Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Fluoxetine-Referenced, 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	2008-002063-13
Trial protocol	Outside EU/EEA
Global end of trial date	20 March 2015

Results information

Result version number	v1 (current)
This version publication date	17 March 2016
First version publication date	17 March 2016

Trial information

Trial identification

Sponsor protocol code	B2061014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01372150
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, clinicaltrials.gove_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	20 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, fluoxetine referenced parallel group study of the efficacy, safety and tolerability of desvenlafaxine succinate sustained release formulation (DVS SR) in the treatment of child (ages 7 to 11 years) and adolescent (ages 12 to 17 years) outpatients with major depressive disorder (MDD).

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 (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 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	Mexico: 30
Country: Number of subjects enrolled	United States: 309
Worldwide total number of subjects	339
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)	130
Adolescents (12-17 years)	209
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 were screened within 28 days of Day 1.

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:

Placebo tablets and capsules administered once daily for 8 weeks (treatment phase), followed by placebo tablets and capsules administered once daily as appropriate for 1 week (taper/transition phase).

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:

Matching placebo tablets administered orally, once daily for 8 weeks (treatment phase), followed by placebo tablets administered once daily as appropriate for 1 week (taper/transition phase).

Investigational medicinal product name	Placebo for fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo capsules administered orally, once daily for 8 weeks (treatment phase), followed by placebo capsules administered once daily as appropriate for 1 week (taper/transition phase).

Arm title	Fluoxetine

Arm description:

Fluoxetine capsules, 10 milligrams (mg), administered once daily for the first week of treatment (titration phase) then 20 mg administered once daily for the next 7 weeks of treatment, followed by placebo capsules administered once daily as appropriate for 1 week (taper/transition phase).

Arm type	Active comparator
Investigational medicinal product name	Fluoxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Fluoxetine capsules 10 mg administered orally once daily for the first week of treatment (titration phase) then 20 mg administered once daily for the next 7 weeks of treatment, followed by placebo capsules administered once daily for 1 week as appropriate (taper/transition phase).

Arm title	Desvenlafaxine Succinate Sustained Release (DVS SR)

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) (taper phase) or 25 mg (transition phase) administered once daily as appropriate for 1 week.

Arm type	Experimental
Investigational medicinal product name	Desvenlafaxine succinate sustained release
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 orally 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) (taper phase) or 25 mg (transition phase) administered once daily as appropriate for 1 week.

Number of subjects in period 1	Placebo	Fluoxetine	Desvenlafaxine Succinate Sustained Release (DVS SR)
Started	112	112	115
Completed	99	99	99
Not completed	13	13	16
Consent withdrawn by subject	2	7	2
Adverse event, non-fatal	2	1	2
Other	1	-	2
Lost to follow-up	4	5	6
Lack of efficacy	3	-	1
Protocol deviation	1	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets and capsules administered once daily for 8 weeks (treatment phase), followed by placebo tablets and capsules administered once daily as appropriate for 1 week (taper/transition phase).	
Reporting group title	Fluoxetine
Reporting group description:	
Fluoxetine capsules, 10 milligrams (mg), administered once daily for the first week of treatment (titration phase) then 20 mg administered once daily for the next 7 weeks of treatment, followed by placebo capsules administered once daily as appropriate for 1 week (taper/transition phase).	
Reporting group title	Desvenlafaxine Succinate Sustained Release (DVS SR)
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) (taper phase) or 25 mg (transition phase) administered once daily as appropriate for 1 week.	

Reporting group values	Placebo	Fluoxetine	Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects	112	112	115
Age categorical Units: Subjects			
Age Continuous | Units: Years arithmetic mean standard deviation	 12.6 ± 2.89	 12.6 ± 2.89	 12.9 ± 3.12
Gender, Male/Female Units: Participants			
Male	48	55	52
Female	64	57	63

Reporting group values	Total		
Number of subjects	339		
Age categorical Units: Subjects			
Age Continuous | Units: Years arithmetic mean standard deviation	 -		
Gender, Male/Female Units: Participants			
Male	155		
Female	184		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo tablets and capsules administered once daily for 8 weeks (treatment phase), followed by placebo tablets and capsules administered once daily as appropriate for 1 week (taper/transition phase).	
Reporting group title	Fluoxetine
Reporting group description:	
Fluoxetine capsules, 10 milligrams (mg), administered once daily for the first week of treatment (titration phase) then 20 mg administered once daily for the next 7 weeks of treatment, followed by placebo capsules administered once daily as appropriate for 1 week (taper/transition phase).	
Reporting group title	Desvenlafaxine Succinate Sustained Release (DVS SR)
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) (taper phase) or 25 mg (transition phase) administered once daily as appropriate for 1 week.	

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 presented.	
End point type	Primary
End point timeframe:	
Baseline and Week 8	

End point values	Placebo	Fluoxetine	Desvenlafaxine Succinate Sustained Release (DVS SR)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	101	99	
Units: Score on a Scale				
arithmetic mean (standard error)	-23.07 (± 1.18)	-24.79 (± 1.17)	-22.61 (± 1.17)	

Statistical analyses

Statistical analysis title	Fluoxetine versus Placebo
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.226
Method	Mixed-effects model for repeated measure
Parameter estimate	Mean difference (final values)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	4.48

Statistical analysis title	DVS SR versus Placebo
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.739
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	2.3

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 presented.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Placebo	Fluoxetine	Desvenlafaxine Succinate Sustained Release (DVS SR)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	101	99	
Units: Score on a Scale				
arithmetic mean (standard error)	-1.71 (± 0.12)	-1.88 (± 0.12)	-1.7 (± 0.11)	

Statistical analyses

Statistical analysis title	Fluoxetine versus Placebo
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.224
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.46

Statistical analysis title	DVS SR versus Placebo
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.944
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.27

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 = more affected.

End point type	Secondary

End point timeframe:

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

End point values	Placebo	Fluoxetine	Desvenlafaxine Succinate Sustained Release (DVS SR)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	105	111	
Units: Percentage of Participants				
number (not applicable)				
Week 1, Very Much Improved (n=102, 101, 111)	1	3	2.7	
Week 1, Much Improved (n=102, 101, 111)	7.8	11.9	6.3	
Week 1, Minimally Improved (n=102, 101, 111)	46.1	35.6	43.2	
Week 1, No Change (n=102, 101, 111)	43.1	47.5	45.9	
Week 1, Minimally Worse (n=102, 101, 111)	2	2	1.8	
Week 1, Much Worse (n=102, 101, 111)	0	0	0	
Week 1, Very Much Worse (n=102, 101, 111)	0	0	0	
Week 2, Very Much Improved (n=103, 105, 110)	3.9	6.7	3.6	
Week 2, Much Improved (n=103, 105, 110)	25.2	26.7	31.8	
Week 2, Minimally Improved (n=103, 105, 110)	38.8	42.9	44.5	
Week 2, No Change (n=103, 105, 110)	30.1	22.9	19.1	
Week 2, Minimally Worse (n=103, 105, 110)	1.9	1	0.9	
Week 2, Much Worse (n=103, 105, 110)	0	0	0	
Week 2, Very Much Worse (n=103, 105, 110)	0	0	0	
Week 3, Very Much Improved (n=105, 102, 107)	13.3	14.7	7.5	
Week 3, Much Improved (n=105, 102, 107)	29.5	36.3	42.1	
Week 3, Minimally Improved (n=105, 102, 107)	41	36.3	38.3	
Week 3, No Change (n=105, 102, 107)	15.2	11.8	11.2	
Week 3, Minimally Worse (n=105, 102, 107)	1	1	0.9	
Week 3, Much Worse (n=105, 102, 107)	0	0	0	
Week 3, Very Much Worse (n=105, 102, 107)	0	0	0	
Week 4, Very Much Improved (n=101, 101, 100)	15.8	13.9	20	

