Clinical trial results:
A phase I/II, open label, escalating dose, pilot study to assess the effect, safety, tolerability and pharmacokinetics of multiple subcutaneous doses of drisapersen in patients with Duchenne muscular dystrophy and to assess the potential for intravenous dosing as an alternative route of administration

Summary

EudraCT number	2007-004819-54
Trial protocol	BE NL SE
Global end of trial date	25 June 2013

Results information

Result version number	v2 (current)
This version publication date	07 May 2020
First version publication date	23 March 2017
Version creation reason	• Correction of full data set This study is split in 2 parts and for te first part the CSR summary was uploaded. Now for the second part, the dataset will be uploaded.

Trial information

Trial identification

Sponsor protocol code	PRO051-02 & DMD114673

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Centre, GlaxoSmithKline., 1 8664357343, GSKClinicalSupportHD@GSK.com
Scientific contact	GSK Response Centre, GlaxoSmithKline., 1 8664357343, GSKClinicalSupportHD@GSK.com
Sponsor organisation name	Prosensa Therapeutics B.V.
Sponsor organisation address	Wassenaarseweg 72, 2333 AL Leiden, Netherlands,
Public contact	Clinical Trails Information, Prosensa Therapeutics B.V., +31(0) 71 3322100, info@prosensa.nl
Scientific contact	Clinical Trails Information, Prosensa Therapeutics B.V., +31(0) 71 3322100, info@prosensa.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	16 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Core study:
To preliminarily assess the effect of PRO051 at different dose levels in patients with DMD.
To assess the safety and tolerability of PRO051 at different dose levels in patients with DMD.
To determine the pharmacokinetics of PRO051 at different dose levels after SC administration in patients with DMD.
Administration of PRO051 beyond the core study period (SC administration):
To assess the effect of PRO051 after SC administration at 6 mg/kg or capped at 300 mg in patients with DMD.
To assess the safety and tolerability of PRO051 after SC at 6 mg/kg or capped at 300 mg in patients with DMD.
To determine the pharmacokinetics of PRO051 after SC administration at 6 mg/kg in patients with DMD.
Administration of PRO051 beyond the core study period (IV administration): IV dosing will be investigated as an alternative route of administration.

Protection of trial subjects:

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents. This study complies with US 21 CFR 312.120, as described in the Ethics and Good Clinical Practice section.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Sweden: 5
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	2
Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 2 study centers in 2 countries.

Pre-assignment

Screening details:

Total of 14 subjects screened, 12 subjects started the PRO051 treatment period. All 12 subjects who participated in the initial Study Period were subsequently enrolled into the Continued Treatment phase.

Period 1

Period 1 title	Initial Study Period - PRO051-02
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I - 0.5 mg/kg

Arm description:

PRO051 at 0.5 mg/kg subcutaneous administration per week, for five weeks.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PRO051 at 0.5 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm title	Group II - 2 mg/kg

Arm description:

PRO051 at 2 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PRO051 at 2 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm title	Group III - 4 mg/kg

Arm description:

PRO051 at 4 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
PRO051 at 4 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm title	Group IV - 6 mg/kg

Arm description:
PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.

Number of subjects in period 1	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Group IV - 6 mg/kg
Started	3
Completed	3

Period 2

Period 2 title	Continued Treatment phase - DMD114673
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Continued Treatment phase - 6 mg/kg

Arm description:
PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm type	Experimental

Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.

Arm title	IV sub-study - 0.5 mg/kg over 4 hours

Arm description:

0.5 mg/kg over 4 hours intravenous infusion at Visit 202.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.5 mg/kg over 4 hours intravenous infusion at Visit 202.

Arm title	IV sub-study - 1.4 mg/kg over 4 hours

Arm description:

1.4 mg/kg over 4 hours intravenous infusion at Visit 205.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/kg over 4 hours intravenous infusion at Visit 205.

Arm title	IV sub-study - 2.7 mg/kg over 4 hours

Arm description:

2.7 mg/kg over 4 hours intravenous infusion at Visit 208.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2.7 mg/kg over 4 hours intravenous infusion at Visit 208.

Arm title	IV sub-study - 2.7 mg/kg over 2 hours

Arm description:

2.7 mg/kg over 2 hours intravenous infusion at Visit 211.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2.7 mg/kg over 2 hours intravenous infusion at Visit 211.

Arm title	IV sub-study - 2.7 mg/kg over 1 hour

Arm description:

2.7 mg/kg over 1 hour intravenous infusion at Visit 214.

Arm type	Experimental
Investigational medicinal product name	Drisapersen
Investigational medicinal product code	BMN051
Other name	PRO051, GSK2402968
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2.7 mg/kg over 1 hour intravenous infusion at Visit 214.

Number of subjects in period 2	Continued Treatment phase - 6 mg/kg	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours
Started	12	7	7
Completed	12	7	7

Number of subjects in period 2	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours	IV sub-study - 2.7 mg/kg over 1 hour
Started	7	7	7
Completed	7	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Group I - 0.5 mg/kg
Reporting group description:	
PRO051 at 0.5 mg/kg subcutaneous administration per week, for five weeks.	
Reporting group title	Group II - 2 mg/kg
Reporting group description:	
PRO051 at 2 mg/kg solution for subcutaneous injection per week, for five weeks.	
Reporting group title	Group III - 4 mg/kg
Reporting group description:	
PRO051 at 4 mg/kg solution for subcutaneous injection per week, for five weeks.	
Reporting group title	Group IV - 6 mg/kg
Reporting group description:	
PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.	

Reporting group values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg
Number of subjects	3	3	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.8	9.09	8.2
standard deviation	± 3.15	± 1.55	± 3.01
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	3	3
Weight Units: kg			
arithmetic mean	27.87	32.2	21.2
standard deviation	± 5.88	± 16.47	± 6.49
Height Units: cm			
arithmetic mean	125	122.33	111.67
standard deviation	± 9.85	± 13.32	± 14.98
Body Mass Index Units: kg/m^2			
arithmetic mean	17.67	20.57	16.63
standard deviation	± 0.9	± 5.87	± 0.99

Reporting group values	Group IV - 6 mg/kg	Total	
Number of subjects	3	12	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	9.71		
standard deviation	± 1.02	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	3	12	
Weight Units: kg			
arithmetic mean	30.07		
standard deviation	± 4.41	-	
Height Units: cm			
arithmetic mean	126.67		
standard deviation	± 11.37	-	
Body Mass Index Units: kg/m^2			
arithmetic mean	18.77		
standard deviation	± 1.7	-	

End points

End points reporting groups

Reporting group title	Group I - 0.5 mg/kg
Reporting group description: PRO051 at 0.5 mg/kg subcutaneous administration per week, for five weeks.	
Reporting group title	Group II - 2 mg/kg
Reporting group description: PRO051 at 2 mg/kg solution for subcutaneous injection per week, for five weeks.	
Reporting group title	Group III - 4 mg/kg
Reporting group description: PRO051 at 4 mg/kg solution for subcutaneous injection per week, for five weeks.	
Reporting group title	Group IV - 6 mg/kg
Reporting group description: PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.	
Reporting group title	Continued Treatment phase - 6 mg/kg
Reporting group description: PRO051 at 6 mg/kg solution for subcutaneous injection per week, for five weeks.	
Reporting group title	IV sub-study - 0.5 mg/kg over 4 hours
Reporting group description: 0.5 mg/kg over 4 hours intravenous infusion at Visit 202.	
Reporting group title	IV sub-study - 1.4 mg/kg over 4 hours
Reporting group description: 1.4 mg/kg over 4 hours intravenous infusion at Visit 205.	
Reporting group title	IV sub-study - 2.7 mg/kg over 4 hours
Reporting group description: 2.7 mg/kg over 4 hours intravenous infusion at Visit 208.	
Reporting group title	IV sub-study - 2.7 mg/kg over 2 hours
Reporting group description: 2.7 mg/kg over 2 hours intravenous infusion at Visit 211.	
Reporting group title	IV sub-study - 2.7 mg/kg over 1 hour
Reporting group description: 2.7 mg/kg over 1 hour intravenous infusion at Visit 214.	
Subject analysis set title	IV Sub-Set - All Doses
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received at least one dose of study medication. This is the primary population for evaluation of safety variables.	

Primary: Production of exon 51 skip mRNA in muscle biopsy during Initial study period by dose group per visit - 0.5 mg/kg

End point title	Production of exon 51 skip mRNA in muscle biopsy during Initial study period by dose group per visit - 0.5 mg/kg[1][2]
End point description: Intention-to-Treat (ITT) sample. A muscle biopsy from the tibialis anterior muscle was taken according to a sparse sampling schedule in order to limit the number of biopsies taken per participant. Endogenous production of the expected mRNA in the muscle biopsy was assessed. Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or conflicting results.	
End point type	Primary

End point timeframe:

At Visit 1 nd Visit 8

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Number of observations				
Visit 1 - No	3			
Visit 1 - Yes	0			
Visit 1 - Y/N	0			
Visit 8 - No	3			
Visit 8 - Yes	0			
Visit 8 - Y/N	0			

Statistical analyses

No statistical analyses for this end point

Primary: Production of exon 51 skip mRNA in muscle biopsy during Initial study period by dose group per visit - 2, 4 and 6mg/kg

End point title	Production of exon 51 skip mRNA in muscle biopsy during Initial study period by dose group per visit - 2, 4 and 6mg/kg[3][4]

End point description:

Intention-to-Treat (ITT) sample.
A muscle biopsy from the tibialis anterior muscle was taken according to a sparse sampling schedule in order to limit the number of biopsies taken per participant.
Endogenous production of the expected mRNA in the muscle biopsy was assessed.

Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or
conflicting results.

End point type	Primary

End point timeframe:

At Visit 8 and Visit 10

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: Number of observations				
Visit 8 - No	2	0	1	
Visit 8 - Yes	1	3	1	
Visit 8 - Y/N	0	0	1	
Visit 10 - No	2	0	0	
Visit 10 - Yes	1	3	1	
Visit 10 - Y/N	0	0	2	

Statistical analyses

No statistical analyses for this end point

Primary: Presence of dystrophin in cross sections of muscle biopsy during Initial study period, by dose group per visit - 0.5 mg/kg

End point title	Presence of dystrophin in cross sections of muscle biopsy during Initial study period, by dose group per visit - 0.5 mg/kg[5][6]

End point description:

Intention-to-Treat (ITT) sample.

A muscle biopsy from the tibialis anterior muscle was taken according to a sparse sampling schedule in order to limit the number of biopsies taken per participant.
Dystrophin expression in the muscle biopsy was assessed

Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or conflicting results.

End point type	Primary

End point timeframe:

At Visit 1 and Visit 8

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Number of observations				
Visit 1 - No	1			
Visit 1 - Yes	0			
Visit 1 - Y/N	2			
Visit 8 - No	0			
Visit 8 - Yes	2			
Visit 8 - Y/N	1			

Statistical analyses

No statistical analyses for this end point

Primary: Presence of dystrophin in cross sections of muscle biopsy during Initial study period, by dose group per visit - 2, 4 and 6 mg/kg

End point title	Presence of dystrophin in cross sections of muscle biopsy during Initial study period, by dose group per visit - 2, 4 and 6 mg/kg[7][8]

End point description:

Intention-to-Treat (ITT) sample.

A muscle biopsy from the tibialis anterior muscle was taken according to a sparse sampling schedule in order to limit the number of biopsies taken per participant.

Dystrophin expression in the muscle biopsy was assessed.

Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or conflicting results.

End point type	Primary

End point timeframe:

At Visit 8 and Visit 10

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: Number of observations				
Visit 8 - No	0	0	0	
Visit 8 - Yes	3	1	2	
Visit 8 - Y/N	0	2	1	
Visit 10 - No	0	0	0	
Visit 10 - Yes	2	3	3	
Visit 10 - Y/N	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Presence of dystrophin in total protein extract during Initial study period,

by dose group per visit - 0.5 mg/kg

End point title	Presence of dystrophin in total protein extract during Initial study period, by dose group per visit - 0.5 mg/kg[9][10]

End point description:

Intention-to-Treat (ITT) sample.

A muscle biopsy from the tibialis anterior muscle was taken according to a sparse sampling schedule in order to limit the number of biopsies taken per participant.
Presence of dystrophin in total protein extract was assessed in the muscle biopsy.

Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or conflicting results.

End point type	Primary

End point timeframe:

At Visit 1 and Visit 8

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Number of observations				
Visit 1 - No	1			
Visit 1 - Yes	0			
Visit 1 - Y/N	2			
Visit 8 - No	1			
Visit 8 - Yes	1			
Visit 8 - Y/N	1			

Statistical analyses

No statistical analyses for this end point

Primary: Presence of dystrophin in total protein extract during Initial study period, by dose group per visit - 2, 4 and 6 mg/kg

End point title	Presence of dystrophin in total protein extract during Initial study period, by dose group per visit - 2, 4 and 6 mg/kg[11][12]

End point description:

Intention-to-Treat (ITT) sample.

A muscle biopsy from the tibialis anterior muscle was taken according to a sparse sampling schedule in order to limit the number of biopsies taken per participant.
Presence of dystrophin in total protein extract was assessed in the muscle biopsy.

Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or conflicting results.

End point type	Primary

End point timeframe:

At Visit 8 and Visit 10

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: Number of observations				
Visit 8 - No	0	0	0	
Visit 8 - yes	1	2	3	
Visit 8 - Y/N	2	1	0	
Visit 10 - No	0	0	0	
Visit 10 - Yes	2	2	3	
Visit 10 - Y/N	1	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Production of exon 51 skip mRNA in peripheral blood mononuclear cells, during Initial Study Period, by dose group per visit

End point title	Production of exon 51 skip mRNA in peripheral blood mononuclear cells, during Initial Study Period, by dose group per visit[13]

End point description:

Intention-to-Treat (ITT) sample.

Whole blood samples were collected to assess exon skipping in mononuclear blood cells.

Y/N is a non-conclusive result due to either technical limitations, poor sample quality or non-reproducible or conflicting results.

End point type	Primary

End point timeframe:

At Visit 1, Visit 3, Visit 5, Visit 6 and Visit 8

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Number of observations				
Visit 1 -No	3	3	3	3
Visit 1 - Yes	0	0	0	0
Visit 1 - Y/N	0	0	0	0
Visit 3 - No	3	3	3	3
Visit 3 - Yes	0	0	0	0
Visit 3 - Y/N	0	0	0	0
Visit 5 - No	3	3	3	3
Visit 5 - Yes	0	0	0	0
Visit 5 - Y/N	0	0	0	0
Visit 6 - No	3	3	3	3
Visit 6 - Yes	0	0	0	0
Visit 6 - Y/N	0	0	0	0
Visit 8 - No	3	2	3	3
Visit 8 - Yes	0	0	0	0
Visit 8 - Y/N	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Muscle function: 10-Meter walk/run test during Initial Study Period, by dose group per visit

End point title	Muscle function: 10-Meter walk/run test during Initial Study Period, by dose group per visit[14]

End point description:

Intention-to-Treat (ITT) sample.

The participant was asked to traverse a marked 10-meter measured walkway as quickly as he safely can. The 10-meter walk/run test was performed preferably barefoot without shoes or orthoses. If this was not possible, testing could have been done with shoes/orthoses. Any use of shoes/orthoses should then be documented. Time was recorded from when his first foot crossed the start line until the second foot crossed the finish line. In case a wall was touched, it was noted how often. Care was taken to ensure that the participant was safe when completing this test.

n = Number of observations.

End point type	Primary

End point timeframe:

At Visits 2, 3, 4, 5, 6, 7, 8, 10 and 12

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: sec				
arithmetic mean (standard deviation)				
Visit 2 (n = 2,3,3,3)	3.90 (± 0.42)	4.83 (± 2.55)	4.07 (± 0.81)	5.63 (± 2.46)
Visit 3 (n = 2,3,3,3)	3.60 (± 0.14)	4.97 (± 2.40)	4.23 (± 0.61)	6.30 (± 2.20)
Visit 4 (n = 2,3,3,3)	3.90 (± 0.57)	4.57 (± 2.21)	4.20 (± 0.61)	6.07 (± 2.04)
Visit 5 (n = 2,3,3,3)	3.85 (± 0.64)	5.17 (± 3.12)	4.43 (± 0.55)	5.90 (± 2.36)
Visit 6 (n = 2,3,3,3)	3.90 (± 0.28)	4.83 (± 2.27)	4.50 (± 0.61)	5.93 (± 2.35)
Visit 7 (n = 2,3,3,3)	3.90 (± 0.85)	4.60 (± 2.10)	4.27 (± 0.90)	6.07 (± 2.37)
Visit 8 (n = 2,3,3,3)	3.90 (± 0.85)	4.70 (± 2.10)	4.57 (± 0.70)	6.17 (± 2.08)
Visit 10 (n = 2,3,3,3)	3.70 (± 0.71)	5.07 (± 2.85)	4.97 (± 1.12)	6.17 (± 2.47)
Visit 12 (n = 2,3,3,3)	3.30 (± 0.00)	6.10 (± 4.93)	4.73 (± 0.90)	6.17 (± 2.18)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle function: Timed rising from floor during Initial Study Period, by dose group per visit

End point title	Muscle function: Timed rising from floor during Initial Study Period, by dose group per visit[15]

End point description:

Intention-to-Treat (ITT) sample.

The participant was told to stand up as quickly as possible from supine position with his arms by his side. The participant was allowed to use his arms for support while rising from the floor. Time was recorded from the initiation of movement until the assumption of upright standing. The area was free from furniture and the participant did not wear orthoses or was using any aids.

n = Number of observations.

End point type	Primary

End point timeframe:

At Visits 2, 3, 4, 5, 6, 7, 8, 10 and 12

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: sec				
arithmetic mean (standard deviation)				
Visit 2 (n = 2,3,3,2)	2.05 (± 0.07)	6.00 (± 6.19)	5.00 (± 4.86)	3.95 (± 1.63)
Visit 3 (n = 2,3,3,2)	2.25 (± 0.35)	6.77 (± 6.46)	3.97 (± 2.63)	4.05 (± 1.77)
Visit 4 (n = 2,3,3,2)	2.45 (± 0.92)	6.07 (± 6.64)	4.40 (± 3.33)	5.30 (± 3.39)
Visit 5 (n = 2,3,3,2)	2.65 (± 0.21)	7.20 (± 8.10)	4.03 (± 2.29)	4.00 (± 1.70)
Visit 6 (n = 2,3,3,2)	2.65 (± 0.49)	5.90 (± 6.67)	2.73 (± 0.51)	3.95 (± 2.19)
Visit 7 (n = 2,3,3,2)	2.50 (± 0.14)	6.37 (± 7.57)	4.17 (± 2.32)	4.40 (± 1.41)

Visit 8 (n = 2,3,3,2)	2.85 (± 0.35)	5.87 (± 6.45)	3.73 (± 2.00)	4.15 (± 1.77)
Visit 10 (n = 2,3,3,2)	2.55 (± 0.21)	6.53 (± 7.62)	4.43 (± 2.66)	4.85 (± 2.62)
Visit 12 (n = 2,3,3,2)	2.15 (± 0.07)	9.03 (± 12.03)	4.87 (± 4.06)	4.70 (± 3.68)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle function: Stair climb during Initial Study Period, by dose group per visit

End point title	Muscle function: Stair climb during Initial Study Period, by dose group per visit[16]

End point description:

Intention-to-Treat (ITT) sample.

The subject was to ascend four steps. Time was recorded from the initiation of movement until the subject stood on the fourth step. If a flight of steps with handrail was available these were used. If not, a box step was used. A plinth or other immovable object was available to provide support.

n = Number of observations.

End point type	Primary

End point timeframe:

At Visit 2, 3, 4, 5, 6, 7, 8, 10 and 12

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: sec				
arithmetic mean (standard deviation)				
Vsit 2 (n = 2,3,3,3)	1.80 (± 0.14)	3.27 (± 3.33)	3.67 (± 2.82)	6.40 (± 7.37)
Vsit 3 (n = 2,3,3,3)	1.80 (± 0.00)	3.97 (± 4.20)	3.37 (± 2.46)	5.70 (± 4.86)
Vsit 4 (n = 2,3,3,3)	1.65 (± 0.07)	3.50 (± 3.82)	3.03 (± 1.50)	5.90 (± 5.48)
Vsit 5 (n = 2,3,3,3)	1.65 (± 0.21)	4.47 (± 5.15)	3.10 (± 1.65)	6.10 (± 6.52)
Vsit 6 (n = 2,3,3,3)	1.60 (± 0.14)	3.33 (± 3.29)	2.87 (± 1.14)	4.67 (± 4.65)
Vsit 7 (n = 2,3,3,3)	1.70 (± 0.14)	3.73 (± 4.05)	2.97 (± 1.10)	5.87 (± 5.51)
Vsit 8 (n = 2,3,3,3)	1.55 (± 0.07)	3.47 (± 3.50)	2.77 (± 1.34)	5.90 (± 5.94)
Vsit 10 (n = 2,3,3,3)	1.65 (± 0.21)	4.47 (± 5.23)	3.43 (± 2.05)	5.83 (± 5.38)
Vsit 12 (n = 2,3,3,3)	1.80 (± 0.28)	5.37 (± 6.61)	3.33 (± 1.97)	6.30 (± 6.24)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle function: 6-Minute walk test, time walked during Initial study period, by dose group per visit

End point title	Muscle function: 6-Minute walk test, time walked during Initial study period, by dose group per visit[17]

End point description:

Intention-to-Treat (ITT) sample.

Subjects were requested to walk for 6-minutes. The subject was asked to walk at his own preferred speed up and down the fixed distance until they were told to stop after six minutes. The test was performed preferably barefoot and without aid. If this was not possible, testing was done with shoes/orthoses/aid. Any use of shoes/orthoses/aid was then documented. The subjects were warned of the time and were told that they may stop earlier if they feel unable to continue. The total time walked within six minutes (or until the subjects stopped in case of early termination of the test) was collected in minutes.

n = Number of observations

End point type	Primary

End point timeframe:

At Visit 1, Visit 8 and Visit 12

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: min				
arithmetic mean (standard deviation)				
Visit 1 (n = 2,3,3,3)	6.00 (± 0.00)	6.00 (± 0.00)	6.00 (± 0.00)	6.00 (± 0.00)
Visit 8 (n = 2,3,3,3)	6.00 (± 0.00)	6.00 (± 0.00)	6.00 (± 0.00)	6.00 (± 0.00)
Visit 12 (n = 2,3,3,2)	6.00 (± 0.00)	6.00 (± 0.00)	6.00 (± 0.00)	6.00 (± 0.00)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle function: 6-Minute walk test, Distance walked during Initial study period, by dose group per visit

End point title	Muscle function: 6-Minute walk test, Distance walked during Initial study period, by dose group per visit[18]

End point description:

Intention-to-Treat (ITT) sample.

Subjects were requested to walk for 6-minutes. The subject was asked to walk at his own preferred speed up and down the fixed distance until they were told to stop after six minutes. The test was performed preferably barefoot and without aid. If this was not possible, testing was done with shoes/orthoses/aid. Any use of shoes/orthoses/aid was then documented. The subjects were warned of the time and were told that they may stop earlier if they feel unable to continue. The total distance walked within six minutes (or until the subjects stopped in case of early termination of the test) was collected in meters.

n = Number of observations.

End point type	Primary

End point timeframe:

At Visit 1, Visit 8 and Visit 12

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: metre				
arithmetic mean (standard deviation)				
Visit 1 (n = 2,3,3,3)	437.00 (± 15.56)	422.67 (± 117.80)	360.33 (± 15.01)	368.33 (± 88.27)
Visit 8 (n = 2,3,3,3)	427.50 (± 17.68)	402.67 (± 121.93)	399.67 (± 46.07)	370.00 (± 86.16)
Visit 12 (n = 2,3,3,2)	420.00 (± 89.10)	399.33 (± 164.39)	361.67 (± 28.36)	373.50 (± 157.68)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle function: 6-Minute walk test, Distance per minute walked during Initial study period, by dose group per visit

End point title	Muscle function: 6-Minute walk test, Distance per minute walked during Initial study period, by dose group per visit[19]

End point description:

Intention-to-Treat (ITT) sample.

Subjects were requested to walk for 6-minutes. The subject was asked to walk at his own preferred speed up and down the fixed distance until they were told to stop after six minutes. The test was performed preferably barefoot and without aid. If this was not possible, testing was done with shoes/orthoses/aid. Any use of shoes/orthoses/aid was then documented. The subjects were warned of the time and were told that they may stop earlier if they feel unable to continue. The total distance walked within six minutes (or until the subjects stopped in case of early termination of the test) was collected in metres/meters.

n = Number of observations.

End point type	Primary

End point timeframe:

At Visit 1, Visit 8 and Visit 12

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: m/min				
arithmetic mean (standard deviation)				
Visit 1 (n = 2,3,3,3)	72.83 (± 2.59)	70.44 (± 19.63)	60.06 (± 2.50)	61.39 (± 14.71)

Visit 8 (n = 2,3,3,3)	71.25 (± 2.95)	67.11 (± 20.32)	66.61 (± 7.68)	61.67 (± 14.36)
Visit 12 (n =2,3,3,2)	70.00 (± 14.85)	66.56 (± 27.40)	60.28 (± 4.73)	62.25 (± 26.28)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle strength: Quantitative muscle testing per muscle site during Initial study period, by dose group per visit, Quantitative muscle (Contraction) testing per muscle site

End point title	Muscle strength: Quantitative muscle testing per muscle site during Initial study period, by dose group per visit, Quantitative muscle (Contraction) testing per muscle site[20]

End point description:

Intention-to-Treat (ITT) sample.

Quantitative muscle testing was performed for knee flexors, knee extensors, grip, elbow flexors and elbow extensors using the CINRG Quantitative Measuring System (CQMS).

n = Number of observations.

End point type	Primary

End point timeframe:

At Visit 2, 3, 4, 5, 6, 7, 8, 10 and 12

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: lbs				
arithmetic mean (standard deviation)				
Elbow extensor left: Vist 2(n = 3,3,3,3)	7.80 (± 4.16)	10.13 (± 4.43)	8.93 (± 2.55)	6.30 (± 2.23)
Elbow extensor right: Vist 2(n = 3,3,3,3)	10.33 (± 5.66)	10.10 (± 5.07)	8.50 (± 4.51)	8.97 (± 2.22)
Elbow flexor left: Vist 2(n = 3,3,3,3)	6.73 (± 2.48)	7.53 (± 2.42)	6.20 (± 2.43)	7.77 (± 2.63)
Elbow flexor right: Vist 2(n = 3,3,3,3)	7.30 (± 2.85)	7.37 (± 2.64)	7.57 (± 1.46)	7.80 (± 2.03)
Grip left: Vist 2(n = 3,3,3,3)	14.00 (± 5.64)	14.77 (± 7.80)	12.33 (± 4.66)	16.40 (± 1.65)
Grip right: Vist 2(n = 3,3,3,3)	14.47 (± 2.54)	18.10 (± 7.22)	13.10 (± 4.65)	18.97 (± 3.36)
Knee extensor left: Vist 2(n = 3,3,3,3)	19.20 (± 12.24)	16.17 (± 3.51)	14.83 (± 5.68)	10.53 (± 8.68)
Knee extensor right: Vist 2(n = 3,3,3,3)	17.90 (± 11.64)	22.07 (± 10.86)	16.13 (± 7.72)	11.77 (± 9.53)
Knee flexor left: Vist 2(n = 3,3,3,3)	13.47 (± 4.75)	9.53 (± 5.80)	12.95 (± 6.86)	9.90 (± 1.23)
Knee flexor right: Vist 2(n = 3,3,3,3)	10.60 (± 4.68)	9.70 (± 2.21)	13.60 (± 4.10)	9.83 (± 0.21)
Elbow extensor left: Vist 3(n = 3,3,3,3)	7.17 (± 3.45)	9.80 (± 4.57)	7.37 (± 2.00)	10.40 (± 5.92)
Elbow extensor right: Vist 3(n = 3,3,3,3)	8.83 (± 4.53)	11.30 (± 5.86)	9.20 (± 2.33)	9.77 (± 5.46)
Elbow flexor left: Vist 3(n = 3,3,3,3)	5.33 (± 1.29)	8.33 (± 2.82)	7.53 (± 1.46)	7.97 (± 1.63)
Elbow flexor right: Vist 3(n = 3,3,3,3)	5.37 (± 1.66)	8.50 (± 2.82)	6.43 (± 1.57)	8.50 (± 2.54)

Grip left: Vist 3(n = 3,3,3,3)	13.20 (± 2.69)	14.00 (± 5.01)	13.03 (± 4.47)	15.90 (± 5.70)
Grip right: Vist 3(n = 3,3,3,3)	13.90 (± 3.03)	17.83 (± 5.67)	14.23 (± 4.94)	16.37 (± 4.80)
Knee extensor left: Vist 3(n = 3,3,3,3)	19.87 (± 12.50)	17.40 (± 5.22)	15.10 (± 7.85)	12.20 (± 10.92)
Knee extensor right: Vist 3(n = 3,3,3,3)	20.97 (± 16.54)	20.43 (± 8.97)	15.00 (± 5.56)	12.47 (± 13.16)
Knee flexor left: Vist 3(n = 3,3,3,3)	9.23 (± 0.65)	11.40 (± 3.39)	9.73 (± 4.26)	6.60 (± 2.76)
Knee flexor right: Vist 3(n = 3,3,3,3)	11.50 (± 3.38)	10.27 (± 4.88)	8.80 (± 2.76)	8.10 (± 2.40)
Elbow extensor left: Vist 4(n = 3,3,3,3)	9.07 (± 5.62)	10.70 (± 5.45)	8.17 (± 3.81)	6.47 (± 2.85)
Elbow extensor right: Vist 4(n = 3,3,3,3)	8.53 (± 4.41)	12.43 (± 6.78)	9.53 (± 2.76)	6.90 (± 2.20)
Elbow flexor left: Vist 4(n = 3,3,3,3)	6.60 (± 2.63)	7.37 (± 1.92)	5.77 (± 0.29)	7.23 (± 3.01)
Elbow flexor right: Vist 4(n = 3,3,3,3)	7.07 (± 3.27)	7.47 (± 2.85)	7.97 (± 1.33)	6.63 (± 3.96)
Grip left: Vist 4(n = 3,3,3,3)	14.27 (± 3.01)	15.87 (± 3.49)	12.83 (± 4.03)	17.23 (± 2.89)
Grip right: Vist 4(n = 3,3,3,3)	16.23 (± 1.59)	17.60 (± 5.02)	13.20 (± 4.31)	18.17 (± 2.67)
Knee extensor left: Vist 4(n = 3,3,3,3)	19.40 (± 13.56)	18.87 (± 4.15)	13.33 (± 5.80)	11.83 (± 10.15)
Knee extensor right: Vist 4(n = 3,3,3,3)	16.77 (± 12.27)	17.17 (± 6.16)	15.17 (± 7.21)	11.23 (± 11.29)
Knee flexor left: Vist 4(n = 3,3,3,3)	11.47 (± 2.76)	11.20 (± 2.78)	10.43 (± 4.91)	11.13 (± 2.51)
Knee flexor right: Vist 4(n = 3,3,3,3)	10.63 (± 1.81)	12.23 (± 1.02)	10.47 (± 3.59)	11.17 (± 0.65)
Elbow extensor left: Vist 5(n = 3,2,3,3)	8.13 (± 3.82)	7.10 (± 1.27)	9.00 (± 2.17)	6.27 (± 2.75)
Elbow extensor right: Vist 5(n = 3,2,3,3)	8.10 (± 3.50)	9.30 (± 3.82)	7.50 (± 3.46)	6.47 (± 2.57)
Elbow flexor left: Vist 5(n = 3,2,3,3)	4.77 (± 0.75)	6.85 (± 1.91)	5.37 (± 1.05)	7.20 (± 3.16)
Elbow flexor right: Vist 5(n = 3,2,3,3)	5.17 (± 0.38)	5.65 (± 2.05)	6.93 (± 0.65)	7.83 (± 3.33)
Grip left: Vist 5(n = 3,3,3,3)	14.83 (± 2.32)	17.63 (± 5.73)	12.77 (± 4.46)	19.37 (± 3.61)
Grip right: Vist 5(n = 3,3,3,3)	15.97 (± 1.89)	18.77 (± 4.36)	13.60 (± 4.20)	17.30 (± 2.23)
Knee extensor left: Vist 5(n = 3,2,3,3)	19.87 (± 13.31)	18.05 (± 7.99)	14.07 (± 6.20)	10.83 (± 10.82)
Knee extensor right: Vist 5(n = 3,2,3,3)	18.03 (± 14.94)	15.40 (± 6.08)	14.10 (± 6.84)	10.33 (± 10.17)
Knee flexor left: Vist 5(n = 3,2,3,3)	11.87 (± 1.70)	7.05 (± 1.06)	9.07 (± 6.29)	14.30 (± 4.15)
Knee flexor right: Vist 5(n = 3,2,3,3)	12.60 (± 2.78)	7.95 (± 2.62)	7.53 (± 4.13)	11.57 (± 2.82)
Elbow extensor left: Vist 6(n = 3,2,3,3)	7.73 (± 4.12)	10.25 (± 7.28)	7.60 (± 2.09)	5.13 (± 2.82)
Elbow extensor right: Vist 6(n = 3,2,3,3)	9.90 (± 4.85)	9.05 (± 4.45)	8.40 (± 2.09)	5.57 (± 3.62)
Elbow flexor left: Vist 6(n = 3,2,3,3)	5.90 (± 1.78)	7.40 (± 0.85)	6.30 (± 1.57)	6.10 (± 3.04)
Elbow flexor right: Vist 6(n = 3,2,3,3)	6.03 (± 1.53)	5.60 (± 0.71)	7.97 (± 2.14)	6.57 (± 3.96)
Grip left: Vist 6(n = 3,3,3,3)	15.50 (± 2.50)	18.40 (± 5.58)	12.60 (± 5.09)	18.13 (± 1.01)
Grip right: Vist 6(n = 3,3,3,3)	16.43 (± 3.26)	18.47 (± 6.15)	14.10 (± 5.07)	18.27 (± 1.40)
Knee extensor left: Vist 6(n = 3,2,3,3)	20.37 (± 12.14)	25.75 (± 10.11)	12.97 (± 6.54)	10.87 (± 12.70)
Knee extensor right: Vist 6(n = 3,2,3,3)	18.37 (± 13.50)	27.95 (± 11.67)	13.53 (± 5.00)	11.40 (± 14.42)
Knee flexor left: Vist 6(n = 3,2,3,3)	10.77 (± 3.37)	13.80 (± 3.82)	10.67 (± 5.75)	8.70 (± 3.11)
Knee flexor right: Vist 6(n = 3,2,3,3)	11.47 (± 1.19)	11.50 (± 2.26)	9.87 (± 4.15)	9.07 (± 4.32)
Elbow extensor left: Vist 7(n = 3,3,3,3)	8.33 (± 4.81)	9.73 (± 3.51)	8.30 (± 3.84)	5.40 (± 2.26)
Elbow extensor right: Vist 7(n = 3,3,3,3)	9.07 (± 4.72)	9.40 (± 3.37)	7.97 (± 3.09)	7.10 (± 1.56)
Elbow flexor left: Vist 7(n = 3,3,3,3)	7.37 (± 2.35)	7.70 (± 3.20)	7.40 (± 3.27)	6.27 (± 3.01)
Elbow flexor right: Vist 7(n = 3,3,3,3)	8.57 (± 4.79)	5.20 (± 1.87)	6.97 (± 2.17)	6.60 (± 3.30)
Grip left: Vist 7(n = 3,3,3,3)	14.10 (± 2.52)	17.10 (± 5.57)	12.33 (± 5.08)	18.47 (± 2.81)
Grip right: Vist 7(n = 3,3,3,3)	16.67 (± 1.91)	19.93 (± 8.00)	13.77 (± 4.79)	18.57 (± 2.15)
Knee extensor left: Vist 7(n = 3,3,3,3)	20.50 (± 13.99)	25.17 (± 12.33)	13.20 (± 5.72)	11.10 (± 7.98)

Knee extensor right: Vist 7(n = 3,3,3,3)	17.27 (± 15.53)	21.97 (± 11.23)	12.87 (± 6.01)	12.23 (± 13.05)
Knee flexor left: Vist 7(n = 3,3,3,3)	10.07 (± 1.07)	9.60 (± 4.69)	10.40 (± 5.17)	11.37 (± 0.49)
Knee flexor right: Vist 7(n = 3,3,3,3)	10.93 (± 1.75)	10.87 (± 5.75)	10.07 (± 4.22)	11.60 (± 1.95)
Elbow extensor left: Vist 8(n = 3,3,3,3)	7.63 (± 3.75)	9.93 (± 3.67)	7.30 (± 2.86)	5.30 (± 1.51)
Elbow extensor right: Vist 8(n = 3,3,3,3)	10.00 (± 5.10)	10.57 (± 4.85)	8.00 (± 2.74)	5.83 (± 2.10)
Elbow flexor left: Vist 8(n = 3,3,3,3)	6.27 (± 0.80)	8.40 (± 4.30)	6.77 (± 1.31)	6.20 (± 4.45)
Elbow flexor right: Vist 8(n = 3,3,3,3)	6.53 (± 1.07)	8.43 (± 3.39)	7.80 (± 2.11)	6.33 (± 3.35)
Grip left: Vist 8(n = 3,3,3,3)	16.87 (± 3.27)	19.03 (± 6.47)	15.63 (± 5.53)	16.60 (± 1.11)
Grip right: Vist 8(n = 3,3,3,3)	17.87 (± 2.58)	19.67 (± 8.23)	14.47 (± 5.19)	16.60 (± 1.04)
Knee extensor left: Vist 8(n = 3,3,3,3)	21.87 (± 15.32)	21.00 (± 4.29)	13.90 (± 7.05)	11.37 (± 10.95)
Knee extensor right: Vist 8(n = 3,3,3,3)	19.97 (± 16.84)	21.83 (± 10.20)	13.10 (± 6.43)	13.50 (± 15.01)
Knee flexor left: Vist 8(n = 3,3,3,3)	13.07 (± 5.49)	10.40 (± 2.36)	12.13 (± 5.54)	9.37 (± 3.26)
Knee flexor right: Vist 8(n = 3,3,3,3)	11.87 (± 2.80)	11.13 (± 2.25)	10.93 (± 6.13)	10.17 (± 3.84)
Elbow extensor left: Vist 10(n = 2,3,3,2)	6.10 (± 3.68)	8.97 (± 4.45)	8.77 (± 1.16)	5.15 (± 1.48)
Elbow extensor right: Vist 10(n = 2,3,3,2)	7.50 (± 5.23)	9.60 (± 5.15)	7.97 (± 2.28)	5.90 (± 2.26)
Elbow flexor left: Vist 10(n = 2,3,3,2)	5.75 (± 1.77)	7.77 (± 3.48)	7.27 (± 0.93)	6.80 (± 0.99)
Elbow flexor right: Vist 10(n = 2,3,3,2)	5.25 (± 0.64)	7.30 (± 1.90)	7.63 (± 1.46)	6.30 (± 0.57)
Grip left: Vist 10(n = 3,3,3,2)	14.03 (± 2.10)	21.10 (± 7.52)	14.43 (± 3.58)	17.05 (± 2.33)
Grip right: Vist 10(n = 3,3,3,2)	15.77 (± 3.46)	19.70 (± 6.05)	15.33 (± 3.40)	18.45 (± 0.92)
Knee extensor left: Vist 10(n = 2,3,3,2)	15.50 (± 12.16)	22.90 (± 9.62)	16.33 (± 5.27)	6.40 (± 2.69)
Knee extensor right: Vist 10(n = 2,3,3,2)	11.05 (± 7.57)	20.57 (± 8.95)	15.30 (± 5.17)	5.80 (± 3.11)
Knee flexor left: Vist 10(n = 2,3,3,2)	11.05 (± 1.48)	11.97 (± 8.10)	11.63 (± 7.10)	10.90 (± 5.66)
Knee flexor right: Vist 10(n = 2,3,3,2)	11.95 (± 1.91)	11.00 (± 5.05)	11.27 (± 4.90)	9.65 (± 3.61)
Elbow extensor left: Vist 12(n = 3,3,3,2)	9.83 (± 6.20)	11.43 (± 6.25)	9.07 (± 1.42)	4.90 (± 0.99)
Elbow extensor right: Vist 12(n = 3,3,3,2)	11.37 (± 5.58)	9.57 (± 5.90)	8.57 (± 2.34)	7.20 (± 2.83)
Elbow flexor left: Vist 12(n = 3,3,3,2)	6.77 (± 1.76)	8.60 (± 3.05)	5.97 (± 1.47)	6.45 (± 0.07)
Elbow flexor right: Vist 12(n = 3,3,3,2)	6.97 (± 2.17)	8.43 (± 2.21)	6.80 (± 1.44)	7.60 (± 1.56)
Grip left: Vist 12(n = 3,3,3,2)	16.07 (± 3.18)	16.30 (± 5.45)	17.43 (± 3.32)	19.50 (± 3.68)
Grip right: Vist 12(n = 3,3,3,2)	14.73 (± 2.94)	20.63 (± 7.48)	16.63 (± 2.23)	19.95 (± 3.46)
Knee extensor left: Vist 12(n = 3,3,3,2)	21.33 (± 14.64)	24.83 (± 10.32)	16.00 (± 6.16)	6.25 (± 0.64)
Knee extensor right: Vist 12(n = 3,3,3,2)	16.83 (± 10.88)	23.27 (± 12.74)	17.57 (± 8.21)	4.55 (± 1.20)
Knee flexor left: Vist 12(n = 3,3,3,2)	9.73 (± 3.09)	13.03 (± 3.46)	11.27 (± 4.56)	10.30 (± 0.85)
Knee flexor right: Vist 12(n = 3,3,3,2)	11.43 (± 3.95)	13.30 (± 2.52)	12.90 (± 4.67)	8.95 (± 0.21)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle strength: Quantitative muscle testing per muscle site during Initial study period, by dose group per visit - Pulmonary function testing

End point title	Muscle strength: Quantitative muscle testing per muscle site during Initial study period, by dose group per visit - Pulmonary

	function testing[21]

End point description:

Intention-to-Treat (ITT) sample.

Spirometry assessment for FVC and FEV1 was performed using the CINRG Quantitative Measuring System (CQMS).

n = Number of observations

FVC = Forced Vital Capacity
FEV1 = Forced Expiratory Volume in 1 Second

End point type	Primary

End point timeframe:

At Visit 2, 3, 4, 5, 6, 7, 8, 10 and 12

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: litres				
arithmetic mean (standard deviation)				
FVC: Visit 2(n = 2,3,3,3)	1.75 (± 0.21)	1.70 (± 0.36)	1.43 (± 0.55)	1.67 (± 0.15)
FEV1: Visit 2(n = 2,3,3,3)	1.60 (± 0.28)	1.63 (± 0.35)	1.30 (± 0.56)	1.60 (± 0.20)
FVC: Visit 3(n = 3,3,3,3)	1.53 (± 0.29)	1.73 (± 0.32)	1.50 (± 0.50)	1.80 (± 0.10)
FEV1: Visit 3(n = 3,3,3,3)	1.43 (± 0.21)	1.63 (± 0.32)	1.30 (± 0.50)	1.60 (± 0.20)
FVC: Visit 4(n = 3,3,3,3)	1.67 (± 0.32)	1.77 (± 0.29)	1.37 (± 0.51)	1.67 (± 0.15)
FEV1: Visit 4(n = 3,3,3,3)	1.47 (± 0.31)	1.60 (± 0.26)	1.23 (± 0.57)	1.47 (± 0.21)
FVC: Visit 5(n = 3,3,3,3)	1.63 (± 0.29)	1.73 (± 0.23)	1.43 (± 0.57)	1.67 (± 0.15)
FEV1: Visit 5(n = 3,3,3,3)	1.47 (± 0.23)	1.63 (± 0.15)	1.20 (± 0.66)	1.47 (± 0.21)
FVC: Visit 6(n = 3,3,3,3)	1.60 (± 0.26)	1.80 (± 0.35)	1.40 (± 0.53)	1.67 (± 0.15)
FEV1: Visit 6(n = 3,3,3,3)	1.47 (± 0.32)	1.57 (± 0.47)	1.23 (± 0.57)	1.53 (± 0.15)
FVC: Visit 7(n = 3,3,3,3)	1.63 (± 0.21)	1.83 (± 0.32)	1.40 (± 0.53)	1.77 (± 0.23)
FEV1: Visit 7(n = 3,3,3,3)	1.47 (± 0.15)	1.67 (± 0.29)	1.23 (± 0.67)	1.30 (± 0.46)
FVC: Visit 8(n = 3,3,3,3)	1.57 (± 0.23)	1.87 (± 0.29)	1.40 (± 0.62)	1.70 (± 0.20)
FEV1: Visit 8(n = 3,3,3,3)	1.47 (± 0.15)	1.70 (± 0.26)	1.20 (± 0.72)	1.40 (± 0.30)
FVC: Visit 10(n = 3,3,3,3)	1.63 (± 0.38)	1.90 (± 0.35)	1.40 (± 0.36)	1.77 (± 0.23)
FEV1: Visit 10(n = 3,3,3,3)	1.57 (± 0.32)	1.77 (± 0.29)	1.30 (± 0.36)	1.67 (± 0.23)
FVC: Visit 12(n = 3,3,3,3)	1.67 (± 0.23)	1.93 (± 0.35)	1.50 (± 0.40)	1.85 (± 0.07)
FEV1: Visit 12(n = 3,3,3,3)	1.63 (± 0.29)	1.77 (± 0.31)	1.37 (± 0.45)	1.70 (± 0.14)

Statistical analyses

No statistical analyses for this end point

Primary: Muscle strength: Manual muscle testing, total score and separate scores during Initial study period, by dose group per visit - Overall scores

End point title	Muscle strength: Manual muscle testing, total score and separate scores during Initial study period, by dose group per visit - Overall scores[22]

End point description:

Intention-to-Treat (ITT) sample.

Manual muscle testing was assessed. The Medical Research Council Scale (MRCS) is composed of a rating of 0-5 assigned to each muscle group tested (See section 9.7.1.2.2 for details on muscle groups tested). The MRCS has been modified and formalized to account for more grades of muscle weakness using a plus or minus designation (see Table 5).

Overall score of the total muscle score, total sitting position, and total prone, side lying and supine position.

End point type	Primary

End point timeframe:

At Visit 1, Visit 8 and Visit 12

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Unit on scale				
median (full range (min-max))				
Total Muscle Score : Visit 1(n=3,3,3,3)	245.0 (186.0 to 254.0)	246.0 (228.0 to 255.0)	248.0 (219.0 to 263.0)	232.0 (208.0 to 280.0)
Total Muscle Score : Visit 8(n=3,3,3,3)	244.0 (201.0 to 252.0)	259.0 (239.0 to 270.0)	253.0 (185.0 to 259.0)	230.0 (216.0 to 265.0)
Total Muscle Score : Visit 12(n=3,3,3,2)	229.0 (198.0 to 254.0)	248.0 (226.0 to 267.0)	247.0 (237.0 to 271.0)	223.0 (216.0 to 230.0)
Total sitting position: Visit 1(n=3,3,3,3)	152.0 (128.0 to 158.0)	150.0 (136.0 to 162.0)	148.0 (132.0 to 160.0)	136.0 (118.0 to 174.0)
Total sitting position: Visit 8(n=3,3,3,3)	148.0 (137.0 to 150.0)	159.0 (144.0 to 162.0)	154.0 (116.0 to 169.0)	136.0 (125.0 to 158.0)
Total sitting position: Visit 12(n=3,3,3,1)	137.0 (134.0 to 151.0)	148.0 (136.0 to 166.0)	156.0 (141.0 to 168.0)	132.0 (132.0 to 132.0)
Total Prone/Side Lying/Supine: Visit 1(n=3,3,3,3)	93.0 (58.0 to 96.0)	93.0 (92.0 to 96.0)	100.0 (87.0 to 103.0)	96.0 (90.0 to 106.0)
Total prone/side lying/supine: Visit 8(n=3,3,3,3)	96.0 (64.0 to 102.0)	100.0 (95.0 to 108.0)	90.0 (69.0 to 99.0)	94.0 (91.0 to 107.0)
Total prone/side lying/supine: Visit 12(n=3,3,3,1)	92.0 (64.0 to 103.0)	100.0 (90.0 to 101.0)	96.0 (91.0 to 103.0)	84.0 (84.0 to 84.0)

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Adverse Events during Initial Study Period

End point title	Number of Subjects with Treatment Emergent Adverse Events during Initial Study Period[23]

End point description:

Intensity was determined by the Investigator. For symptomatic AEs the following definitions were applied.
Mild = AE did not limit usual activities; subject may have experienced slight discomfort.
Moderate = AE resulted in some limitation of usual activities; subject may have experienced significant discomfort.

Severe = AE resulted in an inability to carry out usual activities; subject may have experienced intolerable discomfort/pain.

Relationship to Investigational Medicinal Products (IMP)
Unlikely = Slight, but remote, chance that AE was caused by IMP.
Possible = Reasonable suspicion that the AE was caused by IMP.
Probable = Most likely that AE was caused by IMP.

End point type	Primary

End point timeframe:

Upto Visit 12

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Participants				
TEAE by severity: Mild	2	3	1	2
TEAE by severity: Moderate	1	0	1	1
TEAE by severity: Severe	0	0	1	0
Relationship to IMP - Not related	0	0	0	0
Relationship to IMP - unlikely	0	0	0	0
Relationship to IMP - Possible	2	3	1	0
Relationship to IMP - Probable	1	0	1	2
Relationship to IMP - Definite	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline of 6-Minute Walking Distance (6MWD) in Continued Treatment phase

End point title	Change from Baseline of 6-Minute Walking Distance (6MWD) in Continued Treatment phase[24]

End point description:

Intention-to-Treat (ITT) Population are all treated subjects who received at least one dose of study medication and have at least
one post-Baseline (where Baseline is Visit 13) efficacy parameter. This is the primary population for evaluation of efficacy variable.

Visit 93 to 190 indicate visits during washout.

End point type	Primary

End point timeframe:

At Visit 25, 37, 49, 61, 73, 85, 93, 106, 118, 130, 142, 154, 166, 178 and 190

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: min				
arithmetic mean (standard deviation)				
Visit 25 (N = 11)	29.7 (± 32.71)			
Visit 37 (N = 11)	26.6 (± 65.98)			
Visit 49 (N = 11)	15.9 (± 59.31)			
Visit 61 (N = 11)	19.2 (± 81.85)			
Visit 73 (N = 11)	17.0 (± 113.28)			
Visit 85 (N = 11)	-8.9 (± 138.59)			
Visit 93 (N = 11)	2.9 (± 150.45)			
Visit 106 (N = 11)	3.3 (± 151.37)			
Visit 118 (N = 11)	-1.5 (± 154.52)			
Visit 130 (N = 11)	4.9 (± 157.38)			
Visit 142 (N = 11)	-7.4 (± 157.90)			
Visit 154 (N = 11)	-14.3 (± 153.97)			
Visit 166 (N = 11)	-10.6 (± 160.68)			
Visit 178 (N = 11)	-27.7 (± 147.39)			
Visit 190 (N = 11)	-29.1 (± 153.29)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline of Timed Tests - 10m Walk/run, Rising from floor and Stair Climb in Continued Treatment phase

End point title	Change from Baseline of Timed Tests - 10m Walk/run, Rising from floor and Stair Climb in Continued Treatment phase[25]

End point description:

Intention-to-Treat (ITT) Population

Visit 93 to 190 indicate visits during washout.

End point type	Primary

End point timeframe:

At Visit 21, 25, 29, 33, 37, 41, 49, 61, 73, 85, 93, 106, 118, 130, 142, 154, 166, 178 and 190

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: sec				
arithmetic mean (standard deviation)				
10m Walk/run Visit 21 (N = 11)	0.08 (± 1.184)			
10m Walk/run Visit 25 (N = 11)	0.27 (± 0.515)			
10m Walk/run Visit 29 (N = 11)	0.61 (± 0.621)			
10m Walk/run Visit 33 (N = 10)	0.56 (± 0.761)			
10m Walk/run Visit 37 (N = 10)	0.40 (± 0.388)			
10m Walk/run Visit 41 (N = 10)	0.79 (± 1.133)			
10m Walk/run Visit 49 (N = 10)	0.51 (± 1.010)			
10m Walk/run Visit 61 (N = 10)	0.82 (± 1.181)			
10m Walk/run Visit 73 (N = 10)	0.94 (± 1.696)			
10m Walk/run Visit 85 (N = 9)	1.32 (± 2.446)			
10m Walk/run Visit 93 (N = 9)	2.21 (± 5.229)			
10m Walk/run Visit 106 (N = 8)	0.49 (± 1.080)			
10m Walk/run Visit 118 (N = 8)	0.72 (± 1.360)			
10m Walk/run Visit 130 (N = 8)	0.99 (± 1.695)			
10m Walk/run Visit 142 (N = 8)	1.00 (± 1.360)			
10m Walk/run Visit 154 (N = 8)	1.29 (± 1.925)			
10m Walk/run Visit 166 (N = 8)	1.52 (± 1.789)			
10m Walk/run Visit 178 (N = 8)	1.91 (± 2.059)			
10m Walk/run Visit 190 (N = 8)	1.61 (± 2.039)			
Rising from floor Visit 21 (N = 9)	0.50 (± 1.723)			
Rising from floor Visit 25 (N = 9)	-0.20 (± 0.577)			
Rising from floor Visit 29 (N = 9)	0.06 (± 0.655)			
Rising from floor Visit 33 (N = 9)	1.000 (± 2.632)			
Rising from floor Visit 37 (N = 9)	-0.08 (± 0.923)			
Rising from floor Visit 41 (N = 9)	0.55 (± 0.789)			
Rising from floor Visit 49 (N = 9)	0.82 (± 1.620)			
Rising from floor Visit 61 (N = 8)	0.30 (± 0.656)			
Rising from floor Visit 73 (N = 8)	1.04 (± 2.620)			
Rising from floor Visit 85 (N = 8)	1.75 (± 4.031)			
Rising from floor Visit 93 (N = 8)	1.27 (± 2.472)			
Rising from floor Visit 106 (N = 8)	1.75 (± 4.588)			
Rising from floor Visit 118 (N = 8)	3.09 (± 6.439)			
Rising from floor Visit 130 (N = 7)	1.06 (± 1.976)			
Rising from floor Visit 142 (N = 6)	0.67 (± 0.904)			
Rising from floor Visit 154 (N = 6)	0.44 (± 0.497)			
Rising from floor Visit 166 (N = 6)	0.79 (± 0.625)			
Rising from floor Visit 178 (N = 6)	1.12 (± 1.097)			
Rising from floor Visit 190 (N = 6)	1.05 (± 0.914)			
Stair Climb Visit 21 (N = 11)	-0.85 (± 1.791)			
Stair Climb Visit 25 (N = 11)	-1.07 (± 2.110)			

Stair Climb Visit 29 (N = 11)	-0.40 (± 1.603)			
Stair Climb Visit 33 (N = 10)	-0.45 (± 1.064)			
Stair Climb Visit 37 (N = 9)	-0.18 (± 1.554)			
Stair Climb Visit 41 (N = 10)	-0.61 (± 1.690)			
Stair Climb Visit 49 (N = 9)	-0.37 (± 1.248)			
Stair Climb Visit 61 (N = 9)	-0.50 (± 0.996)			
Stair Climb Visit 73 (N = 10)	-0.15 (± 0.677)			
Stair Climb Visit 85 (N = 9)	0.04 (± 1.201)			
Stair Climb Visit 93 (N = 9)	0.32 (± 0.859)			
Stair Climb Visit 106 (N = 9)	0.76 (± 1.422)			
Stair Climb Visit 118 (N = 8)	1.34 (± 3.041)			
Stair Climb Visit 130 (N = 8)	0.85 (± 2.063)			
Stair Climb Visit 142 (N = 8)	1.62 (± 3.469)			
Stair Climb Visit 154 (N = 8)	1.73 (± 3.446)			
Stair Climb Visit 166 (N = 7)	1.78 (± 4.061)			
Stair Climb Visit 178 (N = 8)	3.48 (± 5.654)			
Stair Climb Visit 190 (N = 7)	4.23 (± 10.382)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline of Muscle Strength Handheld Myometry of Elbow Flexor, Elbow Extensor, Knee Flexor and Knee Extensor in Continued Treatment phase

End point title	Change from Baseline of Muscle Strength Handheld Myometry of Elbow Flexor, Elbow Extensor, Knee Flexor and Knee Extensor in Continued Treatment phase[26]

End point description:

Intention-to-Treat (ITT) Population

Visit 93 to 190 indicate visits during washout

End point type	Primary

End point timeframe:

At Visit 21, 25, 29, 33, 37, 41, 49, 61, 73, 85, 93, 106, 118, 130, 142, 154, 166, 178 and 190

