Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety and Tolerability of Desvenlafaxine Succinate Sustained Release (DVS SR) in the Treatment of Children and Adolescent Outpatients With Major Depressive Disorder

Summary

EudraCT number	2008-001875-32
Trial protocol	Outside EU/EEA
Global end of trial date	04 September 2015

Results information

Result version number	v1 (current)
This version publication date	13 May 2016
First version publication date	13 May 2016

Trial information

Trial identification

Sponsor protocol code	B2061032

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01371734
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase 3, multicentre, randomised, 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 major depressive disorder (MDD). The study was planned to evaluate the efficacy, safety and tolerability of DVS SR in the treatment of child and adolescent outpatients with MDD. Participants who completed the 8 week, double-blind treatment phase of this study were eligible to participate in a 6 month, open label extension study of DVS SR (B2061030).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.
The final protocol and any amendments were reviewed and approved by the Institutional Review Board(s) and/or Independent Ethics Committee(s) at each of the investigational centres participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	United States: 362
Worldwide total number of subjects	363
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	109
Adolescents (12-17 years)	254
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants underwent a comprehensive diagnostic psychiatric evaluation. Criteria for MDD were evaluated by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, as assessed by the KIDDIE Schedule for Affective Disorder & Schizophrenia – Present & Lifetime Version (K-SADS-PL).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matched placebo tablets administered once daily for 8 weeks (treatment phase), followed by placebo tablets administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Arm type	Placebo
Investigational medicinal product name	Placebo for DVS SR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets to match the 10 and 25 mg DVS SR pyramid shaped tablets for oral administration once daily for 8 weeks (treatment phase), followed by placebo tablets administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Arm title	DVS SR Low Dose

Arm description:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 20, 25 or 35 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Arm type	Experimental
Investigational medicinal product name	DVS SR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 20, 25 or 35 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Arm title	DVS SR High Dose

Arm description:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 25, 35 or 50 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Arm type	Experimental
Investigational medicinal product name	DVS SR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 25, 35 or 50 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Number of subjects in period 1	Placebo	DVS SR Low Dose	DVS SR High Dose
Started	120	122	121
Completed	97	103	104
Not completed	23	19	17
Consent withdrawn by subject	3	4	9
Adverse event, non-fatal	8	8	3
Not specified	2	1	2
Lost to follow-up	5	3	1
Protocol deviation	3	1	2
Lack of efficacy	2	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matched placebo tablets administered once daily for 8 weeks (treatment phase), followed by placebo tablets administered once daily for 1 week (taper phase) only for those participants not entering the extension study.	
Reporting group title	DVS SR Low Dose
Reporting group description:	
DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 20, 25 or 35 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.	
Reporting group title	DVS SR High Dose
Reporting group description:	
DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 25, 35 or 50 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.	

Reporting group values	Placebo	DVS SR Low Dose	DVS SR High Dose
Number of subjects	120	122	121
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	36	37	36
Adolescents (12-17 years)	84	85	85
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	13.2	13.1	12.9
standard deviation	± 2.68	± 2.8	± 3.01
Gender, Male/Female Units: Participants			
Female	60	69	76
Male	60	53	45

Reporting group values	Total		
Number of subjects	363		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	109		
Adolescents (12-17 years)	254		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous |			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	205		
Male	158		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Matched placebo tablets administered once daily for 8 weeks (treatment phase), followed by placebo tablets administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Reporting group title	DVS SR Low Dose

Reporting group description:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 20, 25 or 35 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Reporting group title	DVS SR High Dose

Reporting group description:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 25, 35 or 50 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Primary: Change from Baseline to Week 8 in the Children's Depression Rating Scale, Revised (CDRS-R) Total Score

End point title	Change from Baseline to Week 8 in the Children's Depression Rating Scale, Revised (CDRS-R) Total Score

End point description:

Clinician-rated interview-based scale (with both child and parent or guardian) to assess 17 distinct symptom areas to derive an index of depression severity. Discrepancies between informants' responses were resolved by using most impaired rating given by valid informant. Rated on a 7-point scale; range from 1 (no impairment) to 7 (indicates greater impairment). Total score calculated as sum of the 17 items (range 1 to 119); higher score indicates greater impairment. Adjusted mean (common baseline average + adjusted mean change from baseline) presented.

End point type	Primary

End point timeframe:

Baseline and Week 8

End point values	Placebo	DVS SR Low Dose	DVS SR High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	106	
Units: Score on a scale				
least squares mean (standard error)	-22.85 (± 1.13)	-23.7 (± 1.12)	-24.37 (± 1.12)	

Statistical analyses

Statistical analysis title	Analysis of CDRS-R at Week 8
Statistical analysis description:	
Adjusted mean difference = Placebo - DVS SR Low Dose	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.587
Method	Mixed-effects model for repeated measure
Parameter estimate	Mean difference (final values)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	3.94

Statistical analysis title	Analysis of CDRS-R at Week 8
Statistical analysis description:	
Adjusted mean difference = Placebo - DVS SR High Dose	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.333
Method	Mixed-effects model for repeated measure
Parameter estimate	Median difference (final values)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	4.61

Secondary: Change from Baseline to Week 8 in the Clinical Global Impression of Severity (CGI-S) Score

End point title	Change from Baseline to Week 8 in the Clinical Global Impression of Severity (CGI-S) Score
End point description:	
A 7-point clinician rated scale to assess severity of participant's current illness state; range: 1 (normal - not ill at all) to 7 (among the most extremely ill patients). Higher score = more affected. Change: score at observation minus score at baseline. Adjusted mean (common baseline average + adjusted mean change from baseline) presented.	
End point type	Secondary
End point timeframe:	
Baseline and Week 8	

End point values	Placebo	DVS SR Low Dose	DVS SR High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	105	106	
Units: Score on a scale				
least squares mean (standard error)	-1.49 (± 0.11)	-1.51 (± 0.11)	-1.65 (± 0.11)	

Statistical analyses

Statistical analysis title	Analysis of CGI-S at Week 8
Statistical analysis description: Adjusted mean difference = Placebo - DVS SR Low Dose	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.923
Method	Mixed-effects model for repeated measure
Parameter estimate	Median difference (final values)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.32

Statistical analysis title	Analysis of CGI-S at Week 8
Statistical analysis description: Adjusted mean difference = Placebo - DVS SR High Dose	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.302
Method	Mixed-effects model for repeated measure
Parameter estimate	Mean difference (final values)
Point estimate	0.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.47

Secondary: Percentage of Participants by Clinical Global Impression Improvement (CGI-I) Score at Weeks 1, 2, 3, 4, 6, and 8

End point title	Percentage of Participants by Clinical Global Impression Improvement (CGI-I) Score at Weeks 1, 2, 3, 4, 6, and 8

End point description:

A 7-point clinician rated scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved), 2 (much improved), or 3 (minimally improved) on the scale. Higher score equals (=) more affected.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 6, and 8

End point values	Placebo	DVS SR Low Dose	DVS SR High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	115	115	
Units: Percentage of Participants				
number (not applicable)				
Week 1, Very Much Improved (n=113, 112,115)	2.7	0.9	2.6	
Week 1, Much Improved (n=113, 112, 115)	6.2	9.8	12.2	
Week 1, Minimally Improved (n=113, 112, 115)	38.9	37.5	33.9	
Week 1, No Change (n=113, 112, 115)	49.6	51.8	46.1	
Week 1, Minimally Worse (n=113, 112, 115)	2.7	0	5.2	
Week 1, Much Worse (n=113, 112, 115)	0	0	0	
Week 1, Very Much Worse (n=113, 112, 115)	0	0	0	
Week 2, Very Much Improved (n=114, 115, 109)	4.4	6.1	10.1	
Week 2, Much Improved (n=114, 115, 109)	26.3	26.1	23.9	
Week 2, Minimally Improved (n=114, 115, 109)	36.8	38.3	35.8	
Week 2, No Change (n=114, 115, 109)	31.6	25.2	29.4	
Week 2, Minimally Worse (n=114, 115, 109)	0	4.3	0	
Week 2, Much Worse (n=114, 115, 109)	0.9	0	0.9	
Week 2, Very Much Worse (n=114, 115, 109)	0	0	0	
Week 3, Very Much Improved (n=108, 110, 110)	10.2	10.9	18.2	
Week 3, Much Improved (n=108, 110, 110)	20.4	26.4	24.5	
Week 3, Minimally Improved (n=108, 110, 110)	47.2	44.5	35.5	
Week 3, No Change (n=108, 110, 110)	20.4	15.5	21.8	
Week 3, Minimally Worse (n=108, 110, 110)	1.9	1.8	0	

Week 3, Much Worse (n=108, 110, 110)	0	0	0	
Week 3, Very Much Worse (n=108, 110, 110)	0	0.9	0	
Week 4, Very Much Improved (n=104,108,113)	14.4	17.6	15	
Week 4, Much Improved (n=104,108,113)	30.8	36.1	31	
Week 4, Minimally Improved (n=104,108,113)	35.6	30.6	35.4	
Week 4, No Change (n=104,108,113)	19.2	14.8	17.7	
Week 4, Minimally Worse (n=104,108,113)	0	0.9	0.9	
Week 4, Much Worse (n=104,108,113)	0	0	0	
Week 4, Very Much Worse (n=104,108,113)	0	0	0	
Week 6, Very Much Improved (n=106,104,104)	19.8	20.2	26.9	
Week 6, Much Improved (n=106,104,104)	29.2	36.5	24	
Week 6, Minimally Improved (n=106,104,104)	31.1	24	31.7	
Week 6, No Change (n=106,104,104)	16	14.4	14.4	
Week 6, Minimally Worse (n=106,104,104)	2.8	2.9	1.9	
Week 6, Much Worse (n=106,104,104)	0	1.9	1	
Week 6, Very Much Worse (n=106,104,104)	0.9	0	0	
Week 8, Very Much Improved (n=102,105,106)	21.6	19	25.5	
Week 8, Much Improved (n=102,105,106)	34.3	37.1	36.8	
Week 8, Minimally Improved (n=102,105,106)	28.4	24.8	21.7	
Week 8, No Change (n=102,105,106)	15.7	18.1	15.1	
Week 8, Minimally Worse (n=102,105,106)	0	1	0.9	
Week 8, Much Worse (n=102,105,106)	0	0	0	
Week 8, Very Much Worse (n=102,105,106)	0	0	0	

Statistical analyses

Statistical analysis title	Analysis of CGI-I Score at Week 1
Statistical analysis description: Week 1	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.729
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 1
Statistical analysis description: Week 1	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.756
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 2
Statistical analysis description: Week 2	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.765
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 2
Statistical analysis description: Week 2	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.475
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 3
Statistical analysis description: Week 3	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.31
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 3

Statistical analysis description: Week 3	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.105
Method	Chi-squared corrected

Statistical analysis title	Analysis of CGI-I Score at Week 4
Statistical analysis description: Week 4	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.254
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 4
Statistical analysis description: Week 4	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.887
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 6
Statistical analysis description: Week 6	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.475
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 6

Statistical analysis description:	
Week 6	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.407
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 8
Statistical analysis description:	
Week 8	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.696
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Analysis of CGI-I Score at Week 8
Statistical analysis description:	
Week 8	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.462
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of Participants with a CGI-I Response Defined as a Score of 'Very Much Improved' or 'Much Improved'

End point title	Percentage of Participants with a CGI-I Response Defined as a Score of 'Very Much Improved' or 'Much Improved'
End point description:	
A 7-point clinician rated scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved) or 2 (much improved) on the scale. Higher score = more affected.	
End point type	Secondary
End point timeframe:	
Weeks 1, 2, 3, 4, 6, and 8	

End point values	Placebo	DVS SR Low Dose	DVS SR High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	115	115	
Units: Percentage of Participants				
number (not applicable)				
Week 1 (n=113, 112, 115)	8.85	10.71	14.78	
Week 2 (n=114, 115, 109)	30.7	32.17	33.94	
Week 3 (n=108, 110, 110)	30.56	37.27	42.73	
Week 4 (n=104, 108, 113)	45.19	53.7	46.02	
Week 6 (n=106, 104, 104)	49.06	56.73	50.96	
Week 8 (n=102, 105, 106)	55.88	56.19	62.26	

Statistical analyses

Statistical analysis title	Analysis of CGI-I Response at Week 1
Statistical analysis description: Week 1	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.633
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.806
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.333
upper limit	1.951

Statistical analysis title	Analysis of CGI-I Response at Week 1
Statistical analysis description: Week 1	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.172
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.561

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.245
upper limit	1.285

Statistical analysis title	Analysis of CGI-I Response at Week 2
Statistical analysis description: Week 2	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.826
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.536
upper limit	1.644

Statistical analysis title	Analysis of CGI-I Response at Week 2
Statistical analysis description: Week 2	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.599
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.489
upper limit	1.511

Statistical analysis title	Analysis of CGI-I Response at Week 3
Statistical analysis description: Week 3	
Comparison groups	Placebo v DVS SR Low Dose

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.248
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.713
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.402
upper limit	1.265

Statistical analysis title	Analysis of CGI-I Response at Week 3
Statistical analysis description: Week 3	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.048
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.564
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.995

Statistical analysis title	Analysis of CGI-I Response at Week 4
Statistical analysis description: Week 4	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.21
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.708
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.412
upper limit	1.216

Statistical analysis title	Analysis of CGI-I Response at Week 4
Statistical analysis description: Week 4	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.893
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.964
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.564
upper limit	1.646

Statistical analysis title	Analysis of CGI-I Response at Week 6
Statistical analysis description: Week 6	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.228
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.714
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.413
upper limit	1.235

Statistical analysis title	Analysis of CGI-I Response at Week 6
Statistical analysis description: Week 6	
Comparison groups	Placebo v DVS SR High Dose

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.751
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.916
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.531
upper limit	1.579

Statistical analysis title	Analysis of CGI-I Response at Week 8
Statistical analysis description:	
Week 8	
Comparison groups	Placebo v DVS SR Low Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.925
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.561
upper limit	1.689

Statistical analysis title	Analysis of CGI-I Response at Week 8
Statistical analysis description:	
Week 8	
Comparison groups	Placebo v DVS SR High Dose
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.342
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.764
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.438
upper limit	1.331

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from informed consent and assent through the first follow up visit (Week 11) for non-serious AEs; the second follow up visit (Week 13) for serious AEs (SAEs); or at Week 8 for participants entering the extension study.

Adverse event reporting additional description:

The same event may appear as both an AE and an SAE. However, what is presented are distinct events. An event may be categorised as serious in 1 participant and as non-serious in another participant, or 1 participant may have experienced both a serious and non-serious event during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matched placebo tablets administered once daily for 8 weeks (treatment phase), followed by placebo tablets administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Reporting group title	DVS SR Low Dose

Reporting group description:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 20, 25 or 35 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Reporting group title	DVS SR High Dose

Reporting group description:

DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 25, 35 or 50 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study.

Serious adverse events	Placebo	DVS SR Low Dose	DVS SR High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 120 (1.67%)	2 / 122 (1.64%)	1 / 121 (0.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Skin and subcutaneous tissue disorders			
Dermatomyositis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 122 (0.00%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Aggression			
subjects affected / exposed	0 / 120 (0.00%)	1 / 122 (0.82%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 120 (0.83%)	1 / 122 (0.82%)	0 / 121 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 122 (0.00%)	1 / 121 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	DVS SR Low Dose	DVS SR High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 120 (28.33%)	46 / 122 (37.70%)	53 / 121 (43.80%)
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 120 (12.50%)	22 / 122 (18.03%)	25 / 121 (20.66%)
occurrences (all)	23	29	44
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 120 (1.67%)	4 / 122 (3.28%)	9 / 121 (7.44%)
occurrences (all)	3	4	9
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	9 / 120 (7.50%)	7 / 122 (5.74%)	11 / 121 (9.09%)
occurrences (all)	10	7	14
Nausea			

subjects affected / exposed	7 / 120 (5.83%)	12 / 122 (9.84%)	14 / 121 (11.57%)
occurrences (all)	7	13	15
Vomiting			
subjects affected / exposed	4 / 120 (3.33%)	1 / 122 (0.82%)	9 / 121 (7.44%)
occurrences (all)	4	1	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 120 (0.83%)	7 / 122 (5.74%)	4 / 121 (3.31%)
occurrences (all)	1	8	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 120 (1.67%)	8 / 122 (6.56%)	7 / 121 (5.79%)
occurrences (all)	2	8	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2011	The key secondary endpoint was changed from CGI-I to CGI-S. The physical examination assessment performed at the early termination before Week 8 visit was revised for consistency with those performed at other visits. Blood and ketones were added to the urinalysis laboratory assessment and urinalysis microanalysis was deleted.
14 April 2011	Updated stratification factors to indicate that participants would be stratified by both age and country. Exclusion criterion 27 for the screening visit was corrected to reflect that participants who were dependents of investigational site staff members to participants who were dependents of Pfizer employees directly involved in the conduct of the study were not eligible for the study. The tests/procedures/assessments listed for the unscheduled visit were corrected to reflect that vital sign measurements included collection of temperature and respiratory rate and to reflect that concomitant treatment information was collected. Additional details were added to describe the planned interim analysis.
13 July 2011	The schedule of activities was updated to reflect clearly that blood chemistry laboratory assessments completed at screening and Week 8 visits included liver function tests, serum lipids, serum creatinine, and blood urea nitrogen or urea. Inclusion criterion 1 was modified to require participants to be a minimum of 7 years of age at the screening visit. Exclusion criterion 22 for the screening visit was clarified regarding first degree relative with bipolar disorder. Text was clarified to reflect that no repackaging or labelling of study drug containers was done at the site that would obscure the Pfizer label. Text was revised to reflect that participants who reached the age of majority, as recognised by local law, during study participation signed the informed consent document. Text specific to urine drug screen information was updated. Text was corrected to clarify that the efficacy assessments (CDRS-R, CGI-S, and CGI-I) were not completed at the Week 9 visit. Repetitive information describing the interim analysis was removed.
22 May 2013	Revised Inclusion & Exclusion Criteria at Screening & Exclusion Criteria at baseline. Additional instruction regarding contraception requirements, increased post-study contraception requirements & changed "medically approved contraception" to "highly effective contraception" for male & female sexually active participants. Removed text relating to clinical studies in adults with MDD & deleted historical numbers of adult studies. Separated secondary objectives into key & other; clarified other objectives. Revised term "final on-therapy" to "Week 8". Revised text to add storage requirements. Clarified collection requirements for prior psychiatric treatments & added examples of permitted concomitant treatments. Added linezolid, methylene blue & selegiline to monoamine oxidase inhibitor category in prohibited concomitant medications. Added provision for consideration of occasional use of prohibited treatments. Clarified assignment of participant numbers via Impala & clarified sections of K-SADS-PL to be completed. Clarified definition of screen failure. Added requirement for investigator review of baseline echocardiogram; revised a requirement to a recommendation that the first dose should be taken on-site. Clarified study visit schedule for participants who do not taper, & that the taper phase may not have been extended. Clarified several study assessments: general corrections to study visit names, collection timeframes & added rater requirement reference; vital signs, pregnancy test, laboratory, pharmacokinetic sampling (fasting requirements), psychiatric evaluation, various scales, K-SADS-PL, Columbia-Suicide Severity Rating Scale (C-SSRS), & risk assessment was added. Clarified AE/SAE classification, reporting period, causality assessment, Hy's Law criteria, exposure in utero, & overdose: specified the case report forms to be completed. Clarified the timing/population of the interim analysis, the IDMC study responsibilities & the Pfizer record retention policy.

13 June 2014	Grammatical revisions & typographical error corrections: "legal guardian", "legally acceptable guardian" &"legally acceptable representative" revised to "parent(s)/legal guardian(s)"throughout; "clinical trial" revised to "clinical study" throughout & "study medication" & "investigational product" revised to "study drug" throughout where appropriate. Added specific studies "(B2061030 & B2061031)" to follow "extension study" for clarification. Clarified timing of CGI-I endpoint. Clarified requirements for roll-over to extension study. Deleted requirement to enrol approximately the same number of children & adolescents & deleted requirement for an approximate 40-60 gender ratio within each age group. Clarified contraception requirements; clarified the following exclusion criteria: allergy to study drugs, contraception requirements & familial exclusions. Clarified drug storage requirements. Clarified the Medication Error case report form page to be a type of AE case report form page. Specified the placebo swallow test was conducted at the study site. Permitted as-needed use of over-the-counter sleeping preparations & temporary use of a sedative-hypnotic for insomnia. Clarified that informed consent/assent was obtained at the screening visit; clarified that screening tests, assessments & procedures did not need to be completed in a single visit; clarified that where possible the same rater was used for the Tanner, clarified pregnancy tests were for all female participants regardless of age, sexual activity or menstrual status, clarified lifestyle discussion & clarified use of age-appropriate C-SSRS version. Clarified screen failure criteria. Clarified definitions for liver injury, hospitalisation, exposure during pregnancy, occupational exposure definition, and withdrawal for AE. Revised planned interim analysis for when at least 75% of total participants had completed or had the opportunity to complete the 8-week double-blind treatment phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 August 2011	The first study interruption was initiated in Aug 2011 when enrolment was open and the first participant screened on 03 Aug 2011. On 03 Aug 2011, the Food and Drug Administration (FDA) requested information regarding bioanalytical data generated at Cetero Research, Houston (Cetero) from 01 Apr 2005 to 15 Jun 2010; this request resulted in Pfizer's voluntary suspension of the Phase 3 paediatric program until further information was obtained regarding Study 3151A6-2000-US (Study 2000). Study 2000, a DVS SR Phase 2a Paediatric MDD study, utilised Cetero to generate pharmacokinetic data that informed the dosing design of the Phase 3 program during the time period of concern. Pfizer notified the US FDA of the voluntary suspension of this study on 23 Sep 2011. It was determined that changes to results for desvenlafaxine concentrations in urine did not affect the dosing recommendations for the Phase 3 paediatric MDD program.	02 November 2011

26 November 2014	As described in a letter to the FDA, dated 26 Nov 2014, Pfizer temporarily suspended screening and randomisation activities for studies B2061014 and B2061032 as a result of a blister card packaging quality issue identified in study B2061031. Pfizer completed on-site sponsor review of the deactivated blister card inventory and determined that there was no impact to participant safety. On 02 Dec 2014, the sites were notified that a temporary, 14-day extension to the 28-day Screening Period had been granted for participants who entered the screening phase on or before 21 Nov 2014 and who were currently participating in the screening phase of the study. This temporary extension to the Screening Period was provided to accommodate a delay in study drug availability. On 18 Dec 2014, Pfizer notified investigators that the DVS SR Phase 3 Paediatric MDD study B2061032 was restored to the status of actively recruiting and investigators were informed that they could proceed with screening and randomisation activities for participants currently in the screening phase and for new participants.	18 December 2014

Notes:

Limitations and caveats

None reported