



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | B2061032 |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 04 September 2015 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 04 September 2015 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

This was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study of DVS SR in the treatment of child (7 to 11 years of age) and adolescent (12 to 17 years of age) outpatients with major depressive disorder (MDD). The study was planned to evaluate the efficacy, safety and tolerability of DVS SR in the treatment of child and adolescent outpatients with MDD. Participants who completed the 8 week, double-blind treatment phase of this study were eligible to participate in a 6 month, open label extension study of DVS SR (B2061030).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

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

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

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

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

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

Dosage and administration details:

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

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | DVS SR Low Dose |
|------------------|-----------------|

Arm description:

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

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

Dosage and administration details:

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

|   |                  |
|---|------------------|
| <b>Arm title</b>  | DVS SR High Dose |
| Arm description:  |                  |
| DVS SR tablets 10 or 20 mg (based on weight at the baseline visit) administered once daily for the first week of treatment (titration phase) then 25, 35 or 50 mg (based on weight at the baseline visit) administered once daily for the next 7 weeks of treatment, followed by 10 or 20 mg (based on weight at the baseline visit) administered once daily for 1 week (taper phase) only for those participants not entering the extension study. |                  |
| Arm type  | Experimental     |
| Investigational medicinal product name  | DVS SR           |
| Investigational medicinal product code  |                  |
| Other name  |                  |
| Pharmaceutical forms  | Tablet           |
| Routes of administration  | Oral use         |

Dosage and administration details:

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

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

## Baseline characteristics

### Reporting groups

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

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

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 363   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |
| In utero                           | 0     |  |  |

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

## End points

### End points reporting groups

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

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

|  |  |
|--|--|
| End point title  | Change from Baseline to Week 8 in the Children's Depression Rating Scale, Revised (CDRS-R) Total Score |
| End point description:<br>Clinician-rated interview-based scale (with both child and parent or guardian) to assess 17 distinct symptom areas to derive an index of depression severity. Discrepancies between informants' responses were resolved by using most impaired rating given by valid informant. Rated on a 7-point scale; range from 1 (no impairment) to 7 (indicates greater impairment). Total score calculated as sum of the 17 items (range 1 to 119); higher score indicates greater impairment. Adjusted mean (common baseline average + adjusted mean change from baseline) presented. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline and Week 8  |  |

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

## Statistical analyses



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

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

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

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

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

## Statistical analyses

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

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

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

|  |  |
|--|--|
| End point title  | Percentage of Participants by Clinical Global Impression Improvement (CGI-I) Score at Weeks 1, 2, 3, 4, 6, and 8 |
| End point description:   |  |
| A 7-point clinician rated scale ranging from 1 (very much improved) to 7 (very much worse). Improvement is defined as a score of 1 (very much improved), 2 (much improved), or 3 (minimally improved) on the scale. Higher score equals (=) more affected. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Weeks 1, 2, 3, 4, 6, and 8   |  |

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

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

## Statistical analyses

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

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

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

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

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

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Analysis of CGI-I Score at Week 3 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Week 3

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

---

**Statistical analysis title**

Analysis of CGI-I Score at Week 4

Statistical analysis description:

Week 4

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v DVS SR Low Dose |
| Number of subjects included in analysis | 229                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           |                           |
| P-value                                 | = 0.254                   |
| Method                                  | Cochran-Mantel-Haenszel   |

---

**Statistical analysis title**

Analysis of CGI-I Score at Week 4

Statistical analysis description:

Week 4

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v DVS SR High Dose |
| Number of subjects included in analysis | 229                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| P-value                                 | = 0.887                    |
| Method                                  | Cochran-Mantel-Haenszel    |

---

**Statistical analysis title**

Analysis of CGI-I Score at Week 6

Statistical analysis description:

Week 6

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v DVS SR Low Dose |
| Number of subjects included in analysis | 229                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           |                           |
| P-value                                 | = 0.475                   |
| Method                                  | Cochran-Mantel-Haenszel   |

---

**Statistical analysis title**

Analysis of CGI-I Score at Week 6

Statistical analysis description:

Week 6

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

**Statistical analysis title**

Analysis of CGI-I Score at Week 8

Statistical analysis description:

Week 8

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v DVS SR Low Dose |
| Number of subjects included in analysis | 229                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           |                           |
| P-value                                 | = 0.696                   |
| Method                                  | Cochran-Mantel-Haenszel   |

**Statistical analysis title**

Analysis of CGI-I Score at Week 8

Statistical analysis description:

Week 8

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v DVS SR High Dose |
| Number of subjects included in analysis | 229                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| P-value                                 | = 0.462                    |
| Method                                  | Cochran-Mantel-Haenszel    |

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with a CGI-I Response Defined as a Score of 'Very Much Improved' or 'Much Improved' |
|-----------------|--|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

## Statistical analyses

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

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



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

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

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

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>           | Analysis of CGI-I Response at Week 3 |
| Statistical analysis description:<br>Week 3 |                                      |
| Comparison groups                           | Placebo v DVS SR Low Dose            |

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

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

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

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

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

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

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

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

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



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | DVS SR Low Dose |
|-----------------------|-----------------|

Reporting group description:

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

|                       |                  |
|-----------------------|------------------|
| Reporting group title | DVS SR High Dose |
|-----------------------|------------------|

Reporting group description:

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

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

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

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

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

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



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

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

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

Notes:

## Limitations and caveats

None reported