



## Clinical trial results:

### Dose-Ranging Study of AVI-4658 to Induce Dystrophin Expression in Selected Duchenne Muscular Dystrophy (DMD) Patients

#### Summary

EudraCT number	2007-004695-39
Trial protocol	GB
Global end of trial date	08 June 2010

#### Results information

Result version number	v1 (current)
This version publication date	09 June 2016
First version publication date	09 June 2016

#### Trial information

##### Trial identification

Sponsor protocol code	AVI-4658-28
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00844597
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Sarepta Therapeutics
Sponsor organisation address	215 First Street, Cambridge, United States, 02142
Public contact	Shamim Ruff, Sarepta Therapeutics, 1 6172744009, SRuff@Sarepta.com
Scientific contact	Shamim Ruff, Sarepta Therapeutics, 1 6172744009, SRuff@Sarepta.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001722-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	08 June 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2010
Global end of trial reached?	Yes
Global end of trial date	08 June 2010
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this Phase 1b study is to assess the safety of escalating doses of AVI-4658 when administered by 12 weekly doses in boys with Duchenne muscular dystrophy (DMD).

Protection of trial subjects:

In addition to the informed consent process required of the patient's parent(s) or legal guardian(s), all possible steps to ensure the protection of this vulnerable class of trial patients, i.e., a pediatric population with Duchenne muscular dystrophy (DMD) were taken including the requirement of assent by each patient, where appropriate.

The study site was responsible for producing the patient informed assent form and the parent(s)/legal guardian(s) informed consent form. Before initiation of the study, the assent and consent forms were submitted for approval to both the Sponsor and to the EC.

Prior to the conduct of any pre-entry tests not performed routinely in the treatment of the patient, the Investigator fully explained the study to the patient and the patient's parent(s) or legal guardian(s). The explanation was sufficiently detailed to allow for an informed decision to participate made by the patient and the patient's parent(s) or legal guardian(s). If the patient (with permission from the patient's parent[s] or legal guardian[s]) was willing to participate in the study, he was requested to give written informed assent, where appropriate, and the patient's parent(s) or legal guardian(s) were requested to give written informed consent. In accordance with institutional and applicable local regulations, assent and written informed consent were obtained prior to performing any study-related procedures, including (non-routine) Screening assessments and administration of study drug.

Administration via the IV route over 60 minutes was selected for patient comfort and because IV access was needed for safety laboratory and PK sample collection. Anesthetic topical cream was used prior to IV placement.

Background therapy:

Patients continued on their standard of care treatment for DMD. 18 of the 19 patients were on some kind of Corticosteroid Treatment including Prednisoline, Hydrocortisone and Deflazacort.

1 patient - no corticosteroid treatments  
5 patients - Prednisolone regimen  
9 patients - Prednisoline regimen and 1 or more hydrocortisone infusions  
1 patient - Deflazacort regimen  
2 patients - Prednisoline, Hydrocortisone and Deflazacort treatments

Evidence for comparator: -

Actual start date of recruitment	07 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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Notes:

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**Subjects enrolled per age group**

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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)	17
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited at two sites in the United Kingdom in London and Newcastle Upon Tyne. The first subject was enrolled in January 2009 and received their first study drug dose February 18, 2009. The last subject was enrolled November 27, 2009 and received their first study drug dose on December 14, 2009.

### Pre-assignment

Screening details:

The first patient was screened February 11, 2009 and the last was screened December 6, 2009. There were 20 patients screened and 19 of these patients were enrolled. The patient who screened failed did not have the correct mutation to be included in the trial.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort 1 - 0.5mg/kg

Arm description:

Subjects in this group received a 0.5 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Arm type	Experimental
Investigational medicinal product name	Eteplirsen
Investigational medicinal product code	AVI-4658
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eteplirsen, formulated in phosphate buffered solution, was supplied in single-use vials at a concentration of 100 mg/mL. Six cohorts of patients were sequentially allocated to receive 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/wk IV infusions of eteplirsen for 12 weeks. Eteplirsen was diluted up to 50 mL with normal saline solution into a syringe and administered IV over a 60 minute period.

