

**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 occurrences (all) | 0 / 87 (0.00%) 0 | 3 / 92 (3.26%) 3 | 5 / 268 (1.87%) 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 occurrences (all) | 5 / 87 (5.75%) 5 | 6 / 92 (6.52%) 6 | 20 / 268 (7.46%) 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 | | |
| Gastroesophageal 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 | | | |

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

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