Clinical trial results:
6-Month, Multicenter, Open-Label, Flexible-Dose Study To Evaluate Safety, Efficacy, And Tolerability Of Desvenlafaxine Succinate Sustained-Release Tablets In The Treatment Of Child And Adolescent Outpatients With Major Depressive Disorder

Summary

EudraCT number	2008-002067-14
Trial protocol	Outside EU/EEA
Global end of trial date	18 May 2010

Results information

Result version number	v1 (current)
This version publication date	13 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	3151A6-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00669110
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B2061013

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Clinical Trials.gov Call Center, Pfizer Inc, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Clinical Trials.gov Call Center, Pfizer Inc, 001 8007181021, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 March 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 May 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the long-term safety and tolerability of Desvenlafaxine succinate sustained-release (DVS SR) in children and adolescents with major depressive disorder (MDD).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	40
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)	20
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects transitioned from preceding Core study NCT00619619, EudraCT: 2008-002066-57 (3151A6-2000 [B2061012]) on Day 56 to this Extension study NCT00669110, 2008-002067-14 (3151A6-2001 [B2061013]) to continue treatment on a flexible dose schedule. A total of 8 subjects discontinued during Taper/post-study or Follow-up phase of Core study.

Pre-assignment

Screening details:

Baseline (Day-1) in the Extension study = Week 8 (Day 56) in the Core study. However, Baseline for the Clinical Global Impressions Scale -Improvement (CGI-I) and Columbia Suicide-Severity Rating Scale (C-SSRS) = Day-1 in the Core study.

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	DVS SR - Children

Arm description:

Desvenlafaxine succinate sustained-release (DVS SR) formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 10 milligrams (mg), 25 mg, 50 mg, and 100 mg for children 7 to 11 years of age at baseline in the preceding Core study NCT00619619.

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

Dosage and administration details:

DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 10 milligrams (mg), 25 mg, 50 mg, and 100 mg for children 7 to 11 years of age at baseline in the preceding Core study NCT00619619.

Arm title	DVS SR - Adolescents

Arm description:

DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 25 mg, 50 mg, 100 mg, and 200 mg for adolescents 12 to 17 years of age at baseline in the preceding Core study NCT00619619.

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

Dosage and administration details:

DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 25 mg, 50 mg, 100 mg, and 200 mg for adolescents 12 to 17 years of age at baseline in the preceding Core study NCT00619619.

Number of subjects in period 1	DVS SR - Children	DVS SR - Adolescents
Started	20	20
Completed	12	7
Not completed	8	13
Caregiver request	3	2
Physician decision	-	1
Adverse Event	4	3
Withdrawal by Subject	-	2
Protocol Violation	-	5
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	DVS SR - Children
Reporting group description:	
Desvenlafaxine succinate sustained-release (DVS SR) formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 10 milligrams (mg), 25 mg, 50 mg, and 100 mg for children 7 to 11 years of age at baseline in the preceding Core study NCT00619619.	
Reporting group title	DVS SR - Adolescents
Reporting group description:	
DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 25 mg, 50 mg, 100 mg, and 200 mg for adolescents 12 to 17 years of age at baseline in the preceding Core study NCT00619619.	

Reporting group values	DVS SR - Children	DVS SR - Adolescents	Total
Number of subjects	20	20	40
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	9.65	13.55	
standard deviation	± 1.31	± 1.64	-
Gender categorical			
Units: Subjects			
Female	11	9	20
Male	9	11	20

End points

End points reporting groups

Reporting group title	DVS SR - Children

Reporting group description:

Desvenlafaxine succinate sustained-release (DVS SR) formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 10 milligrams (mg), 25 mg, 50 mg, and 100 mg for children 7 to 11 years of age at baseline in the preceding Core study NCT00619619.

Reporting group title	DVS SR - Adolescents

Reporting group description:

DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 25 mg, 50 mg, 100 mg, and 200 mg for adolescents 12 to 17 years of age at baseline in the preceding Core study NCT00619619.

Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

AEs are any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given study treatment. The event does not need to be causally related to the study treatment. SAEs are adverse events that result in death, are ife threatening, require hospitalization or prolongation of hospitalization, result in persistent or significant disability or incapacity, result in cancer, or result in a congenital anomaly or birth defect. Safety population (Baseline=Extension study) includes all treatment assigned subjects with at least 1 dose of study treatment during Extension study NCT00669110.

End point type	Primary

End point timeframe:

Baseline (Extension study) up to Extension study Week 29 Follow up visit

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: Only descriptive data was planned to be reported for this endpoint.

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Adverse Events	13	15		
Serious Adverse Events	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects for Columbia Suicide-Severity Rating Scale (C-SSRS) According to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) Categories

End point title	Number of Subjects for Columbia Suicide-Severity Rating Scale (C-SSRS) According to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) Categories[2]

End point description:

C-SSRS is a subjects rated questionnaire to assess suicidal ideation, suicidal behavior, actual attempts (yes or no responses), and intensity of ideation (rated 1=low severity to 5=high severity). Yes/No responses are mapped to Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories: Completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior, or no suicidal intent. A subjects could have a yes or no response in more than one category. Safety population (Baseline=Core study) includes all treatment assigned subjects with at least 1 dose of study treatment during Core study NCT00619619 and Extension study NCT00669110.

End point type	Primary

End point timeframe:

Postbaseline (greater than equal to [≥] Day 1 in Core study NCT00619619) up to Week 26 (Extension study)

Notes:

[2] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Completed suicide: No	20	20		
Suicide attempt: No	20	20		
Preparatory acts - imminent suicidal behavior: No	20	20		
Suicidal ideation: Yes	0	3		
Suicidal ideation: No	20	17		
Any suicidal behavior and/or ideation: Yes	0	3		
Any suicidal behavior and/or ideation: No	20	17		
Self-injurious behavior, no suicidal intent: No	20	20		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline (Bsl) in Children's Depression Rating Scale – Revised (CDRS-R) Total Score at Final On-therapy Visit

End point title	Change From Baseline (Bsl) in Children's Depression Rating Scale – Revised (CDRS-R) Total Score at Final On-therapy Visit

End point description:

CDRS-R total score: scale measures 17 depressive symptoms, of which 3 are rated 1 to 5 and 14 are rated 1 to 7 (1 = no symptom difficulties; 5 to 7 = severe clinically significant difficulties) for a total score range of 17 to 113. Lower total scores indicate lower intensity of symptoms. Intent to Treat population (ITT): all treatment assigned subjects with a baseline primary efficacy evaluation, at least 1 dose of study treatment, and at least 1 primary efficacy evaluation after first dose in Extension study NCT00669110. Last observation carried forward (LOCF).

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study), Extension study Outpatient Weeks 26 and greater than (>) Week 26 (up to Week 29 or early termination)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline mean	32.4 (± 7.61)	33.7 (± 6.34)		
Change from Bsl Outpatient Week 26	-1.85 (± 5.51)	-1.95 (± 6.85)		
Change from Bsl Outpatient Week >26	-1.85 (± 5.51)	-1.7 (± 6.67)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Remission (Total Score ≤28) Based on Children's Depression Rating Scale – Revised (CDRS-R)

End point title	Percentage of Subjects With Remission (Total Score ≤28) Based on Children's Depression Rating Scale – Revised (CDRS-R)

End point description:

CDRS-R total score: scale measures 17 depressive symptoms, of which 3 are rated 1 to 5 and 14 are rated 1 to 7 (1 = no symptom difficulties; 5 to 7 = severe clinically significant difficulties) for a total score range of 17 to 113. Lower total scores indicate lower intensity of symptoms. Remission defined as a CDRS-R total score ≤28 (coded value of 1). ITT population and LOCF was used.

End point type	Other pre-specified

End point timeframe:

Extension study Outpatient Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26, and >26 (up to Week 29)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of subjects				
number (not applicable)				
Outpatient Week 1	26.7	21.1		
Outpatient Week 2	30	25		
Outpatient Week 4	30	20		
Outpatient Week 6	25	25		
Outpatient Week 10	45	25		
Outpatient Week 14	25	25		
Outpatient Week 18	35	40		
Outpatient Week 22	30	35		

Outpatient Week 26	30	30		
Outpatient Week >26	30	25		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline (Bsl) in Hamilton Rating Scale for Depression 17-item (HAM-D17) Total Score

End point title	Change From Baseline (Bsl) in Hamilton Rating Scale for Depression 17-item (HAM-D17) Total Score

End point description:

HAM-D17 is a clinician-rated interview to measure presence of depressive symptoms in 17 areas (symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss). Total score ranges from 0 to 52; higher scores reflect higher severity of current illness states. ITT population and LOCF was used.

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study), Extension study Outpatient Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26, and >26 (up to Week 29)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline mean	5.15 (± 3.01)	7.45 (± 4.1)		
Change from Bsl Outpatient Week 1	0.53 (± 2.72)	1.79 (± 2.97)		
Change from Bsl Outpatient Week 2	-0.5 (± 2.8)	0.7 (± 3.01)		
Change from Bsl Outpatient Week 4	-0.4 (± 2.28)	-0.95 (± 2.24)		
Change from Bsl Outpatient Week 6	-0.45 (± 2.31)	-0.7 (± 2.68)		
Change from Bsl Outpatient Week 10	-1.3 (± 3.06)	-1.4 (± 2.66)		
Change from Bsl Outpatient Week 14	-0.45 (± 2.58)	-1.65 (± 3.08)		
Change from Bsl Outpatient Week 18	-1.65 (± 2.48)	-2.45 (± 3.1)		
Change from Bsl Outpatient Week 22	-1.05 (± 2.26)	-2.15 (± 3.22)		
Change from Bsl Outpatient Week 26	-1.65 (± 2.94)	-2.35 (± 3.39)		
Change from Bsl Outpatient Week >26	-1.65 (± 2.94)	-2.1 (± 3.37)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With a Categorical Clinical Global Impressions Scales - Severity (CGI-S) Score

End point title	Percentage of Subjects With a Categorical Clinical Global Impressions Scales - Severity (CGI-S) Score

End point description:

CGI-S: 7-point clinician rated scale to assess severity of subject's current illness state; range: 1=normal, not ill at all, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill patients. Higher scores reflect higher severity of current illness states. ITT population and LOCF was used. No subjects had a CGI-S score of 5, 6 or 7 (markedly, severely, or extremely ill), therefore only scores 1 through 4 (normal to moderately ill) are reported.

End point type	Other pre-specified

End point timeframe:

Extension study Outpatient Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26, and >26 (up to Week 29)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of subjects				
number (not applicable)				
Outpatient Week 1: not ill at all	13.3	10.5		
Outpatient Week 1: borderline ill	53.3	10.5		
Outpatient Week 1: mildly ill	26.7	57.9		
Outpatient Week 1: moderately ill	6.7	21.1		
Outpatient Week 2: not ill at all	10	10		
Outpatient Week 2: borderline ill	40	20		
Outpatient Week 2: mildly ill	45	45		
Outpatient Week 2: moderately ill	5	25		
Outpatient Week 4: not ill at all	10	10		
Outpatient Week 4: borderline ill	50	30		
Outpatient Week 4: mildly ill	30	35		
Outpatient Week 4: moderately ill	10	25		
Outpatient Week 6: not ill at all	10	10		
Outpatient Week 6: borderline ill	40	20		
Outpatient Week 6: mildly ill	45	50		
Outpatient Week 6: moderately ill	5	20		
Outpatient Week 10: not ill at all	15	10		
Outpatient Week 10: borderline ill	45	35		
Outpatient Week 10: mildly ill	35	45		
Outpatient Week 10: moderately ill	5	10		
Outpatient Week 14: not ill at all	5	5		
Outpatient Week 14: borderline ill	55	55		
Outpatient Week 14: mildly ill	35	30		
Outpatient Week 14: moderately ill	5	10		
Outpatient Week 18: not ill at all	5	5		
Outpatient Week 18: borderline ill	70	55		
Outpatient Week 18: mildly ill	20	35		
Outpatient Week 18: moderately ill	5	5		
Outpatient Week 22: not ill at all	5	5		
Outpatient Week 22: borderline ill	60	55		
Outpatient Week 22: mildly ill	30	35		
Outpatient Week 22: moderately ill	5	5		
Outpatient Week 26: not ill at all	5	5		

Outpatient Week 26: borderline ill	75	50		
Outpatient Week 26: mildly ill	15	40		
Outpatient Week 26: moderately ill	5	5		
Outpatient Week >26: not ill at all	5	5		
Outpatient Week >26: borderline ill	75	50		
Outpatient Week >26: mildly ill	15	40		
Outpatient Week >26: moderately ill	5	5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With a Categorical Clinical Global Impressions Scales - Improvement (CGI-I) Score

End point title	Percentage of Subjects With a Categorical Clinical Global Impressions Scales - Improvement (CGI-I) Score

End point description:

CGI-I: 7-point clinician rated scale ranging from 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 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. Scores above 4 reflect worsening of illness state as compared to baseline. ITT population and LOCF was used. No subjects had a CGI-I score of 6 or 7 (much worse, very much worse), therefore only scores 1 through 5 (very much improved to minimally worse) are reported. CGI-I data for Inpatient Days 1 to 4 reported in Core study NCT00619619.

End point type	Other pre-specified

End point timeframe:

Baseline (Core study NCT00619619), Extension study Outpatient Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26, and >26 (up to Week 29)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of subjects				
number (not applicable)				
Outpatient Week 1: very much improved	25	10		
Outpatient Week 1: much improved	55	45		
Outpatient Week 1: minimally improved	20	40		
Outpatient Week 1: minimally worse	0	5		
Outpatient Week 2: very much improved	25	15		
Outpatient Week 2: much improved	55	55		
Outpatient Week 2: minimally improved	15	30		
Outpatient Week 4: very much improved	35	20		
Outpatient Week 4: much improved	45	55		
Outpatient Week 4: minimally improved	15	25		
Outpatient Week 4: minimally worse	5	0		

Outpatient Week 6: very much improved	35	20		
Outpatient Week 6: much improved	35	65		
Outpatient Week 6: minimally improved	30	15		
Outpatient Week 10: very much improved	30	30		
Outpatient Week 10: much improved	40	50		
Outpatient Week 10: minimally improved	30	15		
Outpatient Week 10: no change	0	5		
Outpatient Week 14: very much improved	25	40		
Outpatient Week 14: much improved	50	40		
Outpatient Week 14: minimally improved	20	15		
Outpatient Week 14: no change	5	5		
Outpatient Week 18: very much improved	30	40		
Outpatient Week 18: much improved	55	45		
Outpatient Week 18: minimally improved	15	15		
Outpatient Week 22: very much improved	30	45		
Outpatient Week 22: much improved	50	40		
Outpatient Week 22: minimally improved	20	15		
Outpatient Week 26: very much improved	40	40		
Outpatient Week 26: much improved	45	45		
Outpatient Week 26: minimally improved	15	15		
Outpatient Week >26: very much improved	40	40		
Outpatient Week >26: much improved	45	45		
Outpatient Week >26: minimally improved	15	15		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With a Response of Much Improved or Very Much Improved Based on the Clinical Global Impressions Scales - Improvement (CGI-I) Score

End point title	Percentage of Subjects With a Response of Much Improved or Very Much Improved Based on the Clinical Global Impressions Scales - Improvement (CGI-I) Score

End point description:

CGI-I: 7-point clinician rated scale ranging from 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, to 7=very much worse. Subject with response is defined as having a score of 1 (very much improved) or 2 (much improved). ITT population and LOCF was used. CGI-I data for Inpatient Days 1 to 4 reported in Core study NCT00619619.

End point type	Other pre-specified

End point timeframe:

Baseline (Core study NCT00619619), Extension study Outpatient Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26,

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage of subjects				
number (not applicable)				
Outpatient Week 1	80	55		
Outpatient Week 2	80	70		
Outpatient Week 4	80	75		
Outpatient Week 6	70	85		
Outpatient Week 10	70	80		
Outpatient Week 14	75	80		
Outpatient Week 18	85	85		
Outpatient Week 22	80	85		
Outpatient Week 26	85	85		
Outpatient Week >26	85	85		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Number of Subjects for Tanner Assessment at Week 26: Females

End point title	Change From Baseline in Number of Subjects for Tanner Assessment at Week 26: Females

End point description:

Tanner Children and Adolescent Pubertal Staging questionnaire used to document the stage of development of secondary sexual characteristics. Female pubertal development staged by pubic hair development and breast size (test categories). Rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity and size). Change categories: 0=no change in stage, 1=change of 1 stage, 2=change of 2 stages, 3=change of 3 stages, and 4=change of 4 stages. Subjects may be represented in more than 1 test category. Safety population (Baseline=Extension study); No subjects had a change of 3 stages or change of 4 stages reported, therefore only changes for 0 stages through 2 stages are reported.

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study), Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[3]	3[4]		
Units: subjects				
Breasts: 0=no stage change	5	1		
Breasts: 1=change of 1 stage	1	1		

Breasts: 2=change of 2 stages	1	1		
Pubic hair: 0=no stage change	6	2		
Pubic hair: 1=change of 1 stage	1	0		
Pubic hair: 2=change of 2 stages	0	1		

Notes:

[3] - N=number of subjects with evaluable data at observation.

[4] - N=number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Number of Subjects for Tanner Assessment at Week 26: Males

End point title	Change From Baseline in Number of Subjects for Tanner Assessment at Week 26: Males

End point description:

Tanner Children and Adolescent Pubertal Staging questionnaire used to document the stage of development of secondary sexual characteristics. Male pubertal development staged by size of the genitalia and development of pubic hair (test categories). Rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity and size). Change categories: 0=no change in stage, 1=change of 1 stage, 2=change of 2 stages, 3=change of 3 stages, and 4=change of 4 stages. Subjects may be represented in more than 1 test category. Safety population (Baseline=Extension study; No subjects had a change of 3 stages or change of 4 stages reported, therefore only changes for 0 stages through 2 stages are reported.

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study), Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[5]	4[6]		
Units: subjects				
Penis: 0=no stage change	4	3		
Penis: 1=change of 1 stage	1	0		
Penis: 2=change of 2 stages	0	1		
Pubic hair: 0=no stage change	2	2		
Pubic hair: 1=change of 1 stage	3	1		
Pubic hair: 2=change of 2 stages	0	1		
Testes: 0=no stage change	3	3		
Testes: 1=change of 1 stage	2	0		
Testes: 2=change of 2 stages	0	1		

Notes:

[5] - N=number of subjects with evaluable data at observation.

[6] - N=number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Vital Sign Results of Potential Clinical

Importance (PCI): Blood Pressure (BP)

End point title	Number of Subjects With Vital Sign Results of Potential Clinical Importance (PCI): Blood Pressure (BP)

End point description:

PCI criteria for females: systolic BP [SBP] ranges from >110 and diastolic BP [DBP] >73 (>110/73) at age 6 up to BP >124/81 at age 11; BP from >121/79 at age 12 up to BP >132/86 at age 17. Criteria for males: BP ranges from >112/73 at age 6 up to BP >123/82 at age 10; BP from >119/79 at age 11 up to BP >140/89 at age 17. Vitals signs meeting the criteria for PCI categorized as BP elevation for 3 consecutive visits or as postural change in BP (decrease in SBP ≥20 millimeters of mercury [mmHg] or in DBP ≥15 mmHg for the last supine to first standing BP [supine to standing]). Safety population (Baseline=Extension study).

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study) up to Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Elevated supine SBP, 3 consecutive visits	4	0		
Decrease SBP ≥20 mmHg supine to standing	2	0		
Decrease DBP ≥15 mmHg supine to standing	0	3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Vital Sign Results of Potential Clinical Importance (PCI): Weight

End point title	Number of Subjects With Vital Sign Results of Potential Clinical Importance (PCI): Weight

End point description:

Vitals signs meeting the PCI criteria for weight categorized according to an increase of ≥7 percent or a decrease of ≥3.5 percent in body weight. Safety population (Baseline=Extension study).

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study) up to Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Increase ≥7 percent in body weight	11	4		
Decrease of ≥3.5 percent in body weight	1	3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Vital Sign Results of Potential Clinical Importance (PCI): Pulse Rate

End point title	Number of Subjects With Vital Sign Results of Potential Clinical Importance (PCI): Pulse Rate

End point description:

PCI criteria for females: supine pulse rate (beats per minute [bpm]) ranges from <68 or >126 at age 6 to pulse <63 or >121 at age 11; pulse from <63 or >121 at age 12 to <54 or >110 at age 17; pulse from <50 or >104 at age 18. Criteria for males: pulse ranges from <68 or >126 at age 6 to pulse <63 or >121 at age 11; pulse from <58 or >116 at age 12 to <50 or >104 at age 17; pulse from <45 or >99 at age 18. Vitals signs meeting criteria for PCI categorized as Low or as postural change in pulse (increase in pulse ≥20 bpm for last supine to first standing pulse [supine to standing]). Safety population (Baseline=Extension study).

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study) up to Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Low supine pulse rate	1	2		
Increase in pulse rate ≥20 supine to standing	14	12		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Electrocardiogram (ECG) Results of Potential Clinical Importance (PCI)

End point title	Number of Subjects With Electrocardiogram (ECG) Results of Potential Clinical Importance (PCI)

End point description:

ECG results meeting the criteria for PCI categorized as PR interval ≥200 milliseconds (msec); QT

interval ≥480msec; QRS interval ≥120 msec; corrected QT (QTc) ≥500 msec; >450 msec for males and >470 msec for females or increase of ≥60 msec or ≥30 msec change from baseline QTcB=QT corrected using Bazett formula; QTcF=QT corrected using the Fridericia formula. Safety population (Baseline=Extension study). Subjects may be represented in >1 category.

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study) up to Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[7]	14[8]		
Units: subjects				
PR interval ≥200 msec	0	1		
QRS interval ≥120 msec	0	1		
QTcF interval ≥30 msec change from baseline	5	1		
QTcB interval ≥30 msec change from baseline	6	1		
QTcB interval ≥60 msec change from baseline	1	0		
QTcB interval >470 or increase ≥60 msec (females)	1	0		

Notes:

[7] - N=number of subjects with evaluable data at observation.

[8] - N=number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Electrocardiogram (ECG) Results of Potential Clinical Importance (PCI): Heart Rate (Low)

End point title	Number of Subjects With Electrocardiogram (ECG) Results of Potential Clinical Importance (PCI): Heart Rate (Low)

End point description:

PCI criteria for females: heart rate (bpm) ranges from <68 and >126 at age 6 to <63 and >121 at age 11; heart rate from <63 and >121 at age 12 to <54 and >110 at age 17; heart rate <50 and >104 at age 18. Criteria for males: heart rate ranges from < 68 and >126 at age 6 to <63 and >121 at age 11; heart rate <58 and >116 at age 12 up <50 and >104 at age 17; heart rate <45 and >99 at age 18. Heart rates meeting the criteria for PCI categorized as low (less than the lower limit specified for age). Safety population (Baseline=Extension study).

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study) up to Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[9]	14[10]		
Units: subjects	0	2		

Notes:

[9] - N=number of subjects with analyzable ECG data.

[10] - N=number of subjects with analyzable ECG data.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Test Results of Potential Clinical Importance (PCI)

End point title	Number of Subjects With Laboratory Test Results of Potential Clinical Importance (PCI)

End point description:

Laboratory test results meeting the criteria for PCI categorized as bicarbonate increase or decrease from baseline of ≥4 millimoles per liter(mmol/L); hematocrit <0.32 or >0.50 (females) or <0.37 or >0.55 (males) liters per liter (L/L); high density lipoprotein (HDL) cholesterol (fasting or nonfasting / unknown) decrease >0.21 mmol/L and test value ≥1.16 mmol/L; triglycerides (fasting or nonfasting / unknown) ≥2.258 mmol/L or increase ≥1.13 mmol/L and test value ≥3.39 mmol/L; urine specific gravity <1.001 or >1.035; and positive urinalysis result for protein (albumin), hemoglobin, or ketones. Safety population (Baseline=Extension study). Subjects may be represented in >1 category.

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study) up to Week 26 (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[11]	14[12]		
Units: subjects				
Bicarbonate: increase	2	0		
Bicarbonate: decrease	0	1		
Hematocrit: low	4	2		
HDL cholesterol: decrease	2	1		
Triglycerides: high	4	1		
Urine specific gravity: high	3	3		
Urine protein albumin: positive result	9	9		
Urine ketones: positive result	0	1		
Urine hemoglobin: positive result	0	1		

Notes:

[11] - N= number of subjects with analyzable laboratory data.

[12] - N= number of subjects with analyzable laboratory data.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects for Tanner Assessment: Females

End point title	Number of Subjects for Tanner Assessment: Females

End point description:

Female pubertal development of secondary sexual characteristics documented by pubic hair development and breast size (test categories). Rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity and size). N=9 Children, 9 Adolescent subjects at observation. Subjects may be represented in more than 1 test category. Safety population (Baseline=Extension study)

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Breasts Stage 1	4	0		
Breasts Stage 2	4	1		
Breasts Stage 3	1	0		
Breasts Stage 4	0	1		
Breasts Stage 5	0	7		
Pubic hair Stage 1	6	6		
Pubic hair Stage 2	3	5		
Pubic hair Stage 3	0	0		
Pubic hair Stage 4	0	2		
Pubic hair Stage 5	0	5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects for Tanner Assessment: Males

End point title	Number of Subjects for Tanner Assessment: Males

End point description:

Male pubertal development of secondary sexual characteristics documented by size of genitalia and pubic hair development (test categories). Rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity, size). N=9 Children, 10 Adolescent subjects at observation.
Subjects may be represented in more than 1 test category.

End point type	Other pre-specified

End point timeframe:

Baseline (Extension study)

End point values	DVS SR - Children	DVS SR - Adolescents		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: subjects				
Penis Stage 1	5	0		
Penis Stage 2	3	2		
Penis Stage 3	1	2		
Penis Stage 4	0	3		
Penis Stage 5	0	3		
Pubic hair Stage 1	6	0		
Pubic hair Stage 2	2	1		
Pubic hair Stage 3	1	3		
Pubic hair Stage 4	0	4		
Pubic hair Stage 5	0	2		
Testes Stage 1	5	0		
Testes Stage 2	2	1		
Testes Stage 3	2	3		
Testes Stage 4	0	3		
Testes Stage 5	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events collected from the time of the signing of the informed consent form up to Week 29 (Follow up visit)

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non-serious in another, or 1 subject may have experienced both serious, non-serious event during study. EU BR specific AE tables were generated separately as per EU format using latest coding.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	DVS SR Children

Reporting group description:

DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 10 milligrams (mg), 25 mg, 50 mg, and 100 mg for children 7 to 11 years of age at baseline in the preceding Core study NCT00619619.

Reporting group title	DVS SR Adolescents

Reporting group description:

Reporting group description: DVS SR formulation tablet(s) by mouth (PO) administered as flexible dosing adjusted by the investigator as clinically indicated. Total daily dose will be flexible between 25 mg, 50 mg, 100 mg, and 200 mg for adolescents 12 to 17 years of age at baseline in the preceding Core study NCT00619619.

Serious adverse events	DVS SR Children	DVS SR Adolescents	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Negativism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	DVS SR Children	DVS SR Adolescents	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 20 (60.00%)	14 / 20 (70.00%)	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Feeling jittery			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	2	4	
Cough			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	6	1	
Sinus congestion			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	2	3	
Upper respiratory tract congestion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Aggression			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Depressive symptom			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	4	
Investigations			
Chlamydia test positive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	3	2	
Ligament sprain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Muscle strain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Nervous system disorders			

Disturbance in attention			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	4 / 20 (20.00%)	3 / 20 (15.00%)	
occurrences (all)	9	6	
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)	6 / 20 (30.00%)	
occurrences (all)	3	14	
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 20 (15.00%)	3 / 20 (15.00%)	
occurrences (all)	3	5	
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Lip swelling			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 20 (10.00%)	4 / 20 (20.00%)	
occurrences (all)	3	11	
Vomiting			

subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	5	8	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Infections and infestations			
Adenoiditis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lymph gland infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	3 / 20 (15.00%)	
occurrences (all)	2	4	
Sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	2	
Tonsillitis			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Wound infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2008	1. The section describing total volume of blood collected was updated from 20 mL to 21 mL based upon information received from the central laboratory. 2. The test article administration section, study flowchart, and procedures section was revised to reflect that the first dose of test article for study 3151A6-2001-US was to be administered on study day 1, the day after the baseline visit.
14 April 2009	The protocol was updated to allow for an expansion of the flexible dose ranges for each age stratum (children and adolescents).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported