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/BLA #:	NDA 021992
Supplement #:	S-042
Drug Name:	Pristiq® (Desvenlafaxine)
Indication(s):	Major depression
Applicant:	Pfizer, Inc.
Date(s):	Receipt Date: April 6, 2017
	PDUFA Date: Feburary 6, 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Yang (Kelly) Yang, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D. Team Leader
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1 EXECUTIVE SUMMARY

Study B2061014 randomized 340 subjects in a ratio 1:1:1 to DVS SR, fluoxetine, or placebo. The primary endpoint was the change from baseline to Week 8 in the CDRS-R total score. A partial-blinded sample size recalculation was performed based on the primary endpoint at 75% of the initially planned enrollment. This trial showed sufficient power at the interim analysis, so sample size was not increased. Despite the sufficient power to detect a 5-point difference of treatment effect in CDRS-R total score, the study did not demonstrate efficacy of both DVS SR and fluoxetine over placebo in children and adolescent subjects with major depression disorders. Neither DVS SR nor fluoxetine met the primary objective in this trial.

Study 2061032 randomized 363 subjects in a ratio 1:1:1 to placebo, DVS SR low dose, or DVS SR high dose. The primary endpoint was the change from baseline to Week 8 in the CDRS-R total score. A partial-blinded sample size recalculation was performed based on the primary endpoint at 75% of the initially planned enrollment. As a result, the sample size was increased by 9 subjects per arm. Despite the increased sample size to assure the sufficient power to detect a 5-point difference in CDRS-R score, the study did not demonstrate efficacy of both DVS SR low dose and high dose over placebo in children and adolescent subjects with major depression disorders. Neither DVS SR dose met the primary objective in this trial.

However, from a statistical perspective, both studies were adequately powered, so this reviewer considers that this submission satisfies pediatric Written Request, particularly the magnitude of the drug effect appears very small (see Table 3 and Table 6).

2 INTRODUCTION

2.1 Overview

Reference is made to the original NDA for the use of Pristiq® (Desvenlafaxine, DVS SR) as a treatment of Major Depressive Disorder (MDD) in adult patients, which was approved in 2008. The sponsor submitted this sNDA as a Prior Approval Supplement Submission to satisfy the Written Request for pediatric patients with ages 7 to 17 years (children and adolescents). This sNDA includes two Phase 3, 8-week, multicenter, randomized, parallel, double-blind, placebo-controlled studies. One study (B2061014) is designed to evaluate the efficacy of DVS SR compared with placebo with fluoxetine-referenced. The other study (B2061032) is designed to evaluate the efficacy and safety of 2 exposure levels of DVS SR with placebo.

The original protocol of this study was reviewed under IND 64552.

Table 1: List of All Studies Included in Analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
B2061014	*Phase 3*	*8 weeks*	*4 weeks*	*112 subjects in placebo, 115 subjects in DVS SR, and 113 subjects in Fluoxetine*	*child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with MDD*
B2061032	*Phase 3*	*8 weeks*	*4 weeks*	*120 subjects in placebo, 121 subjects in DVS SR high dose, and 122 subjects in DVS SR low dose*	*child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with MDD*

[Source: reviewer's table]

2.2 Data Sources

The datasets for Study B2061014 is located at
\\CDSESUB1\evsprod\NDA021992\0330\m5\datasets\b2061014\analysis\adam\datasets

The datasets for Study B2061032 is located at
\\CDSESUB1\evsprod\NDA021992\0330\m5\datasets\b2061032\analysis\adam\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. This reviewer found the quality of their submissions acceptable and was able to replicate the primary results from the sponsor's Clinical Study Report (CSR).

3.2 Evaluation of Efficacy

3.2.1 Study B2061014

3.2.1.1 Study Design and Endpoints

B2061014 was a Phase 3, multicenter, randomized, double-blind, placebo controlled, fluoxetine-referenced parallel-group study of DVS SR in the treatment of child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with MDD. The study was conducted at 37 centers in the United States and Mexico.

The study was comprised of a screening phase of up to 4 weeks, a double-blind treatment period for 8 weeks, a 1-week double-blind taper or transition phase and a 4-week follow-up phase. Following the screening period, subjects who continue to meet entry criteria were randomly assigned to 1 of 3 double-blind treatment arms: DVS SR, fluoxetine, or placebo (1:1:1 ratio). The randomization was stratified by age (children [baseline age 7-11 years] and adolescents [baseline age 12-17 years] at 1:1 ratio) and country.

The primary efficacy endpoint was the change from baseline to Week 8 in the CDRS-R total score, which is the sum of all 17 items on the scale with a score ranging from 17 to 113 and lower total scores indicating lower intensity of symptoms. The key secondary outcome measure was the change from baseline to Week 8 in the CGI-S score. The CGI-S score ranges from 1 to 7 with 1 representing "Normal, not at all ill" and representing "Among the most extremely ill patients." Both the primary efficacy endpoint and the key secondary outcome were measured at screening, at baseline (Day 1) and in Weeks 1, 2, 3, 4, 6, and 8.

3.2.1.2 Statistical Methodologies

The sample size calculation was based on the CDRS-R total score, assuming a standard deviation (SD) of 12. A total of 105 subjects randomized to each treatment arm was considered to be sufficient to demonstrate a difference of 5 points (CDRS-R score) between the DVS SR and placebo treatment groups, at a significance level of 5% and a power of 85%. An upward adjustment of approximately 5% was assumed to compensate for subjects who failed to qualify for the intent-to-treat (ITT) analysis. Thus, a total sample of approximately 333 subjects (111 subjects per group) was randomly assigned to each of the three treatment arms.

The primary analysis was conducted on the change from baseline in the CDRS-R total score at Week 8 (primary time point) based on the ITT population. A mixed-effects model for repeated measures (MMRM) was used with treatment, week, interaction of treatment and week, age group, and gender as fixed effects and the baseline CDRS-R total score as a covariate. Data from Weeks 1, 2, 3, 4, 6, and 8 were used.

The primary and secondary efficacy analyses all used the MMRM Method. In addition to the model-based missing data approach of the MMRM model, the primary and secondary efficacy analyses were all analyzed using an ANCOVA models based on the last observation carried forward (LOCF), an ANCOVA model based on the observed cases (OC), and a pattern-mixture model as sensitivity analyses.

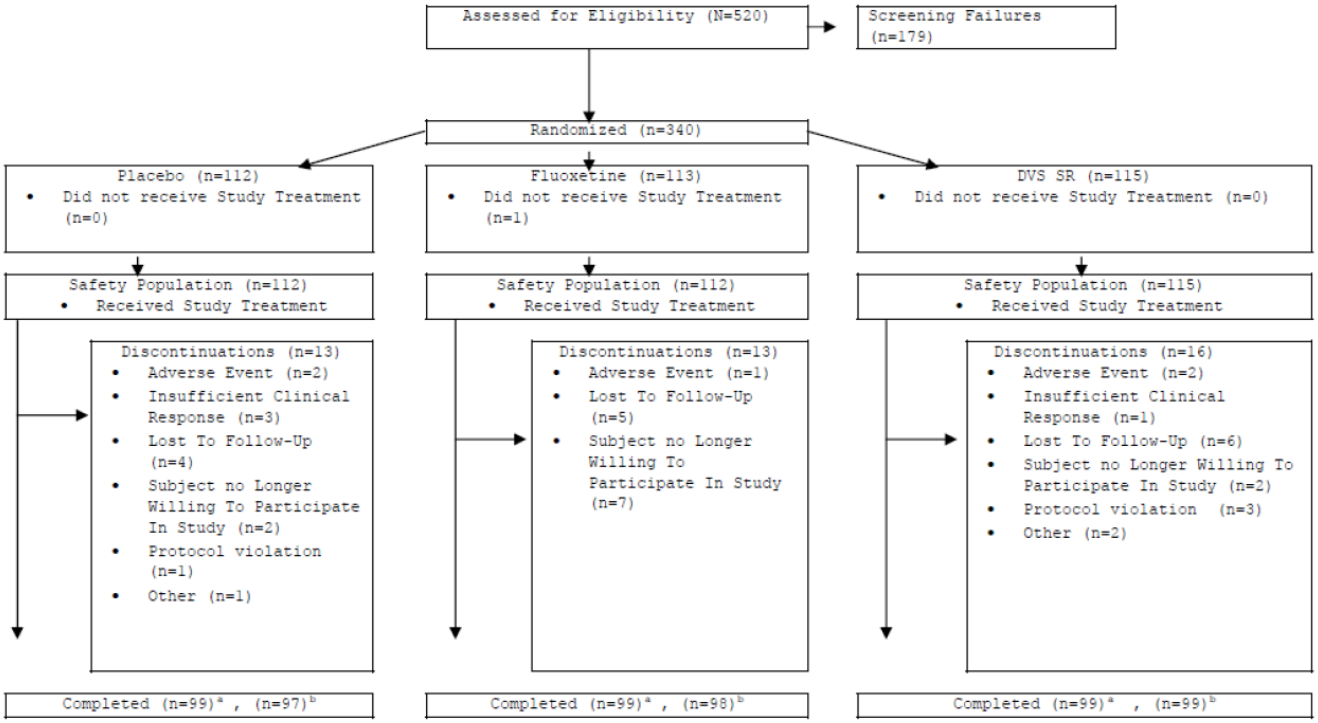
The partially unblinded sample size recalculation was performed when about 75% subjects in the overall population who have had the opportunity to complete the 8-week treatment phase. The sample size would be recalculated based on whether the estimated pooled SD from all available subjects at sample size re-assessment was considerably larger than the assumption (SD=12).

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 340 subjects were randomized to treatment with placebo (N=112), Fluoxetine (N=113), or DVS SR (N=115). A total of 337 subjects were included in the ITT population: 112 subjects in the placebo group, 110 subjects in Fluoxetine group and 115 subjects in the DVS SR group.

The proportions of subjects in the placebo, Fluoxetine, and DVS SR treatment groups who discontinued from treatment during the double-blind treatment period were 11.6%, 11.6%, and 13.9%, respectively. The most common reason for discontinuation in the placebo and DVS SR treatment groups was lost of follow-up (3.6% and 5.2%, respectively). In the Fluoxetine treatment group, the most common reason for discontinuation was no longer willing to participate (6.3%). A total of 297 (87.4%) subjects completed the treatment phase.

Figure 1: Patient Disposition in Study B2061014



[Source: Sponsor's clinical study report B2061014 Figure1, verified by the reviewer]

The overall median age of 13 years was comparable among treatment arms; 38.6% of subjects were children (7 to 11 years of age) and 61.4% were adolescents (12 to 17 years of age). Overall, 45.7% subjects were male and 54.3% were female, 65.0% were white and 26.7% were black; 15.7% were in the weight category between 20 and 35 kg, 53.1% were in the weight category between 35 and 70 kg, and 31.2% weighed ≥ 70 kg. No other meaningful differences were observed among treatment groups for any of the other demographic variables.

Table 2: Demographic Characteristics (Intent-to-Treat Population) in Study B2061014

Characteristic	P-value	Placebo N=112 n (%)	Fluoxetine N=110 n (%)	DVS SR N=115 n (%)	Total N=337 N (%)
Age Group					
7 to 11 years	0.829[b]	42 (37.5)	45 (40.9)	43 (37.4)	130 (38.6)
12 to 17 years		70 (62.5)	65 (59.1)	72 (62.6)	207 (61.4)
Sex					
Male	0.642[b]	48 (42.9)	54(49.09)	52 (45.2)	154(45.70)
Female		64 (57.1)	56(50.91)	63 (54.8)	183(54.30)
Race					
Asian	0.507[b]	1 (0.9)	2 (1.8)	1 (0.9)	4 (1.2)
Black		25 (22.3)	33 (30.0)	32 (27.8)	90 (26.7)
White		81 (72.3)	66 (60.0)	72 (62.6)	219 (65.0)
Other		5 (4.5)	9 (8.2)	10 (8.7)	24 (7.1)
Weight Category					
≥20 to <35 kg	0.155[b]	20 (17.9)	21 (19.1)	12 (10.4)	53 (15.7)
≥35 to <70 kg		63 (56.3)	50 (45.5)	66 (57.4)	179 (53.1)
≥70 kg		29 (25.9)	39 (35.5)	37 (32.2)	105 (31.2)
CDRS-R Total Score, n		112	110	115	337
Mean (SD)	0.767[a]	57.1 (8.9)	56.3 (8.4)	56.3 (9.6)	56.6 (8.9)
Min, max		41, 90	41, 81	33, 77	33, 90
Median		56.0	55.0	56.0	56.0
CGI-S Score, n		112	110	115	337
Mean (SD)	0.638[a]	4.5 (0.6)	4.4 (0.6)	4.5 (0.6)	4.5 (0.6)
Min, max		4, 6	4, 6	3, 6	3, 6
Median		4.0	4.0	4.0	4.0

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CGI-S=Clinical Global Impression of Severity; DVS SR=desvenlafaxine succinate sustained release; n/N=number of subjects; SD=standard deviation

a. P-values for categorical variables were obtained using Chi-square test / Fisher's exact test.

b. P-values for continuous variables were obtained using 1-way analysis of variance with treatment as factor.

[Source: Sponsor's clinical study report B2061014 Table 9, verified by the reviewer]

3.2.1.4 Sponsor's Analysis: Primary Efficacy Analysis and Sensitivity Analysis

A total of 224 subjects had completed the 8-week treatment phase as of 15 Sep 2014. The sample size re-assessment was conducted by a blinded statistician from the (b) (4) based on the clinical database, with a data cut date of September 15, 2014. Since the pooled standard deviation of change from baseline in the CDRS-R total score at Week 8 was less than 12, there was no increase in sample size.

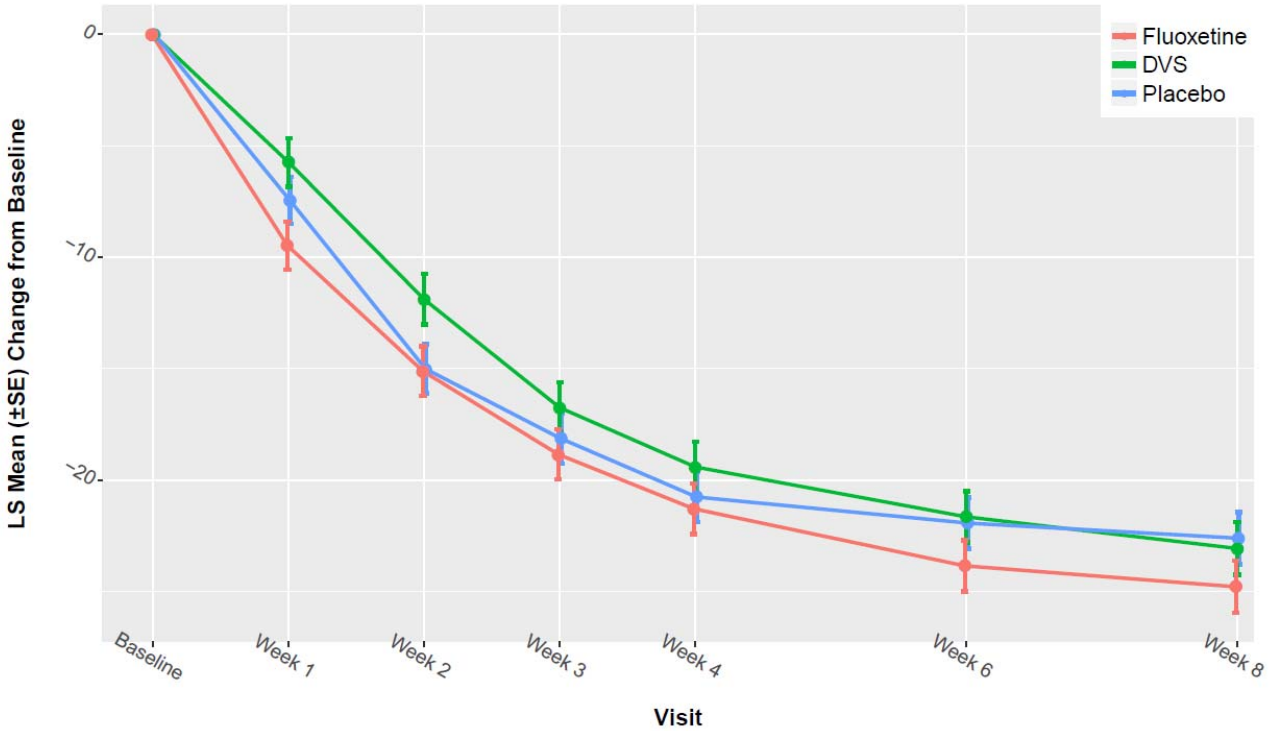
CDRS-R change from baseline in total score for depression was summarized for the ITT population in Table 4 and presented in Figure 2. The primary objective was not met for both Fluoxetine and DVS SR groups. At Week 8, the adjusted change from baseline in CDRS-R total score was -22.61 in DVS SR-treated subjects, as compared to -23.07 in placebo-treated subjects, resulting in a non-statistically significant treatment difference of -0.47 (95% CI -3.23, 2.30) (placebo- DVS SR), p=0.739. The adjusted change from baseline in CDRS-R total score at Week 8 for the group of subjects treated with fluoxetine was -24.79; the treatment difference was 1.71 (95% CI -1.06, 4.48) (placebo- fluoxetine), p=0.226. Overall, the profile of change from baseline in CDRS-R during the course of the 8-week treatment phase was similar for the 3 treatment groups. Various sensitivity analyses also showed consistent results (Table 5). Because the primary objective was not met, no confirmative testing for the key secondary endpoint could be performed.

Table 3: Primary Analysis: Changes from Baseline of CDRS-R Total Score for Depression, through Week 8 Using MMRM Analysis, ITT Population in Study B2061014

Time Point	Treatment Group	n	Adjusted Mean Change from Baseline	SE	Difference in Adjusted Means (placebo-active)	95% CI	P-value
Week 1	Placebo	102	-5.74	1.09			
	Fluoxetine	101	-9.47	1.08	3.73	(1.26, 6.20)	0.003
	DVS SR	111	-7.45	1.06	1.71	(-0.71, 4.13)	0.165
Week 2	Placebo	103	-11.89	1.13			
	Fluoxetine	105	-15.11	1.11	3.22	(0.64, 5.79)	0.015
	DVS SR	110	-15.01	1.10	3.12	(0.57, 5.67)	0.017
Week 3	Placebo	105	-16.75	1.13			
	Fluoxetine	102	-18.85	1.12	2.11	(-0.50, 4.71)	0.112
	DVS SR	107	-18.14	1.11	1.40	(-1.18, 3.97)	0.287
Week 4	Placebo	101	-19.41	1.14			
	Fluoxetine	101	-21.29	1.14	1.88	(-0.76, 4.53)	0.163
	DVS SR	100	-20.76	1.13	1.35	(-1.28, 3.99)	0.312
Week 6	Placebo	100	-21.65	1.15			
	Fluoxetine	100	-23.85	1.15	2.20	(-0.48, 4.88)	0.107
	DVS SR	102	-21.93	1.14	0.28	(-2.38, 2.94)	0.834
Week 8	Placebo	99	-23.07	1.18			
	Fluoxetine	101	-24.79	1.17	1.71	(-1.06, 4.48)	0.226
	DVS SR	99	-22.61	1.17	-0.47	(-3.23, 2.30)	0.739

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; DVS SR=desvenlafaxine succinate sustained release; ITT=intent-to-treat; MMRM=mixed-effects model for repeated measures; n=number of subjects; SE=standard error a. P-value obtained from mixed-effects model for repeated measures: Change from baseline=Treatment+Week+Treatment*Week+Age Group+Country+Gender+Baseline with unstructured covariance structure. [Source: Table 22 on page 79 of clinical study report.]

Figure 2: Change from Baseline (LS Mean ± SE) in the CDRS-R Total Score over Time-Mixed Model for Repeated Measures (ITT Population) in Study B2061014



[Source: Reviewer's Plot]

Table 4: Sensitivity Analyses on Change from Baseline in CDRS-R Total Score for Depression at Week 8 (ITT Population) in Study B2061014

Analysis	Statistic	Placebo (N=112)	Fluoxetine (N=110)	DVS SR (N=115)
OC ANCOVA	LS Mean	-25.21	-26.95	-24.21
	Difference from Placebo			
	LS Mean Difference (SE)		1.74	-1.00
	LS Mean Difference 95% CI		(-0.92, 4.40)	(-3.67, 1.67)
	p-value		0.199	0.461
LOCF ANCOVA	LS Mean	-24.20	-26.15	-24.04
	Difference from Placebo			
	LS Mean Difference		1.95	-0.16
	LS Mean Difference 95% CI		(-0.78, 4.67)	(-2.85, 2.53)
	p-value		0.161	0.908
PMM with Placebo-based Multiple Imputation Result at Week 8	LS Mean	-22.19	-24.98	-22.22
	Difference from Placebo			
	LS Mean Difference (SE)		2.79	0.03
	LS Mean Difference 95% CI		(-0.68,6.25)	(-3.29,3.35)
	p-value		0.115	0.985

Abbreviations: ITT = Intent-to-Treat; LS = least squares; OC = Observed Cases; LOCF = Last-Observation-Carried-Forward; PMM = Pattern Mixed Model.
[Source: Tables 14.2.1.2 - 14.2.1.4 on clinical study report.]

Reviewer's Note: *This reviewer opines that neither the OC ANCOVA nor the LOCF ANCOVA is a sensible sensitivity analysis to assess the impact of the deviation from the missing data mechanism assumed in the primary analysis. This is because they are based on a more rigorous assumption than the primary analysis is.*

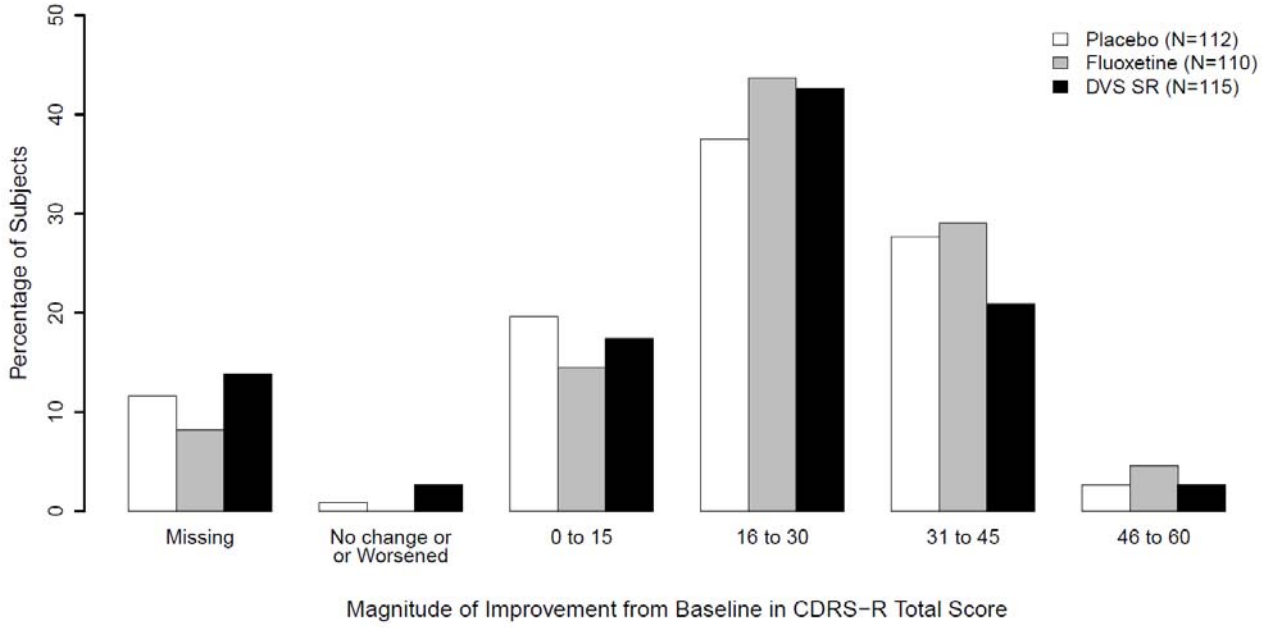
3.2.1.5 Reviewer's Results and Comments

This reviewer confirms the sponsor's analysis results for the primary endpoint. The sensitivity analyses as presented in Tables 5 were confirmed as well. Based on this reviewer's analysis, Figure 3 suggests that the improvements observed on the DVS SR group were generally modest compared with placebo and Fluoxetine, but the DVS SR group had a slightly larger dropout rate.

At the interim look on September 15, 2014, 250 subjects had been randomized and 224 subjects had data on both baseline and Week 8. The estimated SD was 11.82 based on those 224 subjects. Since the estimated pooled SD was smaller than the assumed SD=12, the independent statistical analysis center (ISAC) of the Data and Safety Monitoring Board (DSMB) recommended no sample size increase. Based on the estimated pooled SD 11.82, the calculated powers to conclude at least one effective dose were 86% assuming a treatment difference of 5 points in CDRS-R score.

Despite the sufficient power to detect a 5-point difference in CDRS-R score, the final analysis did not demonstrate superiority to placebo group in either of the treatment groups. The magnitudes of the observed treatment effects were less than 2 points, as compared with the postulated magnitude (5 points). The p-values from the primary analyses were 0.74 and 0.23 for DVS SR group and Fluoxetine, respectively. This study did not demonstrate efficacy of DVS SR over placebo in treating child (ages 7–11) and adolescent (ages 12–17) outpatients with MDD.

Figure 3: Percentage of Subjects with Specific Magnitudes of Improvement in CDRS-R Total Score at Week 8 (ITT Population) in StudyB2061014



[Source: Reviewer's Plot]

Reviewer's Note: *It is noted that the DVS SR group had a slightly larger dropout rate. In this case, if missing values are treated as failures (e.g., imputed by worst scores) regardless of dropout reasons, the efficacy results could be biased in favor of placebo. Hence, such an analysis may not be appropriate to assess efficacy, but it may be considered as "utility" analysis to explore how useful the treatment is in real life.*

3.2.2 Study B2061032

3.2.2.1 Study Design and Endpoints

B2061032 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of DVS SR in the treatment of child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with MDD.

The study was comprised of a screening phase of up to 4 weeks, a double-blind treatment period for 8 weeks, a 1-week double-blind t taper phase or transition phase and a 4-week follow-up phase. Following the screening period, subjects who continue to meet entry criteria were randomly assigned to 1 of 3 double-blind treatment arms: DVS SR high dose, DVS SR low dose, or placebo (1:1:1 ratio). The randomization was stratified by age (children [baseline age 7-11 years] and adolescents [baseline age 12-17 years] at 1:1 ratio) and country.

The primary analysis was conducted on the change from baseline in the CDRS-R total score at Week 8 based on the ITT population, and the key secondary outcome measure was the change from baseline to Week 8 in the CGI-S score. Both the primary efficacy endpoint and the key secondary outcome were measured at screening, at baseline (Day 1) and in Weeks 1, 2, 3, 4, 6, and 8.

3.2.2.2 Statistical Methodologies

The sample size calculation was based on the CDRS-R total score, assuming a standard deviation (SD) of 12. A total of 105 subjects randomized to each treatment arm was considered to be sufficient to demonstrate a difference of 5 points (CDRS-R score) between the DVS SR and placebo treatment groups, at a significance level of 5% and a power of 85%. An upward adjustment of approximately 5% was assumed to compensate for subjects who failed to qualify for the intent-to-treat (ITT) analysis. Thus, a total sample of approximately 333 subjects (111 subjects per group) was randomly assigned to each of the three treatment arms.

The primary analysis was conducted on the change from baseline in the CDRS-R total score at Week 8 (primary time point) based on the ITT population. A mixed-effects model for repeated measures (MMRM) was used with treatment, week, interaction of treatment and week, age group, and gender as fixed effects and the baseline CDRS-R total score as a covariate. Data from Weeks 1, 2, 3, 4, 6, and 8 were used.

The primary and secondary efficacy analyses all used the MMRM Method. In addition to the model-based missing data approach of the MMRM model, the primary and secondary efficacy analyses were all analyzed using an ANCOVA models based on the last observation carried forward (LOCF), an ANCOVA model based on the observed cases (OC), and a pattern-mixture model as sensitivity analyses.

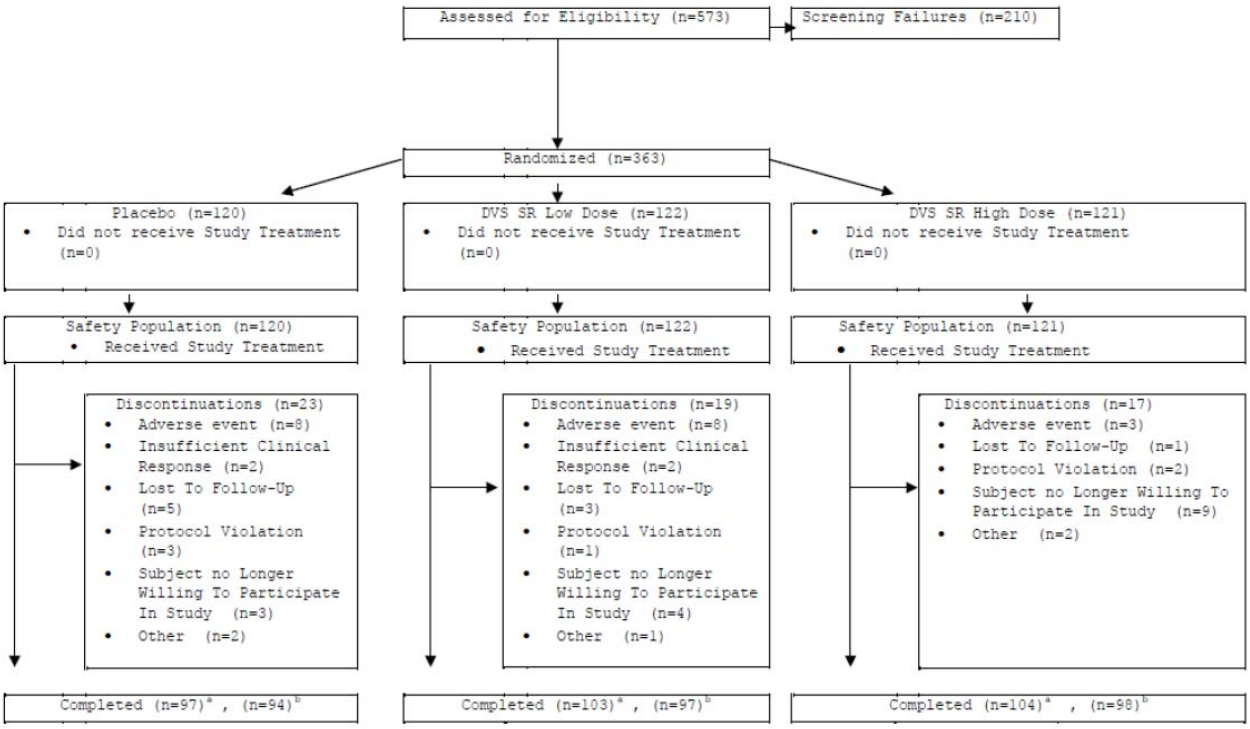
The partially unblinded sample size recalculation was performed when about 75% subject in the overall population who have had the opportunity to complete the 8-week treatment phase. The sample size would be recalculated based on whether the estimated pooled SD from all available subjects at sample size re-assessment was considerably larger than the assumption (SD=12).

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 363 subjects were randomized to treatment with placebo (N=120), DVS SR low dose (N=122), or DVS SR high dose (N=121). A total of 360 subjects were included in the ITT population: 119 subjects in the placebo group, 120 subjects in DVS SR low dose group and 121 subjects in the DVS SR high group.

The proportions of subjects in the placebo, DVS SR low dose, and DVS SR high dose groups who discontinued from treatment during the double-blind treatment period were 19.2%, 15.6%, and 14.0%, respectively. The most common reason for discontinuation in the placebo and DVS SR Low dose treatment groups was adverse event (6.7% and 6.6%, respectively). In the DVS SR High dose treatment group, the most common reason for discontinuation was no longer willing to participate (7.4%). A total of 304 (83.7%) subjects completed the treatment phase.

Figure 4: Patient Disposition in Study B2061032



[Source: Sponsor's clinical study report B2061032 Figure1, verified by the reviewer]

The overall median age of 13 years was comparable among treatment arms; 30.3% of subjects were children (7 to 11 years of age) and 69.7% were adolescents (12 to 17 years of age). Overall, 43.9% subjects were male and 56.1% were female, 68.6% were white and 24.4% were black; 11.7% were in the weight category between 20 and 35 kg, 63.9% were in the weight category between 35 and 70 kg, and 24.4% weighed ≥ 70 kg. No other meaningful differences were observed among treatment groups for any of the other demographic variables.

Table 5: Demographic Characteristics (Intent-to-Treat Population) in Study B2061032

Characteristic	P-value	Placebo N=119 n (%)	DVS SR Low N=120 n (%)	DVS SR High N=121 n (%)	Total N=360 n (%)
Age Group					
7 to 11 years	0.983[b]	36 (30.25)	37 (30.83)	36(29.75)	109(30.28)
12 to 17 years		83 (69.75)	83(69.17)	85(70.25)	251(69.72)
Sex					
Male	0.118[b]	60(50.42)	53 (44.17)	45 (37.19)	158 (43.89)
Female		59(49.58)	67(55.83)	76 (62.81)	202 (56.11)
Race					
Asian	0.436[b]	1(0.84)	1(0.83)	0(0)	2(0.56)
Black		25(21.01)	30(25)	33(27.27)	88(24.44)
White		84(70.59)	85(70.83)	78(64.46)	247(68.61)
Other		9(7.56)	4(3.33)	10(8.26)	23(6.39)
Weight Category					
≥20 to <35 kg	0.235[b]	10 (8.40)	12 (10.00)	20 (16.53)	42 (11.67)
≥35 to <70 kg		80 (67.23)	81 (67.50)	69 (57.02)	230 (63.89)
≥70 kg		29 (24.37)	27 (22.50)	32 (26.45)	88 (24.44)
CDRS-R Total Score, n		119	120	121	360
Mean (SD)	0.415[a]	57.08 (8.71)	58.44 (9.24)	58.45 (9.45)	57.99 (9.14)
Min, max		40, 87	41, 87	41, 82	40, 87
Median		58	58	58	58
CGI-S Score, n		119	120	121	360
Mean (SD)	0.638[a]	4.55 (0.58)	4.60 (0.61)	4.61 (0.58)	4.59 (0.59)
Min, max		4, 6	4, 6	4, 6	4, 6
Median		5	5	5	5

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CGI-S=Clinical Global Impression of Severity; DVS SR=desvenlafaxine succinate sustained release; n/N=number of subjects; SD=standard deviation a. P-values for categorical variables were obtained using Chi-square test / Fisher's exact test.

b. P-values for continuous variables were obtained using 1-way analysis of variance with treatment as factor

[Source: Sponsor's clinical study report B2061032 Table 9, verified by the reviewer]

3.2.2.4 Sponsor's Analysis: Primary Efficacy Analysis and Sensitivity Analysis

A total of 250 subjects had completed the 8-week treatment phase as of 9 February 2015. The sample size re-assessment was conducted by a blinded statistician from the (b) (4) based on the clinical database, with a data cut date of 9 February 2015. The outcome of this IA was that based on the pooled SD the sample size was increased from 333 to 360 total subjects (an additional 9 subjects were randomized to each of the 3 treatment groups).

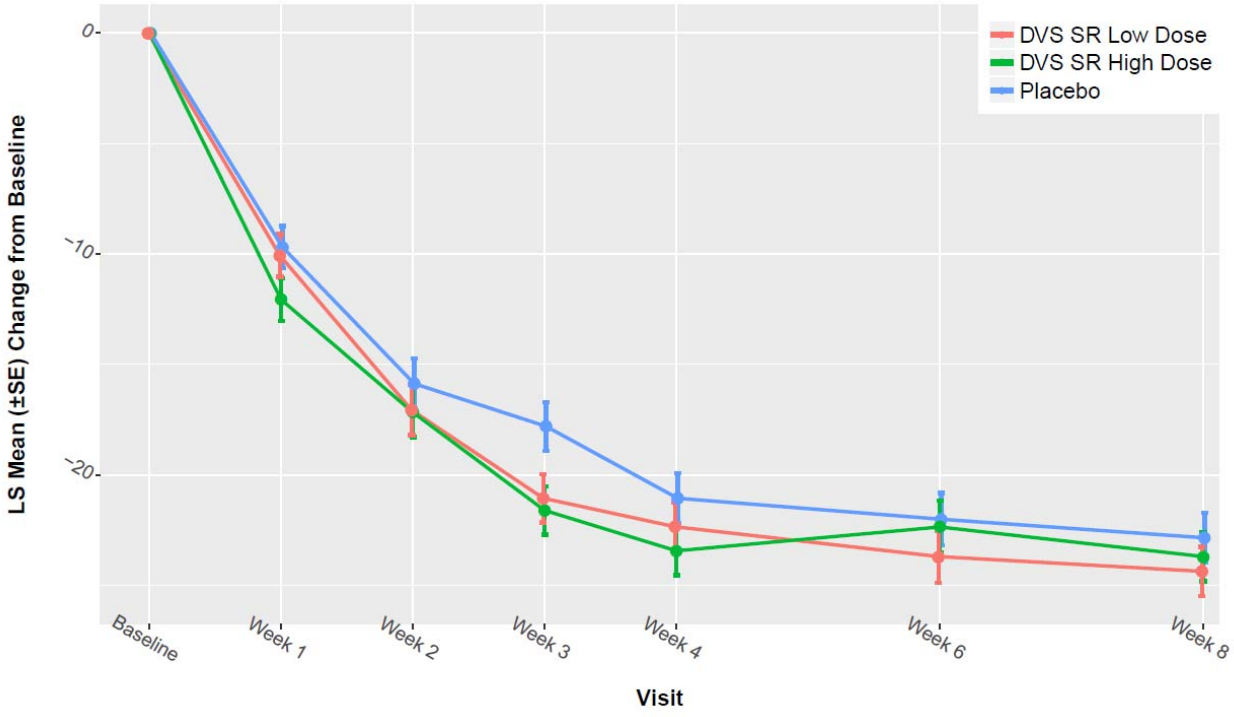
CDRS-R change from baseline in total score for depression is summarized for the ITT population in Table 4 and presented in Figure 4. The primary objective was not met for both DVS SR High and DVS SR Low groups. At Week 8, the adjusted change from baseline in CDRS-R total score was -23.70 in the DVS SR low dose exposure group, as compared to -22.85 in placebo-treated subjects, resulting in a non-statistically significant treatment difference of 0.85 (95% CI -2.23, 3.94) (placebo- DVS SR low), p=0.587. The adjusted change from baseline in CDRS-R total score at Week 8 was -24.37 in the DVS SR high dose exposure group, as compared to -22.85 in placebo-treated subjects, resulting in a non-statistically significant treatment difference of 1.52 (95% CI -1.56, 4.61) (placebo- DVS SR high), p=0.333. Overall, the profile of change from baseline in CDRS-R during the course of the 8-week treatment phase was similar for the 3 treatment groups. Various sensitivity analyses also showed consistent results (Table 7). Because the primary objective was not met, no confirmative testing for the key secondary endpoint could be performed.

Table 6: Primary Analysis: Changes from Baseline of CDRS-R Total Score for Depression, through Week 8 Using MMRM Analysis, ITT Population in Study B2061032

Time Point	Treatment Group	n	Adjusted Mean Change from Baseline	SE	Difference in Adjusted Means (placebo-active)	95% CI	P-value
Week 1	Placebo	113	-9.69	0.96			
	DVS SR Low Dose	112	-12.07	0.96	2.38	(-0.24, 4.99)	0.075
	DVS SR High Dose	116	-10.07	0.96	0.38	(-2.23, 3.00)	0.772
Week 2	Placebo	115	-15.87	1.13			
	DVS SR Low Dose	115	-17.17	1.12	1.29	(-1.79, 4.38)	0.409
	DVS SR High Dose	109	-17.07	1.14	1.20	(-1.91, 4.30)	0.449
Week 3	Placebo	108	-17.80	1.10			
	DVS SR Low Dose	110	-21.61	1.09	3.81	(0.81, 6.80)	0.013
	DVS SR High Dose	110	-21.06	1.10	3.26	(0.25, 6.26)	0.034
Week 4	Placebo	104	-21.06	1.12			
	DVS SR Low Dose	107	-23.44	1.11	2.38	(-0.67, 5.44)	0.126
	DVS SR High Dose	113	-22.35	1.11	1.30	(-1.75, 4.35)	0.404
Week 6	Placebo	106	-22.01	1.18			
	DVS SR Low Dose	105	-22.36	1.18	0.34	(-2.89, 3.57)	0.834
	DVS SR High Dose	104	-23.70	1.18	1.69	(-1.55, 4.93)	0.305
Week 8	Placebo	102	-22.85	1.13			
	DVS SR Low Dose	104	-23.70	1.12	0.85	(-2.23, 3.94)	0.587
	DVS SR High Dose	106	-24.37	1.12	1.52	(-1.56, 4.61)	0.333

Abbreviations: CDRS-R=Children's Depression Rating Scale-Revised; CI=confidence interval; DVS SR=desvenlafaxine succinate sustained release; ITT=intent-to-treat; MMRM=mixed-effects model for repeated measures; n=number of subjects; SE=standard error a. P-value obtained from mixed-effects model for repeated measures: Change from baseline=Treatment+Week+Treatment*Week+Age Group+Country+Gender+Baseline with unstructured covariance structure. [Source: Table 11 on page 76 of clinical study report.]

Figure 5: Change from Baseline (LS Mean ± SE) in the CDRS-R Total Score over Time- Mixed Model for Repeated Measures (ITT Population) in Study B2061032



[Source: Reviewer's Plot]

Table 7: Sensitivity Analyses on Change from Baseline in CDRS-R Total Score for Depression at Week 8 (ITT Population) in Study B2061032

Analysis	Statistic	Placebo (N=119)	DVS SR Low (N=120)	DVS SR High (N=121)
OC ANCOVA	LS Mean	-24.38	-24.48	-24.88
	Difference from Placebo			
	LS Mean Difference		0.09	0.50
	LS Mean Difference 95% CI		(-3.01, 3.20)	(-2.61, 3.61)
	p-value		0.953	0.753
LOCF ANCOVA	LS Mean	-22.39	-23.49	-23.90
	Difference from Placebo			
	LS Mean Difference		1.10	1.51
	LS Mean Difference 95% CI		(-2.02, 4.23)	(-1.62, 4.64)
	p-value		0.487	0.344
PMM with Placebo-based Multiple Imputation Result at Week 8	LS Mean	-19.31	-19.77	-19.86
	Difference from Placebo			
	LS Mean Difference (SE)		0.47	0.55
	LS Mean Difference 95% CI		(-3.30,4.23)	(-3.17,4.28)
	p-value		0.807	0.770

Abbreviations: ITT = Intent-to-Treat; LS = least squares; OC = Observed Cases; LOCF = Last-Observation-Carried-Forward; PMM = Pattern Mixed Model.
[Source: Tables 14.2.1.2 - 14.2.1.4 on clinical study report B2061032.]

Reviewer's Note: *This reviewer opines that neither the OC ANCOVA nor the LOCF ANCOVA is a sensible sensitivity analysis to assess the impact of the deviation from the missing data mechanism assumed in the primary analysis. This is because they are based on a more rigorous assumption than the primary analysis is.*

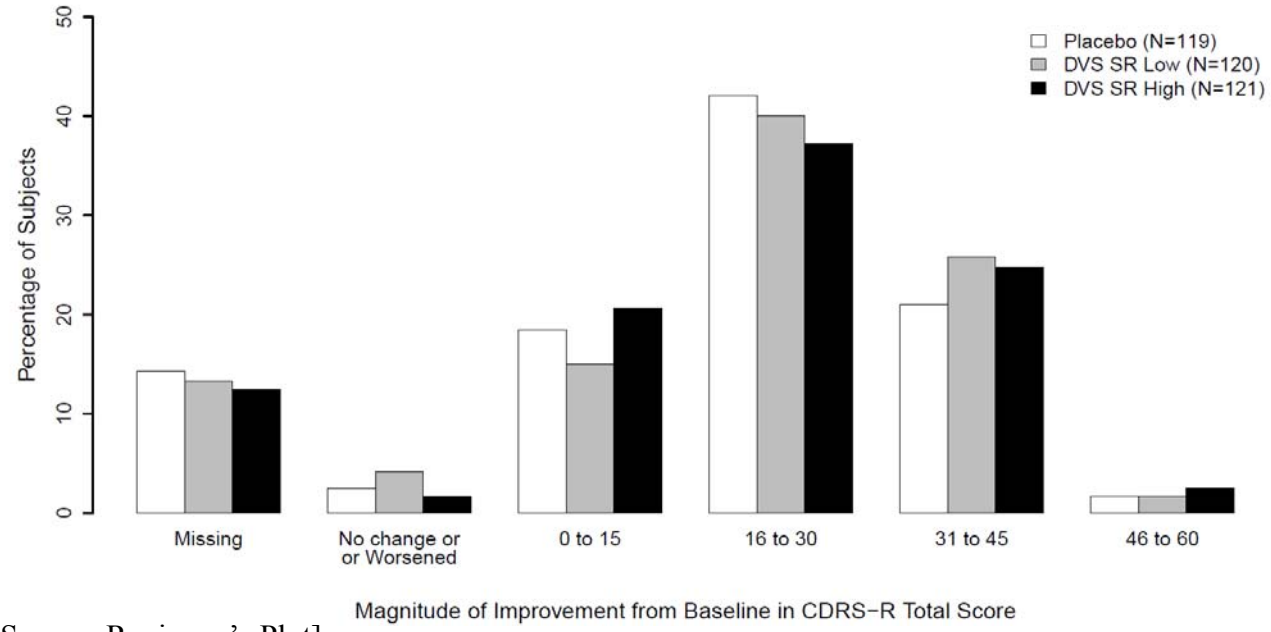
3.2.2.5 Reviewer's Results and Comments

This reviewer confirms the sponsor's analysis results for the primary endpoint. The sensitivity analyses as presented in Tables 8 were confirmed as well. Based on this reviewer's analysis, Figure 6 suggests that the improvements observed on both DVS SR groups were generally modest compared with placebo.

At the interim look on February 9, 2015, 250 subjects had been randomized and 210 subjects had data on both baseline and Week 8. The estimated SD was 12.54 based on those 224 subjects with data at both baseline and Week 8. Since the estimated pooled SD was larger than the assumed SD=12, the independent statistical analysis center (ISAC) of the Data and Safety Monitoring Board (DSMB) recommended that sample size be increased by 9 subjects per arm, to a total of 120 subjects per arm. Based on the estimated pooled SD 12.54 and the updated sample size, the calculated power to conclude at least one effective dose was 84% assuming a treatment difference of 5 points in CDRS-R score.

Despite the sample size increase to assure the sufficient power to detect a 5-point difference in CDRS-R score, the final analysis did not demonstrate superiority to placebo group in either of the treatment groups. The magnitudes of the observed treatment effects were less than 2 points, as compared with the postulated magnitude (5 points). The p-values from the primary analyses were 0.33 and 0.59 for DVS SR high dose group and DVS SR low dose group, respectively. This study did not demonstrate efficacy of both DVS SR high dose and low dose over placebo in treating child (ages 7–11) and adolescent (ages 12–17) outpatients with MDD.

Figure 6: Percentage of Subjects with Specific Magnitudes of Improvement in CDRS-R Total Score at Week 8 (ITT Population) in Study B2061032



[Source: Reviewer's Plot]

Reviewer's Note: *It is noted that the placebo group had a slightly larger dropout rate. In this case, if missing values are treated as failures (e.g., imputed by worst scores) regardless of dropout reasons, the efficacy results could be biased in favor of treatments. Hence, such an analysis may not be appropriate to assess efficacy, but it may be considered as "utility" analysis to explore how useful the treatment is in real life.*

3.3 Evaluation of Safety

Safety was not evaluated in this review. Please refer to the clinical review for details on the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study B2061014

The purpose of the following subgroup analyses was to assess the consistency of treatment effects across subgroups. The change from Baseline to Week 8 in the CDRS-R Total Score was examined by age group, gender and race to explore whether there was a consistent trend in treatment effect across subgroups. Mean differences from placebo in CDRS-R total score for age group, gender and race were shown in Table 7. There was no noticeable trend in favor of any treatment across subgroups. This might be partially explained by the very small treatment effects observed for both DVS SR and Fluoxetine.

Table 8: CDRS-R Total Score: Subgroup Analysis by Age group, Gender and Race in Changes from Baseline to Week 8 (ITT) in Study B2061014

Subgroup Treatment	Treatment	n	LS Mean (SE)	Difference in Adjusted Means (placebo-active) (95% CI)
Age Group				
Children	**Placebo**	38	-25.10 (1.68)	-
	Fluoxetine	41	-24.98 (1.63)	-0.12 (-4.56, 4.32)
	DVS SR	36	-25.70 (1.71)	0.60 (-3.92, 5.12)
Adolescents	**Placebo**	61	-21.41 (1.48)	-
	Fluoxetine	60	-24.30 (1.51)	2.89 (-0.67, 6.44)
	DVS SR	63	-20.31 (1.45)	-1.10 (-4.58, 2.39)
Gender				
Male	**Placebo**	45	-24.89 (1.60)	-
	Fluoxetine	51	-23.29 (1.51)	-1.60 (-5.65, 2.44)
	DVS SR	46	-22.01 (1.55)	-2.88 (-6.99, 1.23)
Female	**Placebo**	54	-21.82 (1.49)	-
	Fluoxetine	50	-26.42 (1.57)	4.60 (0.81, 8.40)
	DVS SR	53	-23.22 (1.52)	1.41 (-2.30, 5.11)
Race				
White	**Placebo**	70	-24.34 (1.33)	-
	Fluoxetine	60	-24.45 (1.41)	0.11 (-3.34, 3.57)
	DVS SR	64	-22.29 (1.37)	-2.04 (-5.43, 1.35)
Black or African American	**Placebo**	23	-19.73 (2.28)	-
	Fluoxetine	30	-25.74 (1.99)	6.01 (0.47, 11.54)
	DVS SR	26	-23.29 (2.06)	3.56 (-2.06, 9.17)
Other	**Placebo**	5	-17.28	-
	Fluoxetine	9	-22.13	-
	DVS SR	8	-20.56	-
Asian	**Placebo**	1	-27.87	-
	Fluoxetine	2	-27.78	-
	DVS SR	1	-29.45	-

Note: LS Means, LS Mean Difference, associated 95% CI and p-value are based on model with treatment, country, age, gender, and treatment-by-subgroup interaction as fixed factors, and baseline CDRS-R total score as a covariate.

[Source: Reviewer's Table.]

4.2 Study B2061032

The purpose of the following subgroup analyses was to assess the consistency of treatment effects across subgroups. The change from Baseline to Week 8 in the CDRS-R Total Score was examined by age group, gender and race to explore whether there was a consistent trend in treatment effect across subgroups. Mean differences from placebo in CDRS-R Total Score for age group, gender, and race were shown in Table 8. There was no noticeable trend in favor of any treatment across subgroups. This might be partially explained by the very small treatment effects observed for both DVS SR doses.

Table 9: CDRS-R Total Score: Subgroup Analysis by Age group, Gender and Race in Changes from Baseline to Week 8 (ITT) in Study B2061032

Subgroup Treatment	Treatment	n	LS Mean (SE)	Difference in Adjusted Means (placebo-active) (95% CI)
Age Group				
Children	**Placebo**	33	-19.54 (4.84)	-
	DVS SR Low Dose	29	-18.38 (4.87)	-1.16 (-6.75, 4.43)
	DVS SR High Dose	33	-23.63 (4.86)	4.09 (-1.44, 9.63)
Adolescents	**Placebo**	69	-16.13 (4.62)	-
	DVS SR Low Dose	75	-17.77 (4.62)	1.64 (-2.03, 5.32)
	DVS SR High Dose	73	-16.71 (4.52)	0.58 (-3.11, 4.26)
Gender				
Male	**Placebo**	54	-17.99 (4.69)	-
	DVS SR Low Dose	46	-17.32 (4.73)	-0.67 (-5.13, 3.80)
	DVS SR High Dose	39	-18.4 (4.79)	0.41 (-4.28, 5.09)
Female	**Placebo**	48	-16.59 (4.72)	-
	DVS SR Low Dose	58	-18.7 (4.68)	2.11 (-2.18, 6.40)
	DVS SR High Dose	67	-19.02 (4.53)	2.43 (-1.74, 6.60)
Race				
White	**Placebo**	70	-17.36 (4.63)	-
	DVS SR Low Dose	75	-20.13(4.62)	2.77 (-0.9, 6.45)
	DVS SR High Dose	65	-18.11 (4.53)	0.75 (-3.04, 4.53)
Black or African American	**Placebo**	22	-18.87 (5.03)	-
	DVS SR Low Dose	24	-14.37 (4.96)	-4.5 (-10.98, 1.98)
	DVS SR High Dose	32	-21.73 (4.87)	2.86 (-3.37, 9.09)
Other	**Placebo**	9	-17.12 (5.89)	-
	DVS SR Low Dose	4	-11.44 (7.32)	-
	DVS SR High Dose	9	-18.88 (5.81)	-
Asian	**Placebo**	1	-17.05 (12.54)	-
	DVS SR Low Dose	1	-27.08 (12.51)	-
	DVS SR High Dose			-

Note: LS Means, LS Mean Difference, associated 95% CI and p-value are based on model with treatment, country, subgroup, and treatment-by-subgroup interaction as fixed factors, and baseline CDRS-R total score as a covariate.

[Source: Reviewer's Table.]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues that impact the overall conclusions.

5.2 Collective Evidence

Despite a sufficient power to detect a 5- point difference in CDRS-R total score, Study B2061014 did not meet the primary objective for both DVS SR and Fluoxetine. The difference in the change from Baseline in CDRS-R total score at Week 8 between DVS SR group and placebo group was -0.47 points (placebo- DVS SR) and was not statistically significant (p-value = 0.74). For the Fluoxetine group, this difference was 1.71 points (placebo- Fluoxetine) and was not statistically significant either (p-value= 0.23).

Study B2061032 did not meet the primary objective for both DVS SR doses although the sample size was increased. The difference in the change from Baseline in CDRS-R total score at Week 8 between DVS SR low group and placebo group was 0.85 points (placebo- DVS SR Low) and was not statistically significant (p-value = 0.59). For the DVS SR high group, this difference was 1.52 points (placebo- DVS SR High) and was not statistically significant (p-value= 0.33).

5.3 Conclusions and Recommendations

Although efficacy was not demonstrated in any of the treatment groups, both studies were adequately powered to detect a targeted treatment difference which we agreed upon. From a statistical perspective, this reviewer considers that this submission satisfies the pediatric Written Request, particularly the magnitude of the drug effect appears very small (see Table 3 and Table 6).

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/s/

YANG YANG
12/27/2017

PEILING YANG
12/27/2017

HSIEN MING J HUNG
12/27/2017