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: lbs				
arithmetic mean (standard deviation)				
Left Elbow Flexor Visit 21 (N = 12)	-1.18 (± 1.968)			
Left Elbow Flexor Visit 25 (N = 12)	-0.73 (± 1.524)			
Left Elbow Flexor Visit 29 (N = 12)	-0.59 (± 1.227)			
Left Elbow Flexor Visit 33 (N = 12)	-0.47 (± 1.828)			
Left Elbow Flexor Visit 37 (N = 12)	-0.68 (± 1.588)			
Left Elbow Flexor Visit 41 (N = 12)	-0.07 (± 2.227)			
Left Elbow Flexor Visit 49 (N = 12)	0.01 (± 1.766)			
Left Elbow Flexor Visit 61 (N = 12)	-1.63 (± 2.308)			
Left Elbow Flexor Visit 73 (N = 12)	-0.64 (± 1.975)			
Left Elbow Flexor Visit 85 (N = 12)	-1.24 (± 1.565)			
Left Elbow Flexor Visit 93 (N = 12)	-1.24 (± 2.021)			
Left Elbow Flexor Visit 106 (N = 12)	-1.44 (± 1.832)			
Left Elbow Flexor Visit 118 (N = 12)	-1.54 (± 2.523)			
Left Elbow Flexor Visit 130 (N = 12)	-0.28 (± 2.312)			
Left Elbow Flexor Visit 142 (N = 12)	-1.05 (± 1.934)			
Left Elbow Flexor Visit 154 (N = 12)	-1.23 (± 2.527)			
Left Elbow Flexor Visit 166 (N = 12)	-1.26 (± 2.200)			
Left Elbow Flexor Visit 178 (N = 12)	-1.62 (± 2.063)			
Left Elbow Flexor Visit 190 (N = 12)	-1.66 (± 1.532)			
Right Elbow Flexor Visit 21 (N = 12)	-0.48 (± 2.020)			
Right Elbow Flexor Visit 25 (N = 12)	0.27 (± 1.721)			
Right Elbow Flexor Visit 29 (N = 12)	-0.88 (± 2.021)			
Right Elbow Flexor Visit 33 (N = 12)	-0.92 (± 1.946)			
Right Elbow Flexor Visit 37 (N = 12)	-1.11 (± 2.017)			
Right Elbow Flexor Visit 41 (N = 12)	-0.18 (± 2.243)			
Right Elbow Flexor Visit 49 (N = 12)	-0.44 (± 1.947)			
Right Elbow Flexor Visit 61 (N = 12)	-1.43 (± 1.971)			

Right Elbow Flexor Visit 73 (N = 12)	-1.07 (± 2.555)			
Right Elbow Flexor Visit 85 (N = 12)	-1.00 (± 2.558)			
Right Elbow Flexor Visit 93 (N = 12)	-1.20 (± 2.649)			
Right Elbow Flexor Visit 106 (N = 12)	-1.60 (± 2.057)			
Right Elbow Flexor Visit 118 (N = 12)	-1.39 (± 2.564)			
Right Elbow Flexor Visit 130 (N = 12)	-0.99 (± 2.886)			
Right Elbow Flexor Visit 142 (N = 12)	-0.73 (± 2.327)			
Right Elbow Flexor Visit 154 (N = 12)	-1.33 (± 2.089)			
Right Elbow Flexor Visit 166 (N = 12)	-0.92 (± 2.664)			
Right Elbow Flexor Visit 178 (N = 12)	-1.80 (± 2.628)			
Right Elbow Flexor Visit 190 (N = 12)	-1.68 (± 2.482)			
Left Elbow Extensor Visit 21 (N = 12)	-1.48 (± 1.937)			
Left Elbow Extensor Visit 25 (N = 12)	-0.77 (± 1.810)			
Left Elbow Extensor Visit 29 (N = 12)	-1.60 (± 1.063)			
Left Elbow Extensor Visit 33 (N = 12)	-0.88 (± 1.419)			
Left Elbow Extensor Visit 37 (N = 12)	-1.38 (± 2.390)			
Left Elbow Extensor Visit 41 (N = 12)	0.46 (± 1.940)			
Left Elbow Extensor Visit 49 (N = 12)	-0.17 (± 2.198)			
Left Elbow Extensor Visit 61 (N = 12)	-1.91 (± 1.441)			
Left Elbow Extensor Visit 73 (N = 12)	-1.26 (± 1.743)			
Left Elbow Extensor Visit 85 (N = 12)	-1.31 (± 1.775)			
Left Elbow Extensor Visit 93 (N = 12)	-1.59 (± 1.508)			
Left Elbow Extensor Visit 106 (N = 12)	-2.38 (± 2.767)			
Left Elbow Extensor Visit 118 (N = 12)	-1.49 (± 1.714)			
Left Elbow Extensor Visit 130 (N = 12)	-1.25 (± 2.482)			
Left Elbow Extensor Visit 142 (N = 12)	-1.52 (± 2.057)			
Left Elbow Extensor Visit 154 (N = 12)	-1.73 (± 2.537)			
Left Elbow Extensor Visit 166 (N = 12)	-1.77 (± 2.117)			
Left Elbow Extensor Visit 178 (N = 12)	-2.14 (± 2.696)			
Left Elbow Extensor Visit 190 (N = 12)	-1.97 (± 2.414)			
Right Elbow Extensor Visit 21 (N = 12)	-0.13 (± 2.401)			

Right Elbow Extensor Visit 25 (N = 12)	-0.15 (± 3.122)			
Right Elbow Extensor Visit 29 (N = 12)	-0.87 (± 2.097)			
Right Elbow Extensor Visit 33 (N = 12)	-0.37 (± 2.447)			
Right Elbow Extensor Visit 37 (N = 12)	-1.61 (± 2.378)			
Right Elbow Extensor Visit 41 (N = 12)	-0.08 (± 2.292)			
Right Elbow Extensor Visit 49 (N = 12)	-0.63 (± 2.782)			
Right Elbow Extensor Visit 61 (N = 12)	-1.88 (± 2.398)			
Right Elbow Extensor Visit 73 (N = 12)	-0.38 (± 1.910)			
Right Elbow Extensor Visit 85 (N = 12)	-1.43 (± 2.969)			
Right Elbow Extensor Visit 93 (N = 12)	-1.54 (± 3.529)			
Right Elbow Extensor Visit 106 (N = 12)	-1.88 (± 3.768)			
Right Elbow Extensor Visit 118 (N = 12)	-1.12 (± 3.164)			
Right Elbow Extensor Visit 130 (N = 12)	-1.63 (± 3.992)			
Right Elbow Extensor Visit 142 (N = 12)	-1.54 (± 2.850)			
Right Elbow Extensor Visit 154 (N = 12)	-1.63 (± 2.842)			
Right Elbow Extensor Visit 166 (N = 12)	-1.87 (± 2.873)			
Right Elbow Extensor Visit 178 (N = 12)	-1.67 (± 2.760)			
Right Elbow Extensor Visit 190 (N = 12)	-1.55 (± 1.614)			
Left Knee Flexor Visit 21 (N = 12)	-0.88 (± 2.982)			
Left Knee Flexor Visit 25 (N = 12)	-0.99 (± 3.170)			
Left Knee Flexor Visit 29 (N = 12)	-1.06 (± 5.171)			
Left Knee Flexor Visit 33 (N = 11)	-1.42 (± 4.101)			
Left Knee Flexor Visit 37 (N = 11)	-1.31 (± 3.894)			
Left Knee Flexor Visit 41 (N = 11)	-0.74 (± 2.604)			
Left Knee Flexor Visit 49 (N = 12)	-1.36 (± 3.282)			
Left Knee Flexor Visit 61 (N = 12)	-2.50 (± 3.177)			
Left Knee Flexor Visit 73 (N = 12)	-1.89 (± 4.518)			
Left Knee Flexor Visit 85 (N = 11)	-1.88 (± 4.602)			
Left Knee Flexor Visit 93 (N = 12)	-1.64 (± 4.498)			
Left Knee Flexor Visit 106 (N = 12)	-4.04 (± 4.782)			
Left Knee Flexor Visit 118 (N = 12)	-3.06 (± 4.522)			

Left Knee Flexor Visit 130 (N = 11)	-2.41 (± 5.280)			
Left Knee Flexor Visit 142 (N = 12)	-2.95 (± 5.588)			
Left Knee Flexor Visit 154 (N = 12)	-3.37 (± 4.673)			
Left Knee Flexor Visit 166 (N = 12)	-3.01 (± 4.751)			
Left Knee Flexor Visit 178 (N = 12)	-3.91 (± 4.284)			
Left Knee Flexor Visit 190 (N = 11)	-3.74 (± 4.801)			
Right Knee Flexor Visit 21 (N = 12)	-1.14 (± 1.874)			
Right Knee Flexor Visit 25 (N = 12)	-0.54 (± 3.358)			
Right Knee Flexor Visit 29 (N = 12)	-1.74 (± 3.504)			
Right Knee Flexor Visit 33 (N = 11)	-1.08 (± 3.563)			
Right Knee Flexor Visit 37 (N = 11)	-1.45 (± 4.435)			
Right Knee Flexor Visit 41 (N = 11)	-1.99 (± 2.221)			
Right Knee Flexor Visit 49 (N = 12)	-2.13 (± 4.209)			
Right Knee Flexor Visit 61 (N = 12)	-2.46 (± 3.520)			
Right Knee Flexor Visit 73 (N = 12)	-1.58 (± 5.070)			
Right Knee Flexor Visit 85 (N = 11)	-2.24 (± 4.360)			
Right Knee Flexor Visit 93 (N = 12)	-2.16 (± 3.830)			
Right Knee Flexor Visit 106 (N = 12)	-3.89 (± 4.880)			
Right Knee Flexor Visit 118 (N = 12)	-3.14 (± 4.848)			
Right Knee Flexor Visit 130 (N = 11)	-2.68 (± 4.706)			
Right Knee Flexor Visit 142 (N = 12)	-3.87 (± 5.562)			
Right Knee Flexor Visit 154 (N = 12)	-4.03 (± 5.447)			
Right Knee Flexor Visit 166 (N = 12)	-3.74 (± 5.233)			
Right Knee Flexor Visit 178 (N = 11)	-4.79 (± 5.185)			
Right Knee Flexor Visit 190 (N = 11)	-3.68 (± 5.214)			
Left Knee Extensor Visit 21 (N = 12)	-0.99 (± 5.692)			
Left Knee Extensor Visit 25 (N = 12)	0.01 (± 2.325)			
Left Knee Extensor Visit 29 (N = 12)	-0.39 (± 2.121)			
Left Knee Extensor Visit 33 (N = 11)	-0.76 (± 3.507)			
Left Knee Extensor Visit 37 (N = 11)	-0.32 (± 3.285)			
Left Knee Extensor Visit 41 (N = 11)	-0.79 (± 2.673)			

Left Knee Extensor Visit 49 (N = 12)	-0.78 (± 3.508)			
Left Knee Extensor Visit 61 (N = 12)	-2.32 (± 3.755)			
Left Knee Extensor Visit 73 (N = 12)	-1.69 (± 3.700)			
Left Knee Extensor Visit 85 (N = 11)	-2.13 (± 2.713)			
Left Knee Extensor Visit 93 (N = 12)	-1.76 (± 3.683)			
Left Knee Extensor Visit 106 (N = 12)	-1.91 (± 4.678)			
Left Knee Extensor Visit 118 (N = 12)	-1.98 (± 4.215)			
Left Knee Extensor Visit 130 (N = 11)	-2.54 (± 4.206)			
Left Knee Extensor Visit 142 (N = 12)	-1.94 (± 4.891)			
Left Knee Extensor Visit 154 (N = 12)	-2.51 (± 4.516)			
Left Knee Extensor Visit 166 (N = 12)	-2.23 (± 4.845)			
Left Knee Extensor Visit 178 (N = 12)	-2.15 (± 3.967)			
Left Knee Extensor Visit 190 (N = 11)	-3.53 (± 2.770)			
Right Knee Extensor Visit 21 (N = 12)	-0.47 (± 2.534)			
Right Knee Extensor Visit 25 (N = 12)	-0.62 (± 3.525)			
Right Knee Extensor Visit 29 (N = 12)	-1.80 (± 2.842)			
Right Knee Extensor Visit 33 (N = 11)	-1.26 (± 2.045)			
Right Knee Extensor Visit 37 (N = 11)	-2.65 (± 2.040)			
Right Knee Extensor Visit 41 (N = 11)	-1.52 (± 3.095)			
Right Knee Extensor Visit 49 (N = 12)	-1.02 (± 3.939)			
Right Knee Extensor Visit 61 (N = 12)	-3.35 (± 4.414)			
Right Knee Extensor Visit 73 (N = 12)	-1.77 (± 4.162)			
Right Knee Extensor Visit 85 (N = 11)	-2.25 (± 4.913)			
Right Knee Extensor Visit 93 (N = 12)	-2.28 (± 3.753)			
Right Knee Extensor Visit 106 (N = 12)	-2.24 (± 3.677)			
Right Knee Extensor Visit 118 (N = 12)	-2.61 (± 4.893)			
Right Knee Extensor Visit 130 (N = 11)	-3.04 (± 3.712)			
Right Knee Extensor Visit 142 (N = 12)	-1.99 (± 5.538)			
Right Knee Extensor Visit 154 (N = 12)	-4.22 (± 7.410)			
Right Knee Extensor Visit 166 (N = 12)	-2.89 (± 6.024)			
Right Knee Extensor Visit 178 (N = 11)	-3.17 (± 5.167)			

Right Knee Extensor Visit 190 (N = 11)	-4.41 (± 5.490)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline Spirometry of Forced vital capacity (FVC) and Forced expiratory volume in 1 second (FEV1) in Continued Treatment phase

End point title	Change from Baseline Spirometry of Forced vital capacity (FVC) and Forced expiratory volume in 1 second (FEV1) in Continued Treatment phase[27]

End point description:

Intention-to-Treat (ITT) Population

Visit 93 to 190 indicate visits during washout

End point type	Primary

End point timeframe:

At Visit 21, 25, 29, 33, 37, 41, 49, 61, 73, 85, 93, 106, 118, 130, 142, 154, 166, 178 and 190

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Litre				
arithmetic mean (standard deviation)				
FVC absolute Visit 21 (N = 12)	0.008 (± 0.1472)			
FVC absolute Visit 25 (N = 12)	-0.030 (± 0.1563)			
FVC absolute Visit 29 (N = 11)	0.029 (± 0.2077)			
FVC absolute Visit 33 (N = 12)	0.023 (± 0.1795)			
FVC absolute Visit 37 (N = 11)	0.039 (± 0.2944)			
FVC absolute Visit 41 (N = 12)	0.048 (± 0.2166)			
FVC absolute Visit 49 (N = 12)	0.058 (± 0.1593)			
FVC absolute Visit 61 (N = 12)	0.079 (± 0.2553)			
FVC absolute Visit 73 (N = 12)	0.078 (± 0.1927)			
FVC absolute Visit 85 (N = 12)	0.045 (± 0.2135)			
FVC absolute Visit 93 (N = 12)	0.061 (± 0.1507)			

FVC absolute Visit 106 (N = 12)	0.150 (± 0.1897)			
FVC absolute Visit 118 (N = 12)	0.092 (± 0.2661)			
FVC absolute Visit 130 (N = 12)	0.073 (± 0.3290)			
FVC absolute Visit 142 (N = 12)	0.066 (± 0.2423)			
FVC absolute Visit 154 (N = 11)	0.053 (± 0.2172)			
FVC absolute Visit 166 (N = 12)	0.057 (± 0.2833)			
FVC absolute Visit 178 (N = 12)	0.063 (± 0.2843)			
FVC absolute Visit 190 (N = 12)	0.057 (± 0.2891)			
FEV1 absolute Visit 21 (N = 12)	-0.006 (± 0.2193)			
FEV1 absolute Visit 25 (N = 12)	-0.040 (± 0.1861)			
FEV1 absolute Visit 29 (N = 11)	0.032 (± 0.1542)			
FEV1 absolute Visit 33 (N = 12)	0.036 (± 0.1841)			
FEV1 absolute Visit 37 (N = 11)	0.035 (± 0.2536)			
FEV1 absolute Visit 41 (N = 12)	0.025 (± 0.2121)			
FEV1 absolute Visit 49 (N = 12)	0.058 (± 0.1668)			
FEV1 absolute Visit 61 (N = 12)	0.066 (± 0.2619)			
FEV1 absolute Visit 73 (N = 12)	0.089 (± 0.1723)			
FEV1 absolute Visit 85 (N = 12)	0.029 (± 0.1900)			
FEV1 absolute Visit 93 (N = 12)	0.043 (± 0.1307)			
FEV1 absolute Visit 106 (N = 12)	0.134 (± 0.1787)			
FEV1 absolute Visit 118 (N = 12)	0.109 (± 0.2309)			
FEV1 absolute Visit 130 (N = 12)	0.076 (± 0.3121)			
FEV1 absolute Visit 142 (N = 12)	0.068 (± 0.2207)			
FEV1 absolute Visit 154 (N = 11)	0.052 (± 0.1670)			
FEV1 absolute Visit 166 (N = 12)	0.078 (± 0.2583)			
FEV1 absolute Visit 178 (N = 12)	0.099 (± 0.2562)			
FEV1 absolute Visit 190 (N = 12)	0.065 (± 0.2878)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline Spirometry of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in Continued Treatment phase

End point title	Change from Baseline Spirometry of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in Continued Treatment phase[28]

End point description:

Intention-to-Treat (ITT) Population

Visit 93 to 190 indicate visits during washout

End point type	Primary

End point timeframe:

At Visit 21, 25, 29, 33, 37, 41, 49, 61, 73, 85, 93, 106, 118, 130, 142, 154, 166, 178 and 190

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: cm H2O				
arithmetic mean (standard deviation)				
MIP absolute Visit 21 (N = 12)	4.0 (± 15.82)			
MIP absolute Visit 25 (N = 12)	-3.7 (± 14.00)			
MIP absolute Visit 29 (N = 11)	6.4 (± 18.51)			
MIP absolute Visit 33 (N = 12)	-1.8 (± 12.88)			
MIP absolute Visit 37 (N = 11)	-6.1 (± 28.58)			
MIP absolute Visit 41 (N = 12)	1.5 (± 12.31)			
MIP absolute Visit 49 (N = 12)	-5.1 (± 14.98)			
MIP absolute Visit 61 (N = 12)	-3.3 (± 12.04)			
MIP absolute Visit 73 (N = 12)	0.4 (± 15.51)			
MIP absolute Visit 85 (N = 12)	1.8 (± 15.15)			
MIP absolute Visit 93 (N = 12)	1.2 (± 14.12)			
MIP absolute Visit 106 (N = 12)	-7.7 (± 17.59)			
MIP absolute Visit 118 (N = 12)	-7.0 (± 17.92)			
MIP absolute Visit 130 (N = 12)	-2.8 (± 15.46)			
MIP absolute Visit 142 (N = 12)	3.3 (± 22.06)			
MIP absolute Visit 154 (N = 11)	5.5 (± 19.21)			
MIP absolute Visit 166 (N = 12)	-0.3 (± 17.51)			
MIP absolute Visit 178 (N = 12)	0.8 (± 15.64)			
MIP absolute Visit 190 (N = 12)	3.7 (± 21.96)			
MEP absolute Visit 21 (N = 12)	-11.2 (± 14.55)			
MEP absolute Visit 25 (N = 12)	-3.3 (± 13.01)			
MEP absolute Visit 29 (N = 11)	-3.5 (± 14.40)			
MEP absolute Visit 33 (N = 12)	-3.6 (± 14.23)			
MEP absolute Visit 37 (N = 11)	-2.7 (± 15.28)			
MEP absolute Visit 41 (N = 12)	-7.6 (± 19.24)			
MEP absolute Visit 49 (N = 12)	-5.7 (± 13.96)			

MEP absolute Visit 61 (N = 12)	-8.7 (± 15.98)			
MEP absolute Visit 73 (N = 12)	-6.0 (± 14.55)			
MEP absolute Visit 85 (N = 12)	-9.6 (± 14.32)			
MEP absolute Visit 93 (N = 12)	-11.9 (± 15.72)			
MEP absolute Visit 106 (N = 12)	-0.8 (± 13.18)			
MEP absolute Visit 118 (N = 12)	-0.5 (± 16.01)			
MEP absolute Visit 130 (N = 12)	-7.6 (± 13.58)			
MEP absolute Visit 142 (N = 12)	-12.5 (± 13.14)			
MEP absolute Visit 154 (N = 11)	-12.7 (± 17.72)			
MEP absolute Visit 166 (N = 12)	-2.6 (± 19.09)			
MEP absolute Visit 178 (N = 12)	-5.7 (± 14.95)			
MEP absolute Visit 190 (N = 12)	-11.4 (± 16.71)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline Spirometry of Peak flow (PF) and Peak cough flow (PCF) in Continued Treatment phase

End point title	Change from Baseline Spirometry of Peak flow (PF) and Peak cough flow (PCF) in Continued Treatment phase[29]

End point description:

Intention-to-Treat (ITT) Population

Visit 93 to 190 indicate visits during washout

End point type	Primary

End point timeframe:

At Visit 21, 25, 29, 33, 37, 41, 49, 61, 73, 85, 93, 106, 118, 130, 142, 154, 166, 178 and 190

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: L/min				
arithmetic mean (standard deviation)				
PF absolute Visit 21 (N = 12)	-3.7 (± 22.38)			
PF absolute Visit 25 (N = 9)	-45.8 (± 29.45)			
PF absolute Visit 29 (N = 9)	13.7 (± 24.05)			
PF absolute Visit 33 (N = 12)	9.0 (± 45.58)			
PF absolute Visit 37 (N = 11)	-2.1 (± 51.17)			
PF absolute Visit 41 (N = 12)	-1.3 (± 36.88)			
PF absolute Visit 49 (N = 12)	15.4 (± 40.37)			

PF absolute Visit 61 (N = 12)	12.9 (± 54.04)			
PF absolute Visit 73 (N = 12)	12.6 (± 36.53)			
PF absolute Visit 85 (N = 12)	9.0 (± 41.13)			
PF absolute Visit 93 (N = 12)	37.8 (± 54.20)			
PF absolute Visit 106 (N = 12)	26.1 (± 44.65)			
PF absolute Visit 118 (N = 11)	31.7 (± 39.46)			
PF absolute Visit 130 (N = 12)	35.5 (± 40.95)			
PF absolute Visit 142 (N = 12)	27.8 (± 53.54)			
PF absolute Visit 154 (N = 11)	33.5 (± 34.17)			
PF absolute Visit 166 (N = 9)	20.9 (± 33.07)			
PF absolute Visit 178 (N = 12)	22.8 (± 42.55)			
PF absolute Visit 190 (N = 12)	9.4 (± 73.06)			
PCF absolute Visit 21 (N = 12)	-4.7 (± 65.20)			
PCF absolute Visit 25 (N = 12)	-6.7 (± 51.93)			
PCF absolute Visit 29 (N = 11)	30.9 (± 55.04)			
PCF absolute Visit 33 (N = 12)	19.2 (± 53.16)			
PCF absolute Visit 37 (N = 11)	19.1 (± 47.63)			
PCF absolute Visit 41 (N = 12)	29.2 (± 63.60)			
PCF absolute Visit 49 (N = 12)	44.2 (± 58.38)			
PCF absolute Visit 61 (N = 12)	19.2 (± 55.83)			
PCF absolute Visit 73 (N = 12)	41.7 (± 66.68)			
PCF absolute Visit 85 (N = 12)	34.2 (± 66.26)			
PCF absolute Visit 93 (N = 12)	50.0 (± 67.01)			
PCF absolute Visit 106 (N = 12)	31.7 (± 53.06)			
PCF absolute Visit 118 (N = 12)	45.8 (± 51.60)			
PCF absolute Visit 130 (N = 12)	70.0 (± 65.51)			
PCF absolute Visit 142 (N = 12)	52.5 (± 69.17)			
PCF absolute Visit 154 (N = 11)	50.0 (± 59.33)			
PCF absolute Visit 166 (N = 12)	42.5 (± 72.13)			
PCF absolute Visit 178 (N = 12)	42.5 (± 66.35)			
PCF absolute Visit 190 (N = 12)	22.5 (± 81.14)			

Statistical analyses

No statistical analyses for this end point

Primary: Responses Summary of Parent Questionnaire to change in condition over the Continued Treatment phase

End point title	Responses Summary of Parent Questionnaire to change in condition over the Continued Treatment phase[30]

End point description:

Intention-to-Treat (ITT) Population

The questionnaires completed at either 4 or 5 visits depending on the study site and the actual visit number varied between subjects.

End point type	Primary

End point timeframe:

At Visit 81 to 89, Visit 109 to 123, Visit 154 to 157 and Visit 178

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of subjects				
General condition: Better at Visit 81-89 (N=11)	4			
General condition: Same at Visit 81-89 (N=11)	5			
General condition: Worse Visit 81-89 (N=11)	2			
General condition: Better at Visit 109-123 (N=12)	3			
General condition: Same at Visit 109-123 (N=12)	5			
General condition: Worse at Visit 109-123 (N=12)	4			
General condition: Better at Visit 154-157 (N=11)	1			
General condition: Same at Visit 154-157 (N=11)	4			
General condition: Worse at Visit 154-157 (N=11)	6			
General condition: Better at Visit 178 (N=12)	1			
General condition: Same at Visit 178 (N=12)	8			
General condition: Worse at Visit 178 (N=12)	3			
Walking: Better at Visit 81-89 (N=11)	4			
Walking: Same at Visit 81-89 (N=11)	5			
Walking: Worse at Visit 81-89 (N=11)	2			
Walking: Better at Visit 109-123 (N=12)	3			
Walking: Same Visit at 109-123 (N=12)	5			
Walking: Worse Visit at 109-123 (N=12)	4			
Walking: Better at Visit 154-157 (N=12)	2			
Walking: Same at Visit 154-157 (N=12)	6			
Walking: Worse at Visit 154-157 (N=12)	4			
Walking: Better at Visit 178 (N=12)	1			
Walking: Same at Visit 178 (N=12)	6			
Walking: Worse at Visit 178 (N=12)	5			
Taking stairs: Better at Visit 81-89 (N=11)	3			
Taking stairs: Same at Visit 81-89 (N=11)	3			
Taking stairs: Worse at Visit 81-89 (N=11)	5			
Taking stairs: Better at Visit 109-123 (N=12)	1			
Taking stairs: Same Visit at 109-123 (N=12)	6			

Taking stairs: Worse Visit at 109-123 (N=12)	5			
Taking stairs: Better at Visit 154-157 (N=12)	1			
Taking stairs: Same at Visit 154-157 (N=12)	4			
Taking stairs: Worse at Visit 154-157 (N=12)	7			
Taking stairs: Better at Visit 178 (N=12)	1			
Taking stairs: Same at Visit 178 (N=12)	3			
Taking stairs: Worse at Visit 178 (N=12)	8			
Endurance: Better at Visit 81-89 (N=11)	4			
Endurance: Same at Visit 81-89 (N=11)	7			
Endurance: Worse at Visit 81-89 (N=11)	0			
Endurance: Better at Visit 109-123 (N=12)	0			
Endurance: Same Visit at 109-123 (N=12)	10			
Endurance: Worse Visit at 109-123 (N=12)	2			
Endurance: Better at Visit 154-157 (N=12)	2			
Endurance: Same at Visit 154-157 (N=12)	7			
Endurance: Worse at Visit 154-157 (N=12)	3			
Endurance: Better at Visit 178 (N=12)	2			
Endurance: Same at Visit 178 (N=12)	8			
Endurance: Worse at Visit 178 (N=12)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Muscle Biopsy Summary of Exon 51 Skip in Continued Treatment phase

End point title	Muscle Biopsy Summary of Exon 51 Skip in Continued Treatment phase[31]

End point description:

Intention-to-Treat (ITT) Population

Y = Clear exon 51 skipping observed, confirmed by sequencing
* = Sequence skip confirmed after additional Polymerase Chain Reaction, despite low quality Ribonucleic Acid
RT-PCR (Reverse Transcription-Polymerase Chain Reaction)

End point type	Primary

End point timeframe:

At Visit 37

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of Subjects				
Exon skip by RT_PCR – Y	6			
Exon skip by RT_PCR - Y*	6			

Statistical analyses

No statistical analyses for this end point

Primary: Muscle Biopsy Summary of Immunofluorescence Qualitative Dystrophin Expression in Continued Treatment phase

End point title	Muscle Biopsy Summary of Immunofluorescence Qualitative Dystrophin Expression in Continued Treatment phase[32]

End point description:

Intention-to-Treat (ITT) Population

Y = dystrophin protein detected at the sarcolemmal membrane
No result = poor quality not allowing analysis

End point type	Primary

End point timeframe:

At Visit 37

Notes:

[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of Subjects				
Immunofluorescence – Y	10			
Immunofluorescence - No result	2			

Statistical analyses

No statistical analyses for this end point

Primary: Muscle Biopsy Summary of Western Blot Qualitative Dystrophin Expression in Continued Treatment phase

End point title	Muscle Biopsy Summary of Western Blot Qualitative Dystrophin Expression in Continued Treatment phase[33]

End point description:

Intention-to-Treat (ITT) Population

Y = suggestive increase of dystrophin levels when compared to earlier visit biopsies and/or pre-treatment samples
N = no clear increase of dystrophin levels when compared to earlier visit
No result = protein degradation not allowing analysis
Inconclusive = no conclusion to be drawn due to presence of revertant fibres or lacking/conflicting data in subsequent experiments
# Compared to earlier sample (on the same gel) from the initial study period

End point type	Primary

End point timeframe:

At Visit 37

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of Subjects				
Western Blot – N	1			
Western Blot - Y	5			
Western Blot – Inconclusive	3			
Western Blot - No result (degraded)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Drisapersen during Initial Study Period

End point title	Maximum Observed Plasma Concentration (Cmax) of Drisapersen during Initial Study Period

End point description:

Pharmacokinetic (PK) sample are all treated subjects who had at least one PK assessment post-baseline.

Pharmacokinetic Parameter Cmax (Maximum measured plasma concentration)

End point type	Secondary

End point timeframe:

0.5, 2, 3, 4, 6, 9, 12 and 24 ±3 hours

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1	1.98 (± 1.38)	4.09 (± 2.45)	5.28 (± 0.38)	9.36 (± 2.68)
Day 29	1.03 (± 0.22)	4.41 (± 1.86)	7.18 (± 3.06)	11.20 (± 2.30)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of Drisapersen during Initial Study Period

End point title	Time to Maximum Observed Concentration (Tmax) of Drisapersen during Initial Study Period

End point description:

Pharmacokinetic (PK) sample

Pharmacokinetic Parameter (Tmax) Time of the maximum measured plasma concentration.

End point type	Secondary

End point timeframe:

0.5, 2, 3, 4, 6, 9, 12 and 24 ±3 hours

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: hr				
arithmetic mean (standard deviation)				
Day 1	2.67 (± 0.58)	4.56 (± 3.53)	2.33 (± 0.58)	3.22 (± 2.26)
Day 29	2.33 (± 0.58)	1.89 (± 1.33)	2.39 (± 0.54)	2.03 (± 0.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration measured 7 days after the injection(Ctrough-D7) of Drisapersen during Initial Study Period

End point title	Plasma concentration measured 7 days after the injection(Ctrough-D7) of Drisapersen during Initial Study

End point description:

Pharmacokinetic (PK) sample

Pharmacokinetic Parameter Ctrough-D7 is the Plasma concentration measured 7 days after the injection.

End point type	Secondary

End point timeframe:

0.5, 2, 3, 4, 6, 9, 12 and 24 ±3 hours

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses were conducted.

End point values	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1	0.0026 (± 0.0006)	0.0024 (± 0.0012)	0.0064 (± 0.0061)	
Day 29	0.0047 (± 0.0027)	0.0075 (± 0.0045)	0.0150 (± 0.0056)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time 0 to 24h(AUC0-24h) of Drisapersen during Initial Study Period

End point title	Area under the plasma concentration-time curve from time 0 to 24h(AUC0-24h) of Drisapersen during Initial Study Period

End point description:

Pharmacokinetic (PK) sample

Pharmacokinetic Parameter AUC0-24h Area under the plasma concentration-time curve from time 0 to 24 h.

End point type	Secondary

End point timeframe:

0.5, 2, 3, 4, 6, 9, 12 and 24 ±3 hours

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: h*µg/mL				
arithmetic mean (standard deviation)				
Day 1	7.6 (± 1.7)	27.0 (± 2.3)	41.0 (± 5.4)	78.9 (± 21.7)
Day 29	5.9 (± 1.1)	26.1 (± 4.1)	44.8 (± 9.6)	106.0 (± 29.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve during one dosing interval (AUC0-D7) of Drisapersen during Initial Study Period

End point title	Area under the plasma concentration-time curve during one dosing interval (AUC0-D7) of Drisapersen during Initial Study Period

End point description:

Pharmacokinetic (PK) sample

Pharmacokinetic Parameter AUC0-D7 is the Area under the plasma concentration-time curve during one dosing interval.

End point type	Secondary

End point timeframe:

0.5, 2, 3, 4, 6, 9, 12 and 24 ±3 hours

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: h*µg/mL				
arithmetic mean (standard deviation)				
Day 1	8.8 (± 2.6)	30.6 (± 4.2)	45.4 (± 5.7)	93.1 (± 32.2)
Day 29	6.2 (± 1.0)	29.7 (± 7.5)	52.7 (± 18.7)	126.7 (± 31.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent plasma clearance (CL/F) of Drisapersen during Initial Study Period

End point title	Apparent plasma clearance (CL/F) of Drisapersen during Initial Study Period

End point description:

Pharmacokinetic (PK) sample

Pharmacokinetic Parameter CL/F is the Apparent plasma clearance.

End point type	Secondary

End point timeframe:

0.5, 2, 3, 4, 6, 9, 12 and 24 ±3 hours

End point values	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg	Group IV - 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: mL/min				
arithmetic mean (standard deviation)				
Day 1	26.6 (± 6.3)	33.8 (± 12.9)	31.5 (± 7.5)	34.6 (± 11.7)
Day 29	39.2 (± 13.5)	35.0 (± 9.0)	29.1 (± 13.1)	24.6 (± 5.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Drisapersen during Continued Treatment phase

End point title	Maximum Observed Plasma Concentration (Cmax) of Drisapersen during Continued Treatment phase

End point description:

Pharmacokinetic (PK) Population are all subjects who had a PK blood sample collected and analyzed for drisapersen.

Pharmacokinetic Parameter Cmax (Maximum measured plasma concentration)

End point type	Secondary

End point timeframe:

0.5 hr (± 5 min), 2 hr (± 15 min), 3 hr (± 15 min), 4 hr (± 15 min), 6 hr (± 15 min), 9 hr (± 30 min), 12 hr (± 30 min) and 24 hr (±3 hrs) at Visit 33.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)	9410.83 (± 4051.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of Drisapersen during Continued Treatment phase

End point title	Time to Maximum Observed Concentration (Tmax) of Drisapersen during Continued Treatment phase

End point description:

Pharmacokinetic (PK) population

Pharmacokinetic Parameter (Tmax) Time of the maximum measured plasma concentration.

End point type	Secondary

End point timeframe:

0.5 hr (± 5 min), 2 hr (± 15 min), 3 hr (± 15 min), 4 hr (± 15 min), 6 hr (± 15 min), 9 hr (± 30 min), 12 hr (± 30 min) and 24 hr (±3 hrs) at Visit 33.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hr				
arithmetic mean (standard deviation)	3.987 (± 2.758)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time 0 to 24h(AUC0-24h) of Drisapersen during Continued Treatment phase

End point title	Area under the plasma concentration-time curve from time 0 to 24h(AUC0-24h) of Drisapersen during Continued Treatment phase

End point description:

Pharmacokinetic (PK) population.

Pharmacokinetic Parameter AUC0-24h Area under the plasma concentration-time curve from time 0 to 24 h.

End point type	Secondary

End point timeframe:

0.5 hr (± 5 min), 2 hr (± 15 min), 3 hr (± 15 min), 4 hr (± 15 min), 6 hr (± 15 min), 9 hr (± 30 min), 12 hr (± 30 min) and 24 hr (±3 hrs) at Visit 33.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h*ng/mL				
arithmetic mean (standard deviation)	110693 (± 45227.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent plasma clearance (CL/F) of Drisapersen during Continued Treatment phase

End point title	Apparent plasma clearance (CL/F) of Drisapersen during Continued Treatment phase

End point description:

Pharmacokinetic (PK) population

Pharmacokinetic Parameter CL/F is the Apparent plasma clearance.

End point type	Secondary

End point timeframe:

0.5 hr (± 5 min), 2 hr (± 15 min), 3 hr (± 15 min), 4 hr (± 15 min), 6 hr (± 15 min), 9 hr (± 30 min), 12 hr (± 30 min) and 24 hr (±3 hrs) at Visit 33.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mL/min				
arithmetic mean (standard deviation)	28.675 (± 6.527)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cpre of Drisapersen during Continued Treatment phase

End point title	Cpre of Drisapersen during Continued Treatment phase

End point description:

Pharmacokinetic (PK) Population

End point type	Secondary

End point timeframe:

0.5 hr (± 5 min), 2 hr (± 15 min), 3 hr (± 15 min), 4 hr (± 15 min), 6 hr (± 15 min), 9 hr (± 30 min), 12 hr (± 30 min) and 24 hr (±3 hrs) at Visit 33.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				

arithmetic mean (standard deviation)	111.417 (± 105.947)			

Statistical analyses

No statistical analyses for this end point

Secondary: C34 of Drisapersen during Continued Treatment phase

End point title	C34 of Drisapersen during Continued Treatment phase

End point description:

Pharmacokinetic (PK) Population

End point type	Secondary

End point timeframe:

0.5 hr (± 5 min), 2 hr (± 15 min), 3 hr (± 15 min), 4 hr (± 15 min), 6 hr (± 15 min), 9 hr (± 30 min), 12 hr (± 30 min) and 24 hr (±3 hrs) at Visit 33.

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)	1697.92 (± 1784.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Drisapersen during IV sub-study

End point title	Maximum Observed Plasma Concentration (Cmax) of Drisapersen during IV sub-study

End point description:

Pharmacokinetic (PK) Population

Pharmacokinetic Parameter Cmax (Maximum measured plasma concentration)

End point type	Secondary

End point timeframe:

Predose, 1, 2, 4, 6, 10.5 and 24hrs at Visit 202, 205, 208, 211 and 214

End point values	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	7
Units: ng/mL				
arithmetic mean (standard deviation)	1784.02 (± 549.816)	5222.78 (± 1413.38)	9907.50 (± 1952.11)	14652.3 (± 3056.57)

End point values	IV sub-study - 2.7 mg/kg over 1 hour			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng/mL				
arithmetic mean (standard deviation)	22261.3 (± 2556.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: C24 of Drisapersen during IV sub-study

End point title	C24 of Drisapersen during IV sub-study
End point description: Pharmacokinetic (PK) Population	
End point type	Secondary
End point timeframe: Predose, 1, 2, 4, 6, 10.5 and 24hrs at Visit 202, Visit 205, Visit 208, Visit 211 and Visit 214	

End point values	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	7
Units: ng/mL				
arithmetic mean (standard deviation)	73.874 (± 88.310)	105.001 (± 78.786)	146.959 (± 98.241)	130.147 (± 111.516)

End point values	IV sub-study - 2.7 mg/kg over 1 hour			
Subject group type	Reporting group			
Number of subjects analysed	7			

Units: ng/mL				
arithmetic mean (standard deviation)	113.353 (± 114.984)			

Statistical analyses

No statistical analyses for this end point

Secondary: C168 of Drisapersen during IV sub-study

End point title	C168 of Drisapersen during IV sub-study
End point description: Intention-to-Treat (ITT) Population	
End point type	Secondary
End point timeframe: Predose, 1, 2, 4, 6, 10.5 and 24hrs at Visit 202, Visit 205, Visit 208, Visit 211 and Visit 214	

End point values	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	7
Units: ng/mL				
arithmetic mean (standard deviation)	50.270 (± 41.325)	47.811 (± 39.649)	56.637 (± 60.946)	62.123 (± 81.155)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of Drisapersen during IV sub-study

End point title	Time to Maximum Observed Concentration (Tmax) of Drisapersen during IV sub-study
End point description: Pharmacokinetic (PK) population Pharmacokinetic Parameter (Tmax) Time of the maximum measured plasma concentration	
End point type	Secondary
End point timeframe: Predose, 1, 2, 4, 6, 10.5 and 24hrs at Visit 202, Visit 205, Visit 208, Visit 211 and Visit 214	

End point values	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	7
Units: hr				
arithmetic mean (standard deviation)	4.120 (± 0.112)	3.709 (± 0.721)	3.519 (± 0.941)	1.926 (± 0.428)

End point values	IV sub-study - 2.7 mg/kg over 1 hour			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hr				
arithmetic mean (standard deviation)	1.003 (± 0.014)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time 0 to24h(AUC0-24h) of Drisapersen during IV sub-study

End point title	Area under the plasma concentration-time curve from time 0 to24h(AUC0-24h) of Drisapersen during IV sub-study

End point description:

Pharmacokinetic (PK) population.

Pharmacokinetic Parameter AUC0-24h Area under the plasma concentration-time curve from time 0 to 24 h.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 4, 6, 10.5 and 24hrs at Visit 202, Visit 205, Visit 208, Visit 211 and Visit 214

End point values	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	7
Units: h*ng/mL				
arithmetic mean (standard deviation)	9240.92 (± 3921.20)	26499.0 (± 8043.45)	51038.5 (± 12998.2)	50439.6 (± 13034.3)

End point values	IV sub-study - 2.7 mg/kg over			

	1 hour			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: h*ng/mL				
arithmetic mean (standard deviation)	48330.0 (± 12668.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-168 of Drisapersen during IV sub-study

End point title	AUC0-168 of Drisapersen during IV sub-study
End point description:	
Pharmacokinetic (PK) population	
End point type	Secondary
End point timeframe:	
Predose, 1, 2, 4, 6, 10.5 and 24hrs at Visit 202, Visit 205, Visit 208, Visit 211 and Visit 214	

End point values	IV sub-study - 0.5 mg/kg over 4 hours	IV sub-study - 1.4 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 4 hours	IV sub-study - 2.7 mg/kg over 2 hours
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	7
Units: h*ng/mL				
arithmetic mean (standard deviation)	17961.7 (± 12357.8)	36804.6 (± 15267.7)	64647.6 (± 23937.2)	63386.7 (± 24050.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events during Continued Treatment phase

End point title	Number of Subjects with Treatment Emergent Adverse Events during Continued Treatment phase

End point description:

Safety population

Related indicate as definite, probable or possible (or missing)

Intensity was determined by the Investigator. For symptomatic AEs the following definitions were applied.
Mild = AE did not limit usual activities; subject may have experienced slight discomfort.
Moderate = AE resulted in some limitation of usual activities; subject may have experienced significant discomfort.
Severe = AE resulted in an inability to carry out usual activities; subject may have experienced intolerable discomfort/pain.

Relationship to Investigational Medicinal Products (IMP)
Unlikely = Slight, but remote, chance that AE was caused by IMP.
Possible = Reasonable suspicion that the AE was caused by IMP.
Probable = Most likely that AE was caused by IMP.

End point type	Secondary

End point timeframe:

Up to Visit 205

End point values	Continued Treatment phase - 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Participants				
Severity: Mild	2			
Severity: Moderate	5			
Severity: Severe	5			
Drug Related Serious Adverse Event	0			
Drug Related Adverse Event	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events during IV sub-study

End point title	Number of Subjects with Treatment Emergent Adverse Events during IV sub-study

End point description:

Safety population

Related indicate as definite, probable or possible (or missing)

Intensity was determined by the Investigator. For symptomatic AEs the following definitions were applied.
Mild = AE did not limit usual activities; subject may have experienced slight discomfort.
Moderate = AE resulted in some limitation of usual activities; subject may have experienced significant discomfort.
Severe = AE resulted in an inability to carry out usual activities; subject may have experienced intolerable discomfort/pain.

Relationship to Investigational Medicinal Products (IMP)
Unlikely = Slight, but remote, chance that AE was caused by IMP.
Possible = Reasonable suspicion that the AE was caused by IMP.
Probable = Most likely that AE was caused by IMP.

End point type	Secondary

End point timeframe:

Up to Visit 229

End point values	IV Sub-Set - All Doses			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Participants				
Severity: Mild	3			
Severity: Moderate	3			
Severity: Severe	1			
Drug Related Serious Adverse Event	0			
Drug Related Adverse Event	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Visit 229	
Adverse event reporting additional description:	
MedDRA 11.0, 11.1 and 12.0 used for the Group I - 0.5 mg/kg, Group II - 2 mg/kg, Group III - 4 mg/kg and Group IV - 6 mg/kg Adverse Event.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	Group I - 0.5 mg/kg
Reporting group description: -	
Reporting group title	Group II - 2 mg/kg
Reporting group description: -	
Reporting group title	Group III - 4 mg/kg
Reporting group description: -	
Reporting group title	Group IV - 6 mg/kg
Reporting group description: -	
Reporting group title	Continued Treatment phase - 6 mg/kg
Reporting group description: -	
Reporting group title	IV sub-study
Reporting group description: -	

Serious adverse events	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Surgical and medical procedures			

Postoperative care			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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 disorders			
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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			
Tendinous contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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
Scoliosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (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	Group IV - 6 mg/kg	Continued	IV sub-study

		Treatment phase - 6 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Surgical and medical procedures			
Postoperative care			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Gastrointestinal disorders			

Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Tendinous contracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Scoliosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (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

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

Non-serious adverse events	Group I - 0.5 mg/kg	Group II - 2 mg/kg	Group III - 4 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Postoperative care			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injection site induration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site atrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site discolouration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site erosion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	1	2	2
Injection site erythema			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
occurrences (all)	6	5	9
Injection site inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site vesicles			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site nodule			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injection site dryness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Application site erosion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site eczema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injection site haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site calcification			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vaccination site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Application site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site irritation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cough			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alpha 1 microglobulin urine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematocrit decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cystatin C increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Complement factor C3 decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haptoglobin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood fibrinogen increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary sediment abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Complement factor C3 increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Protein total decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
pH urine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Troponin I increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Light chain analysis increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bacteria urine identified			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eosinophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Platelet count increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Azotaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Heart rate decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Reticulocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cystatin C increased (serum)			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
MONOCYTE CHEMOTACTIC PROTEIN-1 INCREASED			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Joint sprain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Open wound			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tibia fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lower limb fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tendon rupture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eyelid hematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Convulsion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Post-traumatic headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Lenticular opacities			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Aptyalism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nail bed inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoglobinuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Albuminuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Tendinous contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Scoliosis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Duchenne muscular dystrophy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tendon pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	1	2
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infected bites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Body tinea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infective tenosynovitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Insulin resistance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Group IV - 6 mg/kg	Continued Treatment phase - 6 mg/kg	IV sub-study
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	12 / 12 (100.00%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Postoperative care			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	3 / 3 (100.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 3 (0.00%)	12 / 12 (100.00%)	4 / 7 (57.14%)
occurrences (all)	0	41	7
Injection site atrophy			

subjects affected / exposed	0 / 3 (0.00%)	6 / 12 (50.00%)	0 / 7 (0.00%)
occurrences (all)	0	8	0
Injection site pruritus			
subjects affected / exposed	0 / 3 (0.00%)	6 / 12 (50.00%)	0 / 7 (0.00%)
occurrences (all)	0	15	0
Injection site discolouration			
subjects affected / exposed	0 / 3 (0.00%)	9 / 12 (75.00%)	0 / 7 (0.00%)
occurrences (all)	0	33	0
Injection site erosion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	2 / 3 (66.67%)	10 / 12 (83.33%)	0 / 7 (0.00%)
occurrences (all)	3	58	0
Injection site erythema			
subjects affected / exposed	3 / 3 (100.00%)	12 / 12 (100.00%)	4 / 7 (57.14%)
occurrences (all)	18	60	7
Injection site inflammation			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	1 / 7 (14.29%)
occurrences (all)	0	11	1
Injection site vesicles			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injection site ulcer			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	6	0
Injection site nodule			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	9 / 12 (75.00%)	0 / 7 (0.00%)
occurrences (all)	0	20	0
Injection site dryness			
subjects affected / exposed	3 / 3 (100.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Influenza like illness			

subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	11	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Injection site reaction			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Application site erosion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Injection site eczema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)	1 / 7 (14.29%)
occurrences (all)	0	8	1
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Injection site calcification			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Vaccination site pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Application site erythema			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Injection site rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injection site irritation			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	0 / 7 (0.00%)
occurrences (all)	0	10	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Investigations			
Alpha 1 microglobulin urine increased			
subjects affected / exposed	0 / 3 (0.00%)	12 / 12 (100.00%)	0 / 7 (0.00%)
occurrences (all)	0	24	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Haematocrit decreased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Cystatin C increased			
subjects affected / exposed	0 / 3 (0.00%)	10 / 12 (83.33%)	0 / 7 (0.00%)
occurrences (all)	0	18	0
Complement factor C3 decreased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	9 / 12 (75.00%)	1 / 7 (14.29%)
occurrences (all)	0	13	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	7	0
Haptoglobin increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Blood fibrinogen increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Red blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urinary sediment abnormal			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	0 / 7 (0.00%)
occurrences (all)	0	14	0
Complement factor C3 increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Blood pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
White blood cells urine positive			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Protein total decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
pH urine increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Troponin I increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Light chain analysis increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Bacteria urine identified			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eosinophil count decreased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Platelet count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Azotaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Heart rate decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Reticulocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cystatin C increased (serum)			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
MONOCYTE CHEMOTACTIC PROTEIN-1 INCREASED			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	0 / 7 (0.00%)
occurrences (all)	0	18	0
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Open wound			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Arthropod sting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tibia fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Femur fracture			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Lower limb fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tendon rupture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Foot fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Eyelid hematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Ventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 3 (33.33%)	11 / 12 (91.67%)	1 / 7 (14.29%)
occurrences (all)	1	25	1
Dizziness			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Convulsion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Post-traumatic headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dizziness postural			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyskinesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	1 / 7 (14.29%)
occurrences (all)	0	15	3
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Lenticular opacities			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cataract			

subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Aptyalism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	7 / 12 (58.33%)	0 / 7 (0.00%)
occurrences (all)	0	9	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	8 / 12 (66.67%)	1 / 7 (14.29%)
occurrences (all)	0	29	1
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	5 / 12 (41.67%)	0 / 7 (0.00%)
occurrences (all)	0	10	0
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	4 / 12 (33.33%)	1 / 7 (14.29%)
occurrences (all)	1	8	1
Haemorrhoids			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)	1 / 7 (14.29%)
occurrences (all)	0	4	1
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Nail bed inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Blister			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)	12 / 12 (100.00%)	1 / 7 (14.29%)
occurrences (all)	0	24	1
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0

Haemoglobinuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Albuminuria			
subjects affected / exposed	0 / 3 (0.00%)	11 / 12 (91.67%)	2 / 7 (28.57%)
occurrences (all)	0	24	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Tendinous contracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	7	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Scoliosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	7	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			

subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Muscle tightness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Duchenne muscular dystrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tendon pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 3 (66.67%)	9 / 12 (75.00%)	0 / 7 (0.00%)
occurrences (all)	2	22	0
Rhinitis			
subjects affected / exposed	1 / 3 (33.33%)	4 / 12 (33.33%)	1 / 7 (14.29%)
occurrences (all)	1	7	1
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	6 / 12 (50.00%)	2 / 7 (28.57%)
occurrences (all)	0	10	2
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	6 / 12 (50.00%)	0 / 7 (0.00%)
occurrences (all)	1	46	0
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	4 / 12 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	6	0

Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infected bites			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Injection site infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Folliculitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Onychomycosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Localised infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Body tinea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Infective tenosynovitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 3 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	10	0
Nail infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Eye infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Insulin resistance			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2008	- Extension of the duration of the screening period for skin biopsy and MRI from 4 to 6 weeks, - Validation of a novel, exploratory assay for subject screening, based on confirmation of mutation and PRO051 response on RNA level in peripheral blood mononuclear cells, - Reporting serious adverse events and/or unexpected adverse drug reactions, - Addition of TNF- at assessment of inflammatory response, - Change in choice of complement split factors, - Pre-study diagnostic muscle biopsy, - Manual muscle testing grading scale changed, - Corrections to Schedules of assessments (Tables) and Methodology of assessments (Protocol text sections), - Blood volume of pharmacokinetic samples changed, - All urine samples processed by the local laboratories, and - Minor formatting and typographical errors to improve the clarity and accuracy of the protocol text.
05 May 2008	- Increased monitoring of urine for potential renal effects of PRO051, - Increased frequency of monitoring blood biochemistry parameters, - Clarifications in study design, - List of parameters for routine hematology, biochemistry and urinalysis assessment updated, - Corrections to Schedules of assessment (Table) and Methodology of assessments (Protocol text section), - Sponsor details changed, and - Minor formatting and typographical errors to improve the clarity and accuracy of the protocol text.
27 April 2009	- Implementation of a new template for clinical study protocol, - Muscle biopsy in treatment beyond study period, - Addition of 6-minute walk test in treatment beyond study period, - Replacement of QMT-CINRG by handheld myometry in treatment beyond study period, - Changes in urine analysis, biochemistry parameters and hematology parameters for potential adverse effects of PRO051 in the treatment beyond study period, - Replacement of complement assays at external laboratory by marker complement measurement by the hospitals in treatment beyond study period, - Inflammatory response assay removed from treatment beyond study period, - Pharmacokinetic sampling in treatment beyond study period, - Storage period of the clinical trial samples, - Total blood volumes during treatment beyond study period, - Clarifications on the conditions for the treatment beyond study period, - Clarifications on the subject withdrawal criteria, - New batch of study medication to be used in treatment beyond study period, - Assessment of PRO051 in the muscle biopsy, - Clarification on the methods of the muscle function tests, - Effect parameters adjusted to current technical status of the assay development, - Study centers changed, and - Minor formatting and typographical errors to improve the clarity and accuracy of the protocol text.

02 September 2009	Changes in safety parameters for potential adverse effects of drisapersen in the treatment beyond study period (Continued Treatment phase). These changes included addition of measurements of troponin, fibrinogen, haptoglobin and CRP plus extra measurements of aPTT, cystatin C and ECG recordings, and Addition of echocardiography. Minor formatting and typographical errors to improve the clarity and accuracy of the protocol text. Assessment of drisapersen levels in muscle tissue was to be assessed at the Prosensa laboratory in the remaining material from the muscle biopsy after the results were obtained for the mRNA production and dystrophin expression in the muscle tissue. However, this assessment was not performed as the assay was still being optimized. drisapersen levels in the remaining muscle tissue were to be measured at a later time point and the results reported separately. The anti-dystrophin antibody assay was planned to detect potential IgM and IgG antibodies against dystrophin. IgM antibodies were however not assessed. Different to the original protocol, an assay for IgG but not IgM anti-dystrophin reactivity was performed, because IgM control dystrophin antibodies were not available. Formation of antibodies to dystrophin in blood was to be determined at Visits 13, 25, 37 and 61.
16 July 2010	• Enhanced safety monitoring. • Addition of stopping criteria. • Addition of alternative injection sites for drug administration. • Addition of DEXA scans. • Additional muscle biopsy at 12 months. • Dose capping according to weight. • Allowance for intermittent dosing for any subject reaching any of the study stopping criteria. • Addition of a parent questionnaire. • Change in Clinical Research Manager. • Other minor clarification and corrections. The enhanced safety monitoring was to enable the Sponsor to closely monitor for early signs of potentially drug-related hepatotoxicity and nephrotoxicity as well as thrombocytopenia. Enhanced monitoring consisted of more frequent assessments as well as some changes to the parameters themselves e.g. addition of glutamate dehydrogenase, albumin/globulin ratio and PTT (international normalized ratio [INR]). Changes to urinalysis parameters were also made including removal of the dipstick analysis, and addition of quantitative analysis of glucose, albumin, protein, creatinine, 1 microglobulin, protein/creatinine ratio and microscopy of urine sediment for erythrocytes, leukocytes and casts. The requirement for troponin I concentrations (introduced in Amendment 5) was removed as the relationship of any change in troponin levels in DMD patients (which may be very variable) is not understood relative to any cardiac condition (personal communication, Kate Bushby, Professor of Neuromuscular Genetics, Newcastle University), and were considered to be unlikely to be useful in detecting incipient cardiac damage.
15 November 2010	Further additions to the enhanced safety monitoring implemented in Amendment 6. •Additional detail for stopping criteria. •Change in dosing regimen for all subjects. •Addition of pre-dose pharmacokinetic sampling on a monthly basis from Visit 85 (or as soon as approval of Amendment 7). Ad hoc pharmacokinetic sampling. •Additional instructions on the assessment of local injection site reactions. •Change in blood volumes. •Additions to safety monitoring. •Muscle function (adjustment in visit schedule) •Other minor clarifications and corrections. The amended dosing regimen involved an 8 week washout period for all subjects (Visits 86-93 inclusive). Subjects were then restarted on an intermittent regimen involving 8 weeks of once weekly treatment followed by 4 weeks off drug. New safety monitoring included addition of blood smear for schistocytes (haematology), kidney injury molecule-1 (KIM-1) and cystatin C (urinalysis) and MCP 1 (inflammatory response). Fibrin split products and D dimer were also to be assessed if predefined criteria were met.

09 March 2011	• Extension of the study until 2013. • Change in frequency of efficacy measured in order to reduce the • burden on the subjects. • Change in visit schedule in order to reduce the travel burden on the • families. • Change in blood volumes. • Other minor clarifications and corrections. The frequency of the efficacy measures was changed to every 12 weeks in order to fit in with the new assessment schedule and to assess the effect of the intermittent dosing regimen introduced in Amendment 7. Subjects did not have to return to the hospital for laboratory safety testing during the 4 week treatment break unless there was a medical/safety concern, in which case the subject would be asked to return for further monitoring as determined by the investigator.
14 April 2011	•Change in legal sponsorship from Prosensa Therapeutics B.V. to GlaxoSmithKline (implemented on 21 July 2011). •Change in supply of drisapersen. •Change in frequency of cystatin C measurements to enhance safety monitoring (every 4 weeks rather than every 12 weeks). •Other minor clarifications and corrections.
10 August 2011	•Enhanced safety monitoring and stopping criteria. •Enhanced monitoring and stopping criteria for inflammation. •Modified stopping criteria for coagulation. •Modified stopping criteria for hepatic toxicity. •Change in primary medical contact. •Change in definition of serious adverse events (SAEs). •Other minor clarifications
17 May 2012	•Enhanced safety monitoring and stopping criteria •Enhanced renal monitoring •Modified renal stopping criteria •Clarification to the Disseminated Intravascular Coagulation criteria •Update sponsor signature page •Change in Definition of AEs •Change in study schedule for taking subject height and weight / Parent questionnaire added to flowchart •Option to return to weekly dosing at 6 mg/kg drisapersen

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported