Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Tadalafil for Duchenne Muscular Dystrophy

Summary

EudraCT number	2013-001194-25
Trial protocol	GB IT DE ES BE NL
Global end of trial date	31 March 2016

Results information

Result version number	v1 (current)
This version publication date	16 October 2016
First version publication date	16 October 2016

Trial information

Trial identification

Sponsor protocol code	15122

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01865084
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: H6D-MC-LVJJ, Trial ID: 15122

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	31 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to determine if tadalafil can slow the decline in walking ability of boys who have Duchenne muscular dystrophy (DMD). The study will also assess the safety of tadalafil and any side effects that might be associated with it in boys who have DMD. Participants will receive study treatment (tadalafil or placebo) for the first 48 weeks of the study, and can then continue into an open label extension (OLE) that consists of two periods during which all participants will receive tadalafil. In OLE period 1, all participants will receive tadalafil for 48 weeks. Participants completing OLE period 1 will continue into OLE period 2 and will receive tadalafil for at least another 48 weeks.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

All the participants in the study were receiving corticosteroids.

Evidence for comparator: -

Actual start date of recruitment	03 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 17
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	United States: 107
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Turkey: 20
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Korea, Republic of: 12

Worldwide total number of subjects	331
EEA total number of subjects	105

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)	280
Adolescents (12-17 years)	51
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Long term follow-up duration of 8 months cited in the "Trial Information Section" reflects average actual follow-up duration and is shorter than the planned OLE duration because the study was stopped early.

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Double Blind Period (DB)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo taken orally once daily.

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

Dosage and administration details:

Placebo taken orally once daily.

Arm title	0.3 mg/kg Tadalafil

Arm description:

0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily.

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

Dosage and administration details:

0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily.

Arm title	0.6 mg/kg Tadalafil

Arm description:

0.6 mg/kg tadalafil taken orally once daily.

Arm type	Experimental

Investigational medicinal product name	Tadalafil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.6 mg/kg tadalafil taken orally once daily.

Number of subjects in period 1	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil
Started	116	102	113
Received at least one dose of study drug	116	102	112
Completed	111	98	107
Not completed	5	4	6
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	2	2	1
Withdrawal by Parent/Guardian	2	2	4
Protocol deviation	-	-	1

Period 2

Period 2 title	Open Label Extension (OLE) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	0.3 mg/kg Tadalafil

Arm description:

0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily. There was no control in the open label period.
In period 2 the original placebo arm was randomised to one of the two tadalafil arms. The original tadalafil arms had no randomisation in period 2.

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

Dosage and administration details:

0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily.

Arm title	0.6 mg/kg Tadalafil

Arm description:

0.6 mg/kg tadalafil taken orally once daily. There was no control in the open label period.

In period 2 the original placebo arm was randomised to one of the two tadalafil arms. The original tadalafil arms had no randomisation in period 2.

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

Dosage and administration details:

0.6 mg/kg tadalafil taken orally once daily.

Number of subjects in period 2[1]	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil
Started	150	165
Completed	139	158
Not completed	11	7
Consent withdrawn by subject	2	2
Adverse event, non-fatal	-	1
Withdrawal by Parent/Guardian	8	2
Lost to follow-up	1	-
Lack of efficacy	-	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who were on Placebo during the double blind period were assigned tadalafil during OLE.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo taken orally once daily.	
Reporting group title	0.3 mg/kg Tadalafil
Reporting group description:	
0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily.	
Reporting group title	0.6 mg/kg Tadalafil
Reporting group description:	
0.6 mg/kg tadalafil taken orally once daily.	

Reporting group values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil
Number of subjects	116	102	113
Age categorical Units: Subjects			
Age Continuous			
All participants who were randomized to study drug.			
Units: years			
arithmetic mean	9.4	9.9	9.5
standard deviation	± 1.76	± 2.26	± 1.71
Gender, Male/Female			
All participants who were randomized to study drug.			
Units: participants			
Female	0	0	0
Male	116	102	113
Race (NIH/OMB)			
All participants who were randomized to study drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	15	16	20
Native Hawaiian or Other Pacific Islander	3	1	3
Black or African American	0	0	1
White	96	82	84
More than one race	2	3	2
Unknown or Not Reported	0	0	1
Region of Enrollment			
All participants who were randomized to study drug.			
Units: Subjects			
Argentina	7	4	6
Russian Federation	4	4	4
United States	39	34	34
Japan	6	5	6
Spain	9	7	12
Canada	8	7	8
Netherlands	2	1	3

Turkey	5	7	8
Belgium	8	5	4
Taiwan	6	4	8
Korea, Republic of	3	4	5
Italy	8	8	8
France	3	2	2
Germany	8	10	5

Reporting group values	Total		
Number of subjects	331		
Age categorical Units: Subjects			

Age Continuous			
All participants who were randomized to study drug.			
Units: years arithmetic mean standard deviation	- -		
Gender, Male/Female			
All participants who were randomized to study drug.			
Units: participants			
Female	0		
Male	331		
Race (NIH/OMB)			
All participants who were randomized to study drug.			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	51		
Native Hawaiian or Other Pacific Islander	7		
Black or African American	1		
White	262		
More than one race	7		
Unknown or Not Reported	1		
Region of Enrollment			
All participants who were randomized to study drug.			
Units: Subjects			
Argentina	17		
Russian Federation	12		
United States	107		
Japan	17		
Spain	28		
Canada	23		
Netherlands	6		
Turkey	20		
Belgium	17		
Taiwan	18		
Korea, Republic of	12		
Italy	24		
France	7		
Germany	23		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo taken orally once daily.	
Reporting group title	0.3 mg/kg Tadalafil
Reporting group description:	
0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily.	
Reporting group title	0.6 mg/kg Tadalafil
Reporting group description:	
0.6 mg/kg tadalafil taken orally once daily.	
Reporting group title	0.3 mg/kg Tadalafil
Reporting group description:	
0.3 milligram per kilogram (mg/kg) tadalafil taken orally once daily. There was no control in the open label period. In period 2 the original placebo arm was randomised to one of the two tadalafil arms. The original tadalafil arms had no randomisation in period 2.	
Reporting group title	0.6 mg/kg Tadalafil
Reporting group description:	
0.6 mg/kg tadalafil taken orally once daily. There was no control in the open label period. In period 2 the original placebo arm was randomised to one of the two tadalafil arms. The original tadalafil arms had no randomisation in period 2.	
Subject analysis set title	0.3 mg/kg Tadalafil and 0.6 mg/kg Tadalafil
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
0.3 mg/kg tadalafil taken orally once daily. 0.6 mg/kg tadalafil taken orally once daily.	

Primary: Change from Baseline in Six Minute Walk Distance (6MWD) in Meters

End point title	Change from Baseline in Six Minute Walk Distance (6MWD) in Meters
End point description:	
6MWD measured the distance in meters a participant was able to walk in 6 minutes. The study used 6MWD procedure modified specifically for use in boys with Duchenne muscular dystrophy (DMD), including standardized verbal encouragement at specific intervals to maintain attention to the test, and use of a "safety chaser" to walk behind the participant during testing (McDonald et al., 2010a). The LS mean (LSM) change from baseline, standard error was derived using mixed model repeated measures (MMRM) methodology with factors for pooled country, treatment, visit, treatment-by-visit interaction and baseline 6MWD as a covariate. Analysis Population Description: All randomized participants who received at least one dose of study drug who had a baseline and at least one post-baseline measurement.	
End point type	Primary
End point timeframe:	
Baseline, Week 48	

End point values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	101	111	
Units: Meters				
least squares mean (standard error)	-50.99 (± 9.316)	-64.71 (± 9.809)	-59.08 (± 9.397)	

Statistical analyses

Statistical analysis title	Six Minute Walk Distance (6MWD)
Comparison groups	Placebo v 0.3 mg/kg Tadalafil
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.307 [1]
Method	Mixed models analysis

Notes:

[1] - The p-value is based on the treatment difference LS Mean changes from baseline between tadalafil and placebo.

Statistical analysis title	Six Minute Walk Distance (6MWD)
Comparison groups	Placebo v 0.6 mg/kg Tadalafil
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.538 [2]
Method	Mixed models analysis

Notes:

[2] - The p-value is based on the treatment difference LS Mean changes from baseline between tadalafil and placebo.

Secondary: Change from Baseline in the North Star Ambulatory Assessment (NSAA) Global Score

End point title	Change from Baseline in the North Star Ambulatory Assessment (NSAA) Global Score

End point description:

The NSAA is a functional scale specifically designed for ambulant boys with DMD that can provide additional information on motor functions important in maintaining normal ambulation and other activities important to everyday life. The NSAA is a 17-item evaluation of standing, ability to transition from lying to sitting,sitting to standing,and other mobility assessments.Each of the 17 items is evaluated on an ordinal scale of 0,1, or 2, with higher scores reflecting better performance on the assessment, for a total maximum score of 34.This score was transformed to a 0 to 100 scale for the key analysis (referred to as linearized).The LS mean(LSM) change from baseline standard error was derived using MMRM with factors for pooled country,treatment,visit, treatment-by-visit interaction and Day 1 value as baseline covariate.

Analysis Population Description: All randomized participants who received at least 1 dose of study drug who had a baseline and at least 1 post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	116	102	112	
Units: Units on a scale				
least squares mean (standard error)	-8.8 (± 1.104)	-9.31 (± 1.181)	-8.96 (± 1.115)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Timed Function Tests in Seconds

End point title	Change from Baseline in Timed Function Tests in Seconds

End point description:

Timed function tests included time it took to rise from floor, walk 10 meters, ascend 4 stairs, and descend 4 stairs.The lower the time in seconds taken, the better the performance. The LS mean change from baseline, standard error, was derived using mixed model repeated measures methodology (MMRM) with factors for pooled country, treatment, visit, treatment-by-visit interaction and Day 1 value as baseline covariate.

Analysis Population Description : All randomized participants who received at least one dose of study drug who had a baseline and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	116	96	110	
Units: Seconds				
least squares mean (standard error)				
Rise from the Floor(n=92,75,89)	4.16 (± 1.12)	3.6 (± 1.223)	4.81 (± 1.156)	
10 Meter Walk/Run(n=105,90,100)	1.11 (± 0.204)	0.95 (± 0.226)	1.12 (± 0.217)	
Stair Climb (n=116,96,110)	3.96 (± 1.041)	4.1 (± 1.154)	5.82 (± 1.072)	
Stair Descend(n=115,95,110)	3.19 (± 0.827)	2.07 (± 0.915)	3.27 (± 0.853)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Persistent 10% Worsening in 6MWD

End point title	Time to Persistent 10% Worsening in 6MWD

End point description:

Time on study until the 6MWD becomes 10% less than the baseline 6MWD and continues at that level or lower until the end of study.

Analysis Population Description: All randomized participants who received at least one dose of study drug who had complete evaluable data. Complete evaluable data was defined as having baseline measurement, complete dates at evaluable visits and a post-baseline measurement at each evaluable visit. Censored participants: placebo=71, 0.3 mg/kg=63, 0.6 mg/kg=61.

End point type	Secondary

End point timeframe:

Baseline through Week 48

End point values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115[3]	101[4]	111[5]	
Units: Days				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Notes:

[3] - 999=These statistics were not estimable due to large number of participants who were censored.

[4] - 999=These statistics were not estimable due to large number of participants who were censored.

[5] - 999=These statistics were not estimable due to large number of participants who were censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Persistent 10% Worsening in Timed Function Tests (TFT)

End point title	Time to Persistent 10% Worsening in Timed Function Tests (TFT)

End point description:

Time on study until the TFT becomes 10% worse than the baseline TFT and continues at that level or lower until the end of study. The time to persistent 10% worsening is the observed time after baseline(until the first observed timepoint where their time used for the TFTs is >110% of the baseline time and all the time values observed afterward are also >110% of baseline. If the participant discontinues prior to experiencing persistent worsening, this outcome for the participant is censored at the date of discontinuation of the double-blind period.

Analysis Population Description: All randomized participants who received at least 1 dose of study drug who had complete evaluable data. Censored participants:Rise from Floor;placebo (pl)=40,0.3 mg/kg=39,0.6 mg/kg=43;Stair Climb;pl=55,0.3 mg/kg=45,0.6 mg/kg=52;10 Meter Walk/Run pl=61,0.3 mg/kg=65,0.6 mg/kg=58,Stair Descend;pl=63,0.3 mg/kg=60,0.6 mg/kg=59.

End point type	Secondary

End point timeframe:

Baseline through Week 48

End point values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	116[6]	102[7]	113[8]	
Units: Days				
median (confidence interval 95%)				
Rise from the Floor (n=81,67,77)	253 (170 to 999)	999 (999 to 999)	999 (999 to 999)	
Stair Climb (n=112,91,107)	255 (252 to 999)	259 (176 to 999)	253 (185 to 999)	
10 Meter Walk/Run (n=98,83,91)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	
Stair Descend (n=110,91,108)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Notes:

[6] - 999=These statistics were not estimable due to large number of participants who were censored.

[7] - 999=These statistics were not estimable due to large number of participants who were censored.

[8] - 999=These statistics were not estimable due to large number of participants who were censored.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pediatric Outcomes Data Collection Instrument (PODCI) Scores

End point title	Change from Baseline in Pediatric Outcomes Data Collection Instrument (PODCI) Scores

End point description:

The global functioning score is the mean of the mean scores from 4 of the 5 core scales (all except the happiness core scale). The scores were standardized so that a score of "0" represents a poor outcome/worse health, while "100" is the best possible outcome/best health. The LS mean (LSM) change from baseline, standard error was derived using mixed model repeated measures methodology (MMRM) with factors for pooled country, treatment, visit, treatment-by-visit interaction and baseline PODCI scale as covariate.
Analysis Population Description: All randomized participants who received at least one dose of study drug who had a baseline and at least one post-baseline measurement. The reason the number of participants analyzed is significantly less than the total number of randomized participants is because PODCI was administered only in English.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo	0.3 mg/kg Tadalafil	0.6 mg/kg Tadalafil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	35	34	
Units: Units on a scale				
least squares mean (standard error)				
Global Functioning Scale (n=41,34,34)	-8.81 (± 1.77)	-7.36 (± 1.929)	-7.34 (± 1.888)	
Upper Extremity & Physical Function	-5.47 (± 1.901)	-3.73 (± 2.06)	-2.47 (± 2.042)	
Transfer/Basic Mobility Core Scale	-14.26 (± 3.037)	-12.5 (± 3.26)	-12.78 (± 3.279)	

Sports/Physical Functioning Core Scale	-12.47 (± 2.362)	-11.98 (± 2.552)	-7.88 (± 2.537)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Apparent Clearance (CL/F) of Tadalafil

End point title	Pharmacokinetics (PK): Apparent Clearance (CL/F) of Tadalafil

End point description:

The data reported are the population estimate (geometric mean) and the inter-patient variability (geometric coefficient of variation (%)).

Analysis Population Description : All randomized participants who received at least one dose of study drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Weeks 4, 12, 24 and 36: -1 Hour up to 24 Hours Postdose

End point values	0.3 mg/kg Tadalafil and 0.6 mg/kg Tadalafil			
Subject group type	Subject analysis set			
Number of subjects analysed	210			
Units: Liter per hour (L/hr)				
geometric mean (geometric coefficient of variation)	1.79 (± 29.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-Blind and Open-Label Treatment Periods

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug for Placebo - DB, 0.3 mg/kg tadalafil -DB and 0.6 mg/kg tadalafil -DB arms during the DB period.
All randomized participants who received at least one dose of study drug for 0.3 mg/kg tadalafil - OLE and 0.6 mg/kg tadalafil - OLE arms during the OLE period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo-DB
Reporting group description: -	
Reporting group title	Tadalafil 0.3mg/Kg-DB
Reporting group description: -	
Reporting group title	Tadalafil 0.6mg/Kg-DB
Reporting group description: -	
Reporting group title	Tadalafil 0.3mg/Kg-OLE
Reporting group description: -	
Reporting group title	Tadalafil 0.6mg/Kg-OLE
Reporting group description: -	

Serious adverse events	Placebo-DB	Tadalafil 0.3mg/Kg-DB	Tadalafil 0.6mg/Kg-DB
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 116 (4.31%)	4 / 102 (3.92%)	6 / 112 (5.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fall			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 116 (0.86%)	0 / 102 (0.00%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
femoral neck fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 116 (0.86%)	0 / 102 (0.00%)	0 / 112 (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
femur fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	2 / 112 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower limb fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 116 (0.86%)	0 / 102 (0.00%)	0 / 112 (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
spinal fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
myocarditis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	1 / 102 (0.98%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
extrapyramidal disorder			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
abasia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 116 (0.86%)	0 / 102 (0.00%)	0 / 112 (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
Gastrointestinal disorders			
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
self injurious behaviour			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
muscle contracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	1 / 102 (0.98%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tendinous contracture			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 116 (0.86%)	0 / 102 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tendon disorder			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bronchitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 116 (0.86%)	0 / 102 (0.00%)	0 / 112 (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
gastroenteritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis viral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrointestinal infection			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 116 (0.00%)	1 / 102 (0.98%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
influenza			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pharyngotonsillitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	1 / 102 (0.98%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia adenoviral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
varicella			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 116 (0.00%)	0 / 102 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tadalafil 0.3mg/Kg-OLE	Tadalafil 0.6mg/Kg-OLE	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 150 (4.00%)	9 / 165 (5.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
femoral neck fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower limb fracture			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
myocarditis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
extrapyramidal disorder			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
abasia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
self injurious behaviour			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicidal ideation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
muscle contracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tendinous contracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tendon disorder			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis viral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
influenza			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pharyngotonsillitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

pneumonia adenoviral			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
varicella			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo-DB	Tadalafil 0.3mg/Kg-DB	Tadalafil 0.6mg/Kg-DB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 116 (71.55%)	82 / 102 (80.39%)	92 / 112 (82.14%)
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	24 / 116 (20.69%)	18 / 102 (17.65%)	22 / 112 (19.64%)
occurrences (all)	41	30	41
Vascular disorders			
flushing			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 116 (2.59%)	8 / 102 (7.84%)	8 / 112 (7.14%)
occurrences (all)	3	8	9
Nervous system disorders			

headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	36 / 116 (31.03%)	40 / 102 (39.22%)	43 / 112 (38.39%)
occurrences (all)	92	57	68
General disorders and administration site conditions			
abasia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 116 (5.17%)	14 / 102 (13.73%)	9 / 112 (8.04%)
occurrences (all)	6	14	9
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 116 (3.45%)	11 / 102 (10.78%)	9 / 112 (8.04%)
occurrences (all)	4	11	10
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 116 (5.17%)	4 / 102 (3.92%)	9 / 112 (8.04%)
occurrences (all)	7	4	9
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 116 (6.03%)	5 / 102 (4.90%)	8 / 112 (7.14%)
occurrences (all)	7	6	8
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 116 (8.62%)	6 / 102 (5.88%)	10 / 112 (8.93%)
occurrences (all)	10	9	19
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 116 (1.72%)	7 / 102 (6.86%)	3 / 112 (2.68%)
occurrences (all)	2	8	3
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	14 / 116 (12.07%)	6 / 102 (5.88%)	17 / 112 (15.18%)
occurrences (all)	20	6	25
Reproductive system and breast			

disorders			
erection increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 116 (2.59%)	10 / 102 (9.80%)	17 / 112 (15.18%)
occurrences (all)	3	11	18
spontaneous penile erection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 116 (3.45%)	13 / 102 (12.75%)	13 / 112 (11.61%)
occurrences (all)	6	13	14
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 116 (8.62%)	4 / 102 (3.92%)	5 / 112 (4.46%)
occurrences (all)	11	4	5
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	5 / 116 (4.31%)	10 / 102 (9.80%)	6 / 112 (5.36%)
occurrences (all)	11	15	8
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 116 (6.03%)	3 / 102 (2.94%)	5 / 112 (4.46%)
occurrences (all)	7	3	5
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 116 (7.76%)	11 / 102 (10.78%)	7 / 112 (6.25%)
occurrences (all)	15	12	7
muscle spasms			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 116 (6.03%)	3 / 102 (2.94%)	3 / 112 (2.68%)
occurrences (all)	9	3	4
pain in extremity			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	8 / 116 (6.90%)	6 / 102 (5.88%)	10 / 112 (8.93%)
occurrences (all)	14	6	11
Infections and infestations			
gastroenteritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 116 (5.17%)	4 / 102 (3.92%)	3 / 112 (2.68%)
occurrences (all)	6	4	3
influenza			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 116 (7.76%)	8 / 102 (7.84%)	5 / 112 (4.46%)
occurrences (all)	9	9	5
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	16 / 116 (13.79%)	8 / 102 (7.84%)	18 / 112 (16.07%)
occurrences (all)	26	10	24
sinusitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 116 (5.17%)	4 / 102 (3.92%)	3 / 112 (2.68%)
occurrences (all)	11	5	3
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 116 (8.62%)	10 / 102 (9.80%)	12 / 112 (10.71%)
occurrences (all)	18	21	16

Non-serious adverse events	Tadalafil 0.3mg/Kg-OLE	Tadalafil 0.6mg/Kg-OLE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 150 (45.33%)	84 / 165 (50.91%)	
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	16 / 150 (10.67%)	15 / 165 (9.09%)	
occurrences (all)	22	18	
Vascular disorders			
flushing			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	2 / 150 (1.33%)	2 / 165 (1.21%)	
occurrences (all)	2	2	
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 150 (5.33%)	14 / 165 (8.48%)	
occurrences (all)	12	19	
General disorders and administration site conditions			
abasia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	12 / 150 (8.00%)	16 / 165 (9.70%)	
occurrences (all)	12	16	
pyrexia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 150 (4.67%)	6 / 165 (3.64%)	
occurrences (all)	8	6	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 150 (1.33%)	3 / 165 (1.82%)	
occurrences (all)	2	3	
abdominal pain upper			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 150 (2.67%)	2 / 165 (1.21%)	
occurrences (all)	5	2	
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 150 (6.00%)	7 / 165 (4.24%)	
occurrences (all)	13	7	
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
vomiting			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	9 / 150 (6.00%)	10 / 165 (6.06%)	
occurrences (all)	12	11	
Reproductive system and breast disorders			
erection increased			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 150 (1.33%)	4 / 165 (2.42%)	
occurrences (all)	2	4	
spontaneous penile erection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 150 (2.00%)	4 / 165 (2.42%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 150 (2.67%)	5 / 165 (3.03%)	
occurrences (all)	5	5	
epistaxis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	4 / 150 (2.67%)	3 / 165 (1.82%)	
occurrences (all)	6	5	
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 150 (2.00%)	1 / 165 (0.61%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	7 / 150 (4.67%)	9 / 165 (5.45%)	
occurrences (all)	7	9	
muscle spasms			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	2 / 165 (1.21%)	
occurrences (all)	0	2	

pain in extremity			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 150 (1.33%)	4 / 165 (2.42%)	
occurrences (all)	2	4	
Infections and infestations			
gastroenteritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 150 (2.00%)	2 / 165 (1.21%)	
occurrences (all)	3	2	
influenza			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	3 / 150 (2.00%)	2 / 165 (1.21%)	
occurrences (all)	3	2	
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	8 / 150 (5.33%)	12 / 165 (7.27%)	
occurrences (all)	10	12	
sinusitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 150 (4.00%)	8 / 165 (4.85%)	
occurrences (all)	15	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2013	Updated information brochure (IB) to include a warning about the use of tadalafil with guanylate cyclase stimulators such as riociguat due to the risk of hypotension.
29 April 2015	Adding an additional open label extension phase to the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The Sponsor concluded that the efficacy results do not provide sufficient justification for continuance of the open-label extension (OLE) period of the study, where all participants were receiving daily treatment with tadalafil.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19941337