Week 4, Much Improved (n=101, 101, 100)	38.6	47.5	44	
Week 4, Minimally Improved (n=101, 101, 100)	29.7	27.7	25	
Week 4, No Change (n=101, 101, 100)	13.9	9.9	10	
Week 4, Minimally Worse (n=101, 101, 100)	2	1	1	
Week 4, Much Worse (n=101, 101, 100)	0	0	0	
Week 4, Very Much Worse (n=101, 101, 100)	0	0	0	
Week 6, Very Much Improved (n=100, 100, 102)	18	26	23.5	
Week 6, Much Improved (n=100, 100, 102)	41	45	45.1	
Week 6, Minimally Improved (n=100, 100, 102)	34	24	20.6	
Week 6, No Change (n=100, 100, 102)	6	5	9.8	
Week 6, Minimally Worse (n=100, 100, 102)	0	0	0	
Week 6, Much Worse (n=100, 100, 102)	1	0	0	
Week 6, Very Much Worse (n=100, 100, 102)	0	0	0	
Week 8, Very Much Improved (n=99, 101, 99)	27.3	30.7	23.2	
Week 8, Much Improved (n=99, 101, 99)	35.4	47.5	45.5	
Week 8, Minimally Improved (n=99, 101, 99)	32.3	16.8	21.2	
Week 8, No Change (n=99, 101, 99)	4	4	9.1	
Week 8, Minimally Worse (n=99, 101, 99)	1	1	1	
Week 8, Much Worse (n=99, 101, 99)	0	0	0	
Week 8, Very Much Worse (n=99, 101, 99)	0	0	0	

Statistical analyses

Statistical analysis title	Fluoxetine versus Placebo - Week 1
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.924 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	DVS SR versus Placebo - Week 1
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.698 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	Fluoxetine versus Placebo - Week 2
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.214 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	DVS SR versus Placebo - Week 2
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.113 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	Fluoxetine versus Placebo - Week 3
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.314 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	DVS SR versus Placebo - Week 3
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.659 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	Fluoxetine versus Placebo - Week 4
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.577 [7]
Method	Cochran-Mantel-Haenszel

Notes:

[7] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	DVS SR versus Placebo - Week 4
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.187 [8]
Method	Cochran-Mantel-Haenszel

Notes:

[8] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	Fluoxetine versus Placebo - Week 6
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.051 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	DVS SR versus Placebo - Week 6
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.266 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	Fluoxetine versus Placebo - Week 8
Comparison groups	Placebo v Fluoxetine

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.095 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[11] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

Statistical analysis title	DVS SR versus Placebo - Week 8
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.852 [12]
Method	Cochran-Mantel-Haenszel

Notes:

[12] - P-value obtained from the Cochran-Mantel-Haenszel test for the alternative hypothesis of "Row Mean Scores Differences".

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), 2 (much improved), or 3 (minimally 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	Fluoxetine	Desvenlafaxine Succinate Sustained Release (DVS SR)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	105	111	
Units: Percentage of Participants				
number (not applicable)				
Week 1 (n=102, 101, 111)	8.82	14.85	9.01	
Week 2 (n=103, 105, 110)	29.13	33.33	35.45	
Week 3 (n=105, 102, 107)	42.86	50.98	49.53	
Week 4 (n=101, 101, 100)	54.46	61.39	64	
Week 6 (n=100, 100, 102)	59	71	68.63	
Week 8 (n=99, 101, 99)	62.63	78.22	68.69	

Statistical analyses

Statistical analysis title	Fluoxetine versus Placebo - Week 1
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.186 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.226
upper limit	1.335

Notes:

[13] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	DVS SR versus Placebo - Week 1
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.984 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.382
upper limit	2.567

Notes:

[14] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	Fluoxetine versus Placebo - Week 2
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.462 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.795
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.431
upper limit	1.465

Notes:

[15] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	DVS SR versus Placebo - Week 2
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.297 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.726
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.399
upper limit	1.324

Notes:

[16] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	Fluoxetine versus Placebo - Week 3
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.194 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.391
upper limit	1.21

Notes:

[17] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	DVS SR versus Placebo - Week 3
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.272 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.732

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.419
upper limit	1.277

Notes:

[18] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	Flouxetine versus Placebo - Week 4
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.313 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.748
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.426
upper limit	1.314

Notes:

[19] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	DVS SR versus Placebo - Week 4
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.157 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.663
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.376
upper limit	1.171

Notes:

[20] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	Flouxetine versus Placebo - Week 6
Comparison groups	Placebo v Fluoxetine

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.072 [21]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.319
upper limit	1.05

Notes:

[21] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	DVS SR versus Placebo - Week 6
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.135 [22]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.356
upper limit	1.149

Notes:

[22] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	Flouxetine versus Placebo - Week 8
Comparison groups	Placebo v Fluoxetine
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.017 [23]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.465
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.249
upper limit	0.871

Notes:

[23] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

Statistical analysis title	DVS SR versus Placebo - Week 8
Comparison groups	Placebo v Desvenlafaxine Succinate Sustained Release (DVS SR)
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.343 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.751
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.415
upper limit	1.357

Notes:

[24] - Logistic Regression using Response (Y/N) at each time point (excluding Week 9) as a response variable and treatment, age group and country as factors.

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 9 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 categorized 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	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo tablets and capsules administered once daily for 8 weeks (treatment phase), followed by placebo tablets and capsules administered once daily as appropriate for 1 week (taper/transition phase).

Reporting group title	DVS SR

Reporting group description:

DVS SR capsules 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) (taper phase) or 25 mg (transition phase) administered once daily as appropriate for 1 week.

Reporting group title	Fluoxetine

Reporting group description:

Fluoxetine capsules 10 mg administered once daily for the first week of treatment (titration phase) then 20 mg administered once daily for the next 7 weeks of treatment, followed by placebo capsules administered once daily for 1 week as appropriate (taper/transition phase).

Serious adverse events	Placebo	DVS SR	Fluoxetine
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 112 (0.00%)	2 / 115 (1.74%)	2 / 112 (1.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Disinhibition			
subjects affected / exposed	0 / 112 (0.00%)	1 / 115 (0.87%)	0 / 112 (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
Suicidal ideation			

subjects affected / exposed	0 / 112 (0.00%)	1 / 115 (0.87%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 112 (0.00%)	0 / 115 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 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	Fluoxetine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 112 (39.29%)	47 / 115 (40.87%)	39 / 112 (34.82%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 112 (5.36%)	7 / 115 (6.09%)	3 / 112 (2.68%)
occurrences (all)	6	9	3
Headache			
subjects affected / exposed	21 / 112 (18.75%)	19 / 115 (16.52%)	16 / 112 (14.29%)
occurrences (all)	29	32	24
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 112 (1.79%)	2 / 115 (1.74%)	6 / 112 (5.36%)
occurrences (all)	2	2	6
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 112 (6.25%)	15 / 115 (13.04%)	9 / 112 (8.04%)
occurrences (all)	9	17	9
Nausea			
subjects affected / exposed	10 / 112 (8.93%)	8 / 115 (6.96%)	13 / 112 (11.61%)
occurrences (all)	11	9	14
Vomiting			
subjects affected / exposed	4 / 112 (3.57%)	5 / 115 (4.35%)	7 / 112 (6.25%)
occurrences (all)	5	5	8
Infections and infestations			

Influenza			
subjects affected / exposed	0 / 112 (0.00%)	6 / 115 (5.22%)	2 / 112 (1.79%)
occurrences (all)	0	6	3
Nasopharyngitis			
subjects affected / exposed	8 / 112 (7.14%)	6 / 115 (5.22%)	7 / 112 (6.25%)
occurrences (all)	8	6	7
Upper respiratory tract infection			
subjects affected / exposed	6 / 112 (5.36%)	6 / 115 (5.22%)	4 / 112 (3.57%)
occurrences (all)	6	6	4

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 changed from CGI I to CGI S. The description of the PE assessments at the ET Before Week 8 visit corrected to be consistent with the PE assessments at the other visits. Blood and ketones were added to the U/A assessment and the U/A microanalysis was deleted.
17 May 2011	A correction in the text was necessary to specify that subjects are instructed to take 2 tablets/day during the taper phase or 1 tablet/day during the transition phase.
14 July 2011	Schedule of Activities was updated to clarify that LFTs, serum lipids, serum creatinine and BUN or urea are collected as part of the blood chemistry evaluations, at the Screening and Week 8 visits. Inclusion criterion #1 has been modified requiring subjects to be a minimum of 7 years of age at the screening visit. Exclusion criterion #22 has been clarified regarding first-degree relative with bipolar disorder. Clarification was added to allow additional labeling on the study drug packaging if this does not obscure the Pfizer label. Revised the prohibited timeframe for formal psychotherapy from 90 days to 30 days, and deleted investigational procedures from the prohibited list. Text revised to clarify subjects who must sign an informed consent form are those reaching the age of majority rather than reaching the age of 18 years. Addition of atomoxetine, methaqualone and the phenothiazine class to the UDS testing list.
22 May 2013	Schedule of activities was updated as follows: study visit naming conventions; provided additional wording regarding study visits out of window; provided additional wording regarding subjects who do not taper; clarified the information collected in the comprehensive psychiatric evaluation, added risk assessment wording. Revised term “final on-therapy” to “Week 8” in Endpoints. Inclusion and exclusion criteria were updated, contraception requirements and definition of childbearing were clarified, history of hypertension and suicide behavior ad baseline were clarified, suicidal ideation exclusion and risk assessment wording was also clarified. Lenth of time for post-study contraception was updated; medication error section was added. Double-Blind Treatment section was revised to clarify the study visit treatment phases and changed the requirement that the first dose should be taken on-site to a recommendation. Permitted and prohibited concomitant treatments were modified; definition of screen fail was clarified. Requirement for PI review of baseline ECG was added. Study visit schedule for participants who did not taper was clarified. Hy's Law criteria clarified, causality assessment definition clarified (AEs), reporting of exposures in utero clarified.

13 June 2014	"Legal guardian", "legally acceptable guardian" and "legally acceptable representative" revised to "parent(s)/legal guardian(s)" throughout; "clinical trial" revised to "clinical study" throughout and "study medication" and "investigational product" revised to "study drug" throughout where appropriate. Clarified approved use of fluoxetine and timing of CGI-I endpoint; clarified requirements for roll-over to extension study; revised approximate number of participants to delete requirement to enroll approximately the same number of children and adolescents; deleted requirement for an approximate 40-60 gender ratio within each age group. Clarified contraception requirements (inclusion criteria) and allergy to study drugs, contraception requirements and familial exclusion (exclusion criteria). Clarified that the placebo swallow test will be conducted at the study site; clarified to permit as-needed use of over-the-counter sleeping preparations and temporary use of a sedative-hypnotic for insomnia. Clarified informed consent/assent must be obtained at screening visit and that screening tests, assessments and procedures do not need to be completed in a single screening visit; clarified that same rater should be used for the Tanner and pregnancy tests are for all female participants regardless of age, sexual activity or menstrual status, clarified lifestyle discussion and use of age-appropriate C-SSRS version. Clarified screen failure criteria, specified first dose of study drug to be taken on-site, added study drug compliance assessment to the Weeks 5 & 7 study visits; clarified the liver-injury definition, the hospitalization definition, and the exposure during pregnancy and occupational exposure definitions as well as definition of withdrawal for AE. Revised interim analysis to allow for planned interim analysis when at least 75% of total participants have 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? No

Limitations and caveats

None reported