Lot numbers of eteplirsen used in this study: 44GD-DE01 and 60GD-DE01

<b>Arm title</b>	Cohort 2 - 1.0 mg/kg/wk
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Arm description:

Subjects in this group will receive a 1.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Arm type	Experimental
Investigational medicinal product name	Eteplirsen
Investigational medicinal product code	AVI-4658
Other name	SRP-4658
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eteplirsen, formulated in phosphate buffered solution, was supplied in single-use vials at a concentration of 100 mg/mL. Six cohorts of patients were sequentially allocated to receive 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/wk IV infusions of eteplirsen for 12 weeks. Eteplirsen was diluted up to 50 mL with normal saline solution into a syringe and administered IV over a 60 minute period.

Lot numbers of eteplirsen used in this study: 44GD-DE01 and 60GD-DE01

<b>Arm title</b>	Cohort 3 - 2.0 mg/kg/wk
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**Arm description:**

Subjects in this group will receive a 2.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Arm type	Experimental
Investigational medicinal product name	Eteplirsen
Investigational medicinal product code	AVI-4658
Other name	SRP-4658
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Eteplirsen, formulated in phosphate buffered solution, was supplied in single-use vials at a concentration of 100 mg/mL. Six cohorts of patients were sequentially allocated to receive 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/wk IV infusions of eteplirsen for 12 weeks. Eteplirsen was diluted up to 50 mL with normal saline solution into a syringe and administered IV over a 60 minute period.

Lot numbers of eteplirsen used in this study: 44GD-DE01 and 60GD-DE01

<b>Arm title</b>	Cohort 4 - 4.0 mg/kg/wk
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**Arm description:**

Subjects in this group will receive a 4.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Arm type	Experimental
Investigational medicinal product name	Eteplirsen
Investigational medicinal product code	AVI-4658
Other name	SRP-4658
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Eteplirsen, formulated in phosphate buffered solution, was supplied in single-use vials at a concentration of 100 mg/mL. Six cohorts of patients were sequentially allocated to receive 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/wk IV infusions of eteplirsen for 12 weeks. Eteplirsen was diluted up to 50 mL with normal saline solution into a syringe and administered IV over a 60 minute period.

Lot numbers of eteplirsen used in this study: 44GD-DE01 and 60GD-DE01

<b>Arm title</b>	Cohort 5 - 10 mg/kg/wk
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**Arm description:**

Subjects in this group will receive a 10.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Arm type	Experimental
Investigational medicinal product name	Eteplirsen
Investigational medicinal product code	AVI-4658
Other name	SRP-4658
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Eteplirsen, formulated in phosphate buffered solution, was supplied in single-use vials at a concentration of 100 mg/mL. Six cohorts of patients were sequentially allocated to receive 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/wk IV infusions of eteplirsen for 12 weeks. Eteplirsen was diluted up to 50 mL with normal saline solution into a syringe and administered IV over a 60 minute period.

Lot numbers of eteplirsen used in this study: 44GD-DE01 and 60GD-DE01

<b>Arm title</b>	Cohort 6 - 20mg/kg/wk
Arm description: Subjects in this group will receive a 20.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Arm type	Experimental
Investigational medicinal product name	Eteplirsen
Investigational medicinal product code	AVI-4658
Other name	SRP-4658
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Eteplirsen, formulated in phosphate buffered solution, was supplied in single-use vials at a concentration of 100 mg/mL. Six cohorts of patients were sequentially allocated to receive 0.5, 1.0, 2.0, 4.0, 10.0, or 20.0 mg/kg/wk IV infusions of eteplirsen for 12 weeks. Eteplirsen was diluted up to 50 mL with normal saline solution into a syringe and administered IV over a 60 minute period.

Lot numbers of eteplirsen used in this study: 44GD-DE01 and 60GD-DE01

<b>Number of subjects in period 1</b>	Cohort 1 - 0.5mg/kg	Cohort 2 - 1.0 mg/kg/wk	Cohort 3 - 2.0 mg/kg/wk
Started	4	2	2
Completed	4	2	2
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

<b>Number of subjects in period 1</b>	Cohort 4 - 4.0 mg/kg/wk	Cohort 5 - 10 mg/kg/wk	Cohort 6 - 20mg/kg/wk
Started	3	4	4
Completed	2	4	4
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1 - 0.5mg/kg
Reporting group description: Subjects in this group received a 0.5 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 2 - 1.0 mg/kg/wk
Reporting group description: Subjects in this group will receive a 1.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 3 - 2.0 mg/kg/wk
Reporting group description: Subjects in this group will receive a 2.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 4 - 4.0 mg/kg/wk
Reporting group description: Subjects in this group will receive a 4.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 5 - 10 mg/kg/wk
Reporting group description: Subjects in this group will receive a 10.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 6 - 20mg/kg/wk
Reporting group description: Subjects in this group will receive a 20.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	

Reporting group values	Cohort 1 - 0.5mg/kg	Cohort 2 - 1.0 mg/kg/wk	Cohort 3 - 2.0 mg/kg/wk
Number of subjects	4	2	2
Age categorical Units: Subjects			
Children (2-11 years)	4	2	1
Adolescents (12-17 years)	0	0	1
Age continuous Units: years			
least squares mean	8.3	6	11
standard deviation	± 0.5	± 0	± 2.83
Gender categorical Units: Subjects			
Female	0	0	0
Male	4	2	2

Reporting group values	Cohort 4 - 4.0 mg/kg/wk	Cohort 5 - 10 mg/kg/wk	Cohort 6 - 20mg/kg/wk
Number of subjects	3	4	4
Age categorical Units: Subjects			
Children (2-11 years)	3	3	4
Adolescents (12-17 years)	0	1	0

Age continuous Units: years least squares mean standard deviation	9.7 ± 0.58	8.8 ± 2.75	8.8 ± 1.26
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	4	4

<b>Reporting group values</b>	Total		
Number of subjects	19		
Age categorical Units: Subjects			
Children (2-11 years)	17		
Adolescents (12-17 years)	2		
Age continuous Units: years least squares mean standard deviation	-		
Gender categorical Units: Subjects			
Female	0		
Male	19		

### Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all patients who were enrolled in the study and received at least 1 dose of study treatment.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

Included all patients who received all 12 doses of study treatment.

Subject analysis set title	PK Evaluable Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all patients who provided at least 1 PK sample. The reportable PK population included those patients with at least C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-24</sub> computed from 1 or more of the 3 sampling days (1st, 6th, 12th dose [Weeks 1, 6, and 12]).

<b>Reporting group values</b>	Safety Population	Per Protocol Population	PK Evaluable Population
Number of subjects	19	18	19
Age categorical Units: Subjects			
Children (2-11 years)	17	16	17
Adolescents (12-17 years)	2	2	2
Age continuous Units: years least squares mean standard deviation	8.7 ± 1.91	8.6 ± 1.94	8.7 ± 1.91



Gender categorical			
Units: Subjects			
Female			
Male			

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## End points

### End points reporting groups

Reporting group title	Cohort 1 - 0.5mg/kg
Reporting group description: Subjects in this group received a 0.5 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 2 - 1.0 mg/kg/wk
Reporting group description: Subjects in this group will receive a 1.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 3 - 2.0 mg/kg/wk
Reporting group description: Subjects in this group will receive a 2.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 4 - 4.0 mg/kg/wk
Reporting group description: Subjects in this group will receive a 4.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 5 - 10 mg/kg/wk
Reporting group description: Subjects in this group will receive a 10.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Reporting group title	Cohort 6 - 20mg/kg/wk
Reporting group description: Subjects in this group will receive a 20.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Included all patients who were enrolled in the study and received at least 1 dose of study treatment.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description: Included all patients who received all 12 doses of study treatment.	
Subject analysis set title	PK Evaluable Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Included all patients who provided at least 1 PK sample. The reportable PK population included those patients with at least C <sub>max</sub> , T <sub>max</sub> , and AUC <sub>0-24</sub> computed from 1 or more of the 3 sampling days (1st, 6th, 12th dose [Weeks 1, 6, and 12]).	

### Primary: Safety and Tolerability

End point title	Safety and Tolerability <sup>[1]</sup>
End point description: Number of subjects with 1 or more Treatment Emergent Adverse Event that are possibly related to the investigational drug	
End point type	Primary
End point timeframe: Baseline to 6 months	

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: This study was primarily descriptive in nature; therefore, there were no formal statistical hypothesis tests planned.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Subjects	14			

## Statistical analyses

No statistical analyses for this end point

### Primary: Treatment Emergent Adverse Events

End point title	Treatment Emergent Adverse Events <sup>[2]</sup>
End point description:	
Number of Patients with Treatment Emergent Adverse Events	
End point type	Primary
End point timeframe:	
from Baseline to Follow-up (27 Weeks)	

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: This study was primarily descriptive in nature; therefore, there were no formal statistical hypothesis tests planned.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Patients	19			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics - Mean Peak Plasma Concentration of AVI-4658 after Administration

End point title	Pharmacokinetics - Mean Peak Plasma Concentration of AVI-4658 after Administration
End point description:	
Standard Pharmacokinetic parameters estimated using non-compartmental modeling of plasma concentration data.	
End point type	Secondary
End point timeframe:	
Samples were taken: 30 minutes pre dose; and at 5 ( $\pm 1$ ), 15 ( $\pm 2$ ), 30 ( $\pm 5$ ), 60 ( $\pm 5$ ), and 90 ( $\pm 5$ ) minutes; and 2, 4, 6, 8, 12, and 24 hours (all $\pm 15$ minutes) post dose at Weeks 1, 6, and 12	

End point values	PK Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: ng/mL				
least squares mean (standard deviation)	39000 ( $\pm$ 16900)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Efficacy of Eteplirsen Over 12 Weeks of Dosing

End point title	Efficacy of Eteplirsen Over 12 Weeks of Dosing
End point description: Efficacy was defined as an estimated change in the percentage of dystrophin positive fibers (assessed by IHC) at Week 14 from Baseline after 12 weekly doses of eterplirsen. This outcome measure represents the number of patients to show an increase in the percentage of dystrophin-positive fibers.	
End point type	Secondary
End point timeframe: Biopsies were taken at Baseline and Week 14	

End point values	Per Protocol Population			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: patients	11			

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: Adverse Events >15%

End point title	Adverse Events >15%
End point description: Adverse events that occurred in >15% of overall patient population across dose level arms.	
End point type	Post-hoc
End point timeframe: 27 Weeks	

End point values	Cohort 1 - 0.5mg/kg	Cohort 2 - 1.0 mg/kg/wk	Cohort 3 - 2.0 mg/kg/wk	Cohort 4 - 4.0 mg/kg/wk
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	3
Units: Occurrences				
Cardiomyopathy	0	0	0	1
Tachycardia	0	0	0	1
Abdominal Pain	0	1	0	1
Nausea	0	0	1	1
Vomiting	0	0	1	1
Influenza like Illness	0	0	2	0
Rhinitis	1	0	0	1
Upper respiratory tract infection	2	1	0	1
Fall	2	0	0	2
Arthralgia	1	0	1	1
Back Pain	1	0	1	2
Myalgia	1	1	1	0
Dizziness	0	0	1	1
Headache	2	1	2	0

End point values	Cohort 5 - 10 mg/kg/wk	Cohort 6 - 20mg/kg/wk	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	4	19	
Units: Occurrences				
Cardiomyopathy	0	2	3	
Tachycardia	0	2	3	
Abdominal Pain	1	0	3	
Nausea	0	1	3	
Vomiting	1	0	3	
Influenza like Illness	1	0	3	
Rhinitis	4	1	7	
Upper respiratory tract infection	2	2	8	
Fall	0	1	5	
Arthralgia	0	0	3	
Back Pain	2	1	7	
Myalgia	1	0	4	
Dizziness	0	1	3	
Headache	2	1	8	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Event data for this study was collected from Baseline to Follow-up (27 Weeks)

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	Cohort 1 - 0.05mg/kg
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Reporting group description:

Subjects in this group received a 0.5 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Reporting group title	Cohort 2 - 1.0 mg/kg/wk
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Reporting group description:

Subjects in this group will receive a 1.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Reporting group title	Cohort 3 - 2.0 mg/kg/wk
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Reporting group description:

Subjects in this group will receive a 2.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Reporting group title	Cohort 4 - 4.0 mg/kg/wk
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Reporting group description:

Subjects in this group will receive a 4.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Reporting group title	Cohort 5 - 10 mg/kg/wk
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Reporting group description:

Subjects in this group will receive a 10.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Reporting group title	Cohort 6 - 20mg/kg/wk
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Reporting group description:

Subjects in this group will receive a 20.0 mg/kg/wk dose of AVI-4658 over 12 weekly IV infusions in 50 mL of normal saline solution over a 60-minute period

Serious adverse events	Cohort 1 - 0.05mg/kg	Cohort 2 - 1.0 mg/kg/wk	Cohort 3 - 2.0 mg/kg/wk
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Post-Operative Nausea and Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
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			
Fracture of Left Medial Malleolus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (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

<b>Serious adverse events</b>	Cohort 4 - 4.0 mg/kg/wk	Cohort 5 - 10 mg/kg/wk	Cohort 6 - 20mg/kg/wk
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Post-Operative Nausea and Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Fracture of Left Medial Malleolus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (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

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

<b>Non-serious adverse events</b>	Cohort 1 - 0.05mg/kg	Cohort 2 - 1.0 mg/kg/wk	Cohort 3 - 2.0 mg/kg/wk
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	2 / 2 (100.00%)	2 / 2 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Pallor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	2 / 2 (100.00%)
occurrences (all)	0	0	2
Abasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Application site rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Catheter Site Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Disease Progression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vaccination site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Cough			



subjects affected / exposed	2 / 4 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 4 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Ankle Fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Arthropod sting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Excoriation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Heat stroke			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Lumbar vertebral fracture			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Post procedural haematoma subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Procedural Pain subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Vaccination complication subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Cardiomyopathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	1 / 2 (50.00%) 1	2 / 2 (100.00%) 2
Dizziness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1
Blood and lymphatic system disorders Platelet anisocytosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Eye disorders			

Enteritis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1
Abdominal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 2 (50.00%) 1	0 / 2 (0.00%) 0
Abdominal Pain - Upper subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Lip Dry subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Skin and subcutaneous tissue disorders			
Drug eruption subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Skin irritation subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Renal and urinary disorders			
Enuresis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Musculoskeletal and connective tissue			

disorders			
Back Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	1	1	1
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Coccydynia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 4 (50.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Incision site infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Tinea infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Viral Infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

<b>Non-serious adverse events</b>	Cohort 4 - 4.0 mg/kg/wk	Cohort 5 - 10 mg/kg/wk	Cohort 6 - 20mg/kg/wk
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pallor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Abasia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Application site rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Catheter Site Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vaccination site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vessel puncture site haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Productive cough			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Ankle Fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Excoriation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Head injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Heat stroke			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Post procedural haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Procedural Pain			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Vaccination complication subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	2 / 4 (50.00%) 2
Cardiomyopathy subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2	1 / 4 (25.00%) 1
Dizziness subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Blood and lymphatic system disorders Platelet anisocytosis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Eye disorders Enteritis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders Nausea			



subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Abdominal Pain - Upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lip Dry			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
Myalgia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Coccydynia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 3 (33.33%)	4 / 4 (100.00%)	1 / 4 (25.00%)
occurrences (all)	1	4	1
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	1	2	2
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Incision site infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Respiratory tract infection viral subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Tinea infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Viral Infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2009	Decreased duration of follow-up period from 40 to 14 weeks, decreased number of patients per each dose cohort, updated DSMB responsibilities, modified inclusion and exclusion criteria to expand patient qualification, modified study termination criteria, eliminated most overnight stays after dosing visits.  Altered various data collection requirements in the Schedule of Assessments, including: frequency of ECG and PFT assessments, ECHO procedures, lab assessments, muscle function tests, blood and urine collection. Added 6MWT and changed drug diluent to normal saline.
23 June 2009	Added 2 additional dose cohorts with dosage of 10.0 and 20.0 mg/kg/wk. Added 10 day window to obtain Baseline StepWatch data, lab assessments, physical exam and vitals Added lab assessments at Week 3
02 March 2010	Added exon skipping as a measurement of exploratory efficacy Removed reference to full passive range of ankle dorsiflexion bilaterally throughout the protocol Specified that assays relevant to muscle biopsy were to be performed at GOSH

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.

Due to the small number of study participants, a single adverse event (AE) in 1 patient exceeds the reporting threshold of 5%. Refer to the "Post-Hoc Outcome Measures" for a summary of frequent and related AEs.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/21784508>