Clinical trial results:
A 6-MONTH, OPEN-LABEL, MULTI-CENTER, FLEXIBLE-DOSE EXTENSION STUDY TO THE B2061014 STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF DESVENLAFAXINE SUCCINATE SUSTAINED-RELEASE (DVS SR) TABLETS IN THE TREATMENT OF CHILDREN AND ADOLESCENT OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER

Summary

EudraCT number	2008-002064-34
Trial protocol	Outside EU/EEA
Global end of trial date	21 October 2015

Results information

Result version number	v1 (current)
This version publication date	07 May 2016
First version publication date	07 May 2016

Trial information

Trial identification

Sponsor protocol code	B2061031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	3151A6-3357: 3151A6-3357

Notes:

Sponsors

Sponsor organisation name	10017
Sponsor organisation address	235 E 42nd Street, New York, NY, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center,, Pfizer Inc., 01 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 01 18007181021, 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?	Yes
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	21 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2015
Global end of trial reached?	Yes
Global end of trial date	21 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a 6-month, open-label, flexible-dose study evaluating desvenlafaxine succinate sustained release (DVS SR) in the treatment of child and adolescent outpatients with major depressive disorder (MDD) to evaluate safety, tolerability and efficacy of DVS SR.

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

Evidence of a personally signed and dated informed consent and assent documents indicating that the subject and a legally acceptable representative were informed of all pertinent aspects of the study was required.

The investigator was to inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator became aware of.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2012
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: 28
Country: Number of subjects enrolled	United States: 240
Worldwide total number of subjects	268
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)	108
Adolescents (12-17 years)	160
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who completed the 8-week, double-blind treatment phase of Desvenlafaxine Succinate Sustained Release (DVS SR B2061014 and completed the 1-week transition phase (week 9) of the short-term study were eligible to participate in this study (DVS SR B2061031).

Pre-assignment

Screening details:

Subjects met all eligibility requirements at the Baseline visit prior to randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / DVS SR

Arm description:

Placebo in previous study B2061014 / DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

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

Dosage and administration details:

placebo plus DVS SR flexible dose 20 mg – 50 mg

Arm title	Fluoxetine / DVS SR

Arm description:

Fluoxetine 20 mg in previous study B2061014 /DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

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

Dosage and administration details:

Fluoxetine plus DVS SR flexible dose 20 mg – 50 mg

Arm title	Desvenlafaxine Succinate Sustained Release / DVS SR

Arm description:

DVS SR weight based (25 mg, 35 mg, 50 mg) in previous study B2061014 / DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

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:

Desvenlafaxine Succinate Sustained Release plus DVS SR flexible dose 20 mg – 50 mg

Number of subjects in period 1	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR
Started	87	89	92
Completed	59	65	62
Not completed	28	24	30
Consent withdrawn by subject	5	7	11
Adverse event, non-fatal	5	4	5
Not specified	2	3	-
Lost to follow-up	8	2	6
Protocol deviation	6	4	5
Lack of efficacy	2	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo / DVS SR
Reporting group description:	
Placebo in previous study B2061014 / DVS SR flexible dose 20 mg – 50 mg in extension study B2061031	
Reporting group title	Fluoxetine / DVS SR
Reporting group description:	
Fluoxetine 20 mg in previous study B2061014 /DVS SR flexible dose 20 mg – 50 mg in extension study B2061031	
Reporting group title	Desvenlafaxine Succinate Sustained Release / DVS SR
Reporting group description:	
DVS SR weight based (25 mg, 35 mg, 50 mg) in previous study B2061014 / DVS SR flexible dose 20 mg – 50 mg in extension study B2061031	

Reporting group values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR
Number of subjects	87	89	92
Age categorical Units: Subjects			
Children (2-11 years)	35	38	35
Adolescents (12-17 years)	52	51	57
Age Continuous | Units: years			
arithmetic mean	12.5	12.4	12.8
standard deviation	± 2.9	± 3.01	± 3.14
Gender, Male/Female			
Safety population - included all randomized participants who received at least 1 dose of study drug. Total = sum across Arm/Groups = Combination of 3 groups from previous study B2061014 who received DVS SR flexible dose 20 mg – 50 mg in extension study B2061031.			
Units: Participants			
Female	47	39	49
Male	40	50	43

Reporting group values	Total		
Number of subjects	268		
Age categorical Units: Subjects			
Children (2-11 years)	108		
Adolescents (12-17 years)	160		
Age Continuous | Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Safety population - included all randomized participants who received at least 1 dose of study drug. Total = sum across Arm/Groups = Combination of 3 groups from previous study B2061014 who received DVS SR flexible dose 20 mg – 50 mg in extension study B2061031.			
Units: Participants			
Female	135		

Male	133		

End points

End points reporting groups

Reporting group title	Placebo / DVS SR
Reporting group description:	
Placebo in previous study B2061014 / DVS SR flexible dose 20 mg – 50 mg in extension study B2061031	
Reporting group title	Fluoxetine / DVS SR
Reporting group description:	
Fluoxetine 20 mg in previous study B2061014 /DVS SR flexible dose 20 mg – 50 mg in extension study B2061031	
Reporting group title	Desvenlafaxine Succinate Sustained Release / DVS SR
Reporting group description:	
DVS SR weight based (25 mg, 35 mg, 50 mg) in previous study B2061014 / DVS SR flexible dose 20 mg – 50 mg in extension study B2061031	

Primary: Percentage of Participants Experiencing a Treatment Emergent Adverse Event

End point title	Percentage of Participants Experiencing a Treatment Emergent Adverse Event[1]
End point description:	
End point type	Primary
End point timeframe:	
Week 9 (B2061014)/Day 1 (B2061031) to Week 26 of the B2061031 Study	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analyses was planned for this primary endpoint	

End point values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	89	92	
Units: Percentage of Participants				
number (not applicable)	70.1	75.3	73.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 26 in the Children's Depression Rating Scale, Revised (CDRS-R) Total Score Based on Observed Cases

End point title	Change From Baseline at Week 26 in the Children's Depression Rating Scale, Revised (CDRS-R) Total Score Based on Observed Cases

End point description:

End point type	Secondary

End point timeframe:

Week 9 (B2061014)/Day 1 (B2061031) to Week 26 of the B2061031 Study

End point values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	61	56	
Units: Score on a Scale				
arithmetic mean (standard deviation)	-5.55 (± 10.8)	-6.41 (± 11.5)	-5.32 (± 7.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 26 in the Clinical Global Impression of Severity (CGI-S) Score Based on Observed Cases

End point title	Change From Baseline at Week 26 in the Clinical Global Impression of Severity (CGI-S) Score Based on Observed Cases

End point description:

End point type	Secondary

End point timeframe:

Week 9 (B2061014)/Day 1 (B2061031) to Week 26 of the B2061031 Study

End point values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	61	56	
Units: Score on a Scale				
arithmetic mean (standard deviation)	-0.78 (± 1.23)	-0.77 (± 1.16)	-0.82 (± 0.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a CGI-I Response Defined as a Score of 'Very Much Improved' or 'Much Improved' at Week 26

End point title	Percentage of Participants With a CGI-I Response Defined as a Score of 'Very Much Improved' or 'Much Improved' at Week 26

End point description:

End point type	Secondary

End point timeframe:

Week 9 (B2061014)/Day 1 (B2061031) to Week 26 of the B2061031 Study

End point values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	61	56	
Units: Percentage of Participants				
number (not applicable)	90.9	93.4	92.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Remission as Determined by a 'Remission' CDRS-R Score of ≤28 at Week 26 Based on Observed Cases

End point title	Percentage of Participants With Remission as Determined by a 'Remission' CDRS-R Score of ≤28 at Week 26 Based on Observed Cases

End point description:

End point type	Secondary

End point timeframe:

Week 9 (B2061014)/Day 1 (B2061031) to Week 26 of the B2061031 Study

End point values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	61	56	
Units: Percentage of Participants				
number (not applicable)	74.5	78.7	73.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Clinical Global Impression Improvement (CGI-I) Score at Week 26 Based on Observed Cases

End point title	Percentage of Participants by Clinical Global Impression Improvement (CGI-I) Score at Week 26 Based on Observed Cases

End point description:

End point type	Secondary

End point timeframe:

Week 9 (B2061014)/Day 1 (B2061031) to Week 26 of the B2061031 Study

End point values	Placebo / DVS SR	Fluoxetine / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	61	56	
Units: Percentage of Participants				
number (not applicable)				
Very Much Improved	63.6	63.9	57.1	
Much Improved	27.3	29.5	35.7	
Minimally Improved	3.6	3.3	5.4	
No Change	3.6	1.6	1.8	
Minimally Worse	0	1.6	0	
Much Worse	1.8	0	0	
Very Much Worse	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) recorded from informed consent and assent through Week 30 and Serious Adverse events (SAEs) collected through Week 32 visit. Participants discontinuing prior to Week 28 visit, AEs collected for 14 days and SAEs for 28 days.

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	18.1

Reporting groups

Reporting group title	Placebo / DVS SR

Reporting group description:

Placebo in previous study B2061014/DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

Reporting group title	Desvenlafaxine Succinate Sustained Release / DVS SR

Reporting group description:

DVS SR weight based (25 mg, 35 mg, 50 mg) in previous study B2061014/DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

Reporting group title	Combination

Reporting group description:

Combination of 3 groups from previous study B2061014 who received DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

Reporting group title	Fluoxetine / DVS SR

Reporting group description:

Fluoxetine 20 mg in previous study B2061014 /DVS SR flexible dose 20 mg – 50 mg in extension study B2061031

Serious adverse events	Placebo / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	Combination
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)	3 / 92 (3.26%)	10 / 268 (3.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 87 (0.00%)	1 / 92 (1.09%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 87 (0.00%)	0 / 92 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 87 (1.15%)	0 / 92 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Frustration			
subjects affected / exposed	1 / 87 (1.15%)	0 / 92 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	1 / 87 (1.15%)	0 / 92 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritability			
subjects affected / exposed	1 / 87 (1.15%)	0 / 92 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Self injurious behaviour			
subjects affected / exposed	1 / 87 (1.15%)	0 / 92 (0.00%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	3 / 87 (3.45%)	1 / 92 (1.09%)	5 / 268 (1.87%)
occurrences causally related to treatment / all	3 / 3	1 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 92 (1.09%)	1 / 268 (0.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fluoxetine / DVS SR		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 89 (2.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Frustration			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination, auditory			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Irritability			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Self injurious behaviour			

subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo / DVS SR	Desvenlafaxine Succinate Sustained Release / DVS SR	Combination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 87 (54.02%)	62 / 92 (67.39%)	170 / 268 (63.43%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 87 (0.00%)	3 / 92 (3.26%)	6 / 268 (2.24%)
occurrences (all)	0	3	6
Weight increased			
subjects affected / exposed	7 / 87 (8.05%)	12 / 92 (13.04%)	30 / 268 (11.19%)
occurrences (all)	7	12	30
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 87 (0.00%)	3 / 92 (3.26%)	5 / 268 (1.87%)
occurrences (all)	0	4	6
Fall			
subjects affected / exposed	0 / 87 (0.00%)	2 / 92 (2.17%)	5 / 268 (1.87%)
occurrences (all)	0	2	5
Ligament sprain			

subjects affected / exposed	0 / 87 (0.00%)	3 / 92 (3.26%)	5 / 268 (1.87%)
occurrences (all)	0	3	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 87 (5.75%)	8 / 92 (8.70%)	18 / 268 (6.72%)
occurrences (all)	6	8	19
Headache			
subjects affected / exposed	12 / 87 (13.79%)	19 / 92 (20.65%)	47 / 268 (17.54%)
occurrences (all)	13	38	71
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 87 (2.30%)	3 / 92 (3.26%)	8 / 268 (2.99%)
occurrences (all)	2	3	8
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 87 (3.45%)	3 / 92 (3.26%)	9 / 268 (3.36%)
occurrences (all)	3	3	9
Abdominal pain upper			
subjects affected / exposed	7 / 87 (8.05%)	7 / 92 (7.61%)	22 / 268 (8.21%)
occurrences (all)	7	9	28
Constipation			
subjects affected / exposed	2 / 87 (2.30%)	1 / 92 (1.09%)	6 / 268 (2.24%)
occurrences (all)	4	1	8
Diarrhoea			
subjects affected / exposed	3 / 87 (3.45%)	2 / 92 (2.17%)	10 / 268 (3.73%)
occurrences (all)	5	2	13
Dyspepsia			
subjects affected / exposed	2 / 87 (2.30%)	3 / 92 (3.26%)	5 / 268 (1.87%)
occurrences (all)	2	3	5
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 87 (0.00%)	3 / 92 (3.26%)	4 / 268 (1.49%)
occurrences (all)	0	3	4
Nausea			
subjects affected / exposed	9 / 87 (10.34%)	8 / 92 (8.70%)	31 / 268 (11.57%)
occurrences (all)	11	8	34
Vomiting			

subjects affected / exposed	5 / 87 (5.75%)	6 / 92 (6.52%)	20 / 268 (7.46%)
occurrences (all)	5	6	21
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 87 (1.15%)	5 / 92 (5.43%)	6 / 268 (2.24%)
occurrences (all)	1	6	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 87 (6.90%)	4 / 92 (4.35%)	11 / 268 (4.10%)
occurrences (all)	7	5	13
Epistaxis			
subjects affected / exposed	1 / 87 (1.15%)	1 / 92 (1.09%)	5 / 268 (1.87%)
occurrences (all)	2	1	6
Oropharyngeal pain			
subjects affected / exposed	6 / 87 (6.90%)	1 / 92 (1.09%)	10 / 268 (3.73%)
occurrences (all)	6	1	10
Sinus congestion			
subjects affected / exposed	0 / 87 (0.00%)	3 / 92 (3.26%)	3 / 268 (1.12%)
occurrences (all)	0	3	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 87 (2.30%)	0 / 92 (0.00%)	7 / 268 (2.61%)
occurrences (all)	2	0	7
Irritability			
subjects affected / exposed	3 / 87 (3.45%)	2 / 92 (2.17%)	8 / 268 (2.99%)
occurrences (all)	3	2	8
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 87 (2.30%)	3 / 92 (3.26%)	7 / 268 (2.61%)
occurrences (all)	2	3	7
Myalgia			
subjects affected / exposed	4 / 87 (4.60%)	2 / 92 (2.17%)	6 / 268 (2.24%)
occurrences (all)	5	2	7
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 87 (0.00%)	4 / 92 (4.35%)	5 / 268 (1.87%)
occurrences (all)	0	4	5
Gastroenteritis			
subjects affected / exposed	2 / 87 (2.30%)	2 / 92 (2.17%)	7 / 268 (2.61%)
occurrences (all)	2	2	9
Gastroenteritis viral			
subjects affected / exposed	4 / 87 (4.60%)	5 / 92 (5.43%)	12 / 268 (4.48%)
occurrences (all)	4	5	12
Influenza			
subjects affected / exposed	5 / 87 (5.75%)	1 / 92 (1.09%)	7 / 268 (2.61%)
occurrences (all)	6	1	8
Nasopharyngitis			
subjects affected / exposed	11 / 87 (12.64%)	6 / 92 (6.52%)	21 / 268 (7.84%)
occurrences (all)	12	8	26
Pharyngitis			
subjects affected / exposed	1 / 87 (1.15%)	4 / 92 (4.35%)	7 / 268 (2.61%)
occurrences (all)	1	4	8
Pharyngitis streptococcal			
subjects affected / exposed	2 / 87 (2.30%)	3 / 92 (3.26%)	7 / 268 (2.61%)
occurrences (all)	2	4	8
Sinusitis			
subjects affected / exposed	2 / 87 (2.30%)	3 / 92 (3.26%)	8 / 268 (2.99%)
occurrences (all)	2	3	8
Upper respiratory tract infection			
subjects affected / exposed	7 / 87 (8.05%)	8 / 92 (8.70%)	24 / 268 (8.96%)
occurrences (all)	7	9	26
Viral infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 92 (1.09%)	4 / 268 (1.49%)
occurrences (all)	0	1	4
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 87 (1.15%)	3 / 92 (3.26%)	6 / 268 (2.24%)
occurrences (all)	1	3	6
Decreased appetite			

subjects affected / exposed	3 / 87 (3.45%)	1 / 92 (1.09%)	5 / 268 (1.87%)
occurrences (all)	3	1	5

Non-serious adverse events	Fluoxetine / DVS SR		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 89 (68.54%)		
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	11 / 89 (12.36%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Ligament sprain			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	16 / 89 (17.98%)		
occurrences (all)	20		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3		
Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 89 (8.99%) 12		
Constipation subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 6		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 89 (0.00%) 0		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1		
Nausea subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 15		
Vomiting subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 10		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 89 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1		
Epistaxis subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3		
Oropharyngeal pain			

subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Sinus congestion			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Irritability			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	5		
Gastroenteritis viral			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	6		
Pharyngitis			

subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	3		
Pharyngitis streptococcal			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	10		
Viral infection			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2011	Provided clarification for: dosing rationale, additional labeling on study drug packaging, informed consent text revised, added methaqualone to UDS testing, change in study drug blister packaging, deleted investigational procedures from Prohibited Concomitant Treatment.
22 May 2013	Combined / clarified efficacy endpoints. Deleted Final On-Therapy Visit reference. Clarified omission of taper. Updated Schedule of activities: study visit naming conventions and out of window wording; subjects who do not taper wording, comprehensive psychiatric evaluation information collected, risk assessment wording. Inclusion/Exclusion criteria updated: "legally acceptable representative" changed to "legal guardian", contraception requirements and definition of childbearing were clarified, length of time for post-study contraception was updated. Subjects requiring a prohibited medication to control a medical condition should not be enrolled, suicidal ideation exclusion and history of suicide behavior exclusion since last visit and risk assessment wording. Medication error section was added and protocol sponsor qualified medical personnel section, rater qualifications, and storage requirement text. Permitted and prohibited concomitant treatments were modified. Subject withdrawal to include those who could not comply with scheduled or required procedures, instruction for lost to follow-up subjects, risk assessment wording. Clarified: study visit schedule for subjects that did not taper, Hy's Law criteria, causality assessment definition (AEs), reporting of exposures in utero. Clarification regarding review of available laboratory/ECG results before randomization. Assessments updated : CRF be completed, weight be measured without shoes; requirement to a recommendation for BP measurement timing, additional details for pregnancy testing, fasting status recommendations, microscopic analysis, types of sympathomimetic drugs, provision of guidance materials text and rater requirements / training, requirements for risk assessment and discontinuation, added risk assessment, added vendor information, deleted End of Trial in a Member State section, added the table of diagnostician and rater requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported