

Table 5: Number and Percentage of Patients Discontinued From the Study – Safety Population [LVM-MD-01]

Patient Status	*Placebo (N = 176) n (%)*	*F2695 SR*			*Total (N = 713) n (%)*
		40 mg/d (N = 178) n (%)	*80 mg/d (N = 179) n (%)*	*120 mg/d (N = 180) n (%)*	
Completed study[a]	138 (78.4)	130 (73.0)	121 (67.6)	117 (65.0)	506 (71.0)
Prematurely discontinued	38 (21.6)	48 (27.0)	58 (32.4)[b]	63 (35.0)[b]	207 (29.0)
Adverse event	3 (1.7)	13 (7.3)[b]	26 (14.5)[b]	12 (6.7)[b]	54 (7.6)
Insufficient therapeutic response	7 (4.0)	4 (2.2)	1 (0.6)[b]	3 (1.7)	15 (2.1)
Protocol violation	9 (5.1)	5 (2.8)	9 (5.0)	10 (5.6)	33 (4.6)
Withdrawal of consent	9 (5.1)	12 (6.7)	11 (6.1)	23 (12.8)[b]	55 (7.7)
Lost to follow-up	10 (5.7)	14 (7.9)	8 (4.5)	15 (8.3)	47 (6.6)
Other reasons	0	0	3 (1.7)	0	3 (0.4)
Entered down-taper period[c]	130 (73.9)	123 (69.1)	122 (68.2)	117 (65.0)	492 (69.0)

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

b Difference between placebo and F2695 SR group was statistically significant ($p < 0.05$) based on the Fisher exact test.

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

N = number of patients in the Safety Population; n = number of patients in the specified category; SR = sustained release.

(Source: Study report p. 79)

Demographic data for the Safety Population are presented in Table 6. There were no statistically significant differences among the treatment groups with respect to age, sex, or race. Most patients were white and the average age was about 41 years. Females comprised approximately 63% of the Safety Population.

Table 6: Demographic Characteristics – Safety Population [LVM-MD-01]

Characteristic	*Placebo (N = 176)*	*F2695 SR*			*Total (N = 713)*
		40 mg/d (N = 178)	*80 mg/d (N = 179)*	*120 mg/d (N = 180)*	
Age, y					
Mean ± SD	41.3 ± 11.3	41.6 ± 13.1	41.0 ± 12.8	40.3 ± 11.9	41.1 ± 12.3
Median (min, max)	42.0 (19, 64)	43.0 (19, 64)	42.0 (18, 65)	41.0 (18, 64)	42.0 (18, 65)
Age group, y, n (%)					
< 20	1 (0.6)	2 (1.1)	4 (2.2)	2 (1.1)	9 (1.3)
≥ 20-29	31 (17.6)	43 (24.2)	44 (24.6)	42 (23.3)	160 (22.4)
≥ 30-39	47 (26.7)	34 (19.1)	33 (18.4)	38 (21.1)	152 (21.3)
≥ 40-49	44 (25.0)	36 (20.2)	48 (26.8)	46 (25.6)	174 (24.4)
≥ 50-59	46 (26.1)	48 (27.0)	36 (20.1)	41 (22.8)	171 (24.0)
≥ 60	7 (4.0)	15 (8.4)	14 (7.8)	11 (6.1)	47 (6.6)
Sex, n (%)					
Male	68 (38.6)	56 (31.5)	68 (38.0)	74 (41.1)	266 (37.3)
Female	108 (61.4)	122 (68.5)	111 (62.0)	106 (58.9)	447 (62.7)
Race, n (%)					
White	134 (76.1)	133 (74.7)	129 (72.1)	130 (72.2)	526 (73.8)
All Other Races	41 (23.3)	45 (25.3)	50 (27.9)	50 (27.8)	186 (26.1)
Black or African American	29 (16.5)	36 (20.2)	39 (21.8)	41 (22.8)	145 (20.3)
Asian	8 (4.5)	3 (1.7)	5 (2.8)	3 (1.7)	19 (2.7)
American Indian or Alaska native	1 (0.6)	0	2 (1.1)	1 (0.6)	4 (0.6)
Native Hawaiian or other Pacific Islander	0	0	0	1 (0.6)	1 (0.1)
Other	3 (1.7)	6 (3.4)	4 (2.2)	4 (2.2)	17 (2.4)
Ethnicity, n (%)					
Hispanic or Latino	20 (11.4)	22 (12.4)	28 (15.6)	22 (12.2)	92 (12.9)
Not Hispanic or Latino	156 (88.6)	155 (87.1)	151 (84.4)	158 (87.8)	620 (87.0)

max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients in the specified category; SR = sustained release; y = years.

(Source: Study report p. 83)

The baseline scores of the efficacy parameters for the ITT Population are presented in Table 7. The scores were similar among the treatment groups.

Table 7: Baseline Efficacy Assessments – ITT population [LVM-MD-01]

Efficacy parameter	*Placebo (N = 175)*	*F2695 SR*			*P-Value*
		40 mg/d (N = 176)	*80 mg/d (N = 177)*	*120 mg/d (N = 176)*	
MADRS-CR total score, mean ± SD	35.6 ± 4.5	36.0 ± 4.1	36.1 ± 3.9	36.0 ± 3.9	0.6950
SDS total score, mean ± SD	21.5 ± 4.8	21.1 ± 4.8	21.4 ± 4.9	21.3 ± 5.0	0.9164
HAMD-17 total score, mean ± SD	24.6 ± 4.3	24.7 ± 3.8	24.9 ± 3.8	25.0 ± 3.8	0.5660
CGI-S score, mean ± SD	4.9 ± 0.6	4.8 ± 0.6	4.9 ± 0.6	4.9 ± 0.6	—
Average pain level, mean ± SD	4.0 ± 2.9	4.1 ± 2.7	4.2 ± 2.7	4.0 ± 2.9	0.9511

Note: For continuous variables, p-values are from an analysis-of-variance model with treatment group and pooled study center as factors. For categorical variables, p-values are from the Cochran Mantel-Haenszel test controlling for pooled study centers.

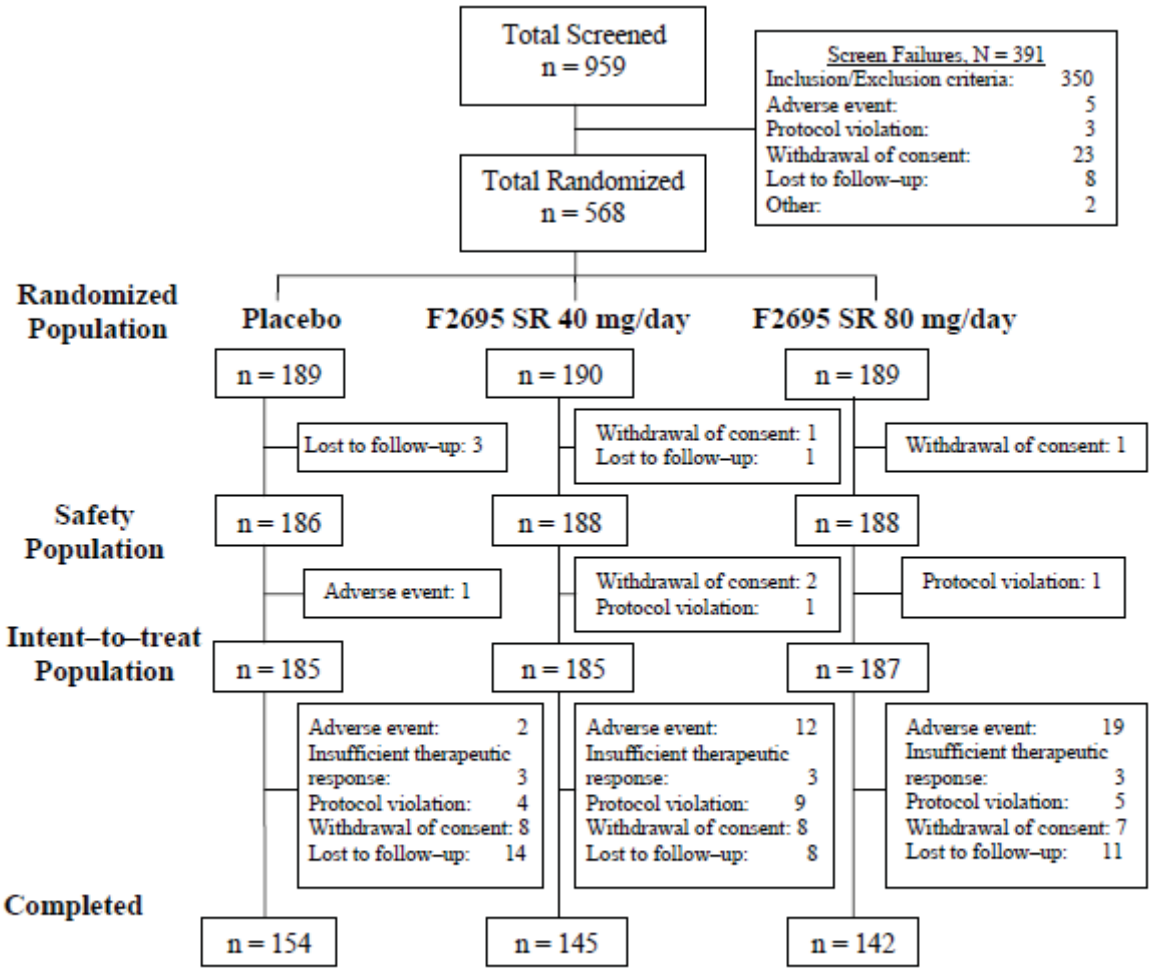
CGI-S = Clinical Global Impression–Severity; HAMD = Hamilton Rating Scale for Depression; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; N = number of patients in the ITT Population; SR = sustained release.

(Source: Study report p. 86)

3.2.3.2 LVM-MD-10

A total of 568 patients were randomized to receive double-blind treatment. Of the 562 patients who received at least one dose of double-blind treatment, 557 had at least one post-baseline MADRS assessment (ITT population). A total of 441 subjects (79%) completed the study (see Figure 11 below). Most (96%) of the randomized patients were enrolled at 47 sites in the United States, and about 4% were enrolled at four sites in Canada.

Figure 11: Patient Populations and Disposition [LVM-MD-10]



SR = sustained release
(Source: Study report p. 79)

Reasons for discontinuation from the study are provided in Table 8. Statistically significant more patients discontinued prematurely due to adverse events in the levomilnacipran 40 mg (6.4%) and 80 mg (10.1%) groups compared to the placebo group (1.6%).

Table 8: Number and Percentage of Patients Discontinued From the Study – Safety Population [LVM-MD-10]

	Placebo (N = 186)	*F2695 SR 40 mg/day (N = 188)*	*F2695 SR 80 mg/day (N = 188)*	*Total (N = 562)*
Patient Status	n (%)			
Completed study	154 (82.8)	145 (77.1)	142 (75.5)	441 (78.5)
Prematurely discontinued	32 (17.2)	43 (22.9)	46 (24.5)	121 (21.5)
Reasons for premature discontinuation				
Adverse event	3 (1.6)	12 (6.4)[a]	19 (10.1)[a]	34 (6.0)
Insufficient therapeutic response	3 (1.6)	3 (1.6)	3 (1.6)	9 (1.6)
Protocol violation	4 (2.2)	10 (5.3)	6 (3.2)	20 (3.6)
Withdrawal of consent	8 (4.3)	10 (5.3)	7 (3.7)	25 (4.4)
Lost to follow-up	14 (7.5)	8 (4.3)	11 (5.9)	33 (5.9)
Entered double-blind down-taper period[b]	147 (79.0)	136 (72.3)	141 (75.0)	424 (75.4)

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.

N = number of patients in the Safety Population; n = number of patients in the specified category; SR = sustained release.

(Source: Study report p. 80)

Demographic characteristics are presented in Table 9. The mean patient age was 42.8 years; most patients where white (74%) and female (63.5%). The treatment groups appear balanced with respect to age, sex and race.

Table 9: Demographic Characteristics – Safety Population [LVM-MD-10]

Characteristic	*Placebo (N = 186)*	*F2695 SR 40 mg/day (N = 188)*	*F2695 SR 80 mg/day (N = 188)*	*Total (N = 562)*
Age, years				
Mean ± SD	42.3 ± 13.2	42.9 ± 13.4	43.1 ± 12.8	42.8 ± 13.1
Median (min, max)	42.5 (19, 74)	44.0 (18, 74)	43.0 (18, 74)	43.0 (18, 74)
Age group,(years) n (%)				
< 20	3 (1.6)	1 (0.5)	5 (2.7)	9 (1.6)
≥ 20-29	35 (18.8)	35 (18.6)	28 (14.9)	98 (17.4)
≥ 30-39	43 (23.1)	40 (21.3)	44 (23.4)	127 (22.6)
≥ 40-49	45 (24.2)	49 (26.1)	53 (28.2)	147 (26.2)
≥ 50-59	43 (23.1)	42 (22.3)	36 (19.1)	121 (21.5)
≥ 60	17 (9.1)	21 (11.2)	22 (11.7)	60 (10.7)
Sex, n (%)				
Male	70 (37.6)	71 (37.8)	64 (34.0)	205 (36.5)
Female	116 (62.4)	117 (62.2)	124 (66.0)	357 (63.5)
Race, n (%)				
White	135 (72.6)	142 (75.5)	139 (73.9)	416 (74.0)
All other races	51 (27.4)	46 (24.5)	49 (26.1)	146 (26.0)
Black or African-American	35 (18.8)	37 (19.7)	36 (19.1)	108 (19.2)
Asian	7 (3.8)	4 (2.1)	3 (1.6)	14 (2.5)
American Indian of Alaska Native	3 (1.6)	0	0	3 (0.5)
Native Hawaiian or other Pacific Islander	1 (0.5)	0	0	1 (0.2)
Other	5 (2.7)	5 (2.7)	10 (5.3)	20 (3.6)
Ethnicity, n (%)				
Hispanic	23 (12.4)	24 (12.8)	15 (8.0)	62 (11.0)
Non-Hispanic	163 (87.6)	164 (87.2)	173 (92.0)	500 (89.0)

max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients in the specified category; SD = standard deviation; SR = sustained release.

(Source: Study report p. 84)

The baseline scores for the efficacy parameters are displayed in Table 10 and are similar across treatment groups (see Table 10).

Table 10: Baseline Efficacy Assessments – ITT Population [LVM-MD-10]

Efficacy Parameter	*Placebo (N = 185)*	*F2695 SR 40 mg/day (N = 185)*	*F2695 SR 80 mg/day (N = 187)*	*p-Value*
MADRS total score, mean ± SD	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5	0.5305
SDS total score, mean ± SD	16.4 ± 6.1	16.7 ± 6.6	17.6 ± 6.0	0.2364
CGI-S score, mean ± SD	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.1524
HAMD-17 total score, mean ± SD	21.7 ± 4.1	21.5 ± 3.9	21.8 ± 4.1	0.7789

Note: For continuous variables, p-values are from an ANOVA model with treatment group and pooled study center as factors. CGI-S p-value is derived from the categorical data using the CMH test controlling for pooled study centers.

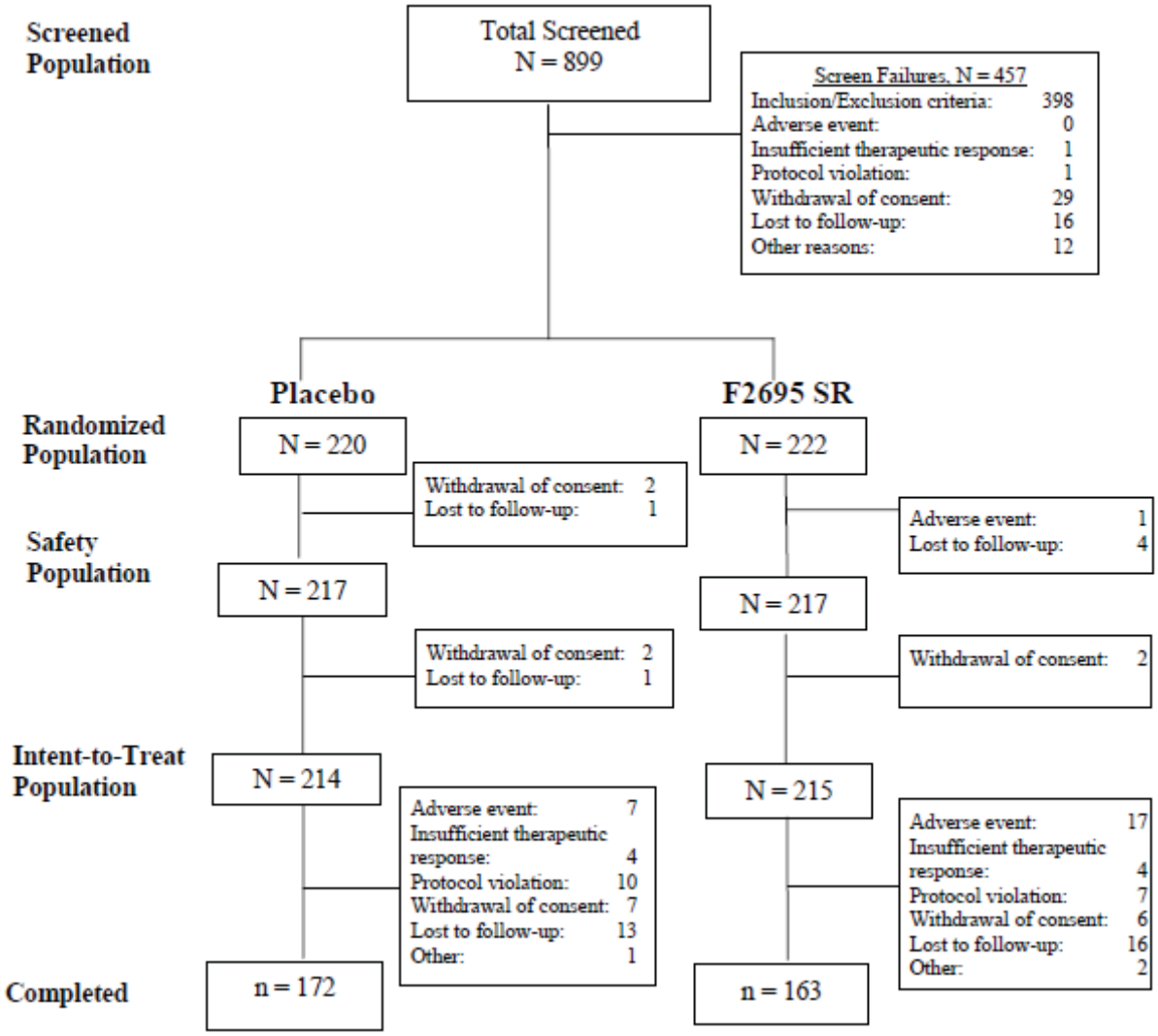
ANOVA = analysis of variance; CGI-S = Clinical Global Impressions-Severity; CMH = Cochran-Mantel-Haenszel test; HAMD-17 = 17-item Hamilton Rating Scale for Depression; ITT = intent to treat; MADRS = Montgomery-Åsberg Depression Rating Scale; N = number of patients in the ITT population; SD = standard deviation; SDS = Sheehan Disability Scale; SR = sustained release.

(Source: Study report p. 90)

3.2.3.3 LVM-MD-03

A total of 442 patients were randomized to receive double-blind treatment in Study MD-03. Of the 434 patients who received at least one dose of double-blind treatment, 429 had at least one post-baseline MADRS-CR assessment and were included in the ITT Population. A total of 172 patients (79.3%) in the placebo group and 163 patients (75.1%) in the levomilnacipran group completed the study (see Figure 12).

Figure 12: Patient Populations and Dispositions [LVM-MD-03]



(Source: Study report p. 85)

The overall rate of premature discontinuation was slightly higher in the levomilnacipran group (24.9%) compared to the placebo group (20.7%). The incidence of patients with adverse events associated with premature discontinuation was higher in the levomilnacipran group than in the placebo group (7.8% vs. 3.2%). The difference however is not statistically significant at alpha = 0.05. The proportions are similar for all other reasons for discontinuation (see Table 11).

Table 11: Number and Percentage of Patients Discontinued From the Study – Safety Population [LVM-MD-03]

Patient Status	*Placebo (N = 217)*	*F2695 SR 40-120 mg/day (N = 217)*	*Total (N = 434)*
	n (%)		
Completed study[a]	172 (79.3)	163 (75.1)	335 (77.2)
Prematurely discontinued	45 (20.7)	54 (24.9)	99 (22.8)
Reason for discontinuation			
Adverse event	7 (3.2)	17 (7.8)	24 (5.5)
Insufficient therapeutic response	4 (1.8)	4 (1.8)	8 (1.8)
Protocol violation	10 (4.6)	7 (3.2)	17 (3.9)
Withdrawal of consent	9 (4.1)	8 (3.7)	17 (3.9)
Lost to follow-up	14 (6.5)	16 (7.4)	30 (6.9)
Other	1 (0.5)	2 (0.9)	3 (0.7)
Entered down-taper period[b]	171 (78.8)	164 (75.6)	335 (77.2)

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.

N = number of patients in the Safety Population; n = number of patients in the specified category; SR = sustained release

(Source: Study report p. 86)

Demographic characteristics are shown in Table 12 below. No imbalances were observed between the treatment groups. The mean age in the Safety population was 44.8 years. Most patients were white (82.7%) and female (65.2%).

Table 12: Demographic Characteristics – Safety Population [LVM-MD-03]

Characteristic	*Placebo (N = 217)*	*F2695 SR 40-120 mg/day (N = 217)*	*Total (N = 434)*
Age, y			
Mean ± SD	44.6 ± 13.9	45.0 ± 13.2	44.8 ± 13.5
Median (min, max)	46.0 (18, 76)	46.0 (19, 74)	46.0 (18, 76)
Age (years) group, n (%)			
< 20	2 (0.9)	2 (0.9)	4 (0.9)
≥ 20-29	38 (17.5)	34 (15.7)	72 (16.6)
≥ 30-39	37 (17.1)	44 (20.3)	81 (18.7)
≥ 40-49	51 (23.5)	40 (18.4)	91 (21.0)
≥ 50-59	57 (26.3)	68 (31.3)	125 (28.8)
≥ 60	32 (14.7)	29 (13.4)	61 (14.1)
Sex, n (%)			
Male	74 (34.1)	77 (35.5)	151 (34.8)
Female	143 (65.9)	140 (64.5)	283 (65.2)
Race, n (%)			
White	182 (83.9)	177 (81.6)	359 (82.7)
All Other Races	35 (16.1)	40 (18.4)	75 (17.3)
Black or African American	28 (12.9)	33 (15.2)	61 (14.1)
Asian	2 (0.9)	2 (0.9)	4 (0.9)
American Indian or Alaska native	1 (0.5)	1 (0.5)	2 (0.5)
Other	4 (1.8)	4 (1.8)	8 (1.8)
Ethnicity, n (%)			
Hispanic or Latino	17 (7.8)	21 (9.7)	38 (8.8)
Not Hispanic or Latino	200 (92.2)	196 (90.3)	396 (91.2)

max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients in the specified category; SD = standard deviation; SR = sustained release.

(Source: Study report p. 90)

Baseline scores of the efficacy parameters for the ITT Population were similar for the levomilnacipran and placebo groups (see Table 13).

Table 13: Baseline Efficacy Assessments – ITT Population [LVM-MD-03]

Efficacy parameter	*Placebo (N = 214)*	*F2695 SR 40-120 mg/day (N = 215)*	*p-Value*
MADRS-CR total score, mean ± SD	35.2 ± 3.8	35.0 ± 3.6	0.3508
SDS total score, mean ± SD	19.7 ± 5.2	20.1 ± 5.0	0.4274
CGI-S score, mean ± SD	4.8 ± 0.7	4.7 ± 0.7	0.3820
HAMD-17 total score, mean ± SD	22.9 ± 4.1	23.3 ± 4.1	0.2850
MEI-SF total score, mean ± SD	30.19 ± 15.14	29.25 ± 15.61	0.5683

Note: For continuous variables, p-values are from an ANOVA model with treatment group and pooled study center as factors. The p-value presented for the CGI-S is the value for the categorical scale and is from the CMH test controlling for pooled study centers.

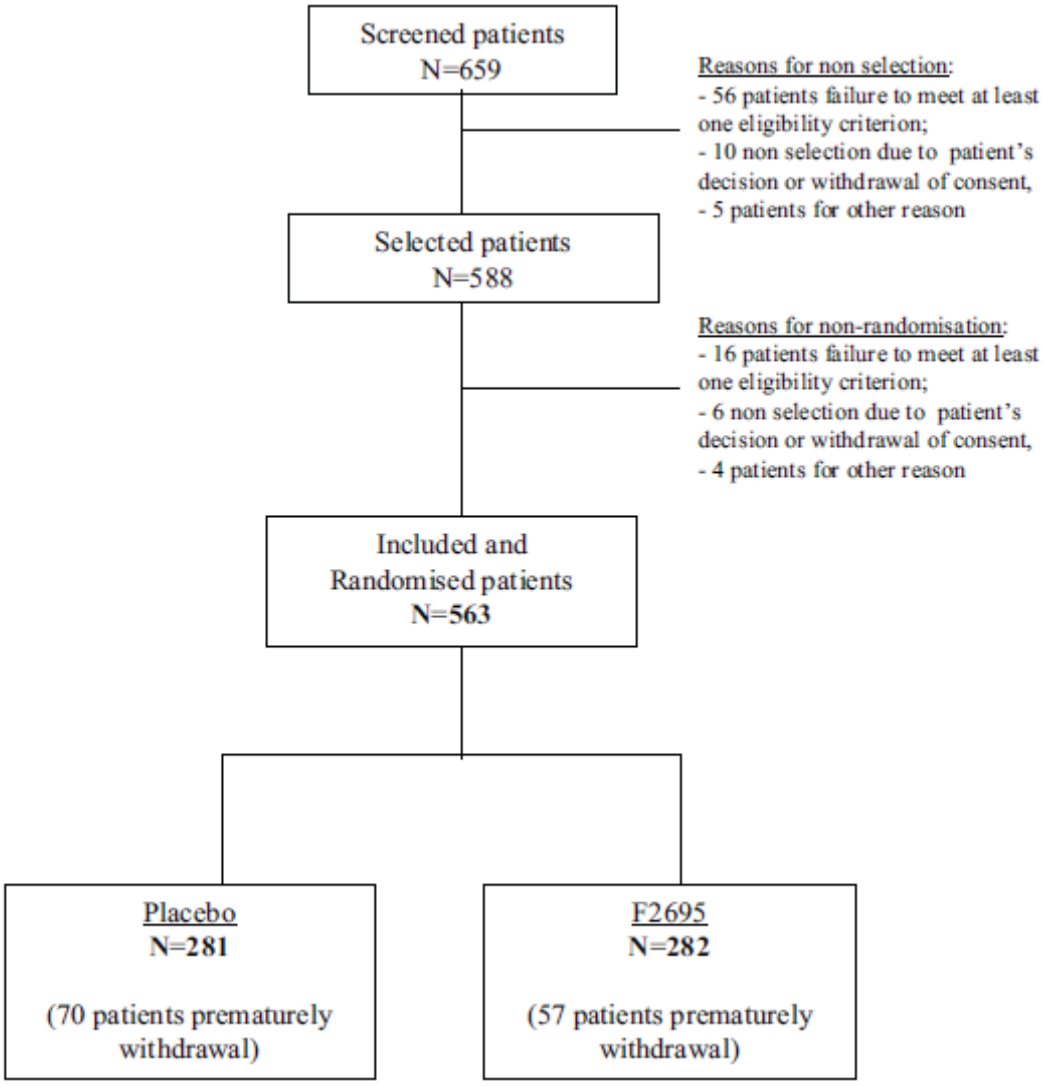
ANOVA = analysis of variance; CGI-S = Clinical Global Impression–Severity (scale); CMH = Cochran-Mantel-Haenszel test; HAMD-17 = 17-item Hamilton Rating Scale for Depression; ITT = intent to treat; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MEI-SF = Motivation and Energy Inventory–Short Form; N = number of patients in the ITT population; SD = standard deviation; SDS = Sheehan Disability Scale; SR = sustained release.

(Source: Study report p. 94)

3.2.3.4 F02695 LP 2 02 (Phase 2)

A total of 659 patients were screened for Study LP 2 02 and 563 were randomized (281 to the placebo and 282 to the levomilnacipran group). At the end of the dose escalation period 189 (71.6%) of patients were on 100 mg and 75 (28.4%) were on 75 mg of levomilnacipran in the active treatment arm (Study report p. 88).

Figure 13: Disposition of Patients [LP 2 02]



(Source: Study report p. 84)

In total, 22.6% (127/563) of patients withdrew from the study. The proportion of patients discontinuing early was slightly higher in the placebo group (24.9%) compared to the levomilnacipran group (20.2%). Table 14 gives the reasons for premature withdrawal.

Table 14: Number and Percentage of Patients Discontinued From the Study [LP 2 02]

	Placebo n=281	F2695 n=282	Total n=563
Number of withdrawn patients	70 (24.9 %)	57 (20.2 %)	127 (22.6 %)
Significant Suicidal Risk	6 (2.1 %)	1 (0.4 %)	7 (1.2 %)
Serious Adverse Event/Non Serious Adverse Event	17 (6.0 %)	26 (9.2 %)	43 (7.6 %)
Therapeutic Failure:	40 (14.2 %)	22 (7.8 %)	62 (11.0 %)
- Worsening of MDD	17 (6.0 %)	11 (3.9 %)	28 (5.0 %)
- Insufficient response	33 (11.7 %)	16 (5.7 %)	49 (8.7 %)
Patient's decision - Consent withdrawal	37 (13.2 %)	29 (10.3 %)	66 (11.7 %)
Patient lost to follow up	-	1 (0.4 %)	1 (0.2 %)
Other reason	10 (3.6 %)	8 (2.8 %)	18 (3.2 %)

Note : *several reasons may have led to the premature withdrawal of a given patient*

(Source: Study report p. 85)

Overall, 11.0% of patients were classified as withdrawing due to insufficient clinical response and/or worsening of MDD (combined under term "Therapeutic Failure"). The percentage of withdrawal due to therapeutic failure was 14.2% in the placebo group and 7.8% in the levomilnacipran group. The percentage of patients who withdrew due to significant suicidal risk was greater in the placebo group (2.1% vs. 0.4%).

Table 15 shows the number of patients analyzed in each data set. Data for 6 randomized patients from one site were removed by the sponsor due to suspicion of misconduct at this site. The safety data set included all randomized patients who received at least one dose of the study treatment. The primary efficacy analysis set is the Full Analysis Set (FAS), which 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 measure. This set included 553 patients, with 277 in the placebo and 276 in the levomilnacipran group.

Table 15: Patient Populations [LP 2 02]

	Placebo n=281	F2695 n=282	Total n=563
Safety Data Set	279 (99.3 %)	278 (98.6 %)	557 (98.9 %)
Full Analysis Set (FAS)	277 (98.6 %)	276 (97.9 %)	553 (98.2 %)
Per Protocol Data Set (PP Data Set)	254 (90.4 %)	251 (89.0 %)	505 (89.7 %)
Rebound Analysis Data Set	202 (71.9 %)	221 (78.4 %)	423 (75.1 %)
Cardiovascular History Data Set	34 (12.1 %)	37 (13.1 %)	71 (12.6 %)

(Source: Study report p. 91)

Demographic characteristics of the ITT study population are presented in Table 16. There are no notable differences between the two treatment groups. About two thirds of patients were females and the mean age was 44.1 years. The majority of patients were Caucasian (91.1%).

Table 16: Demographic Characteristics – ITT Population [LP 2 02]

	Placebo n=277	F2695 n=276	Total n=553
Sex			
Missing	-	-	-
Male	95 (34.3 %)	90 (32.6 %)	185 (33.5 %)
Female	182 (65.7 %)	186 (67.4 %)	368 (66.5 %)
Age at selection (years)			
Missing	-	-	-
Mean (SD)	44.6 (11.7)	43.7 (12.6)	44.1 (12.1)
Min/Median/Max	19 / 45.0 / 69	18 / 44.0 / 70	18 / 44.0 / 70
Weight (kg)			
Missing	-	-	-
Mean (SD)	73.22 (17.47)	71.79 (16.87)	72.50 (17.17)
Min/Median/Max	36.0 / 72.50 / 165.0	42.0 / 70.40 / 150.0	36.0 / 71.00 / 165.0
Height (cm)			
Missing	1	-	1
Mean (SD)	167.8 (9.5)	167.7 (9.2)	167.7 (9.3)
Min/Median/Max	142 / 167.0 / 199	150 / 167.0 / 190	142 / 167.0 / 199
Body Mass Index (kg/m²)			
Missing	1	-	1
Mean (SD)	25.92 (5.53)	25.38 (5.09)	25.65 (5.32)
Min/Median/Max	14.6 / 25.25 / 55.1	16.7 / 24.75 / 56.5	14.6 / 25.05 / 56.5
Body Mass Index Class (kg/m²)			
Missing	1	-	1
<18.5	10 (3.6 %)	12 (4.3 %)	22 (4.0 %)
[18.5;25[	124 (44.9 %)	128 (46.4 %)	252 (45.7 %)
[25;30[	91 (33.0 %)	93 (33.7 %)	184 (33.3 %)
>=30	51 (18.5 %)	43 (15.6 %)	94 (17.0 %)
Ethnic origin			
Missing	-	-	-
Hispanic or latino	5 (1.8 %)	3 (1.1 %)	8 (1.4 %)
Other	272 (98.2 %)	273 (98.9 %)	545 (98.6 %)
Race			
Missing	-	-	-
Caucasian	251 (90.6 %)	253 (91.7 %)	504 (91.1 %)
Black	-	1 (0.4 %)	1 (0.2 %)
Asian	21 (7.6 %)	17 (6.2 %)	38 (6.9 %)
American-Indian or Alaska Native	-	-	-
Native Hawaiian or Other Pacific Islander	-	-	-
Other	5 (1.8 %)	5 (1.8 %)	10 (1.8 %)

(Source: Study report p. 94)

Baseline efficacy values are given in Table 17 and were similar for both treatment groups.

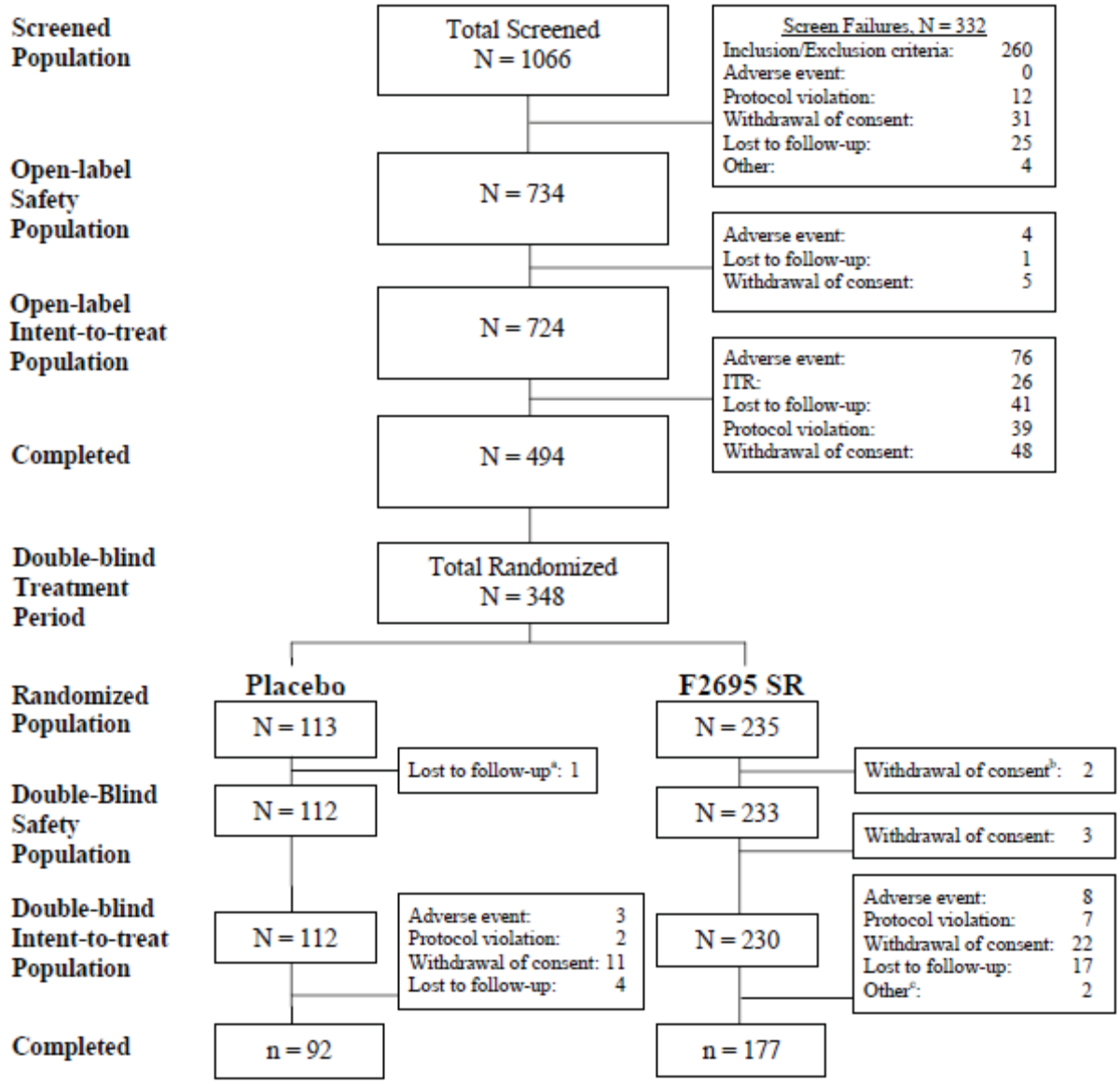
Table 17: Baseline Efficacy Assessments – ITT Population [LP 2 02]

	Placebo n=277	F2695 n=276	Total n=553
MADRS Total score			
Missing	-	-	-
Mean (SD)	30.5 (3.7)	30.9 (4.1)	30.7 (3.9)
Min/Median/Max	22 / 30.0 / 43	22 / 31.0 / 44	22 / 30.0 / 44
HAM-D Total score			
Missing	-	-	-
Mean (SD)	25.8 (2.6)	26.2 (2.6)	26.0 (2.6)
Min/Median/Max	21 / 25.0 / 35	22 / 26.0 / 36	21 / 25.0 / 36
Sheehan Total score			
Missing	1	-	1
Mean (SD)	20.82 (3.76)	21.25 (3.93)	21.03 (3.85)
Min/Median/Max	12.0 / 21.00 / 30.0	10.0 / 21.00 / 30.0	10.0 / 21.00 / 30.0
CGI - Severity			
Missing	-	-	-
Normal / not at all ill	-	-	-
Borderline mentally ill	-	-	-
Mildly ill	-	1 (0.4 %)	1 (0.2 %)
Moderately ill	113 (40.8 %)	106 (38.4 %)	219 (39.6 %)
Markedly ill	137 (49.5 %)	133 (48.2 %)	270 (48.8 %)
Severely ill	27 (9.7 %)	36 (13.0 %)	63 (11.4 %)
Among the most extremely ill patients	-	-	-
COVI Total Score			
Missing	-	-	-
Mean (SD)	5.4 (2.0)	5.6 (1.9)	5.5 (1.9)
Min/Median/Max	0 / 5.0 / 11	1 / 6.0 / 10	0 / 6.0 / 11

(Source: Study report p. 95)

3.2.3.5 LVM-MD-05 (Maintenance Study)

Figure 14: Patient Populations and Disposition [LVM-MD-05]



a PID 0110519 was randomized but was lost to follow-up before receiving double-blind investigational product.

b PID 0180534 and PID 0240536 were randomized but withdrew consent before receiving double-blind investigational product.

c Other reasons for discontinuation included positive serum pregnancy test result (PID 0060516 and PID 0290525).

ITR = insufficient therapeutic response; PID = patient identification; SR = sustained release.

(Source: Study report p. 80)

In Study MD-05 a total of 1066 patients were screened and 734 patients were enrolled and received at least 1 dose of open-label levomilnacipran ER during the 12-week open-label treatment period (Open-label Safety population). Of these, 724 patients had at least 1 MADRS assessment during this period (Open-label ITT Population). A total of 494 patients completed the open-label treatment period. Of those, 348 patients met the randomization criteria and entered the double-blind treatment period for treatment with either levomilnacipran ER (n = 235) or placebo (n = 113) in a 2 to 1 ratio. Note that the number of 348 patients in the randomized population is somewhat below the number of 360 from the sample size calculation. The Double-blind ITT population consisted of 342 patients who received at least 1 dose of double-blind treatment and had at least 1 post-randomization MADRS assessment. The double-blind treatment period was completed by 269 patients.

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 (5 out of 6 were discontinued early, some already in the open-label phase).

Table 18 presents the discontinuation reasons. Discontinuations in the double-blind period were somewhat higher in the levomilnacipran ER group (24.0%) compared to the placebo group (17.9%). Withdrawal of consent was the most frequent reason for discontinuation (9.8% for placebo and 9.4% for levomilnacipran ER group) followed by lost to follow-up (3.6% for placebo and 7.3% for levomilnacipran ER group).

Table 18: Number and Percentages of Patients Discontinued During the Open-label and Double-blind Treatment Periods – Safety Populations [LVM-MD-05]

Patient Status	*Open–label Treatment Period*	*Double-blind Treatment Period*		
	F2695 SR 40-120 mg/d n (%) (N = 734)	*Placebo n (%) (N = 112)*	*F2695 SR 40-120 mg/d n (%) (N = 233)*	*Total n (%) (N = 345)*
Completed treatment period	494 (67.3)	92 (82.1)	177 (76.0)	269 (78.0)
Prematurely discontinued	240 (32.7)	20 (17.9)	56 (24.0)	76 (22.0)
Adverse event	80 (10.9)	3 (2.7)	8 (3.4)	11 (3.2)
Insufficient therapeutic response	26 (3.5)	—	—	—
Protocol violation	39 (5.3)	2 (1.8)	7 (3.0)	9 (2.6)
Withdrawal of consent	53 (7.2)	11 (9.8)	22 (9.4)	33 (9.6)
Lost to follow-up	42 (5.7)	4 (3.6)	17 (7.3)	21 (6.1)
Other[a]	0	0	2 (0.9)	2 (0.6)
Entered down-taper[b]	179 (24.4)	80 (71.4)	165 (70.8)	245 (71.0)

a Other reasons included positive serum pregnancy test result (PID 0060516 and PID 0290525).

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

N = number of patients in the Open–label or Double-blind Safety Population; n = number of patients in the specified category; SR = sustained release

(Source: Study report p. 83)

Demographic characteristics are presented in Table 19. There appear to be no imbalances between the two treatment groups. The majority of patients were white (75.1%) and female (58%) with a mean age of 43.3 years. Also, the treatment groups were similar with respect to psychiatric history (for details see study report p. 93).

Table 19: Demographic Characteristics – Safety Populations [LVM-MD-05]

Characteristic	*Open–label Safety Population*	*Double–blind Safety Population*		
	F2695 SR 40-120 mg/d (N = 734)	*Placebo (N = 112)*	*F2695 SR 40-120 mg/d (N = 233)*	*Total (N = 345)*
Age, y				
Mean ± SD	42.2 ± 12.3	44.7 ± 12.7	42.6 ± 12.0	43.3 ± 12.3
Median (min, max)	44.0 (18, 65)	48.0 (18, 65)	45.0 (19, 65)	45.0 (18, 65)
Age (y) group, n (%)				
< 20	8 (1.1)	1 (0.9)	2 (0.9)	3 (0.9)
≥ 20-29	151 (20.6)	18 (16.1)	43 (18.5)	61 (17.7)
≥ 30-39	127 (17.3)	20 (17.9)	40 (17.2)	60 (17.4)
≥ 40-49	208 (28.3)	23 (20.5)	68 (29.2)	91 (26.4)
≥ 50-59	186 (25.3)	38 (33.9)	63 (27.0)	101 (29.3)
≥ 60	54 (7.4)	12 (10.7)	17 (7.3)	29 (8.4)
Sex, n (%)				
Male	309 (42.1)	51 (45.5)	94 (40.3)	145 (42.0)
Female	425 (57.9)	61 (54.5)	139 (59.7)	200 (58.0)
Race, n (%)				
White	519 (70.7)	83 (74.1)	176 (75.5)	259 (75.1)
All Other Races	215 (29.3)	29 (25.9)	57 (24.5)	86 (24.9)
Black or African American	162 (22.1)	22 (19.6)	42 (18.0)	64 (18.6)
Asian	24 (3.3)	3 (2.7)	6 (2.6)	9 (2.6)
American Indian or Alaska native	8 (1.1)	2 (1.8)	2 (0.9)	4 (1.2)
Native Hawaiian or Other Pacific Islander	2 (0.3)	0	1 (0.4)	1 (0.3)
Other	19 (2.6)	2 (1.8)	6 (2.6)	8 (2.3)
Ethnicity, n (%)				
Hispanic or Latino	94 (12.8)	13 (11.6)	29 (12.4)	42 (12.2)
Not Hispanic or Latino	640 (87.2)	99 (88.4)	204 (87.6)	303 (87.8)

d = day; max = maximum; min = minimum; N = number of patients in the Open–label or Double-blind Safety Population; n = number of patients in the specified category; SD = standard deviation; SR = sustained release; y = years.

(Source: Study report p. 89)

Baseline scores for the efficacy parameters for the Open-Label and DB ITT Populations are presented in Table 20. There are no apparent imbalances.

Table 20: Baseline Efficacy Assessments – Open-label and Double-blind ITT Populations [LVM-MD-05]

Efficacy parameter	*Open–label ITT Population*	*Double–blind ITT Population*[a]		
	F2695 SR 40-120 mg/d (N = 724)	*Placebo (N = 112)*	*F2695 SR 40-120 mg/d (N = 230)*	*p–Value*
MADRS total score, mean ± SD	30.7 ± 5.1	5.9 ± 3.8	6.0 ± 3.6	0.8409
SDS total score, mean ± SD	19.6 ± 4.7	4.9 ± 5.7	5.0 ± 4.7	0.9485
CGI-S score, n (%)				
Normal, not at all ill	0	45 (40.2)	104 (45.2)	0.9722
Borderline ill	0	60 (53.6)	99 (43.0)	—
Mildly ill	2 (0.3)	7 (6.3)	27 (11.7)	—
Moderately ill	425 (58.7)	0	0	—
Markedly ill	250 (34.5)	0	0	—
Severely ill	46 (6.4)	0	0	—
Among the most extremely ill	1 (0.1)	0	0	—

a Baseline for the double-blind treatment period was the last assessment at the end of the open-label treatment period (Visit 9).

Note: For continuous variables, p-values are from an ANOVA model with treatment group and pooled study center as factors. For categorical variables, p-values are from the CMH test controlling for pooled study centers.

ANOVA = analysis of variance; CGI-S = Clinical Global Impression–Severity; CMH = Cochran Mantel-Haenszel test; d = day; ITT = intent-to-treat; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; N = number of patients in the Open-label or Double-blind ITT population; SD = standard deviation; SDS = Sheehan Disability Scale; SR = sustained release.

(Source: Study report p. 95)

3.2.4 Results and Conclusions

Table 21 presents a summary of the efficacy results for the completed Phase 2 and 3 Studies in the levomilnacipran program for MDD. The table includes results from the failed/negative studies MD-02 and MD-05.

Table 21: Summary of Efficacy for Completed Phase 2 and 3 Studies

Study Identifier Study Centers/ Location	*Start (FPFV) - Stop (LPLV) Enrollment[a] Actual/Planned*	*Design, Control Type*	*Diagnosis and Criteria for Inclusion*	*Investigational Product(s) Dosage*	*No. of Patients Treated[b]/ Completed[c]*	*Study Duration*	*Sex: M/F Mean Age, y (range)*	*Efficacy Conclusions*
Pivotal Studies								
LVM-MD-01 38 centers/ US	14 Sep 2009 - 09 May 2011 724/700	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study	MDD (DSM-IV-TR) MADRS-CR ≥ 30, MADRS-SR ≥ 26	Levomilnacipran 40 mg Levomilnacipran 80 mg Levomilnacipran 120 mg Placebo	178/130 179/121 180/117 176/138	11 weeks: 1-week, single-blind placebo run-in period, 8 weeks double-blind treatment, 2 weeks down-taper	266 M/447 F 41 (18-65)	Primary Δ MADRS-CR total score, LSMD 40 mg vs PBO = –3.23, p = 0.0186 80 mg vs PBO = –3.99, p = 0.0038 120 mg vs PBO = –4.86, p = 0.0005 Secondary Δ SDS total score, LSMD 40 mg vs PBO = –1.41, p = 0.1687 80 mg vs PBO = –2.51 p = 0.0151 120 mg vs PBO = –2.57, p = 0.0141
LVM-MD-10 51 centers/ US and Canada	13 Jun 2011 - 01 Mar 2012 568/510	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study	MDD (DSM-IV-TR) MADRS ≥ 26, CGI-S ≥ 4	Levomilnacipran 40 mg Levomilnacipran 80 mg Placebo	188/145 188/142 186/154	70 days: 1-week, single-blind placebo run-in period, 8 weeks double-blind treatment, 1 week down-taper	205 M/357 F 43 (18-74)	Primary Δ MADRS-CR total score, LSMD 40 mg vs PBO = –3.30, p = 0.0027 80 mg vs PBO = –3.14, p = 0.0043 Secondary Δ SDS total score, LSMD 40 mg vs PBO = –1.83, p = 0.0459 80 mg vs PBO = –2.72, p = 0.0028
LVM-MD-03 23 centers/ US	21 Dec 2009 - 19 Dec 2011 442/440	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study	MDD (DSM-IV-TR) MADRS-CR ≥ 30, MADRS-SR ≥ 26	Levomilnacipran 40-120 mg Placebo	217/163 217/172	11 weeks: 1-week, single-blind, placebo run-in period, 8 weeks double-blind treatment, 2 weeks down-taper	151 M/283 F 45 (18-76)	Primary Δ MADRS-CR total score, LSMD, active vs PBO = –3.10, p = 0.0051 Secondary Δ SDS total score, LSMD active vs PBO = –2.63, p = 0.0010
Supportive Study								
F02695 LP 2 02 68 centers/ Non-US	13 Dec 2006 - 22 Oct 2007 563/534	Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study	MDD (DSM-IV) HAMD-17 > 22, SDS ≥ 10, at least 1 SDS subscale score ≥ 6	Levomilnacipran 75-100 mg Placebo	278/225 279/211	11 weeks: 70 days double-blind treatment, 1 week down-taper	185 M/368 F 44 (18-70)	Primary Δ MADRS-CR total score, LSMD active vs PBO = –4.2, p < 0.0001 Secondary Δ SDS total score, LSMD active vs PBO = –3.4, p < 0.0001
Other MDD Studies								
LVM-MD-02 24 centers/ US	14 Sep 2009 - 29 Oct 2010 362/360	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study	MDD (DSM-IV-TR) MADRS-CR ≥ 30, MADRS-SR ≥ 26	Levomilnacipran 40-120 mg Placebo	175/135 182/149	11 weeks: 1-week, single-blind, placebo run-in period, 8 weeks double-blind treatment, 2 weeks down-taper	142 M/ 215 F 43 (19-78)	Primary Δ MADRS-CR total score, LSMD active vs PBO = –1.49, p = 0.2492 Secondary Δ SDS total score, LSMD active vs PBO = –0.54, p = 0.5625

Study Identifier Study Centers/ Location	*Start (FPFV) - Stop (LPLV) Enrollment[a] Actual/Planned*	*Design, Control Type*	*Diagnosis and Criteria for Inclusion*	*Investigational Product(s) Dosage*	*No. of Patients Treated[b]/ Completed[c]*	*Study Duration*	*Sex: M/F Mean Age, y (range)*	*Efficacy Conclusions*
LVM-MD-05 36 centers/ US and Canada	11 Mar 2010 - 12 Oct 2011 348/360	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study with an open-label, flexible-dose treatment period and a double-blind, fixed-dose treatment period	MDD (DSM-IV-TR) MADRS-CR ≥ 22	Open-label Levomilnacipran 40-120 mg Double-blind Levomilnacipran 40-120 mg Placebo	Open-label 734/494 Double-blind 233/177 112/92	39 weeks: up to 1 week screening, 12-week open-label treatment, 24-week double-blind treatment, 2 week down-taper	145 M/200 F 43 (18-65)	Primary Time to relapse, active vs PBO, Hazard ratio = 0.68, p = 0.1651

Note: Investigational product was taken orally in all studies.

a Enrollment reflects the number of patients randomized or assigned to treatment with the investigational product.

b Number of patients who received at least 1 dose of double-blind treatment.

c Patients who completed the double-blind treatment period were considered completers.

Δ = change; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition Text Revision; F = female; FPFV = first patient first visit; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LPLV = last patient last visit; LSMD = least squares mean difference; M = male; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MADRS-SR = Montgomery-Åsberg Depression Rating Scale, Self-Rated; MDD = major depressive disorder; PBO = placebo; SDS = Sheehan Disability Scale; y = years.

(Source: Summary of Clinical Effectiveness p. 30-33)

3.2.4.1 LVM-MD-01

After 8 weeks of double-blind treatment, a statistically significant improvement ($p < 0.05$) in MADRS total score was observed in all levomilnacipran ER groups (total score decrease of 14.8, 15.6, and 16.5 points for the 40 mg, 80 mg, and 120 mg groups, respectively, compared with a 11.6 point mean decrease in placebo-treated patients). Table 22 provides the detailed results.

Table 22: Primary Efficacy Parameter: Change from Baseline to Week 8 (or final assessment day) in the MADRS Total Score (MMRM) – ITT Population [LVM-MD-01]

	Placebo (N = 175)	*Levomilnacipran*		
		40 mg/day (N = 176)	*80 mg/day (N = 177)*	*120 mg/day (N = 176)*
Baseline, mean ± SD	35.6 ± 4.5	36.0 ± 4.1	36.1 ± 3.9	36.0 ± 3.9
Change at Week 8				
LS mean (SE)	–11.6 (0.97)	–14.8 (0.99)	–15.6 (1.00)	–16.5 (1.02)
LSMD (95% CI)	—	–3.23 (–5.92, –0.54)	–3.99 (–6.69, –1.29)	–4.86 (–7.59, –2.12)
p-Value[a]	—	0.0186	0.0038	0.0005

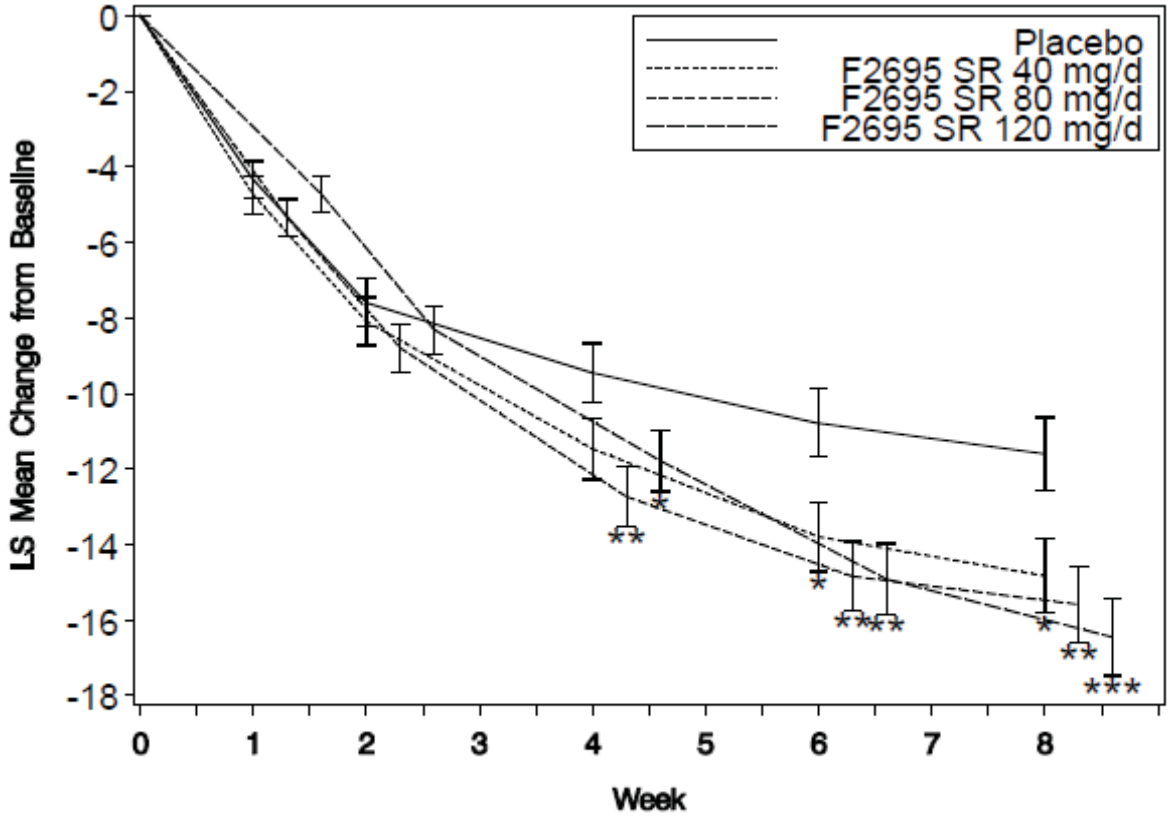
a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS-CR total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 35; results confirmed by this reviewer)

Figure 15 gives a graphical representation of the LS mean MADRS total score change from baseline over the course of the eight week study by treatment group.

Figure 15: LS Mean (SE) of Change from Baseline to Week 8 in MADRS Total Score (MMRM) – ITT Population [LVM-MD-01]



* = p <0.05, ** = p<0.01, *** = p<0.001.
ITT = intent to treat; LS = least squares; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; SE = standard error; SR = sustained release.
(Source: Summary of Clinical Effectiveness p. 36)

Recall that the primary endpoint is the change from baseline to week 8. However, week 8 encompasses quite a wide range of days (see apparently staggered end of curves in Figure 15 above). According to the SAP (p. 29 Table 16.1-1.) the visit time window for the week 8 visit with a scheduled visit at day 57 includes any day ≥ 51 days and within the double-blind treatment period. However, there is no definite end point (in days) set for the double-blind treatment period. Note that the maximum number of days at which the week 8 assessment was conducted varies considerably between the treatment groups: 71 days (placebo), 78 days (40mg), 66 days (80mg), and 77 days (120mg). The fact that the mean "analysis relative day" for subjects with a week 8 visit is about the same for the placebo group and all three drug dose groups (57.9

[n=141], 57.6 [n=130], 57.6 [n=123], 57.7 [n=120]) is a redeeming factor lending more credibility to the sponsor's "open ended" approach.

This reviewer conducted an exploratory MMRM analysis restricting the "Analysis Relative Day" variable to be less than 58 days in an attempt to reduce the variability in the endpoint assessment time for the different treatment groups. A word of caution regarding this approach: it leads to missing values for the week 8 assessment when this assessment was conducted later than day 57. The analysis produces primary endpoint results that are consistent with the sponsor's (i.e., the 40, 80, 120 mg doses are all statistically significant). See table 23 below.

Table 23: Primary Efficacy Parameter: Change from Baseline to Week 8 (up to day 57) in the MADRS Total Score (MMRM) – ITT Population [LVM-MD-01]

	Placebo *(N = 175)*	***Levomilnacipran***		
		40 mg/day (N=176)	*80 mg/day (N=177)*	*120 mg/day (N=177)*
Baseline, mean ± SD	35.6 ± 4.5	36.0 ± 4.1	36.1 ± 3.9	36.0 ± 3.9
Change at Week 8 (only include assessments up to day 57)				
LS mean (SE)	-11.8 (1.08)	-15.2 (1.08)	-15.3 (1.10)	-17.4 (1.12)
LSMD (95% CI)	__	-3.37 (-6.35, -0.40)	-3.54 (-6.55, -0.53)	-5.64 (-8.68, -2.60)
p-value	__	0.0264	0.0212	0.0003

(Source: computed by reviewer)

The sponsor added a definition of what is considered the double-blind treatment period on page 11 of the SAP for the subsequent Study MD-10: "The double-blind treatment period starts with the first dose of double-blind investigational product and ends with the last assessment date up to the first dose of down-taper investigational product or early termination".

Table 24 shows the results of two sensitivity analyses (LOCF and PMM). The LOCF analysis of change in MADRS total score at week 8 showed statistically significant improvements among all levomilnacipran ER treatment groups. Note that the p-value for the 40 mg group with 0.041 is close to the threshold value of 0.05.

For all selected values of the shift parameter in the PMM analysis, the mean decrease in MADRS total score from baseline remained greater in patients treated with levomilnacipran ER compared

with patients in the placebo group, indicating that the result of the primary efficacy analysis is robust.

Table 24: Sensitivity Analyses: Change from Baseline to Week 8 in MADRS Total Score (LOCF and PMM) – ITT Population [LVM-MD-01]

	Placebo (N = 175)	*Levomilnacipran*		
		40 mg/day (N =176)	*80 mg/day (N =177)*	*120 mg/day (N =176)*
LOCF				
Baseline, mean ± SD	35.6 ± 4.5	36.0 ± 4.1	36.1 ± 3.9	36.0 ± 3.9
Change at Week 8				
LS mean (SE)	–10.7 (0.93)	–13.3 (0.92)	–14.1 (0.92)	–14.1 (0.92)
LSMD (95% CI)	—	–2.56 (–5.01, –0.11)	–3.45 (–5.90, –1.00)	–3.43 (–5.88, –0.97)
p-Value[a]	—	0.0410	0.0058	0.0063
PMM[b]				
Shift parameter, LSMD (95% CI):				
0	—	–3.16 (–5.77, –0.55)	–3.92 (–6.57, –1.28)	–4.90 (–7.70, –2.09)
2	—	–3.01 (–5.65, –0.36)	–3.87 (–6.54, –1.19)	–4.76 (–7.53, –1.99)
4	—	–3.05 (–5.74, –0.37)	–3.71 (–6.44, –0.97)	–4.58 (–7.35, –1.81)
6	—	–3.05 (–5.80, –0.29)	–3.51 (–6.33, –0.70)	–4.07 (–6.92, –1.21)
8	—	–2.93 (–5.75, –0.12)	–3.22 (–5.99, –0.44)	–3.62 (–6.54, –0.70)

a p-Value was obtained from an ANCOVA model with treatment group and pooled study centers as factors and baseline MADRS-CR total score as covariate.

b For each shift parameter value, missing values were imputed multiple times using a PMM assuming non-future dependence. For each imputed dataset, MMRM analysis was performed.

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; PMM = pattern-mixture model; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 37; LOCF results confirmed by this reviewer)

The sponsor's analysis results of the SDS total score (secondary efficacy parameter) are presented in Table 25.

Table 25: Key secondary Efficacy Parameter: Change from Baseline to Week 8 in the SDS Total Score (MMRM) – ITT Population [LVM-MD-01]

	Placebo (N = 175)	*Levomilnacipran*		
		40 mg/day (N = 176)	*80 mg/day (N = 177)*	*120 mg/day (N = 176)*
SDS Total Score				
Baseline, mean ± SD	21.5 ± 4.8	21.1 ± 4.8	21.4 ± 4.9	21.3 ± 5.0
Change at Week 8				
LS mean (SE)	–7.2 (0.74)	–8.6 (0.75)	–9.7 (0.77)	–9.7 (0.78)
LSMD (95% CI)	—	–1.41 (–3.42, 0.60)	–2.51 (–4.54, -0.49)	–2.57 (–4.62, –0.52)
p-Value	—	0.1687	0.0151	0.0141

Note: p-Values were obtained from an MMRM model with treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects, and baseline and baseline-by-visit as covariates using an unstructured covariance matrix.

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

(Source: Summary of Clinical Effectiveness p. 38; results confirmed by this reviewer)

Note that the difference in the SDS total score is not statistically significant in the 40 mg group (p = 0.1687). However, the p-value for the 80 mg group with 0.0151 is less than 0.05/2 = 0.025 (Hochberg multiplicity procedure). Because the 80 mg group difference to placebo is statistically significant it follows that the 120 mg group difference (associated with a smaller p-value) is statistically significant as well.

Sensitivity analysis results (ANCOVA LOCF) for the SDS measure are given in Table 26. Note that the 40 mg/day difference to placebo in change scores is also not statistically significant in the LOCF analysis.

Table 26: Sensitivity Analyses: Change from Baseline to Week 8 in SDS Total Score (LOCF) – ITT Population [LVM-MD-01]

Visit* / Measurement / Statistics	Placebo (N=175)	F2695 SR 40 mg/d (N=176)	F2695 SR 80 mg/d (N=177)	F2695 SR 120 mg/d (N=176)
Week 8				
Actual				
Mean	14.7	13.1	12.3	12.4
SD	9.4	8.8	8.7	9.3
SEM	0.8	0.7	0.7	0.8
Median	17.0	14.0	12.0	11.5
Min, Max	0, 30	0, 30	0, 30	0, 30
n	158	151	155	146
Change From Baseline				
Mean	-6.9	-8.0	-9.0	-9.1
SD	8.6	8.9	8.9	8.2
SEM	0.7	0.7	0.7	0.7
Median	-5.0	-8.0	-8.0	-8.5
Min, Max	-27, 10	-27, 20	-28, 12	-27, 6
n	158	151	155	146
LS mean (SE)	-6.8 (0.71)	-8.0 (0.72)	-9.2 (0.71)	-9.1 (0.73)
LSMD vs Placebo (95% CI)		-1.204 (-3.093, 0.684)	-2.364 (-4.237, -0.491)	-2.284 (-4.189, -0.379)
P-value		0.2109	0.0134	0.0189

Notes: The estimates and p-values for F2695 SR dose groups vs. placebo comparison are based on last observation carried forward (LOCF) values using ANCOVA model with treatment group, pooled study center as factors and corresponding baseline as covariate. * Visit = Derived.
n = Number of patients with available analysis value at both baseline and a specific time point in the Intent-to-Treat Population. LSMD = difference in least squares mean. LS Mean = least squares mean, CI = confidence interval, SD = standard deviation, SEM = standard error of the mean, Min = minimum, Max = maximum, SE = standard error.

(Source: Study report p. 254; results confirmed by this reviewer)

This reviewer confirmed the sponsor's results for study MD-01 for the primary analyses (MMRM) and the sensitivity analyses (LOCF) for MADRS and SDS.

3.2.4.2 LVM-MD-10

The primary efficacy parameter in Study MD-10 is the change from baseline to week 8 in the MADRS total score and was analyzed by the sponsor using an MMRM approach. Treatment with levomilnacipran ER at doses of 40 mg/day and 80 mg/day produced a statistically significant improvement in the MADRS total score at week 8 ($p = 0.0027$ and $p = 0.0043$, respectively; for details see Table 27).

Table 27: Primary Efficacy Parameter: Change from Baseline to Week 8 in the MADRS Total Score (MMRM) – ITT Population [LVM-MD-10]

	Placebo (N = 185)	*Levomilnacipran*	
		40 mg/day (N = 185)	*80 mg/day (N = 187)*
Baseline, mean ± SD	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5
Change at Week 8			
LS mean (SE)	–11.3 (0.77)	–14.6 (0.79)	–14.4 (0.79)
LSMD (95% CI)	—	–3.303 (–5.457, –1.148)	–3.141 (–5.293, –0.988)
p-Value[a]	—	0.0027	0.0043

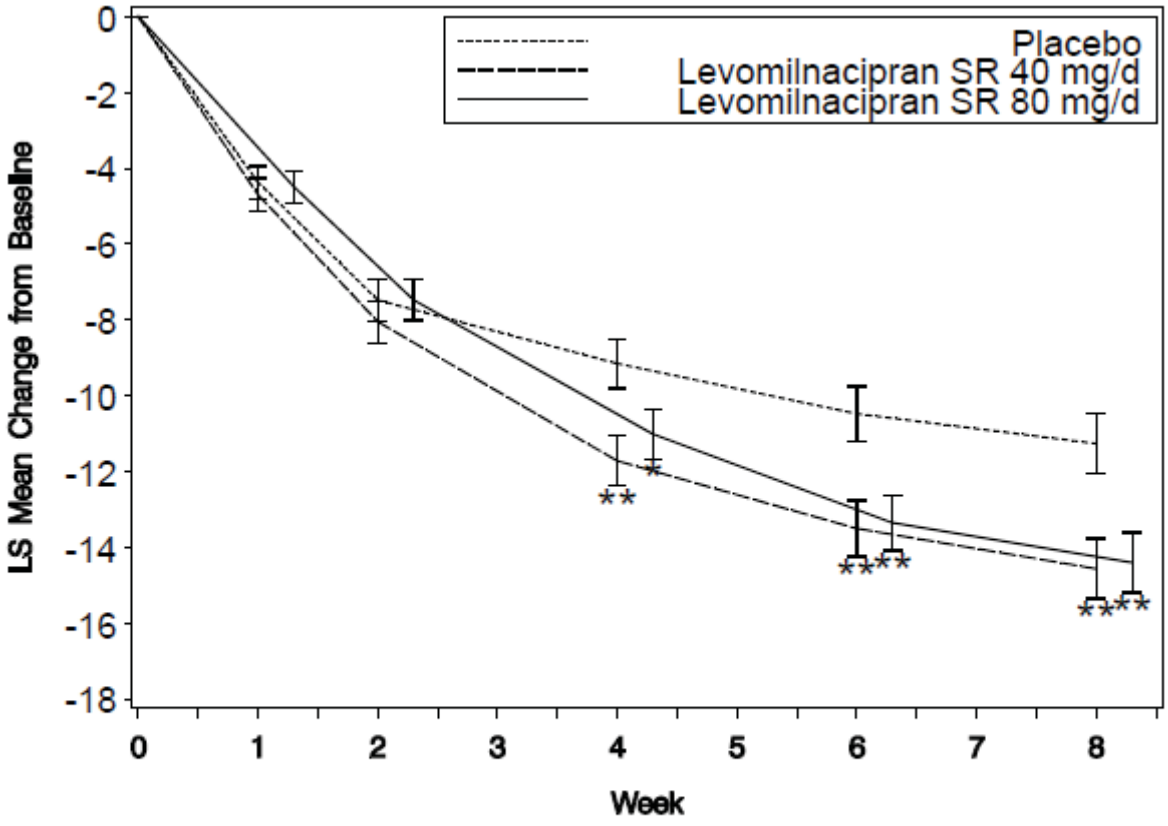
a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS-CR total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 43; results confirmed by this reviewer)

A graphical presentation of the change from baseline in MADRS total score over the course of the 8 week study is given in Figure 16.

Figure 16: LS Mean (SE) of Change from Baseline to Week 8 in MADRS Total Score (MMRM) – ITT Population [LVM-MD-10]



* = p <0.05, ** = p<0.01.

ITT = intent to treat; LS = least squares; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; SE = standard error; SR = sustained release.

(Source: Summary of Clinical Effectiveness p. 44)

The results of the supportive analysis using the LOCF approach are consistent with the results of the MMRM analysis with statistically significant improvements relative to placebo for both doses. The sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions confirms the robustness of the primary analysis, with both levomilnacipran ER groups demonstrating statistically significant improvement compared to placebo at each selected value of the shift parameter (see Table 28).

Table 28: Sensitivity Analyses: Change from Baseline to Week 8 in MADRS Total Score (LOCF and PMM) – ITT Population [LVM-MD-10]

	Placebo (N = 185)	*Levomilnacipran*	
		40 mg/day (N = 185)	*80 mg/day (N = 187)*
LOCF			
Baseline, mean ± SD	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5
Change at Week 8			
LS mean (SE)	–10.7 (0.77)	–13.1 (0.79)	–13.1 (0.76)
LSMD (95% CI)	—	–2.415 (–4.521, –0.309)	–2.380 (–4.451, –0.308)
p-Value[a]	—	0.0247	0.0244
PMM[b]			
Shift parameter, LSMD (95% CI):			
0	—	–3.342 (–5.453, –1.231)	–3.138 (–5.242, –1.034)
2	—	–3.263 (–5.392, –1.134)	–3.073 (–5.242, –0.904)
4	—	–3.267 (–5.371, –1.164)	–3.043 (–5.236, –0.850)
6	—	–3.319 (–5.480, –1.157)	–2.936 (–5.136, –0.737)
8	—	–3.318 (–5.624, –1.011)	–2.727 (–4.969, –0.485)

a p-Value was obtained from an ANCOVA model with treatment group and pooled study centers as factors and baseline MADRS-CR total score as covariate.

b For each shift parameter value, missing values were imputed multiple times using a PMM assuming non-future dependence. For each imputed dataset, MMRM analysis was performed.

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS-CR= Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; PMM = pattern-mixture model; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 45; LOCF results confirmed by this reviewer)

This reviewer confirmed the primary analysis results for the primary endpoint as well as the LOCF results. Results for the key secondary parameter for Study MD-10 are presented in Table 29.

Table 29: Key secondary Efficacy Parameter: Change From Baseline to Week 8 in the SDS Total Score and SDS Subscale Scores (MMRM) – ITT Population [LVM-MD-10]

	Placebo (N = 185)	*F2695 SR 40 mg/day (N = 185)*	*F2695 SR 80 mg/day (N = 187)*
SDS total score			
Baseline, mean ± SD	16.4 ± 6.1	16.7 ± 6.6	17.6 ± 6.0
Change at Week 8, LS mean (SE)	–5.4 (0.66)	–7.3 (0.68)	–8.2 (0.66)
LSMD vs placebo (95% CI)	—	–1.827 (–3.620, –0.033)	–2.720 (–4.494, –0.946)
p-Value[a]	—	0.0459	0.0028
SDS work/school subscale			
Baseline, mean ±SD	5.1 ± 2.5	5.1 ± 2.7	5.4 ± 2.3
Change at Week 8, LS mean (SE)	–1.4 (0.23)	–2.3 (0.24)	–2.5 (0.23)
LSMD vs placebo (95% CI)	—	–0.909 (–1.546, –0.272)	–1.108 (–1.737, –0.478)
p-Value[a]	—	0.0053	0.0006
SDS social life subscale			
Baseline, mean ±SD	6.0 ± 2.3	6.2 ± 2.5	6.3 ± 2.4
Change at Week 8, LS mean (SE)	–2.0 (0.21)	–2.5 (0.22)	–2.4 (0.21)
LSMD vs placebo (95% CI)	—	–0.561 (–1.147, 0.025)	–0.443 (–1.026, 0.140)
p-Value[a]	—	0.0604	0.1363
SDS family life subscale			
Baseline, mean ±SD	5.7 ± 2.2	5.8 ± 2.4	6.1 ± 2.3
Change at Week 8, LS mean (SE)	–1.8 (0.21)	–2.4 (0.21)	–2.3 (0.21)
LSMD vs placebo (95% CI)	—	–0.562 (–1.142, 0.017)	–0.501 (–1.078, 0.076)
p-Value[a]	—	0.0570	0.0888

a p-Values are from a MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline SDS total score and baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores.

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT population; SDS = Sheehan Disability Scale; SD = standard deviation; SE = standard error; SR = sustained release.

(Source: Study Report p. 95; SDS total score results confirmed by this reviewer)

Note that the p-value for 40 mg/day dose with 0.0459 from the MMRM analysis for the key secondary endpoint SDS is close to 0.05. Also, the sponsor fails to mention in the body of the study report (despite inclusion of the relevant SAS output on p. 2568 of study report) that the LOCF analysis of the SDS total score returns a p-value of 0.0607 for the 40 mg group (see Table 30).

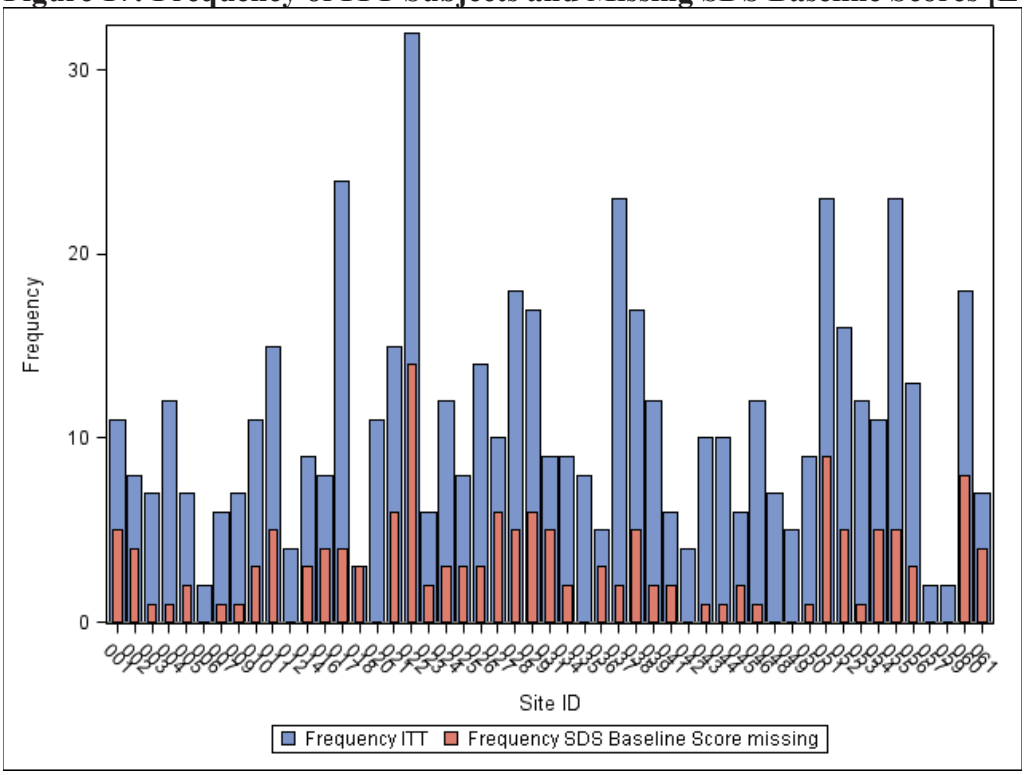
Table 30: Sensitivity Analysis: Change from Baseline to Week 8 in SDS Total Score (LOCF) – ITT Population [LVM-MD-10]

	Placebo	Levomilnacipran	
		40 mg/day	80 mg/day
	(N = 185)	(N = 185)	(N = 187)
Baseline, mean (SD)	16.4 (6.1)	16.7 (6.6)	17.6 (6.0)
Change at Week 8			
LS mean (SE)	-5.0 (0.66)	-6.7 (0.67)	-7.4 (0.63)
LSMD (95% CI)		-1.681 (-3.438, 0.076)	-2.446 (-4.168, -0.725)
p-value		0.0607	0.0055

(Source: Reviewer's analysis; see also study report p. 2568)

This reviewer confirmed the SDS total score results from the MMRM and LOCF analysis.

Figure 17: Frequency of ITT Subjects and Missing SDS Baseline Scores [LVM-MD-10]



(Source: Computed by reviewer)

Most sites in Study MD-10 have some subjects that have no SDS baseline score. For example, at site 22 there are 14 out of 32 baseline SDS scores missing. Overall (for study MD-10) about 27% of ITT patients did not have a SDS baseline score and hence were excluded from the SDS change from baseline to week 8 analysis.

The sponsor did not mention this issue explicitly. He lists the ITT based numbers for each treatment group in Table 11.4.1.2-1 pertaining to the key secondary efficacy parameter in the main body of the study report (p. 95). However, he refers to the SAS output in Table 16.1.9.3.2. (Study report p. 2558). There it can be seen that only 362 subjects were used in the analysis (compared to 557 for the MADRS analysis). The number of subjects that are included in the reviewer's bar graph above is slightly higher (number of subjects with SDS baseline score = 404) because all ITT subjects are included (no exclusion of subjects due to no post-baseline SDS data). The issue of a high proportion of missing SDS baseline data is limited to this study. Not nearly as many sites are affected by missing SDS baseline data in Studies LVM-MD-01 and LVM-MD-03.

My conjecture about the reasons for the high proportion of missing baseline SDS scores: The definition of the ITT population and the inclusion/exclusion criteria reference the MADRS but not the SDS. Recall the definition of ITT population for this study: The ITT population consists of all patients in the Safety Population (i.e., randomized and took at least 1 dose of double-blind investigational product) who had at least one post-baseline assessment of the MADRS total score.

3.2.4.3 LVM-MD-03

The overall mean modal and final daily doses administered during the double-blind treatment period are given in Table 31. The overall mean daily dose received by patients in the levomilnacipran group was approximately 73 mg.

Table 31: Overall Mean, Modal, and Final Daily Doses and Capsules during the Double-blind Treatment Period – Safety Population

	Placebo (N = 217)	*F2695 SR 40-120 mg/day (N = 217)*
Overall mean (caps/day)[a]		
Mean ± SD	2.1 ± 0.5	1.9 ± 0.5
Median	2.3	1.9
Min, max	1, 3	1, 3
Overall mean (mg/day)[a]		
Mean ± SD	—	72.9 ± 20.5
Median	—	74.3
Min, max	—	20, 97
Overall modal dose (caps/day), n (%)[b]		
1 capsule	27 (12.4)	49 (22.6)
2 capsules	66 (30.4)	81 (37.3)
3 capsules	124 (57.1)	87 (40.1)
Overall modal dose (mg/day), n (%)[b]		
40 mg/day	—	44 (20.3)
80 mg/day	—	87 (40.1)
120 mg/day	—	85 (39.2)
Final daily dose (caps/day), n (%)[c]		
1 capsule	20 (9.2)	47 (21.7)
2 capsules	62 (28.6)	74 (34.1)
3 capsules	135 (62.2)	96 (44.2)
Final daily dose (mg/day), n (%)[c]		
40 mg/day	—	46 (21.2)
80 mg/day	—	74 (34.1)
120 mg/day	—	96 (44.2)

a Overall mean daily dose was defined as the total dose divided by total duration of the double-blind treatment period (days)

b Overall modal daily dose was defined as the total daily dose (capsules/mg) taken for the maximum number of days during the double-blind treatment period. If there is a tie, the highest dose was used. Overall modal dose was 20 mg/day for 1 patient in the F2695 SR group.

c Final daily dose was defined as the last daily dose taken during the double-blind treatment period. Final daily dose was 20 mg/day for 1 patient in the F2695 SR group.

caps = capsules; max = maximum; min = minimum; N = number of patients in the Safety Population; n = number of patients who received the specified dose; SR = sustained release.

(Source: Study report p. 111)

The results of the primary efficacy analysis in Study MD-03 for the change from baseline to week 8 in the MADRS total score are presented in Table 32. Based on the MMRM approach the treatment with levomilnacipran ER 40-120 mg/day resulted in a statistically significant improvement in the MADRS total score at week 8 relative to placebo (p = 0.0051).

Table 32: Primary Efficacy Parameter: Change from Baseline to Week 8 in the MADRS Total Score (MMRM, LOCF, and PMM) – ITT Population [LVM-MD-03]

		Placebo (N = 214)	*Levomilnacipran 40-120 mg/day (N = 215)*	*LSMD (95% CI)*	*p-Value*
Primary Analysis—MMRM					
Baseline, mean ± SD		35.2 ± 3.8	35.0 ± 3.6	—	—
Change at Week 8					
LS mean (SE)		–12.2 (0.78)	–15.3 (0.79)	–3.095 (–5.256, –0.935)	0.0051[a]
Sensitivity Analysis—LOCF					
Baseline, mean ± SD		35.2 ± 3.8	35.0 ± 3.6	—	—
Change at Week 8					
LS mean (SE)		–11.4 (0.76)	–13.9 (0.75)	–2.553 (–4.557, –0.549)	0.0127[b]
Sensitivity Analysis—PMM[c]					
Change at Week 8, LS mean (SE)	Shift parameter				
	0	–12.1 (0.77)	–15.3 (0.77)	–3.135 (–5.255, –1.016)	0.0038
	2	–11.8 (0.77)	–14.8 (0.77)	–3.015 (–5.128, –0.902)	0.0052
	4	–11.4 (0.79)	–14.4 (0.79)	–2.925 (–5.051, –0.800)	0.0070
	6	–11.1 (0.80)	–13.9 (0.82)	–2.870 (–5.087, –0.652)	0.0112
	8	–10.7 (0.81)	–13.5 (0.82)	–2.792 (–5.057, –0.526)	0.0158

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

b p-Value was obtained from an ANCOVA model with treatment group and pooled study centers as factors and baseline MADRS-CR total score as covariate.

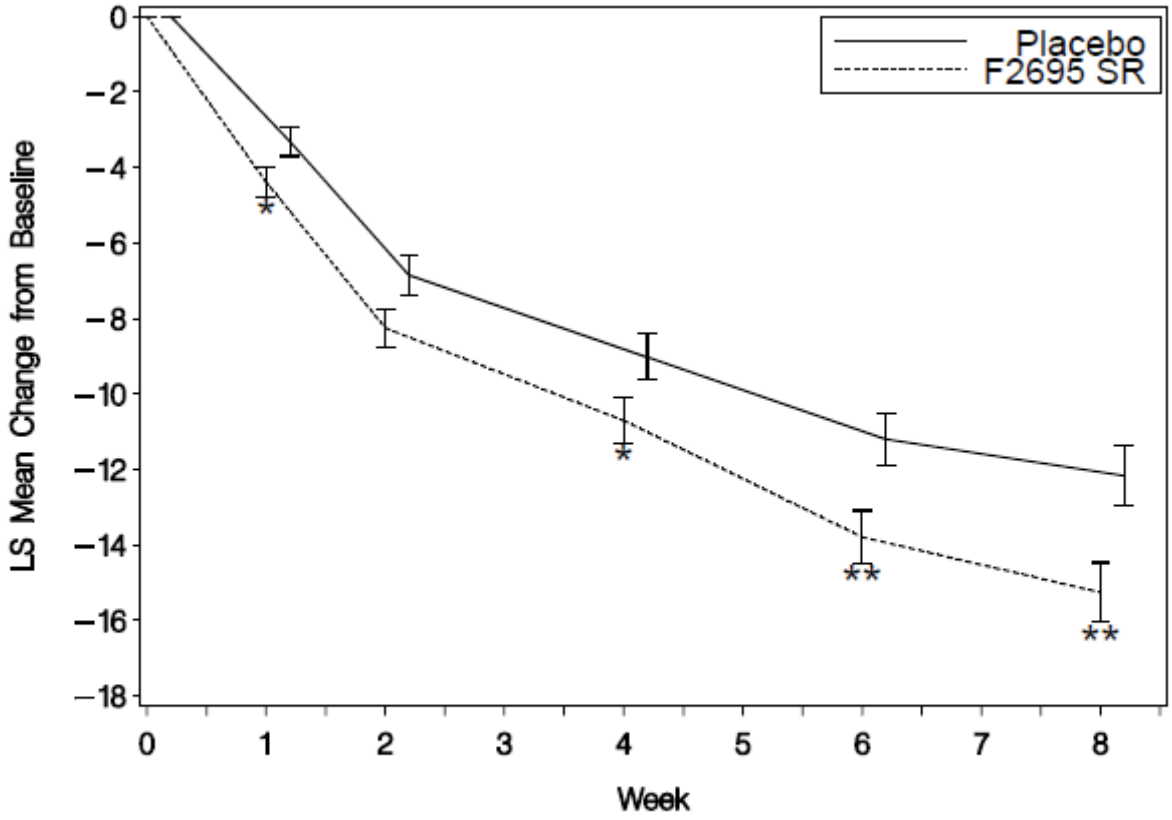
c For each shift parameter value, missing values were imputed multiple times using a PMM assuming non-future dependence. For each imputed dataset, MMRM analysis was performed. The p-value was obtained from combining all the results from each individual analysis of the same shift parameter value.

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; n = number of patients in the ITT Population with available values at baseline and at a specific timepoint; PMM = pattern-mixture model; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 51; MMRM and LOCF results confirmed by this reviewer)

Statistically significant improvement was also seen in the LOCF analysis (p = 0.0127) and the PMM analysis at each selected value of the shift parameter, confirming the robustness of the primary efficacy analysis. The MMRM estimates of change from baseline in MADRS total score at each visit are displayed in Figure 18.

Figure 18: LS Mean (SE) of Change from Baseline to Week 8 in MADRS Total Score (MMRM) – ITT Population [LVM-MD-03]



* = p <0.05, ** = p<0.01.
ITT = intent to treat; LS = least squares; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; SE = standard error; SR = sustained release.
(Source: Summary of Clinical Effectiveness p. 52)

This reviewer confirmed the sponsor's MMRM and LOCF analysis results.

The sample size was increased from 360 to 440 while Study MD-03 was ongoing after results from another similarly designed study (LVM-MD-02) showed a smaller than expected effect size (Amendment 2 to the protocol, Amendment 1 to SAP). The effect size estimate was adjusted from 0.38 to 0.33 and the sample size increased by 40 patients per treatment group (see study

report p. 2084). The FDA communicated the following comment to Forest on July 5, 2011: "In order to maintain the integrity of trial conduct, major changes to the protocol such as sample size increase at a very late stage of a trial are normally discouraged. If you have already completed the enrollment of the additional 80 patients for Study LVM-MD-03, the impact of the sample size increase on the study outcomes would become a review issue". The FDA requested to conduct an exploratory analysis for the first 360 randomized subjects.

The MADRS total score results for the first 360 randomized subjects (exploratory analysis, Table 33 below) are consistent with results after the increase in sample size. This exploratory analysis was pre-specified in an SAP amendment after the above mentioned FDA request.

Table 33: Change from Baseline in MADRS Total Score to Week 8 Based on the first 360 Randomized Patients – ITT Population [LVM-MD-03]

		Placebo (N=170)		F2695 SR (N=182)		F2695 SR - Placebo LSMD (95% CI) P-value
	Statistics	Actual	Change	Actual	Change	
MMRM [1]	Mean	23.2	-12.1	19.5	-15.6	
	SD	12.0	11.4	10.3	10.0	
	SEM	1.0	1.0	0.9	0.9	
	Median	26.0	-10.0	18.0	-16.0	
	Min, Max	0, 50	-41, 17	2, 44	-49, 5	
	n	139	139	137	137	
	LS Mean (se)		-12.2 (0.88)		-15.4 (0.86)	-3.241 (-5.639, -0.843) 0.0082

Notes: [1] P-values are from a MMRM model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as factors, and baseline MADRS-CR total score and baseline-by-visit interaction as covariates. MMRM = Mixed-effects Model for Repeated Measures.
N = Number of patients in the first 360 randomized patients who satisfies ITT population definition.
n = Number of patients with available analysis values at both baseline and a specific time point in the first 360 randomized patients who satisfies ITT population definition.
LSMD = Difference in Least Squares Mean, LS Mean = Least Squares Mean, CI = Confidence Interval, SD = Standard Deviation, SEM = Standard Error of the Mean, Min = Minimum, Max = Maximum, se = standard error of the least square mean.

(Source: Study report p. 2092; results confirmed by this reviewer)

This reviewer obtains similar results when conducting the MMRM analysis for the first 360 randomized patients.

Treatment with levomilnacipran ER 40-120 mg/day also produced a statistically significant decrease relative to placebo in the secondary efficacy parameter – the SDS total score. The LS Mean difference was estimated to be -2.632 with a p-value of 0.0010 based on data from 371 subjects with at least one post baseline assessment of SDS (see Table 34).

Table 34: Key secondary Efficacy Parameter: Change from Baseline to Week 8 in the SDS Total Score (MMRM) – ITT Population [LVM-MD-03]

	Placebo (N = 214)	*Levomilnacipran 40-120 mg/day (N = 215)*	*LSMD (95% CI)*	*p-Value*
SDS Total Score				
Baseline, mean ± SD	19.7 ± 5.2	20.1 ± 5.0	—	—
Change at Week 8				
LS mean (SE)	–5.4 (0.57)	–8.0 (0.58)	–2.632 (–4.193, –1.070)	0.0010[a]

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

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; n = number of patients in the ITT Population with available values at baseline and at the specific timepoint; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 53; results confirmed by this reviewer)

The MMRM analysis for SDS including only the first 360 subjects randomized performed by this reviewer is consistent with the analysis using all randomized patients (LSMD [95% CI]: -2.601 [-4.305, -0.898]).

Results from the LOCF analysis of the SDS total score are in line with the primary analysis results (see Table 35).

Table 35: Change from Baseline in SDS Total Score to Week 8 (LOCF) – ITT Population [LVM-MD-03]

Visit*	Statistics	Placebo (N=214) Actual	Placebo (N=214) Change	F2695 SR (N=215) Actual	F2695 SR (N=215) Change	F2695 SR - Placebo LSMD (95% CI) P-value [1]
Week 8	Mean	14.8	-5.0	12.6	-7.7	
	SD	8.1	8.0	7.5	7.6	
	SEM	0.6	0.6	0.6	0.6	
	Median	16.0	-4.0	12.0	-8.0	
	Min, Max	0, 30	-25, 16	0, 30	-29, 12	
	n	190	190	181	181	
	LS Mean (se)		-5.2 (0.56)		-7.6 (0.57)	-2.390 (-3.892, -0.888) 0.0019

Notes: [1] Analyses are based on an ANCOVA model with treatment group and pooled study center as factors and corresponding baseline as covariate. LOCF = Last Observation Carried Forward.
* Visit = Derived.
n = Number of patients with available analysis values at both baseline and a specific time point in the Intent-to-Treat Population.
LSMD = Difference in Least Squares Mean, LS Mean = Least Squares Mean, CI = Confidence Interval.
SD = Standard Deviation, SEM = Standard Error of the Mean, Min = Minimum, Max = Maximum, se = standard error of the least square mean.

(Source: Study report p. 264; results confirmed by this reviewer)

This reviewer obtained the same MMRM and LOCF analyses results as the sponsor for the SDS total score.

3.2.4.4 F02695 LP 2 02 (Phase 2)

According to the primary MMRM model there was a statistically significant greater LS Mean change (improvement) in total MADRS score from baseline to week 10 in the levomilnacipran ER group compared to the placebo group ($p < 0.0001$). The difference between the two groups in the LS mean change from baseline was -4.2 (95%: -5.7, -2.6), with an LS mean change from baseline to week 10 of -14.5 in the placebo and -18.7 in the levomilnacipran ER group (see Table 36).

LOCF ANCOVA of the change in MADRS score from baseline to week 10 in the ITT population supports the results of the primary analysis. The magnitude of change is slightly smaller but the difference between the two groups with -3.7 is about the same.

Table 36: Primary Efficacy Parameter: Change from Baseline to Week 10 in the MADRS Total Score (MMRM and LOCF) – ITT Population [LP 2 02]

	Placebo (N =277)	*Levomilnacipran 75-100 mg/day (N =276)*	*LSMD (95% CI)*	*p-Value*
Primary Analysis—MMRM				
Baseline, mean ± SD	30.5 ± 3.7	30.9 ± 4.1	—	—
Change at Week 10				
LS mean (SE)	–14.5 (0.56)	–18.7 (0.56)	–4.2 (–5.7, –2.6)	< 0.0001[a]
Sensitivity Analysis—LOCF				
Baseline, mean ± SD	30.5 ± 3.7	30.9 ± 4.1	—	—
Change at Week 10				
LS mean (SE)	–13.2 (0.57)	–16.9 (0.57)	–3.7 (–5.2, –2.1)	< 0.0001[b]

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

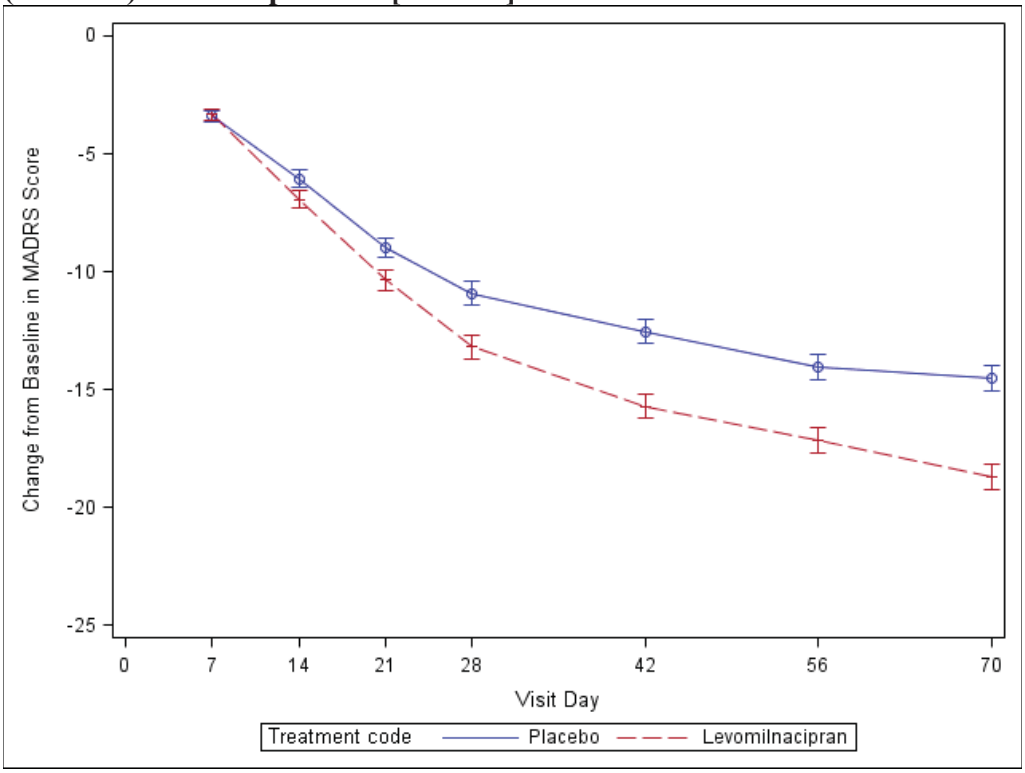
b p-Value was obtained from an ANCOVA model with treatment group and pooled study centers as factors and baseline MADRS-CR total score as covariate.

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 58, see also study report p. 101; MMRM results confirmed by this reviewer)

The mean MADRS total score decreased at each study visit during the double-blind period for both the placebo and levomilnacipran group; at each visit the change from baseline in MADRS score was greater in the levomilnacipran group. Figure 19 displays the change from baseline in MADRS total score over time by treatment group based on the MMRM model.

Figure 19. LS Mean (SE) of Change from Baseline to Week 10 in MADRS Total Score (MMRM) – ITT Population [LP 2 02]



(Source: Computed by reviewer based on primary MMRM model; SE = Standard Error; compare to graph in Summary of Clinical Effectiveness p. 59; see also figures and table in Study Report p. 102 - 104)

One of several secondary efficacy criteria in Study LP 2 02 is the SDS total score. It was not defined a priori as key secondary endpoint. The LS mean change (MMRM) from baseline in SDS total score at week 10 is statistically significant greater in the levomilnacipran group (-11.1) compared to the placebo group (-7.7). The difference between the two groups in LS mean changes at week 10 is -3.4 (95% CI: -4.6, -2.2). Details are provided in table 37.

Table 37: Key secondary Efficacy Parameter: Change from Baseline to Week 10 in the SDS Total Score (MMRM) – ITT Population [LP 2 02]

	Placebo (N=277)	*Levomilnacipran 75-100 mg/day (N=276)*	*LSMD (95% CI)*	*p-Value[a]*
SDS Total Score				
Baseline, mean ± SD	20.82 ± 3.76	21.25 ± 3.93	—	—
Change at Week 10				
LS mean (SE)	–7.7 (0.44)	–11.1 (0.43)	–3.4 (–4.6, –2.2)	< 0.0001

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

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

(Source: Summary of Clinical Effectiveness p. 60)

3.2.4.5 Summary for Positive Studies

A summary of the primary efficacy parameter (MADRS total score) results for the four positive studies is provided in Table 38. Recall that Study LP 2 02 is a Phase II study evaluating doses of 75 and 100 mg/day over 10 weeks of double-blind treatment.

Table 38: Summary of the Primary Efficacy Parameter results in the Positive Studies: Change from Baseline to Endpoint in the MADRS Total Score (MMRM) – ITT Population

	LVM-MD-01				*LVM-MD-10*			*LVM-MD-03*		*F02695 LP 2 02*	
	Placebo (N = 175)	*40 mg/d (N = 176)*	*80 mg/d (N = 177)*	*120 mg/d (N = 176)*	*Placebo (N = 185)*	*40 mg/d (N = 185)*	*80 mg/d (N = 187)*	*Placebo (N = 214)*	*40-120 mg/d (N = 215)*	*Placebo (N = 277)*	*75-100 mg/d (N = 276)*
Baseline, Mean ± SD	35.6 ± 4.5	36 ± 4.1	36.1 ± 3.9	36.0 ± 3.9	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5	35.2 ± 3.8	35.0 ± 3.6	30.5 ± 3.7	30.9 ± 4.1
Change, LS mean (SE)	–11.6 (0.97)	–14.8 (0.99)	–15.6 (1.00)	–16.5 (1.02)	–11.3 (0.77)	–14.6 (0.79)	–14.4 (0.79)	–12.2 (0.78)	–15.3 (0.79)	–14.5 (0.56)	–18.7 (0.56)
LSMD (95% CI)	—	–3.23 (–5.9, –0.5)	–3.99 (–6.7, –1.3)	–4.86 (–7.6, –2.1)	—	–3.30 (–5.5, –1.1)	–3.14 (–5.3, –1.0)	—	–3.10 (–5.3, –0.9)	—	–4.2 (–5.7, –2.6)
p-Value[a]	—	**0.0186**	**0.0038**	**0.0005**	—	**0.0027**	**0.0043**	—	**0.0051**	—	**< 0.0001**

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

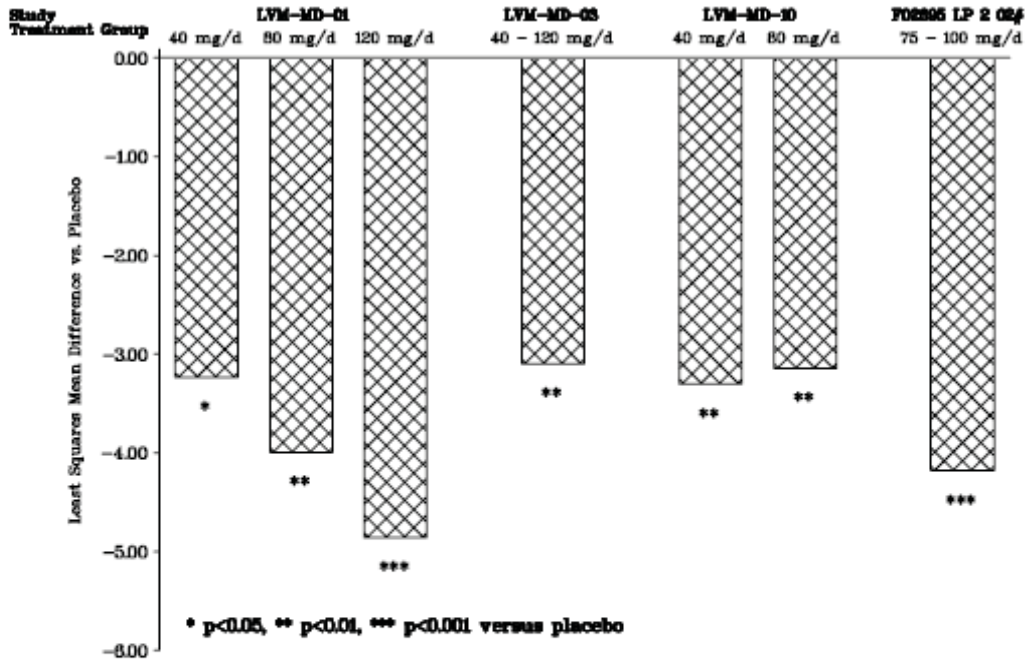
a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS = Montgomery-Åsberg Depression Rating Scale; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 69)

A graphical summary of the LS mean difference at endpoint in MADRS total score is presented in Figure 20.

Figure 20: Treatment Difference for Change from Baseline in MADRS Total Score at Endpoint (MMRM) – ITT Population



Note: Analysis based on observed cases using a mixed model for repeated measures with treatment group, pooled study center (nested within study), visit, and treatment group-by-visit interaction as fixed effects and baseline and baseline-by-visit as covariates using an unstructured covariance matrix to model the covariance of within-patient scores.

Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

ITT = intent to treat; MADRS = Montgomery-Åsberg Depression Rating Scale; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures.

(Source: Summary of Clinical Effectiveness p. 70)

A summary of the primary analysis results for the key secondary parameter SDS is given in Table 39. Note that the difference between the levomilnacipran 40 mg dose group and the placebo group is not statistically significant at alpha = 0.05 in Study MD-01 and is right below the significance threshold with p = 0.0459 in Study MD-10.

Table 39: Summary of the Key Secondary Efficacy Parameter Results in the Positive Studies: Change from Baseline to Endpoint in the SDS Total Score (MMRM) – ITT Population

	LVM-MD-01				*LVM-MD-10*			*LVM-MD-03*		*F02695 LP 2 02*	
	Placebo (N = 175)	*40 mg/d (N = 176)*	*80 mg/d (N = 177)*	*120 mg/d (N = 177)*	*Placebo (N = 185)*	*40 mg/d (N = 185)*	*80 mg/d (N = 187)*	*Placebo (N = 214)*	*40-120 mg/d (N = 215)*	*Placebo (N = 277)*	*75-100 mg/d (N = 276)*
Baseline, Mean ± SD	21.5 ± 4.8	21.1 ± 4.8	21.4 ± 4.9	21.3 ± 5	16.4 ± 6.1	16.7 ± 6.6	17.6 ± 6.0	19.7 ± 5.2	20.1 ± 5.0	20.8 ± 3.8	21.3 ± 3.9
Change, LS mean (SE)	–7.2 (0.74)	–8.6 (0.75)	–9.7 (0.77)	–9.7 (0.78)	–5.4 (0.66)	–7.3 (0.68)	–8.2 (0.66)	–5.4 (0.57)	–8.0 (0.58)	–7.7 (0.44)	–11.1 (0.43)
LSMD (95% CI)	—	–1.41 (–3.4, 0.6)	–2.51 (–4.5, -0.5)	–2.57 (–4.6, –0.5)	—	–1.83 (–3.6, –0.0)	–2.72 (–4.5, –1.0)	—	–2.63 (–4.2, –1.1)	—	–3.4 (–4.6, –2.2)
p-Value[a]	—	0.1687	**0.0151**	**0.0141**	—	**0.0459**	**0.0028**	—	**0.0010**	—	**< 0.0001**

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

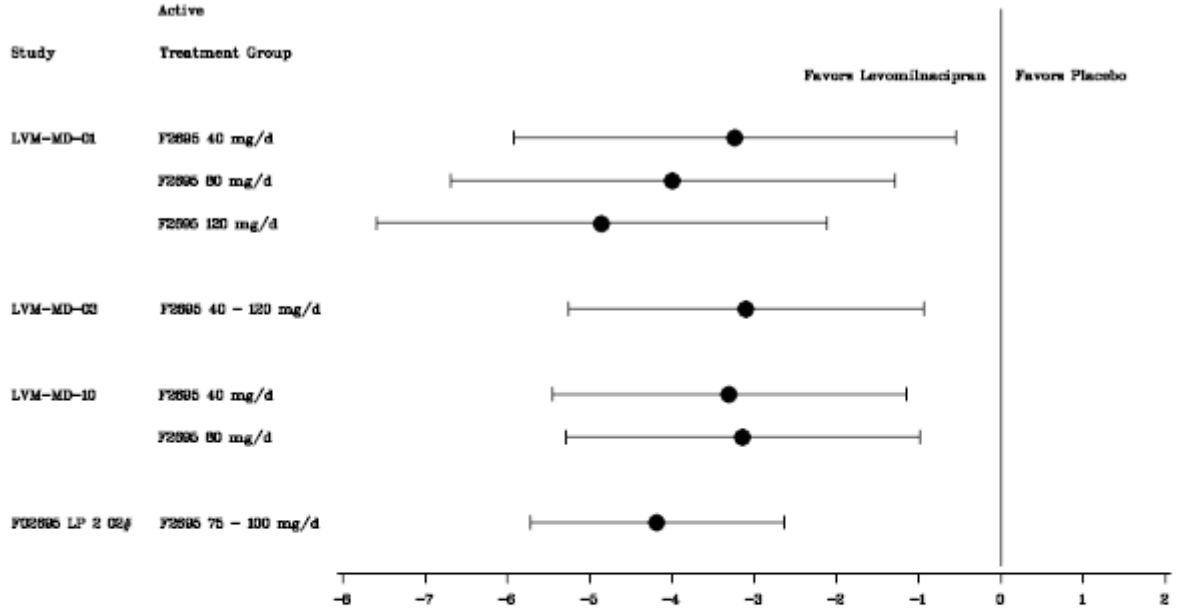
a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS-CR total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SDS = Sheehan Disability Scale; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 71)

Another graphical summary of the primary and key secondary results that incorporates (unadjusted) 95% confidence intervals for each dose is shown in figures 21 and 22.

Figure 21: Treatment Differences and 95% CIs of Change from Baseline in MADRS Total Score at Endpoint (MMRM) – ITT Population



Note: Analysis based on observed cases using a mixed model for repeated measures with treatment group, pooled study center (nested within Study), visit, and treatment group-by-visit interaction, as fixed effects and baseline and baseline-by-visit as covariates using an unstructured covariance matrix to model the covariance of within-patient scores.

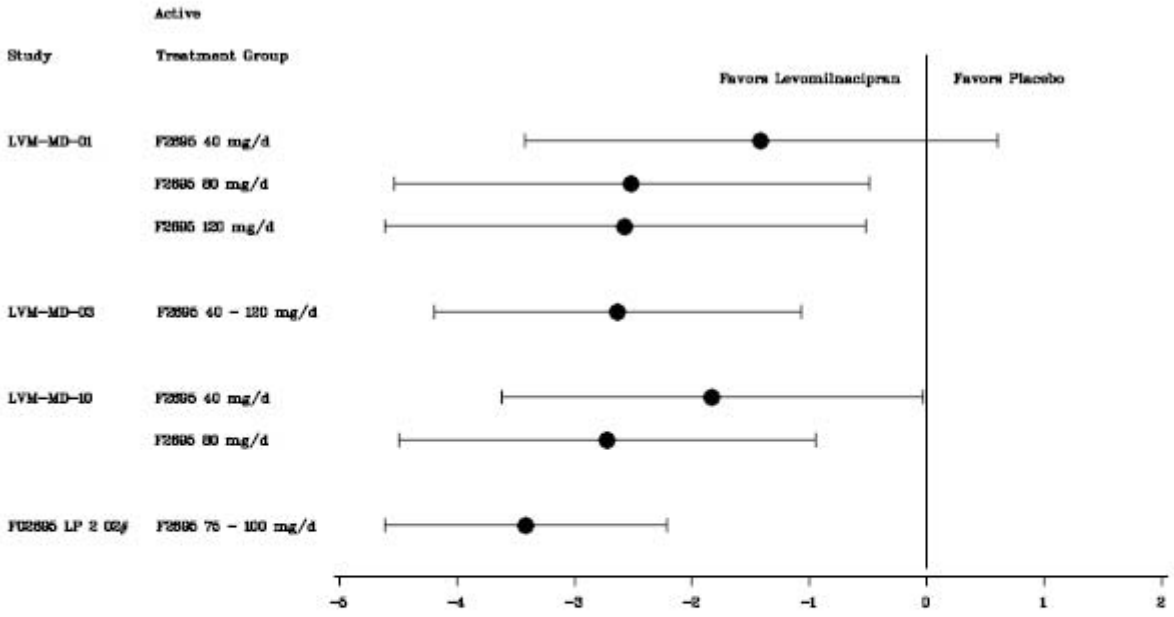
Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

All values in the levomilnacipran group were statistically significant versus placebo.

CI = confidence interval; F2695 = levomilnacipran; ITT = intent to treat; MADRS = Montgomery-Åsberg Depression Rating Scale; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures.

(Source: Summary of Clinical Effectiveness p. 83)

Figure 22: Treatment Differences and 95% CIs of Change from Baseline in SDS Total Score at Endpoint (MMRM) – ITT Population



Note: Analysis based on observed cases using a mixed model for repeated measures with treatment group, pooled study center (nested within Study), visit, and treatment group-by-visit interaction, as fixed effects and baseline and baseline-by-visit as covariates using an unstructured covariance matrix to model the covariance of within-patient scores.

Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

All values in the levomilnacipran group were statistically significant versus placebo, with the exception of the levomilnacipran 40 mg/day group in Study LVM-MD-01.

CI = confidence interval; F2695 = levomilnacipran; ITT = intent to treat; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; SDS = Sheehan Disability Scale.

(Source: Summary of Clinical Effectiveness p. 84)

3.2.4.6 Summary for Negative/Failed Studies

LVM-MD-02

Study MD-02 failed to reject the Null hypothesis of no treatment effect for the primary and key secondary endpoints. The study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study conducted in the US which evaluated levomilnacipran ER for the treatment of MDD. Male and female MDD patients 19 to 78 years of age were enrolled in the study provided they had a clinician rated MADRS total score of 30 or higher. The ITT Population included 355 patients (181 on placebo and 174 on levomilnacipran ER 40 – 120 mg/day). The overall mean daily dose of active drug was approximately 75 mg and about 50% of patients on active treatment received 120 mg/day as their final dose. Approximately 80% of the patients completed the 8 week double-blind treatment phase. The LS Mean Difference in MADRS total score at week 8 is (b) (4) with a p-value of (b) (4) MMRM results for the primary efficacy parameter, MADRS total score, are summarized in Table 40.

Table 40: Negative Study - Primary Efficacy Parameter: Change from Baseline to Week 8 in the MADRS Total Score (MMRM) – ITT Population [LVM-MD-02]

	Placebo (N = 181)	*Levomilnacipran 40-120 mg/day (N = (b) (4)*	*LSMD (95% CI)*	*p-Value*
Baseline, mean ± SD	35.5 ± 4.0	(b) (4)	—	—
Change at Week 8			(b) (4)	
LS mean (SE)	–14.2 (0.90)			

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

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS-CR = Montgomery-Åsberg Depression Rating Scale, Clinician-Rated; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SD = standard deviation; SE = standard error.

(Source: Summary of Clinical Effectiveness p. 64)

There was almost no differentiation at week 8 for the key secondary parameter SDS between the levomilnacipran and placebo groups (Change from baseline at week 8 of (b) (4) and -8.2, respectively).

The sponsor conjectures that the failure of this study "was likely due to a large placebo response" (Summary of Clinical Effectiveness p. 64).

LVM-MD-05 (Maintenance Study)

The primary efficacy parameter in Study MD-05 was the time to relapse during the double-blind treatment period. The estimated hazard ratio (levomilnacipran/placebo) of (b) (4) indicates a reduced risk of relapsing for the levomilnacipran group but it is not statistically significant at alpha = (b) (4).

Table 41: Negative Study – Primary Efficacy Parameter: Time to Relapse – Double-blind ITT Population [LVM-MD-05]

Time to Relapse	*Placebo (N = 112)*	*Levomilnacipran 40-120 mg/day* (b) (4)
Primary Analysis		
Number of patients relapsed, n (%)	23 (20.54)	(b) (4)
Number of patients censored, n (%)	89 (79.46)	
Hazard ratio (95% CI)[a]		(b) (4)
p-Value[b]		

a Percentiles (95% CI) were based on Kaplan Meier estimates.

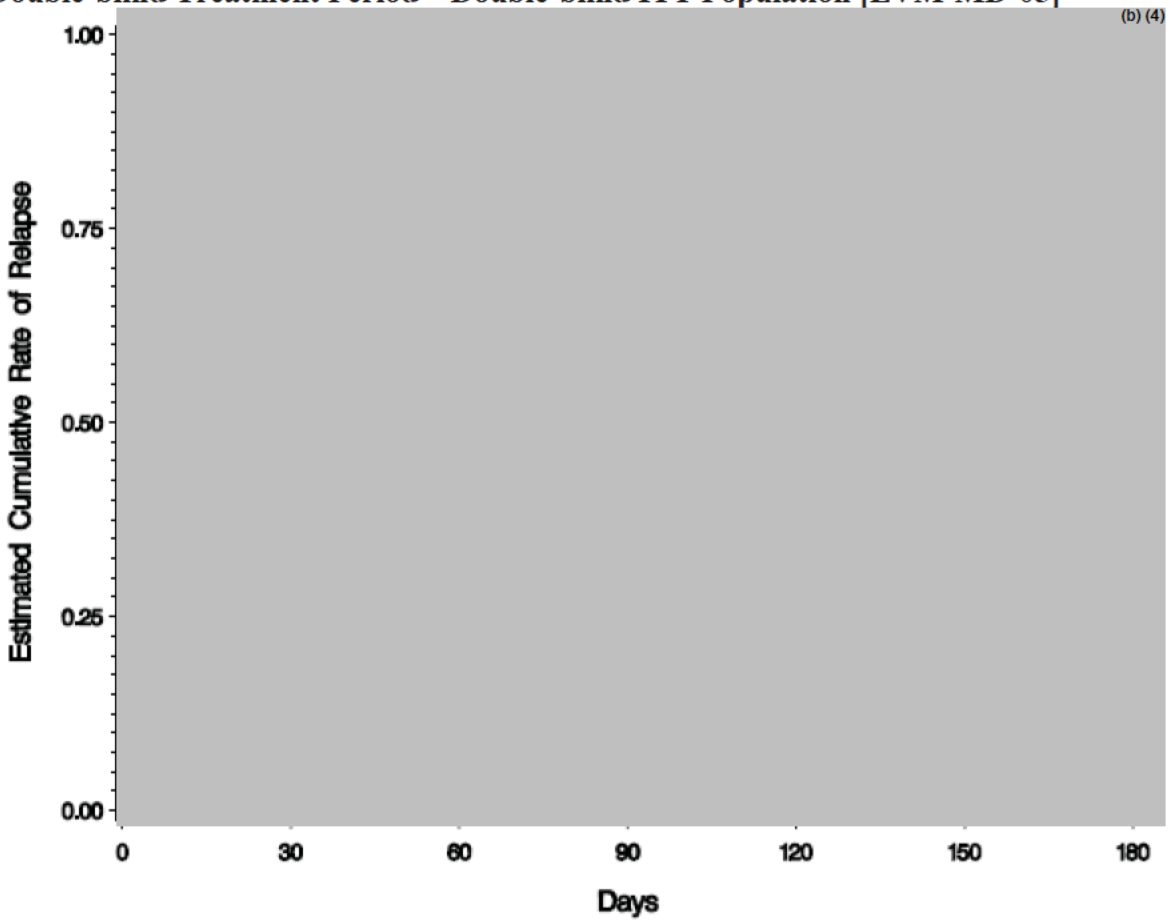
b Hazard ratio (levomilnacipran/placebo) and p-value were based on Cox proportional hazards regression model, with treatment group and double-blind MADRS total score as explanatory variables.

CI = confidence interval; ITT = intent to treat; N = number of patients in the Double-blind ITT Population; n = number of patients in the Double-blind ITT Population with available values at baseline and at a specific time point.

(Source: Summary of Clinical Effectiveness p. 66; results confirmed by this reviewer)

This reviewer obtained the same results for the Cox proportional hazards regression model as the sponsor. The Kaplan-Meier curves are presented in Figure 23.

Figure 23: Negative Study – Kaplan-Meier Estimates of Cumulative Rate of Relapse during Double-blind Treatment Period – Double-blind ITT Population [LVM-MD-05]



Note: Day to relapse was calculated as date of relapse – date of randomization + 1.
ITT = intent to treat; SR = sustained release.
(Source: Study report p. 100; results confirmed by this reviewer)

A summary of relapse by treatment, dose, and relapse category during the DB treatment period is presented in Table 42.

Table 42: Summary of Relapse during the Double-blind Treatment Period, by Dose – Double-blind ITT Population [LVM-MD-05]

Relapse Category	*Placebo (N = 112) n (%)*	*F2695 SR* (b) (4)			
		40 mg/d n (%)	*80 mg/d n (%)*	*120 mg/d n (%)*	*Total n (%)*
Number of patients	**112**	(b) (4)			
Any relapse[a]	23 (20.5)				
MADRS total score ≥ 22 at 2 consecutive visits	6 (5.4)				
Increase of ≥ 2 points in CGI-I score at 2 consecutive visits compared with CGI-I score at Visit 9[b]	10 (8.9)				
Premature discontinuation due to insufficient therapeutic response	12 (10.7)				
MADRS item 10 score ≥ 4	0				

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.

CGI-I = Clinical Global Impressions-Improvement; ITT = intent to treat; MADRS = Montgomery-Åsberg Depression Rating Scale; N = number of patients in the Double-blind ITT Population; n = number of patients in the Double-blind ITT Population with available values at baseline and at a specific time point; SR = sustained release.

(Source: Study report p. 101)

Requirement of 12-week stabilization period

The open-label phase in Study MD-05 has a total length of 12 weeks (see Figure 10 of this review). The sponsor proposed that patients who meet responder criteria (MADRS total score ≤ 12 and CGI-I score ≤ 2) at week 10 and week 12 of the open-label phase will be randomized. The requirement of a 12-week stabilization period was communicated to the sponsor in an email on July 5, 2011. The goal of a stabilization period of at least 12 weeks is to only randomize subjects who can be regarded as true responders. In the response from August 31, 2011 (SN 138) the sponsor states that "Patient enrollment in the open-label phase and randomization to double-blind treatment have been completed. […] Thus, it is not feasible to implement the additional stabilization period, as requested at this point in time." In response the FDA requested "additional analysis to find out how many patients (or percentage of patients) meet the required stabilization criteria …, and how long those patients continuously met the stabilization criteria during the run in phase" (email to Forest from October 4, 2011).

The results of this analysis are presented in Table 43, which gives the number and percentage of patients who met the stabilization criteria consecutively starting at week 4, week 6 or week 8. Using the number of randomized patients as denominator we see that overall (b) (4) of patients met the randomization criteria consecutively starting at week 4, 6, and 8, respectively. The treatment groups are fairly balanced regarding the proportion of patients stabilized with a trend for placebo patients to have been stable earlier compared to the levomilnacipran ER patients (b) (4) at week 4).

Overall this table emphasizes that the 12 week stabilization requirement has not been met in this trial (b) (4) of patients were not stable responders at 6 weeks of open-label treatment and more than (b) (4) were not stabilized by week 8. This finding questions whether mostly true and stable responders were randomized to the double-blind phase at week 12. It appears plausible that the shortcoming in stringently selecting the appropriate patients (i.e., stable responders) was the main reason for the failure to show a difference in time to relapse between the two treatment groups.

Table 43: Number of Patients Achieved Sustained Response during Open-label Treatment Phase – Randomized Population [LVM-MD-05]

Visit Patient Achieved Sustained Response [1]	Placebo (N = 113) n (%)	F2695 SR (N = 235) n (%)	Total (N = 348) n (%)
Week 4	(b) (4)		
Week 6			
Week 8			

Notes: [1] Patient is considered to have achieved sustained response at a visit if the patient's MADRS total score <=12 and CGI-I<=2 at the visit and at all subsequent visits till randomization (Week 12). Visit Weeks 4, 6, and 8 are based on nominal Visits 5, 6, and 7, respectively.
Percentage is calculated using the number of patients in the treatment group as the denominator.

(Source: Study report p. 326)

Table 44 presents an exploratory analysis of time to relapse for the patient groups stabilized at week 4, 6 or 8. The sponsor states that the hazard ratios (levomilnacipran ER/placebo) neither markedly favor the placebo nor the levomilnacipran ER group.

Table 44: Analysis of Time to Relapse – Exploratory Analysis (Double-blind ITT Population) [LVM-MD-05]

Visit Patient Achieved Sustained Response [1]	Placebo (N=112)			F2695 SR (b) (4)			Hazard Ratio [2]	
	N1	n	%	N1	n	%	Estimate (95% CI)	p-value
Week 4	39	8	20.51	(b) (4)				
Week 6	58	10	17.24					
Week 8	82	17	20.73					

Notes: [1] Patient is considered to have achieved sustained response at a visit during open-label treatment phase if the patient's MADRS total score <=12 and CGI-I<=2 at the visit and at all subsequent visits till randomization (Week 12). Visit Weeks 4, 6, and 8 are based on nominal Visits 5, 6, and 7, respectively.
Time to relapse (days) is calculated as Date of Relapse - date of randomization + 1.
[2] Hazard ratio (F2695 SR/Placebo) and p-value are based on Cox proportional hazards regression model, with treatment group and double-blind baseline MADRS total score as explanatory variables.
N1 = number of patients achieved sustained response at the visit during open-label; n = number of patients relapsed;
CI = confidence interval

(Source: Study report p. 327)

Conjectures why Study MD-05 failed:

a) The open label period with 12 weeks in total duration was too short and the requirement to meet response criteria at weeks 10 and 12 is too narrow (requiring 12 weeks of stable response could have potentially led to a more reliable selection of true responders).

b) The sample size was calculated with an expectation of higher relapse rates in both treatment groups. The relapse rates observed in this study (20.5% for placebo and (b) (4) for levomilnacipran) were much lower than those used for the sample size calculations (38% for placebo and (b) (4) for levomilnacipran) [see study report p. 181].

c) Instead of the 360 patients required by the sample size calculation only (b) (4) were actually included in the randomized ITT population.

3.3 Evaluation of Safety

Safety was not evaluated in this review. Please refer to the clinical review for the assessment of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Geographic Region

Subgroup analyses were conducted by the sponsor to assess the consistency of the treatment effect across studies. The following cutoffs were used for subgroups:

- Sex (male, female)
- Age (< 55 years, ≥ 55 years)
- Race (white, all other races)

The sponsor states, that the examination of subgroups did not reveal any clear evidence of differential response.

4.1.1 Gender

Table 45: Summary of Change from Baseline to Endpoint in the MADRS Total Score by Sex (LOCF) – ITT Population

	LVM-MD-01				*LVM-MD-10*			*LVM-MD-03*		*F02695 LP 2 02*	
	Placebo	*40 mg/d*	*80 mg/d*	*120 mg/d*	*Placebo*	*40 mg/d*	*80 mg/d*	*Placebo*	*40-120 mg/d*	*Placebo*	*75-100 mg/d*
Males											
N	68	56	68	72	70	69	64	73	75	95	90
Baseline, Mean ± SD	35.9 ± 4.8	36.3 ± 4.1	36.0 ± 3.2	36.2 ± 3.6	31.3 ± 3.8	30.7 ± 3.5	31.0 ± 3.9	34.8 ± 3.5	34.6 ± 3.1	30.8 ± 4.0	30.4 ± 3.5
Change, Mean ± SD	−10.6 ± 11.3	−12.8 ± 12.1	−15.0 ± 11..2	−14.9 ± 11.0	−9.7 ± 9.9	−15.1 ± 10.1	−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
Baseline, Mean ± SD	35.5 ± 4.4	35.9 ± 4.2	36.1 ± 4.3	35.9 ± 4.1	30.8 ± 3.8	30.8 ± 3.4	31.3 ± 3.3	35.5 ± 3.9	35.2 ± 3.8	30.4 ± 3.6	31.1 ± 4.3
Change, Mean ± SD	−11.0 ± 12.4	−13.7 ± 12.0	−13.9 ± 11.8	−13.7 ± 11.2	−11.3 ± 9.6	−12.2 ± 10.3	−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

Note: Mean treatment difference is levomilnacipran minus placebo.
Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.
(Source: Summary of Clinical Effectiveness p. 76)

Both males and females exhibit greater improvements in the MADRS totals score on average when on active treatment compared to placebo. Note that the greatest divergence in the differences by gender was estimated for Study MD-10, with males showing stronger efficacy

results compared to females (LS Mean differences for the 40 and 80 mg dose groups: -5.4 and -5.1 for males vs. -0.9 and -1.1 for females).

4.1.2 Age

Table 46 provided by the sponsor presents MADRS efficacy results when grouping patients by age with an age of 55 delimiting the two groups.

Table 46: Summary of Change from Baseline to Endpoint in the MADRS Total Score by Age Group (LOCF) – ITT Population

	LVM-MD-01				*LVM-MD-10*			*LVM-MD-03*		*F02695 LP 2 02*	
	Placebo	*40 mg/d*	*80 mg/d*	*120 mg/d*	*Placebo*	*40 mg/d*	*80 mg/d*	*Placebo*	*40-120 mg/d*	*Placebo*	*75-100 mg/d*
< 55 years											
N	152	139	142	154	148	150	148	163	158	215	210
Baseline, mean ± SD	35.6 ± 4.5	36.2 ± 4.1	36.2 ± 3.8	36.0 ± 3.8	30.8 ± 3.9	30.9 ± 3.5	31.0 ± 3.4	35.3 ± 3.7	34.8 ± 3.7	30.5 ± 3.8	31.0 ± 4.2
Change, mean ± SD	−10.8 ± 11.9	−13.4 ± 12.4	−14.4 ± 11.7	−14.5 ± 10.9	−10.4 ± 9.9	−13.4 ± 10.4	−13.1 ± 10.4	−11.8 ± 11.0	−13.6 ± 10.5	−12.7 ± 10.2	−17.1 ± 10.2
Difference	—	−2.6	−3.6	−3.7	—	−3.0	−2.8	—	−1.8	—	−4.4
≥ 55 years											
N	23	37	35	22	37	35	39	51	57	62	66
Baseline, mean ± SD	36.2 ± 5.1	35.5 ± 4.2	35.6 ± 4.5	35.6 ± 4.4	31.8 ± 3.3	30.3 ± 3.1	31.9 ± 3.8	34.9 ± 4.0	35.5 ± 3.2	30.6 ± 3.5	30.4 ± 3.5
Change, mean ± SD	−11.3 ± 12.7	−13.5 ± 10.4	−14.1 ± 11.2	−12.0 ± 12.6	−11.9 ± 8.9	−13.0 ± 10.2	−13.5 ± 9.9	−10.1 ± 10.3	−14.4 ± 9.7	−13.2 ± 8.8	−16.7 ± 10.4
Difference	—	−2.2	−2.8	−0.7	—	−1.0	−1.5	—	−4.3	—	−3.5

Note: Mean treatment difference is levomilnacipran minus placebo.
Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.
(Source: Summary of Clinical Effectiveness p. 78)

The sponsor notes in the draft label that efficacy was demonstrated in "adult (18-78 years of age) outpatients". The oldest participants this reviewer could find in the ITT population were two participants 76 years of age in study LVM-MD-03.

Figures A4a-A4d in the appendix provide the ITT frequencies for each age in years for the three Phase 3 and the one supportive Phase 2 study for patients ≥ 55. The purpose of those descriptive figures is to explore whether the upper age range (e.g., ≥ 65) is represented well enough to potentially derive a claim. Table 47 summarizes the frequencies of older patients in each study.

Table 47: Frequency of Participants Equal/Greater a Specified Age – ITT Population

Study	Age in years				
	≥55	≥60	≥65	≥70	≥75
(1) LVM-MD-01	117	47	1	0	0
(2) LVM-MD-10	111	59	25	12	0
(3) LVM-MD-03	108	60	23	11	3
Total of (1), (2), (3)	**336**	**166**	**49**	**23**	**3**
F02695 LP 2 02	128	58	20	2	0
Total of (1), (2), (3) and LP 2 02	464	224	69	25	3

(Source: Computed by reviewer)

There are only 23 patients in the Phase 3 studies 70 years of age or older (25 when including the Phase 2 study). This reviewer subdivided the equal or greater 55 age group further to explore the consistency of the results over different age strata. Tables A5a-A5d in the appendix display exploratory efficacy results for the three Phase 3 and for the one Phase 2 study. Considering those exploratory efficacy results, support for a claim in this patient group could only be derived from Study LVM-MD-03 (11 patients ≥ 70) which shows a trend in favor of levomilnacipran, while the trend in Study LVM-MD-10 (12 patients ≥ 70) is in favor of placebo. Given those results (whose reliability is limited by the small sample sizes) more studies in patients aged 70 and older (or even 65 years and older) appear necessary to obtain sufficient evidence of efficacy.

4.1.3 Race

Table 48: Summary of Change from Baseline to Endpoint in the MADRS Total Score by Race Group (LOCF) – ITT Population

	LVM-MD-01				*LVM-MD-10*			*LVM-MD-03*		*F02695 LP 2 02*	
	Placebo	*40 mg/d*	*80 mg/d*	*120 mg/d*	*Placebo*	*40 mg/d*	*80 mg/d*	*Placebo*	*40-120 mg/d*	*Placebo*	*75-100 mg/d*
White											
N	133	131	128	128	134	141	139	180	176	251	253
Baseline, mean ± SD	35.4 ± 4.5	35.9 ± 3.8	36.0 ± 3.9	35.7 ± 3.8	31.1 ± 3.8	30.9 ± 3.3	31.2 ± 3.5	35.3 ± 3.8	34.9 ± 3.5	30.4 ± 3.6	30.9 ± 4.1
Change, mean ± SD	−11.1 ± 11.7	−14.1 ± 11.8	−15.1 ± 12.0	−14.9 ± 11.3	−10.3 ± 10.1	−13.9 ± 9.9	−13.3 ± 10.1	−11.1 ± 10.9	−14.3 ± 10.3	−12.8 ± 9.7	−17.5 ± 9.6
Difference	—	−3.1	−4.0	−3.8	—	−3.6	−3.0	—	−3.2	—	−4.6
All Other Races											
N	41	45	49	48	51	44	48	34	39	26	23
Baseline, mean ± SD	36.1 ± 4.5	36.4 ± 5.0	36.3 ± 4.2	36.7 ± 4.0	30.8 ± 3.9	30.4 ± 3.8	31.4 ± 3.4	34.9 ± 3.8	35.5 ± 3.9	31.3 ± 4.5	30.6 ± 4.4
Change, mean ± SD	−9.9 ± 12.7	−11.3 ± 12.4	−12.3 ± 10.1	−12.4 ± 10.7	−11.7 ± 8.8	−11.5 ± 11.3	−12.9 ± 10.8	−12.7 ± 11.0	−11.3 ± 10.1	−12.3 ± 12.1	−11.9 ± 14.6
Difference	—	−1.4	−2.3	−2.5	—	0.3	−1.1	—	1.4	—	0.4

Note: Mean treatment difference is levomilnacipran minus placebo.
Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.
(Source: Summary of Clinical Effectiveness p. 80)

All treatment differences (levomilnacipran minus placebo) estimated in the three pivotal trials and the one supportive study are larger for "Whites" compared to "All Other Races". Also, the reduction in the MADRS total score is consistently larger for "Whites" on levomilnacipran compared to "Whites" on placebo. That is not the case for the group "All Other Races". However, the size of the "All Other Races" group is fairly small per study and dose. The results should be considered with caution.

4.1.4 Geographic Region

An exploration of potential differences by geographic region is not warranted since all studies, besides the supportive Phase 2 study, were conducted in the US and Canada.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The sample size for Study MD-03 was increased while the study was ongoing after external information about a smaller than expected effect size became available, however the results are consistent with results without the added subjects.

The large proportion of missing SDS baseline scores (27% of ITT subjects) in Study MD-10 reduced the available sample size for analysis and contributed to the p-value close to the nominal alpha level of 0.05 for the primary analysis and a p-value greater than 0.05 for the supportive analysis.

5.2 Collective Evidence

Statistically significant results were obtained for the primary endpoint for all evaluated doses and for the 80 and 120 mg doses for the key secondary endpoint. Evidence of efficacy for the 40 mg dose at the key secondary endpoint is weak (MD-01 SDS not statistically significant in 40 mg group [p = 0.1687]; MD-10 SDS 40 mg p = 0.0459 (MMRM), p = 0.0607 (ANCOVA LOCF)).

Tables 38 and 39 in section 3.2.4.5 provide a summary of the primary and key secondary endpoint results.

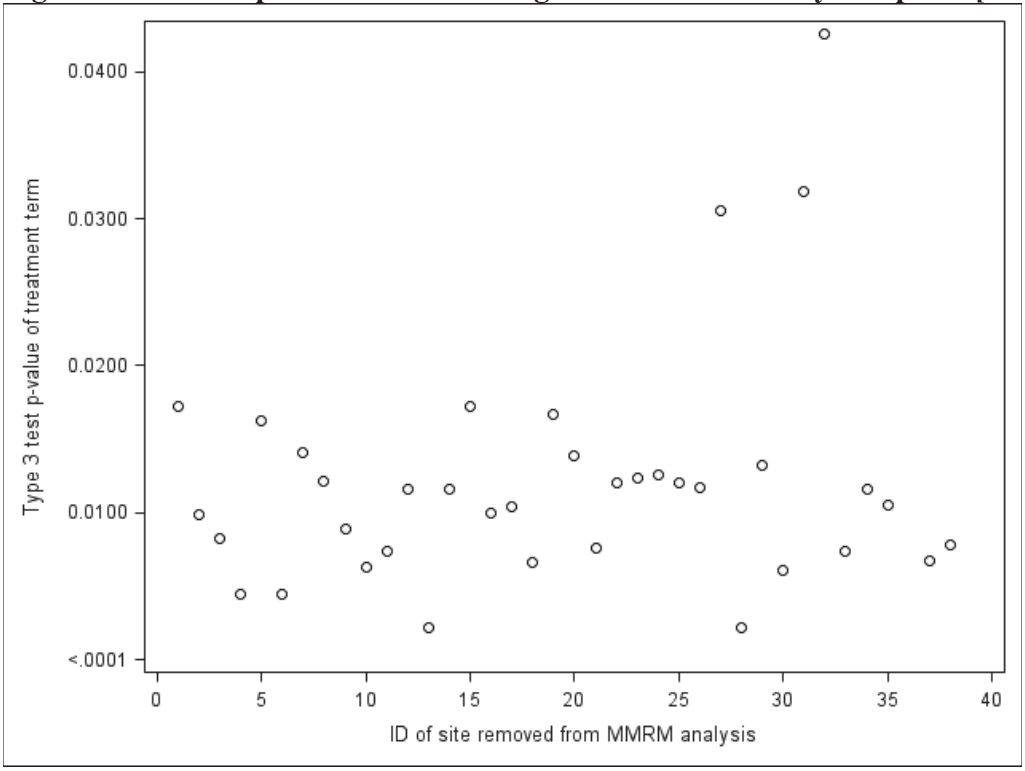
5.3 Conclusions and Recommendations

The statistical results provide adequate evidence to support the claims proposed in the NDA.

5.4 Labeling Recommendations

APPENDICES

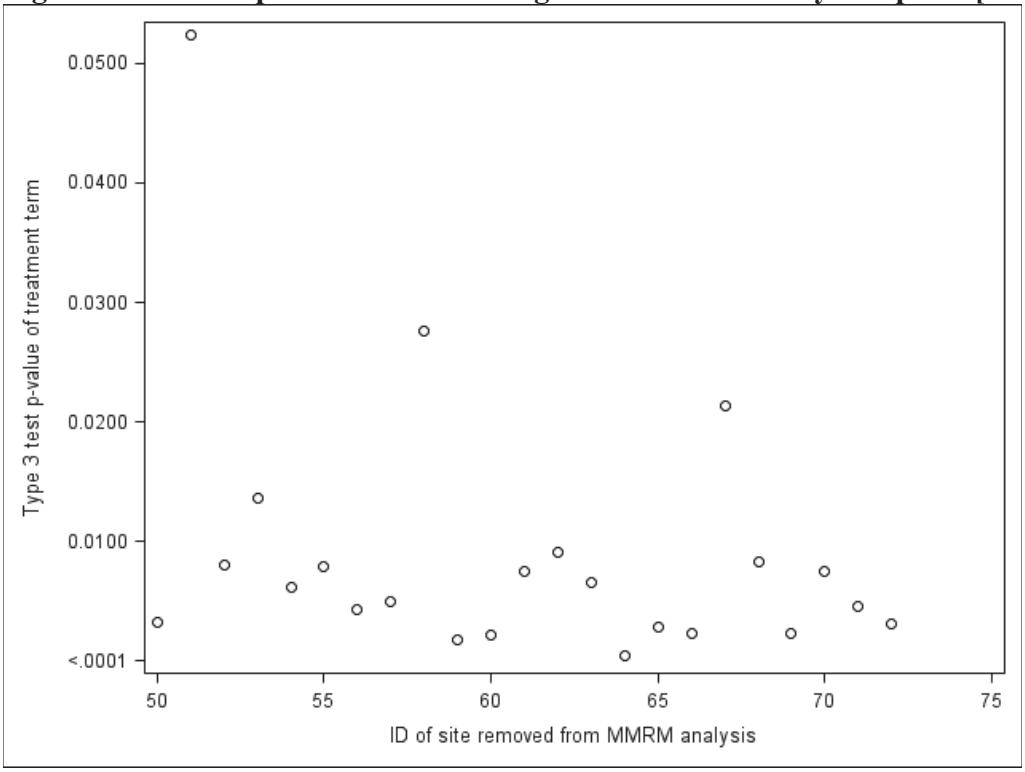
Figure A1. Site Impact on Statistical Significance of Primary Endpoint [LVM-MD-01]



(Source: Computed by reviewer)

For Study MD-01 removal of data from Site 32 would increase the type 3 test p-value of the treatment term in the MMRM model the most (p = 0.0426). Sites 31 and 27 are in second and third place with respect to supporting efficacy.

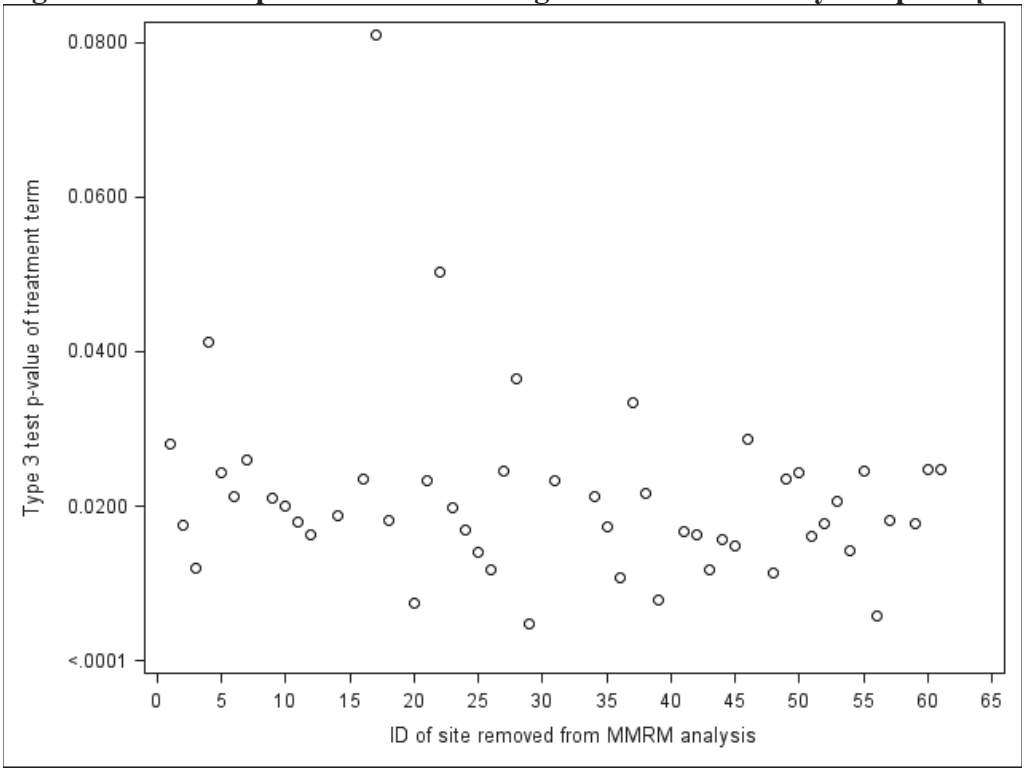
Figure A2. Site Impact on Statistical Significance of Primary Endpoint [LVM-MD-03]



(Source: Computed by reviewer)

For Study MD-03 site 51 has the strongest impact on the statistical significance of the treatment effect. Without this site the p-value for the treatment coefficient in the MMRM model would increase to 0.0524. Sites 58 and 67 also strongly support efficacy.

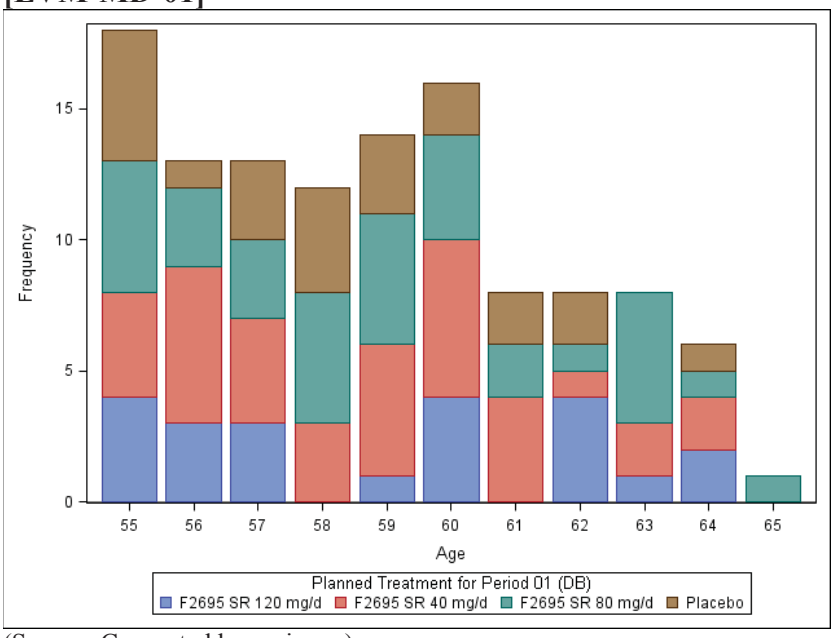
Figure A3. Site Impact on Statistical Significance of Primary Endpoint [LVM-MD-10]



(Source: Computed by reviewer)

In Study MD-10 site 17 provides the strongest support for efficacy. Removing this site would result in a p-value for the treatment term in the MMRM analysis of p = 0.0810. Sites 22 and 4 are the second and third most impactful sites. Without data from site 22 the p-value for the treatment coefficient would increase to 0.0502.

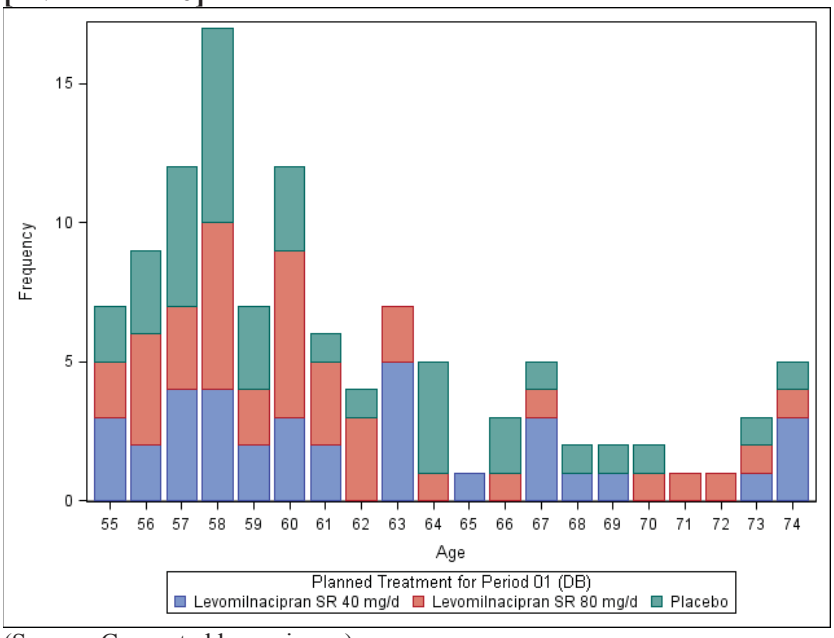
Figure A4a: Age Distribution for Participants 55 Years of Age and Older – ITT Population [LVM-MD-01]



(Source: Computed by reviewer)

There were 47 participants between 60 and 65 years of age in Study LVM-MD-01. The oldest participant in the ITT population in this study was 65 years.

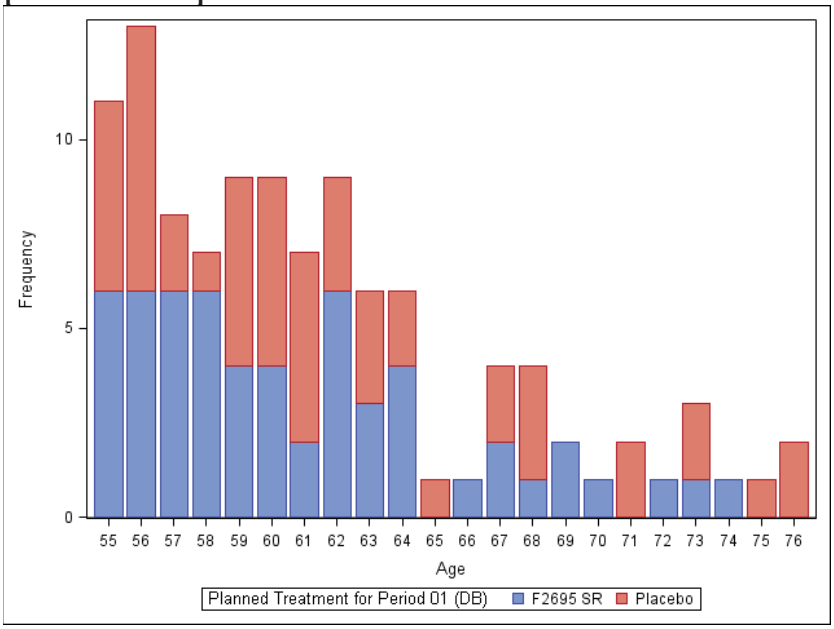
Figure A4b: Age Distribution for Participants 55 Years of Age and Older – ITT Population [LVM-MD-10]



(Source: Computed by reviewer)

In Study LVM-MD-10 there were 59 participants between 60 and 74 years of age. Of those 25 participants were 65 years of age or older. The oldest person in the ITT population was 74 years of age.

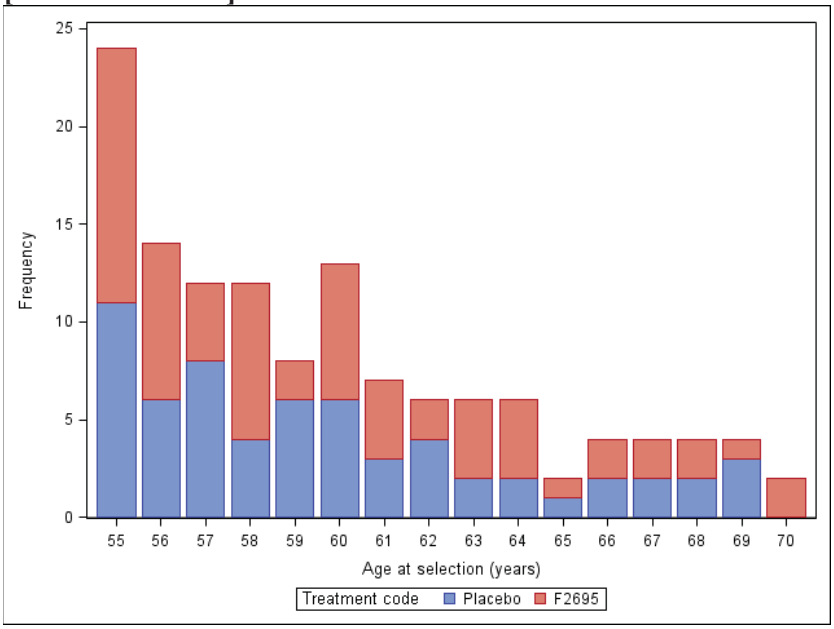
Figure A4c: Age Distribution for Participants 55 years of Age and Older – ITT Population [LVM-MD-03]



(Source: Computed by reviewer)

Study LVM-MD-03 had 108 participants 55 years or older, 60 participants 60 years or older, and 23 participants 65 years of age or older. The oldest person in the ITT population was 76 years.

Figure A4d: Age Distribution for Participants 55 Years of Age and Older – ITT Population [F02695 LP 2 02]



(Source: Computed by reviewer)

Table A5a: Summary of Change from Baseline to Endpoint in the MADRS Total Score for Patients ≥60 Years of Age (MMRM*) – ITT Population [LVM-MD-01]

Age (N)	LS Mean Change from Baseline (SE)			
	Placebo	Levomilnacipran 40 mg/day	Levomilnacipran 80 mg/day	Levomilnacipran 120 mg/day
≥60 (47)	-9.4 (6.16)	-16.8 (3.99)	-20.9 (4.51)	-13.4 (4.69)

(Source: Computed by reviewer)
*Primary MMRM model

Study LVM-MD-01 did not enroll patients older than 65. The results based on the 47 subjects older than 60 years of age indicate a benefit of treatment with levomilnacipran.

Table A5b: Summary of Change from Baseline to Endpoint in the MADRS Total Score by Age Group for Patients ≥60 Years of Age (MMRM*) – ITT Population [LVM-MD-10]

Age (N)	LS Mean Change from Baseline (SE)		
	Placebo	Levomilnacipran 40 mg/day	Levomilnacipran 80 mg/day
≥60 (59)	-13.4 (2.32)	-15.3 (2.20)	-13.9 (2.18)
≥65 (25)	-15.5 (2.54)	-16.3 (2.37)	-7.1 (2.93)
≥70 (12)	-18.6 (6.27)	-15.0 (5.23)	-0.8 (6.18)

(Source: Computed by reviewer)
*Modified primary MMRM model (deleted "pooled site variable" due to convergence issues)

A trend favoring levomilnacipran is noted for Study LVM-MD-10 when considering all patients equal or greater 60 years of age in this trial, but this trend disappears when the age limit is increased to patients equal/greater 65 or 70 years of age. There is some indication that the lower dose provides a greater benefit compared to the higher dose, with placebo competing with the lower dose. Those findings are based on a small sample size, but they do not support an efficacy claim for patients age 65 and older.

Table A5c: Summary of Change from Baseline to Endpoint in the MADRS Total Score by Age Group for Patients ≥60 Years of Age (MMRM*) – ITT Population [LVM-MD-03]

Age (N)	LS Mean Change from Baseline (SE)	
	Placebo	Levomilnacipran 40-120 mg/day
≥60 (60)	-10.8 (1.75)	15.2 (1.81)
≥65 (23)	-7.4 (2.90)	-16.9 (3.29)
≥70 (11)	-4.9 (2.78)	-17.8 (3.63)

(Source: Computed by reviewer)
*Modified primary MMRM model (deleted "pooled site variable" due to convergence issues)

Opposite of what was noted for Study LVM-MD-10 the results in the flexible dose study (LVM-MD-03) for patients 60 years of age and above trend consistently in favor of levomilnacipran 40-120 mg/day when considering consecutively older groups of patients.

Table A5d: Summary of Change from Baseline to Endpoint in the MADRS Total Score by Age Group for Patients ≥60 Years of Age (MMRM*) – ITT Population [F02695 LP 2 02]

Age (N)	LS Mean Change from Baseline (SE)	
	Placebo	Levomilnacipran 75-100 mg/day
≥60 (58)	-14.5 (1.80)	-18.8 (1.71)
≥65 (20)	-17.1 (2.69)	-18.4 (2.90)

(Source: Computed by reviewer)
*Modified primary MMRM model (deleted "grouped centre variable" due to convergence issues). Also, there are two patients 70 years of age and both on levomilnacipran. They are not shown within a separate age category.

The results of the flexible dose Phase 2 study trend in favor of levomilnacipran but the sample size is very small for patients 65 and older.

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/s/

THOMAS BIRKNER
06/14/2013

PEILING YANG
06/14/2013
I concur with the review.

HSIEN MING J HUNG
06/14/2013

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 204-168
Drug Name:	F2695 (Levomilnacipran HCL)
Indication(s):	104 Week Rat and 26 Week Mouse Carcinogenicity Studies
Applicant:	**Sponsor:** (b) (4) [redacted]
	Testing Facility: (b) (4) [redacted]
Documents Reviewed:	Electronic submission: Submission date 9/25/2012 Electronic data: Submission date 9/25/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products
Reviewing Pharmacologist:	Arippa Ravindran, Ph.D.
Project Manager:	Juliette T. Toure
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of F2695 (Levomilnacipran HCL) when administered orally by gavage once daily at appropriate drug levels in rats for 104 weeks and in mice for 26 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Ravindran.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two identical vehicle control groups. Three hundred Sprague Dawley CD [Crl:CD®(SD)] rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 10, 30, and 90 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The controls received the vehicle (distilled water) by gavage.

Beginning in Week 45, the dose level administered to males at 90 mg/kg/day was reduced to 70 mg/kg/day. Beginning on Week 87 (Day 605), dosing was discontinued for females administered 90 mg/kg/day, and all surviving females at this dose level were sacrificed on Week 93 (Day 646).

During the administration period all rats were observed for morbidity, mortality, injury, and the availability of food and water twice daily. Beginning on Week 53, a third mortality check in the evening was also conducted. A detailed clinical examination of all animals was performed prior to randomization and weekly during the study. On occasions, clinical observations were made at unscheduled intervals. The observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and bizarre behavior. Palpation of tissue masses were performed monthly for the first 6 months and twice monthly thereafter.

Body weights for all rats were measured and recorded the day following receipt (Day -13) and prior to randomization (Day -1). During the study, the rats were weighed weekly during the study for the first 13 weeks and once every 4 weeks thereafter.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and was presented graphically. An overall test comparing all groups was conducted using a log-rank test. When this overall test was significant ($p < 0.05$), a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

Sponsor's findings: The sponsor's analysis showed 33%, 35%, 30%, 23%, and 43% survival of male rats and 37%, 38%, 35%, 27%, and 0% (27% for Week 93) survival of female rats in control 1, control 2, low, medium, and high dose groups, respectively. The sponsor concluded that the overall survival was generally

similar to that of controls for males at all dose levels. For females the overall survival was also similar to that of controls for dose of 10 and 30 mg/kg/day, but was statistically significantly decreased for dose of 90 mg/kg/day when compared to control 1, control 2, and the combined control groups.

The sponsor further concluded that there were no test article-related effects on cause of death/morbidity in either sex. All causes of death/morbidity were of the type commonly seen in this type of study in rats. The most common cause of death/morbidity was pituitary tumor or undetermined in both sexes and mammary tumor in females.

2.1.2. Tumor data analysis

Tumor incidence data were analyzed using both survival unadjusted and survival adjusted tests. The survival unadjusted tests were conducted using the Cochran-Armitage test, while the survival adjusted tests were conducted using the methods outlined in the paper of Peto et al. (1980). The pair wise comparisons of control groups with the treated groups were conducted using the Fisher's exact.

Adjustment for multiple testing: For the adjust for multiple testing, the sponsor used the method suggested in the draft FDA guidance for the carcinogenicity data analysis namely, the use of test levels of 0.005 for common tumors and 0.025 for rare tumors, respectively for dose response relationship tests, and the use of test levels of 0.01 for common tumors and 0.05 for rare tumors, respectively for pairwise comparisons. The common tumors were defined as tumors with historical background of 1% and rare otherwise.

Reviewer's comment: *The above mentioned multiple testing adjustment methods, given in the FDA guidance for the carcinogenicity data analysis, were suggested for submission with two long term (two year) studies in rats and mice. In the present submission the rat study was two years long and the mouse study was 6 months long. The application of the present rule in this submission may be slightly conservative. For submission with one long term study and one short or medium term study, the recommendation form the biometrics group for dose response relationship tests is to use test levels of 0.005 for common tumors and 0.025 rare tumors, respectively for long term study, and the use of test levels of 0.05 for all tumors for short or medium term study.*

Sponsor's findings: Sponsor's analyses did not show statistically significant positive dose response relationship among the treated groups, or higher tumor rates in the treated groups in any of the observed tumor types compared to the controls in either sex.

The sponsor's analysis, using both the survival unadjusted and survival adjusted tests, showed statistically significant negative dose response relationship for the incidence of benign pheochromocytoma in adrenal glands in male rats. The pairwise comparisons showed statistically significant decreased incidence of benign pheochromocytoma of the adrenal glands in the treaded groups compared to control 2 and combined control groups.

In female rats, both the survival unadjusted and survival adjusted tests showed statistically significant negative dose response relationship for the incidence of granular cell tumor of vagina and uterus. The survival unadjusted test showed statistically significant negative dose response relationship for the incidence of c-cell adenoma of the thyroid gland and adenoma of the pars distalis of the pituitary gland. The pairwise comparisons with control 1 showed statistically significant decreased incidence of c-cell adenoma of the thyroid gland at 30 mg/kg/day, adenoma of the pars distalis of the pituitary gland at 90 mg/kg/day. The pairwise comparisons with control 1 showed statistically significant decreased incidence of c-cell adenoma of the thyroid gland at 30 mg/kg/day, adenoma of the pars distalis of the pituitary gland at 90 mg/kg/day. Also

in female rats, the survival unadjusted test using the combined control showed statistically significant negative dose response relationship for the incidence of adenoma of the pars distalis of the pituitary gland. The pairwise comparisons using the combined control, showed statistically significant decreased incidence of this tumor type at 90 mg/kg/day.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. For combined control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed 35%, 35%, 30%, 23%, and 47% survival of male rats and 40%, 40%, 37%, 28%, and 0% survival of female rats in control 1, control 2, low, medium, and high dose groups, respectively. Tests showed statistically significant dose response relationship in mortality across treatment groups in female rats. The pairwise comparisons in female rats showed statistically significant increased mortality in the high dose group compared to the combined control.

Reviewer's comment: *There were some differences in the percentages of survivals in different treatment groups calculated by the sponsor and this reviewer. These differences are due to the fact that the following animals died due to natural reasons during the terminal sacrifice weeks. The sponsor did not count them with the terminally sacrificed animals, while this reviewer counted them with the terminally sacrificed animals.*

Animal Numbers Died Due to Natural Causes During Terminal Sacrifice Weeks

Treatment Group	*Control 1*	*Control 2*	*Low*	*Medium*	*High*
Male	*#1054*				*#1285*
Female	*#1373* *#1405*	*#1451*	*#1480*	*#1566*	

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of

the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

Multiple testing adjustment: Noting that present submission had a long term study in rats and a medium term study in mouse, the adjustment of multiple testing of dose response relationship was conducted using the division of biometrics recommendation, mentioned in the reviewers comment in section 2.1.2, i.e. for dose response relationship tests use test levels of α=0.005 for common tumors and α=0.025 for rare tumors in rat study and use test levels of α=0.05 for all tumors in mouse study. For pairwise comparisons of treated group with control use levels α=0.01 for common tumors and α=0.05 for rare tumors in the rat study and use α=0.05 for all tumor types in the mouse study.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Rats

							P_Value		
			Com C#	Low	Med	High	Dose	Com C	Com C	Com C
Sex	Organ Name	Tumor Name	N=120	N=60	N=60	N=60	Resp	vs. L	vs. M	vs. H
Male	skin, subcutis	LIPOMA	2	1	1	4	0.0468	0.6925	0.6682	0.1111

Com C: Combined Control

Based on the criteria of adjustment for multiple testing discussed above, none of the tested tumor types was considered to have statistically significant dose response relationship in either sex. The pairwise comparisons also did not show statistically significant increased incidence of any tumor types in any of the treated groups compared to the control.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and fifteen Tg.rasH2 mice of each sex were assigned randomly to the treated and vehicle control groups in equal size of 25 animals per group. The positive control group had 15 animals. The dose levels for treated groups were 15, 50 and 150 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle controls received the vehicle (sterile water for injection)

by gavage. Positive control animals were dosed via intraperitoneal (i.p.) injections of urethane in saline on Days 1, 3 and 5, at a dose level of 1000 mg/kg/day. A dose volume of 10 mL/kg body weight was used for all groups.

All mice were observed twice daily at least 6 hours apart for morbidity and mortality, and were observed for clinical signs of toxicity daily, within 2 hours after dosing. For the positive control animals, the cage side observations were performed on Days 1, 3, and 5 also within 2 hours after dose administration. In addition, detailed hands-on examinations were performed on all animals on Day 1 and weekly thereafter. Body weights of all animals were recorded on Day 1, weekly through week 13, and biweekly thereafter.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor presented a summary table of the mortalities of animals by sex. Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and was presented graphically. An overall test comparing all groups was conducted using the Wilcoxon test.

Sponsor's findings: The sponsor analysis showed 2, 7, 1, 0, and 1 death of male mice and 0, 8, 0, 0, and 1 death of female mice in vehicle control, positive control, low, medium, and high dose groups, respectively. The sponsor concluded that these deaths were not treatment related and the study drug did not increase mortality at the doses used in the study in either sex.

3.1.2. Tumor data analysis

The sponsor analyzed the tumor data using the method proposed by Peto et al. (1980) for dose response relationships and the Fisher exact test for pairwise comparisons of treated groups with control groups.

Adjustment for multiple testing: No adjustment for multiple testing was performed.

Sponsor's findings: The sponsor's analysis showed a statistically significant increase in the incidence of spleen hemangiosarcomas in the high dose group of male mice. There was no statistically significant increase in the incidence of any tumor in the female mice. There was a numerical increase in the combined incidence of hemangiomas and hemangiosarcomas in multiple organs in the high dose group of both male and female mice but did not reach statistical significance. The incidence of pulmonary tumors in vehicle and test article treated mice was comparable and fell within the historical control range established at (b) (4)

The sponsor's analysis further showed that in the positive control animals, there was a statistically significant increase in the incidence of pulmonary tumors (multiple adenomas and carcinomas) as well as a statistically significant increase in the incidence of splenic hemangiosarcomas when compared to the control mice.

3.2. Reviewer's analyses

Similar to the rat study, to verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data this reviewer used similar methods as he used for the

analysis of the rat data.

3.2.1. Survival analysis

The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals, for vehicle control, low, medium, and high dose groups, are given in Tables 25 and 5B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 2, 15, 1, 0, and 1 death of male mice, and 0, 15, 0, 0, and 1 death of female mice in vehicle control, positive control, low, medium, and high dose groups, respectively. Tests showed no statistically significant dose response relationship in mortality across vehicle control, low, medium, and high dose groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in the low, medium, and high dose groups compared to the vehicle control group in either sex. The positive control showed statistically significant increased mortality compared to any of the treated groups or vehicle control group.

Reviewer's comment: *The sponsor's calculation showed 7 and 8 deaths in the male and the female positive dose groups, while this reviewer's calculation showed 15 deaths in both the male and the female positive dose groups. These differences are due to the fact that prior to the scheduled terminal sacrifice (on Week 27), 7 and 8 male and female mice died due to natural causes and 8 and 7 male and female mice were interimly sacrificed due to their morbidity conditions. The sponsor listed the animals killed in the interim sacrifice as terminally sacrificed, while this reviewer listed them as dead before the terminal sacrificed.*

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumors are listed in Tables 6A and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of treated groups with control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Mice

							P-Value		
			Veh C#	Low	Med	High	Dose	Veh C	Veh C	Veh C
Sex	Organ Name	Tumor Name	N=25	N=25	N=25	N=25	Resp	vs. L	vs. M	vs. H
Male	spleen	hemangiosarcoma	1	0	1	5	0.0058*	0.5000	0.2551	0.0941
Female	spleen	hemangiosarcoma	0	1	0	3	0.0326*	0.5000	.	0.1173

Veh C: Vehicle Control

Based on the criteria of adjustment for multiple testing discussed in the rat data analysis section, the dose response relationship for the incidences of hemangiosarcoma in spleen in both sexes were considered to be statistically significant. The pairwise comparisons did not show statistically significant increase of splenic hemangiosarcoma or any other tested tumor types in any of the treated groups compared to the vehicle control.

The pairwise comparisons showed statistically significant increased incidence of lung and spleen tumors in the positive control group compared to the vehicle. The results of this analysis are given in table 7A and 7B in the appendix.

4. Evaluation of validity of the design of the mouse study

As has been noted, the tumor data analyses from the long term study in rats did not show statistically significant dose-response relationship or increased incidence in the treated groups in any of the tested tumor types. The medium term study in transgenic mice showed a significant dose response relationship in splenic hemangiosarcoma but did not show statistically significant increased incidence of splenic hemangiosarcoma or any other tumor types in any of the treated groups compared to the vehicle control. However, before drawing any conclusion regarding the non-carcinogenic potential of the study drug in rats, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with about fifty to sixty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field.

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

It should be noted that the above mentioned guidelines for study validity were suggested only for two year long

term studies. Hence these rules are not applicable for the present medium term transgenic mouse study.

We will now investigate the validity of the present rat carcinogenicity study, in the light of the above mentioned guidelines. The following is the summary of survival data of rats in the high dose groups:

Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	95%	80%	63%
Female	87%	50%	28%

Based on the survival criterion Haseman proposed, it may be concluded that enough rats were exposed to the high dose for a sufficient amount of time in both sexes.

The following table shows the percent difference in mean body weight gain in rats from the combined control, defined as:

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Combined Control

Male			Female		
10 mg	30 mg	90 mg	10 mg	30 mg	90 mg
7.15	0.21	-9.15	1.15	-9.13	N/A

Source: Tables 4 of sponsor's submission

Therefore, relative to the combined control the male and female rats in high dose group had slightly over 9% decrement in their body weight gain.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End# of the Experiment

	Comb Control	**10 mg**	**30 mg**	**90 mg**
Male	65%	70%	77%	53%
Female	60%	63%	72%	73%

 # End of the Experiment for Female high dose group was Week 93

This shows that the morality rate in the male high dose group was about 12% lower, but about 12% higher in the medium dose group compared to the combined control. In female rats the mortality in the high dose groups was 13% higher compared to the combined control. In female rats the mortality of medium dose group was also 12% higher compared to the combined control.

Thus, considering the mortality and body weight gain data of high and medium dose groups it can be concluded

that the used high dose level in rat study might have reached the MTD in both sexes. The used medium dose level may also be adequate. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of F2695 (Levomilnacipran HCL) when administered orally by gavage once daily at appropriate drug levels in rats for 104 weeks and in mice for 26 weeks.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two identical vehicle control groups. Three hundred Sprague Dawley CD [Crl:CD®(SD)] rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 10, 30, and 90 mg/kg/day. The controls received the vehicle (distilled water) by gavage.

Beginning in Week 45, the dose level administered to males at 90 mg/kg/day was reduced to 70 mg/kg/day. Beginning on Week 87 (Day 605), dosing was discontinued for females administered 90 mg/kg/day, and all surviving females at this dose level were sacrificed on Week 93 (Day 646).

During the administration period all rats were observed for morbidity, mortality, injury, and the availability of food and water twice daily. Beginning on Week 53, a third mortality check in the evening was also conducted. A detailed clinical examination of all animals was performed prior to randomization and weekly during the study. Palpation of tissue masses were performed monthly for the first 6 months and twice monthly thereafter.

Body weights for all rats were measured and recorded the day following receipt (Day -13) and prior to randomization (Day -1). During the study the rats were weighed weekly during the study for the first 13 weeks, then once every 4 weeks thereafter.

The tests showed statistically significant dose response relationship in mortality across treatment groups in female rats. The pairwise comparisons in female rats showed statistically significant increased mortality in the high dose group compared to the combined control. The tests did not show statistically significant positive dose response relationship in any of the observed tumor types. The pairwise comparisons also did not show statistically significant increased incidence of any tumor type in any of the treated groups compared to the combined control.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and fifteen Tg.rasH2 mice of each sex were assigned randomly to the treated and vehicle control groups in equal size of 25 animals per group. The positive control group had 15 animals. The dose levels for treated groups were 15, 50 and 150 mg/kg/day. The vehicle controls received the vehicle (Sterile Water for Injection) by gavage. Positive control animals were dosed via intraperitoneal (i.p.) injections of urethane in saline on Days 1, 3 and 5, at a dose level of 1000 mg/kg/day.

All mice were observed twice daily at least 6 hours apart for morbidity and mortality, and were observed for clinical signs of toxicity daily, within 2 hours after dosing. For the positive control animals, the cage side observations were performed on Days 1, 3, and 5 also within 2 hours after dose administration. In addition, detailed hands-on examinations were performed on all animals on Day 1 and weekly thereafter. Body weights of all animals were recorded on Day 1, weekly through week 13, and biweekly thereafter.

Tests showed no statistically significant dose response relationship in mortality across vehicle control, low, medium, and high dose groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in the low, medium, and high dose groups compared to the vehicle control group in either sex. The positive control showed statistically significant increased mortality compared to any of the treated groups or vehicle control group. Tests showed statistically significant dose response relationship in the incidences of hemangiosarcoma in spleen in both sexes. The pairwise comparisons did not show statistically significant increased splenic hemangiosarcoma or any other tested tumor types in any of the treated groups compared to the vehicle control.

The pairwise comparisons showed statistically significant increased incidence of lung and spleen tumors in the positive control group compared to the vehicle.

Evaluation of rat study design: From the mortality and body weight gain data it can be concluded that the used high dose level for rat study might have reached the MTD in both sexes. The used medium dose level may also be adequate. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Evaluation of mouse study design: Using the statistical criteria used for the long term rat study, no evaluation of the mouse study could be performed.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 204-168
Dr. Ravindran
Ms. Toure
Dr. Machado
Dr. Lin
Dr. Rahman
Ms. Patrician

6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Control 1		Control 2		Low		Medium		High	
Week	No. of Death	Cum. %#	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	5.00	4	6.67	5	8.33	6	10.00	3	5.00
53 - 78	13	26.67	7	18.33	15	33.33	14	33.33	9	20.00
79 - 91	12	46.67	12	38.33	13	55.00	12	53.33	10	36.67
92 - 104	11	65.00	16	65.00	9	70.00	14	76.67	10	53.33
Ter. Sac.	21	35.00	21	35.00	18	30.00	14	23.33	28	46.67
Total	N=60		N=60		N=60		N=60		N=60	

 # Cum. %: Cumulative percentage

Table 1B: Intercurrent Mortality Rate
Female Rats

	Control 1		Control 2		Low		Medium		High**	
Week	No. of Death	Cum. %*	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	3.33	2	3.33	3	5.00	3	5.00	8	13.33
53 - 78	14	26.67	9	18.33	16	31.67	15	30.00	22	50.00
79 - 91	12	46.67	15	43.33	10	48.33	14	53.33	13	71.67
92 - 104	8	60.00	10	60.00	9	63.33	11	71.67	1	73.33
Ter. Sac.	24	40.00	24	40.00	22	36.67	17	28.33	16	26.67
Total	N=60		N=60		N=60		N=60		N=60	

 # Cum. %: Cumulative percentage

**** Terminal sacrifice of animals in high dose group was held on Week 93**

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.2600
Homogeneity	Log-Rank	0.0737

#P-Values were calculated using data from Combined Control, Low. Medium, and High dose groups

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.0001
Homogeneity	Log-Rank	0.0007

#P-Values were calculated using data from Combined Control, Low. Medium, and High dose groups

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
adipose tissue,	HIBERNOMA	0	0	1	0	0.4030	.	0.3109	.
adrenal glands	ADENOMA, CORTICAL	4	2	1	0	0.9334	0.6320	0.4963	0.8253
	CARCINOMA, C-CELL	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	CARCINOMA, CORTICAL	1	2	1	0	0.7214	0.2353	0.5189	0.3492
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	PHEOCHROMOCYTOMA	28	4	4	5	0.9963	0.9917	0.9899	0.9936
bone marrow, fe	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	2	0	0.6822	0.5313	0.3727	0.5747
	PHEOCHROMOCYTOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
bone marrow, st	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	2	0	0.6822	0.5313	0.3727	0.5747
	PHEOCHROMOCYTOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
bone marrow, ti	LYMPHOMA	0	0	1	0	0.4030	.	0.3109	.
	PHEOCHROMOCYTOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
bone, sternum	PHEOCHROMOCYTOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
bone, tibia	CHONDROMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
brain	ASTROCYTOMA	4	0	2	1	0.6107	0.7837	0.6026	0.5678
	CARCINOMA, PARS DIST	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	CARCINOMA, PARS INTE	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	LYMPHOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	MIXED GLIOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
cavity, abdomin	FIBROMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	HEMANGIOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LIPOMA	0	0	0	1	0.2200	.	.	0.3492
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	SARCOMA, UNDIFFERENT	0	1	0	0	0.3980	0.3223	.	.
cavity, oral	CARCINOMA, SQUAMOUS	0	0	1	0	0.4000	.	0.3051	.
cavity, thoraci	CARCINOMA, C-CELL	0	0	1	0	0.4000	.	0.3051	.
	LIPOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	MESOTHELIOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	NEUROENDOCRINE TUMOR	1	0	0	0	0.5871	0.3140	0.3025	0.3465

Com C: Combined Control

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
cavity, thoraci	OSTEOSARCOMA	0	0	0	1	0.2239	.	.	0.3543
	PHEOCHROMOCYTOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
coagulating gla	LEIOMYOMA	0	0	0	1	0.2200	.	.	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
epididymides	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	MESOTHELIOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
esophagus	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
eyes	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	1	0	0.6942	0.5313	0.6728	0.5747
	MELANOMA, AMELANOTIC	1	0	1	0	0.4929	0.3167	0.5189	0.3492
gingiva	SCHWANNOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
harderian gland	CARCINOMA, SQUAMOUS	0	0	1	0	0.4000	.	0.3051	.
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
head	SCHWANNOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
heart	HEMANGIOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LIPOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LYMPHOMA	2	0	0	0	0.8307	0.5313	0.5153	0.5747
	SCHWANNOMA	2	0	0	0	0.8307	0.5313	0.5153	0.5747
joint, tibiofem	LYMPHOMA	0	0	1	0	0.4030	.	0.3109	.
kidneys	CARCINOMA, TUBULAR C	4	1	2	0	0.8779	0.5036	0.5915	0.8161
	HEMANGIOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LIPOSARCOMA	0	1	0	0	0.4000	0.3167	.	.
	LYMPHOMA	2	0	1	0	0.6942	0.5313	0.6728	0.5747
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
lacrimal glands	LYMPHOMA	2	0	1	0	0.6942	0.5313	0.6728	0.5747
large intestine	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
larynx	CARCINOMA, C-CELL	1	0	1	0	0.4901	0.3140	0.5153	0.3465
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465

Com C: Combined Control

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
liver	ADENOMA, HEPATOCELLU	3	2	0	2	0.5009	0.5142	0.6644	0.5777
	CARCINOMA, HEPATOCEL	1	1	1	0	0.6070	0.5313	0.5153	0.3465
	HEMANGIOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	2	0	0.6822	0.5313	0.3727	0.5747
	PHEOCHROMOCYTOMA	2	0	0	0	0.8331	0.5349	0.5189	0.5783
	SARCOMA, HISTIOCYTIC	2	0	0	0	0.8307	0.5313	0.5153	0.5747
lung	ADENOMA, BRONCHIOLAR	0	0	1	0	0.4030	.	0.3109	.
	CARCINOMA, C-CELL	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	CARCINOMA, CORTICAL	0	1	0	0	0.4000	0.3167	.	.
	CARCINOMA, SEBACEOUS	0	0	1	0	0.4030	.	0.3109	.
	HEMANGIOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	1	0	0.6942	0.5313	0.6728	0.5747
	PHEOCHROMOCYTOMA	2	0	0	0	0.8331	0.5349	0.5189	0.5783
	SARCOMA, HISTIOCYTIC	2	0	0	0	0.8307	0.5313	0.5153	0.5747
lymph node, ing	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
lymph node, man	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	2	0	0.6822	0.5313	0.3727	0.5747
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
lymph node, med	HEMANGIOSARCOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	0	0	2	0	0.4237	.	0.0985	.
	MESOTHELIOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
lymph node, mes	HEMANGIOSARCOMA	1	1	1	1	0.3616	0.5349	0.5189	0.5783
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
	PHEOCHROMOCYTOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
mammary gland	FIBROADENOMA	0	0	1	1	0.1308	.	0.3109	0.3543
mesentery/perit	ADENOCARCINOMA	0	1	0	0	0.3980	0.3223	.	.
multicentric ne	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	2	0	0.6822	0.5313	0.3727	0.5747
	SARCOMA, HISTIOCYTIC	2	0	0	1	0.5488	0.5313	0.5153	0.2753
nose, level a	ADENOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465

Com C: Combined Control

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
nose, level b	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
nose, level c	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
nose, level d	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
pancreas	ADENOCARCINOMA	0	1	0	0	0.3980	0.3223	.	.
	ADENOMA, ACINAR CELL	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	ADENOMA, ISLET CELL	12	5	5	6	0.5303	0.4754	0.4317	0.4560
	CARCINOMA, ACINAR CE	3	0	0	0	0.9311	0.6809	0.6644	0.7244
	CARCINOMA, ISLET CEL	7	2	2	0	0.9766	0.5729	0.5418	0.9521
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
parathyroid gla	ADENOMA	2	0	2	0	0.6817	0.5313	0.3520	0.5747
peyers patch	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
pharynx	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
pituitary gland	ADENOMA, PARS DISTAL	83	42	36	36	0.9305	0.5001	0.8391	0.8819
	CARCINOMA, PARS DIST	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	CARCINOMA, PARS INTE	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
preputial gland	ADENOCARCINOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
prostate gland	ADENOCARCINOMA	0	1	0	1	0.2150	0.3223	.	0.3543
	ADENOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	0	0	0.8307	0.5313	0.5153	0.5747
salivary gland,	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
seminal vesicle	ADENOCARCINOMA	0	1	0	2	0.0653	0.3223	.	0.1237
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465

Com C: Combined Control

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
skeletal muscle	ADENOCARCINOMA	0	1	0	0	0.3980	0.3223	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	1	0	1	0	0.4938	0.3167	0.5270	0.3492
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.2200	.	.	0.3492
skin	ADENOMA, BASAL CELL	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	ADENOMA, SEBACEOUS C	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	HAIR FOLLICLE TUMOR	3	1	0	0	0.9176	0.3681	0.6607	0.7209
	KERATOACANTHOMA	3	1	0	0	0.9193	0.3727	0.6644	0.7244
	PAPILLOMA, SQUAMOUS	0	1	2	0	0.5503	0.3167	0.0949	.
skin, subcutis	FIBROMA	6	2	3	4	0.3320	0.4859	0.5646	0.4922
	FIBROSARCOMA	2	0	1	1	0.4563	0.5313	0.6644	0.2823
	LIPOMA	2	1	1	4	0.0468	0.6925	0.6682	0.1111
	LIPOSARCOMA	0	0	1	1	0.1271	.	0.3051	0.3492
	LYMPHOMA	1	0	1	0	0.4911	0.3140	0.5234	0.3465
	OSTEOSARCOMA	0	1	0	0	0.3980	0.3223	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.2200	.	.	0.3492
	SARCOMA, UNDIFFERENT	0	0	1	1	0.1299	.	0.3051	0.3543
	SCHWANNOMA	1	0	0	1	0.3925	0.3167	0.3051	0.5783
small intestine	ADENOCARCINOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
spleen	HEMANGIOSARCOMA	2	0	0	0	0.8331	0.5349	0.5189	0.5783
	LEIOMYOSARCOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	LYMPHOMA	2	0	2	0	0.6822	0.5313	0.3727	0.5747
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
stomach, glandu	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
stomach, nongla	CARCINOMA, SQUAMOUS	0	0	1	0	0.4000	.	0.3051	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
testes	ADENOMA, INTERSTITIA	3	1	1	1	0.5862	0.3774	0.3566	0.4359
	LEUKEMIA, GRANULOCYT	0	0	1	0	0.4030	.	0.3109	.
	MESOTHELIOMA	1	0	0	0	0.5900	0.3167	0.3051	0.3492
thymus	LYMPHOMA	1	0	0	0	0.5871	0.3140	0.3025	0.3465
thyroid gland	ADENOMA, C-CELL	16	8	9	9	0.4478	0.5275	0.3476	0.5458
	ADENOMA, FOLLICULAR	1	2	0	2	0.2457	0.2353	0.3051	0.2861
	CARCINOMA, C-CELL	2	2	1	1	0.5340	0.3727	0.6644	0.2753
tongue	CARCINOMA, SQUAMOUS	0	0	1	0	0.4000	.	0.3051	.

Com C: Combined Control

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
trachea	CARCINOMA, C-CELL	1	0	1	0	0.4901	0.3140	0.5153	0.3465
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
urinary bladder	LYMPHOMA	2	0	0	0	0.8307	0.5313	0.5153	0.5747
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5871	0.3140	0.3025	0.3465
zymbal`s gland	CARCINOMA, SEBACEOUS	0	0	1	0	0.4030	.	0.3109	.

Com C: Combined Control

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
adrenal glands	ADENOMA, CORTICAL	5	2	1	0	0.9350	0.3919	0.5984	0.8041
	PHEOCHROMOCYTOMA	10	2	1	0	0.9961	0.8059	0.8959	0.9644
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
bone marrow, fe	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	2	0	0	0	0.8109	0.5359	0.5129	0.4716
bone marrow, st	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
bone marrow, ti	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
bone, tibia	OSTEOSARCOMA	0	0	1	0	0.3628	.	0.3089	.
brain	ASTROCYTOMA	2	0	1	0	0.6306	0.5394	0.6736	0.4745
	CARCINOMA, PARS DIST	5	2	2	1	0.6846	0.3919	0.3660	0.5377
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
cavity, abdomin	LEIOMYOSARCOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	SARCOMA, HISTIOCYTIC	0	0	0	1	0.1674	.	.	0.2794
cavity, thoraci	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
clitoral glands	ADENOCARCINOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	CARCINOMA, SQUAMOUS	0	0	1	0	0.3656	.	0.3089	.
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5664	0.3200	0.3033	0.2741
eyes	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
heart	ADENOCARCINOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
kidneys	ADENOMA, TUBULAR CEL	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	CARCINOMA, TUBULAR C	1	0	0	0	0.5639	0.3175	0.3008	0.2721
	LIPOSARCOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	NEPHROBLASTOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	SARCOMA, HISTIOCYTIC	1	0	0	1	0.3062	0.3175	0.3008	0.4793
liver	ADENOMA, HEPATOCELLU	0	0	0	1	0.1637	.	.	0.2741
	CARCINOMA, ISLET CEL	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	LEUKEMIA, LARGE GRAN	2	0	0	0	0.8131	0.5394	0.5163	0.4745
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	PHEOCHROMOCYTOMA	2	0	0	0	0.8131	0.5394	0.5163	0.4745
	SARCOMA, HISTIOCYTIC	1	0	0	1	0.3062	0.3175	0.3008	0.4793
lung	ADENOCARCINOMA	2	0	0	1	0.4481	0.5359	0.5129	0.6207
	ADENOMA, BRONCHIOLAR	0	1	0	0	0.3612	0.3254	.	.

Com C: Combined Control

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
lung	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	OSTEOSARCOMA	0	0	1	0	0.3628	.	0.3089	.
	PHEOCHROMOCYTOMA	2	0	0	0	0.8131	0.5394	0.5163	0.4745
	SARCOMA, HISTIOCYTIC	1	0	0	1	0.3062	0.3175	0.3008	0.4793
lymph node, ing	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5664	0.3200	0.3033	0.2741
lymph node, man	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
lymph node, med	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
lymph node, mes	LEIOMYOSARCOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
mammary gland	ADENOCARCINOMA	36	12	19	15	0.2845	0.8393	0.3241	0.4844
	ADENOMA	4	3	5	1	0.4850	0.4106	0.1091	0.4300
	CARCINOSARCOMA	0	1	0	0	0.3628	0.3200	.	.
	FIBROADENOMA	57	27	24	17	0.9690	0.6277	0.7373	0.9532
multicentric ne	LEUKEMIA, LARGE GRAN	2	0	0	0	0.8131	0.5394	0.5163	0.4745
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	2	1	0	1	0.4954	0.6856	0.5129	0.6259
nose, level a	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
nose, level b	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
nose, level c	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
nose, level d	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
ovaries	CYSTADENOMA	0	1	0	0	0.3628	0.3200	.	.
	GRANULOSA CELL TUMOR	0	1	0	0	0.3628	0.3200	.	.
	LUTEOMA	0	0	1	0	0.3628	.	0.3089	.
	SEX-CORD/STROMAL TUM	1	0	0	0	0.5664	0.3200	0.3033	0.2741
pancreas	ADENOMA, ISLET CELL	4	2	0	1	0.7166	0.6217	0.7661	0.4143
	CARCINOMA, ISLET CEL	4	1	0	0	0.9502	0.5096	0.7661	0.7270
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
parathyroid gla	ADENOMA	1	0	0	1	0.3074	0.3200	0.3033	0.4822
	CARCINOMA, C-CELL	2	0	0	0	0.8131	0.5394	0.5163	0.4745
pituitary gland	ADENOMA, PARS DISTAL	96	47	41	35	0.9208	0.6346	0.8665	0.8644

Com C: Combined Control

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Com C N=120	10 mg Low N=60	30 mg Med N=60	70 mg High N=60	P_Value Dose Resp	P_Value Com C vs. L	P_Value Com C vs. M	P_Value Com C vs. H
pituitary gland	ADENOMA, PARS INTERM	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	CARCINOMA, PARS DIST	5	2	2	1	0.6846	0.3919	0.3660	0.5377
	PITUICYTOMA, PARS NE	0	0	1	0	0.3628	.	0.3089	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
skin	ADENOMA, BASAL CELL	0	0	0	1	0.1674	.	.	0.2794
	CARCINOMA, SQUAMOUS	0	1	0	0	0.3612	0.3200	.	.
	PAPILLOMA, SQUAMOUS	2	0	0	0	0.8131	0.5394	0.5163	0.4745
skin, subcutis	FIBROMA	2	2	0	0	0.8524	0.3834	0.5163	0.4745
	FIBROSARCOMA	2	1	3	1	0.3174	0.6966	0.1707	0.6207
	LIPOMA	0	0	0	1	0.1674	.	.	0.2794
	OSTEOSARCOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	SARCOMA, HISTIOCYTIC	1	1	0	0	0.6358	0.5394	0.3033	0.2741
small intestine	ADENOCARCINOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
spinal cord, ce	ASTROCYTOMA	0	0	1	0	0.3656	.	0.3089	.
spleen	LEUKEMIA, LARGE GRAN	2	0	0	0	0.8131	0.5394	0.5163	0.4745
	LYMPHOMA	0	0	1	0	0.3656	.	0.3089	.
	MESOTHELIOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	SARCOMA, HISTIOCYTIC	1	0	0	1	0.3062	0.3175	0.3008	0.4793
stomach, nongla	PAPILLOMA, SQUAMOUS	1	0	0	0	0.5664	0.3200	0.3033	0.2741
thymus	THYMOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
thyroid gland	ADENOMA, C-CELL	17	5	2	3	0.9554	0.7619	0.9647	0.8629
	ADENOMA, FOLLICULAR	0	2	2	0	0.4905	0.1006	0.0972	.
	CARCINOMA, C-CELL	3	0	0	0	0.9199	0.6892	0.6655	0.6207
	CARCINOMA, FOLLICULA	1	0	1	0	0.4216	0.3200	0.5163	0.2741
tongue	CARCINOMA, SQUAMOUS	1	0	0	0	0.5664	0.3200	0.3033	0.2741
urinary bladder	PAPILLOMA, TRANSITIO	0	0	0	1	0.1637	.	.	0.2741
uterus with cer	GRANULAR CELL TUMOR	7	1	1	0	0.9762	0.7866	0.7663	0.9001
	LEIOMYOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741
	LEIOMYOSARCOMA	1	0	1	0	0.4216	0.3200	0.5163	0.2741
	POLYP, STROMAL	7	3	1	2	0.7021	0.4110	0.7554	0.4837
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.5639	0.3175	0.3008	0.2721
	SARCOMA, STROMAL	1	0	0	1	0.3074	0.3200	0.3033	0.4822
vagina	GRANULAR CELL TUMOR	8	3	2	0	0.9753	0.4914	0.6493	0.9290
	LEIOMYOSARCOMA	1	0	0	0	0.5664	0.3200	0.3033	0.2741

Com C: Combined Control

Table 4A: Intercurrent Mortality Rate in Male Mice

	Veh Cont#		Pos Cont#		Low		Medium		High	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 10	.	.	.	.	1	4.00	.	.	1	4.00
11 - 20	.	.	15	100.00	.	.	.	.	.	.
21 - 26	2	8.00	.	.	.	.	.	.	.	.
Ter. Sac.	23	92.00	.	.	24	96.00	25	100.00	24	96.00
Total	N=25		N=15		N=25		N=25		N=25	

Veh Cont: Vehicle Control and Pos Cont: Positive Control

Table 4B: Intercurrent Mortality Rate Female Mice

	Veh Cont#		Pos Cont#		Low		Medium		High	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
11 - 20	.	.	15	100.00	.	.	.	.	.	.
21 - 26	.	.	.	.	.	.	.	.	1	4.00
Ter. Sac.	25	100.00	.	.	25	100.00	25	100.00	24	96.00
Total	N=25		N=15		N=25		N=25		N=25	

Veh Cont: Vehicle Control and Pos Cont: Positive Control

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value#
Dose-Response	Likelihood Ratio	0.6584
Homogeneity	Log-Rank	0.5723

#P-Values were calculated using data from Vehicle Control, Low. Medium, and High dose groups

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value#
Dose-Response	Likelihood Ratio	0.0959
Homogeneity	Log-Rank	0.3916

#P-Values were calculated using data from Vehicle Control, Low. Medium, and High dose groups

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Mice

Organ Name	Tumor Name	0 mg Veh C# N=25	15 mg Low N=25	50 mg Med N=25	150 mg High N=25	P_Value Dos Resp	P_Value Veh C vs. L	P_Value Veh C vs. M	P_Value Veh C vs. H
harderian gland	adenoma	1	1	0	0	0.8170	0.7553	0.5102	0.5000
lungs with bron	alveolar-bronchiolar	3	1	3	1	0.7363	0.6957	0.3535	0.6957
perineum	papilloma	1	0	0	0	0.7526	0.5000	0.5102	0.5000
spleen	hemangiosarcoma	1	0	1	5	0.0058*	0.5000	0.2551	0.0941

#Veh C: Vehicle Control

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0 mg Veh C# N=25	15 mg Low N=25	50 mg Med N=25	150 mg High N=25	P_Value Dos Resp	P_Value Veh C vs. L	P_Value Veh C vs. M	P_Value Veh C vs. H
cavity, nasal	hemangiosarcoma	0	1	0	0	0.4949	0.5000	.	.
harderian gland	adenoma	2	1	0	1	0.6180	0.5000	0.7551	0.4844
	carcinoma	1	0	0	0	0.7475	0.5000	0.5000	0.4898
lungs with bron	alveolar-bronchiolar	0	1	1	0	0.4898	0.5000	0.5000	.
perineum	hemangiosarcoma	0	0	0	1	0.2424	.	.	0.4898
	papilloma	0	1	1	0	0.4898	0.5000	0.5000	.
salivary glands	adenocarcinoma	0	0	1	0	0.2424	.	0.5000	.
	hemangioma	0	0	1	0	0.2424	.	0.5000	.
spleen	hemangiosarcoma	0	1	0	3	0.0326*	0.5000	.	0.1173
thymus	thymoma	3	1	2	1	0.7256	0.6954	0.5000	0.6798
uterus	deciduoma	0	0	0	1	0.2424	.	.	0.4898
	sarcoma	0	0	1	0	0.2424	.	0.5000	.

#Veh C: Vehicle Control

Table 7A: Pairwise Comparisons of Positive Control and Vehicle Groups
Male Mice

Organ Name	Tumor Name	Veh C# N=25	Pos C# N=15	P-Value Veh C vs. Pos C
harderian gland	adenoma	1	0	0.1429
lungs with bron	alveolar-bronchiolar adenoma	3	15	<0.001*
	alveolar-bronchiolar carcinoma	0	8	<0.001*
	hemangiosarcoma	0	7	<0.001*
perineum	papilloma	1	0	0.1429
spleen	hemangiosarcoma	1	14	<0.001*

#Veh C: Vehicle Control; Pos C: Positive Control

Table 7B: Pairwise Comparisons of Positive Control and Vehicle Groups
Female Mice

Organ Name	Tumor Name	Veh C# N=25	Pos C# N=15	P-Value Veh C vs. Pos C
cavity, nasal	hemangiosarcoma	0	0	.
harderian gland	adenoma	2	0	0.2611
	carcinoma	1	0	0.1379
lungs with bron	alveolar-bronchiolar adenoma	0	15	<0.001*
	alveolar-bronchiolar carcinoma	0	11	<0.001*
perineum	papilloma	0	0	.
salivary glands	adenocarcinoma	0	0	.
	hemangioma	0	0	.
spleen	hemangiosarcoma	0	15	<0.001*
thymus	thymoma	3	0	0.3706
uterus	sarcoma	0	0	.

#Veh C: Vehicle Control; Pos C: Positive Control

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

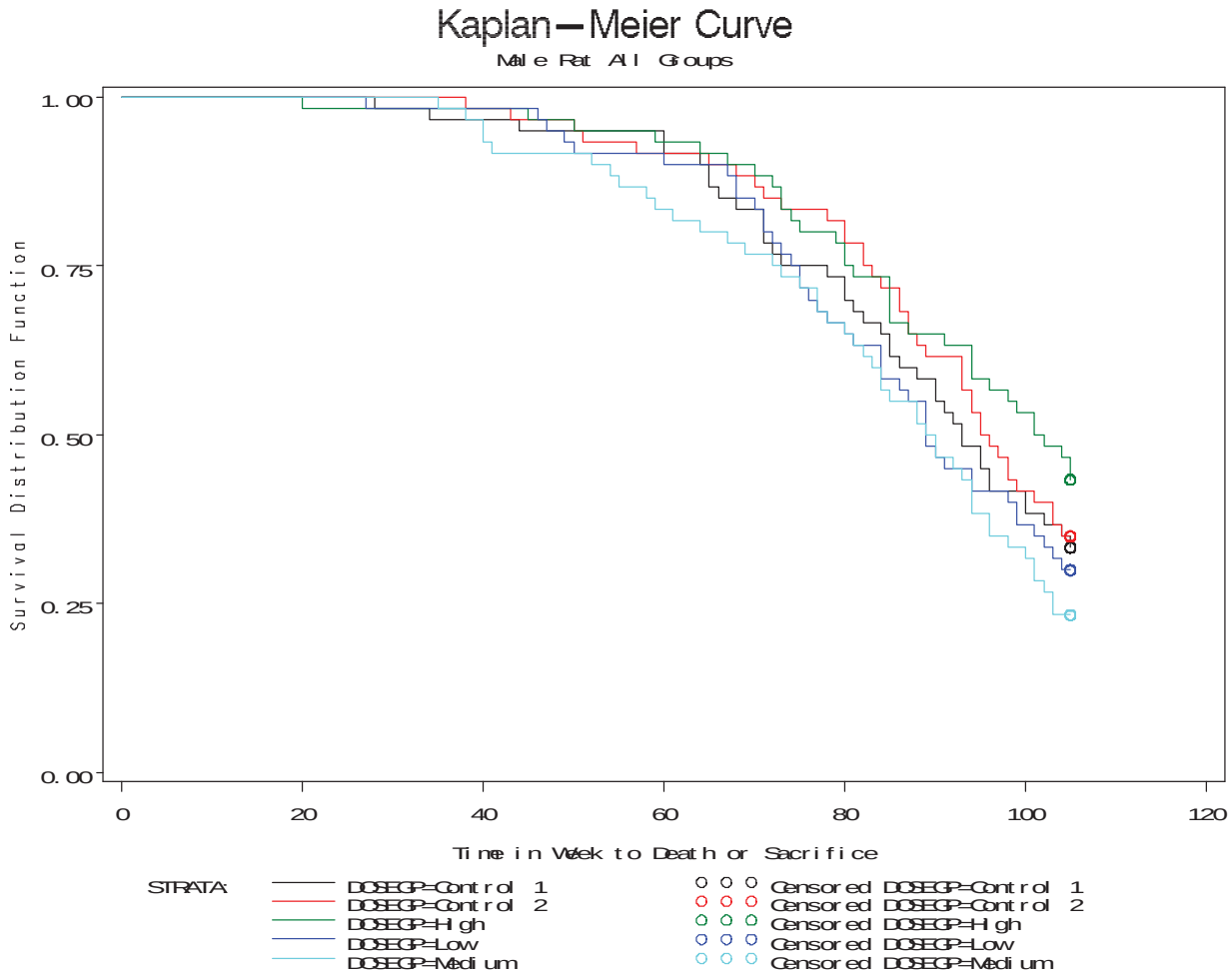


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

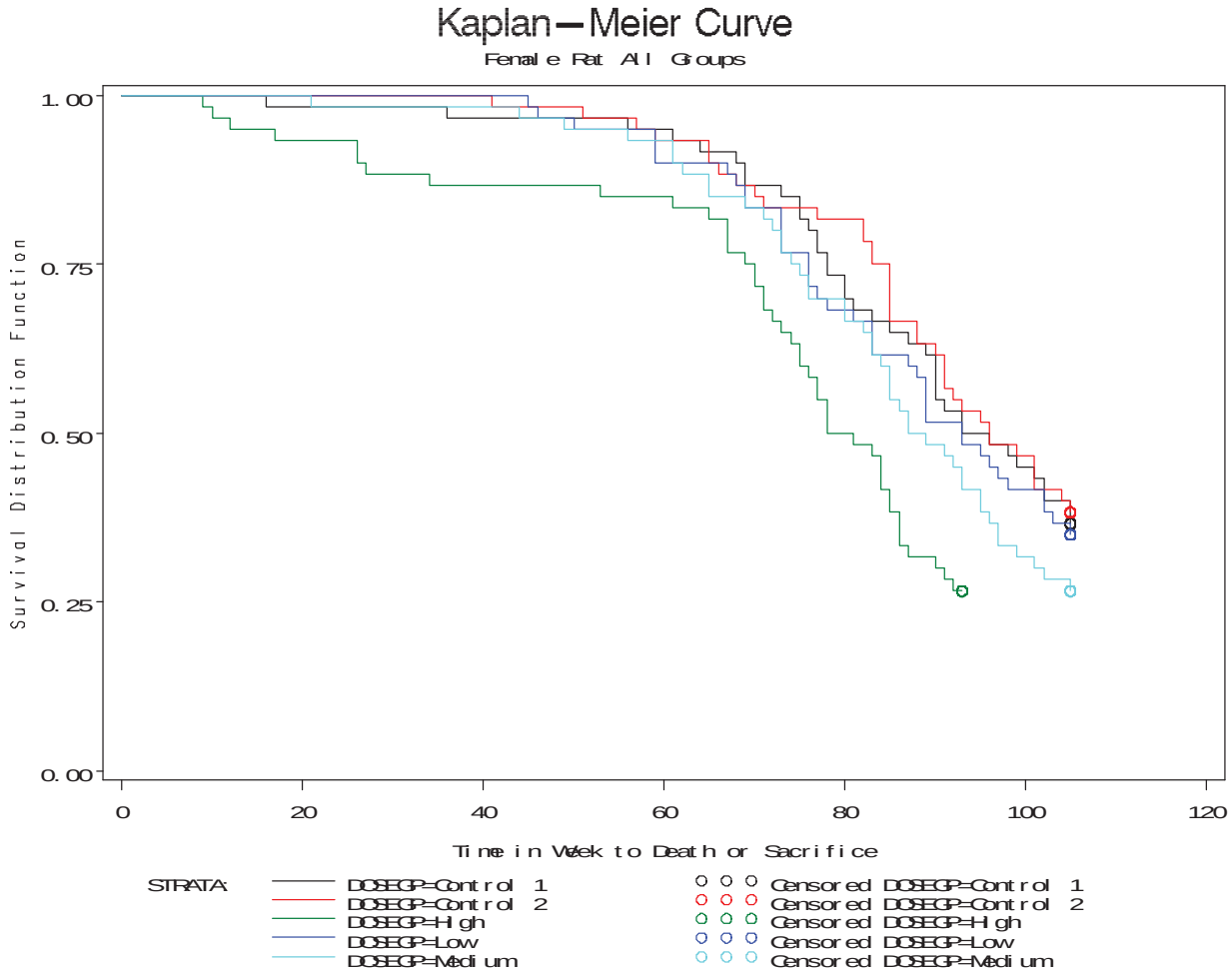


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

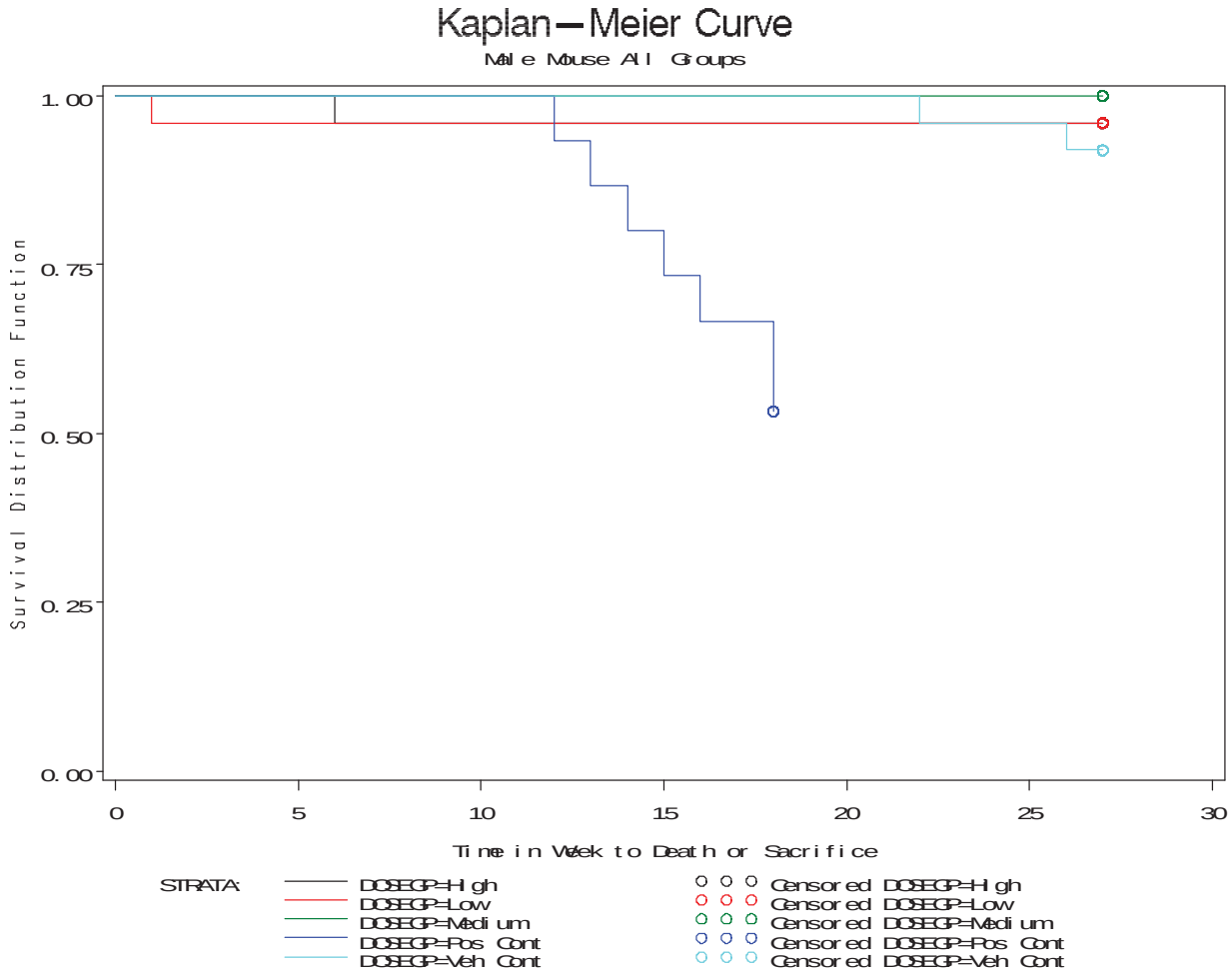
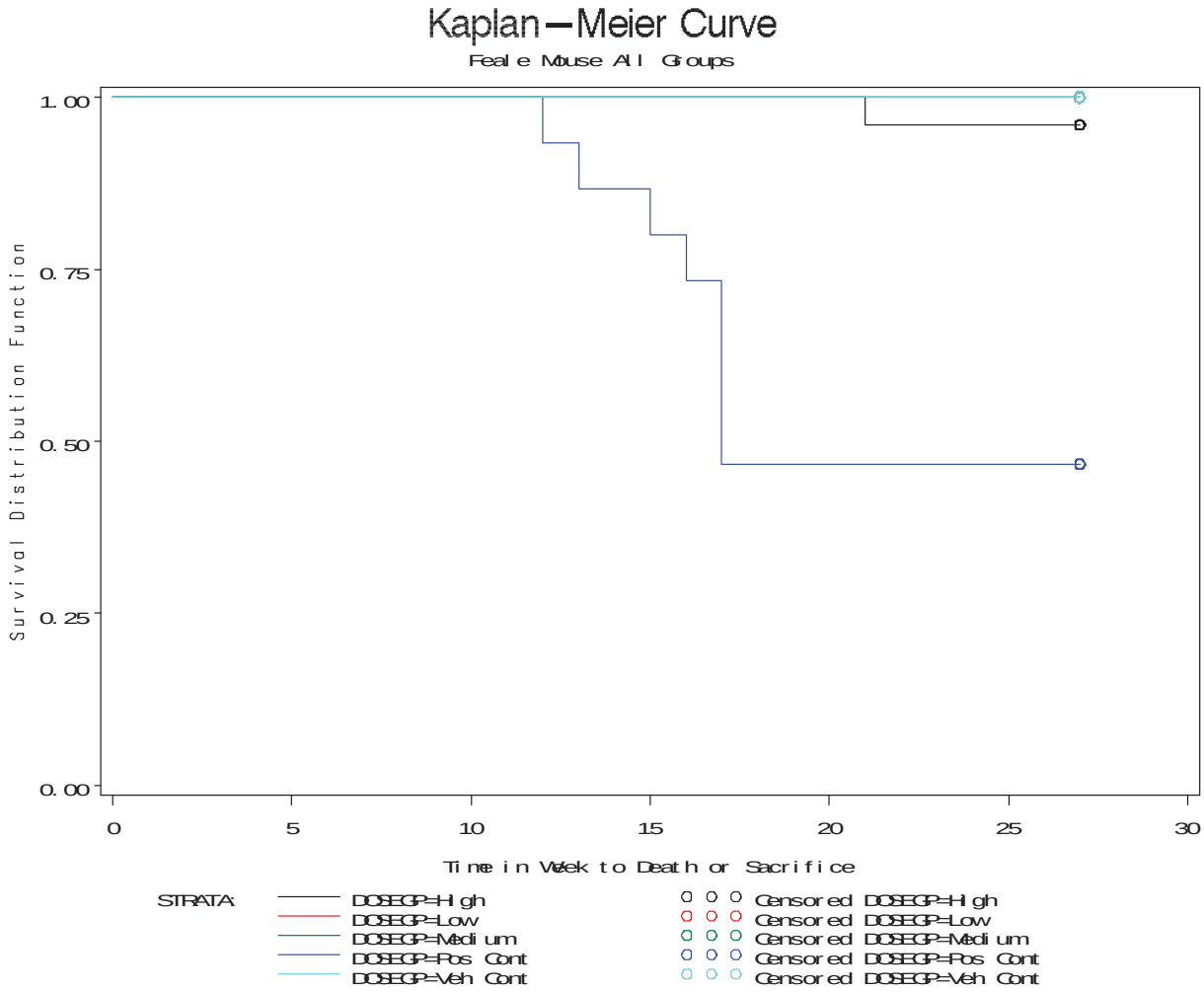


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

MOHAMMAD A RAHMAN
03/19/2013

KARL K LIN
03/19/2013
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204168 **Applicant:** Forest **Stamp Date:** 09/25/2012

Drug Name: levomilnacipran HCl sustained-release **NDA/BLA Type:** original 505 b(1)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Thomas Birkner	11/06/2012
Reviewing Statistician	Date
Peiling Yang	11/06/2012
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

THOMAS BIRKNER
11/06/2012

PEILING YANG
11/06/2012