



## 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	04 August 2016

### Results information

Result version number	v1
This version publication date	23 March 2017
First version publication date	23 March 2017

### Trial information

#### Trial identification

Sponsor protocol code	PRO051-02
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01254019
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trialregister: NTR1241, Protocol code: DMD114673

Notes:

### Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, CA94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 August 2016
Was the trial ended prematurely?	Yes

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:

Please refer to page no.25 of protocol.

Protection of trial subjects:

Not applicable

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: -

### Pre-assignment

Screening details:

Patient selection will first be based on a search in a coded database with DNA diagnostic data of DMD patients. Patients will be asked for consent and subsequently screened according to the in- and exclusion criteria. Screening includes a full DNA diagnostic report, an interview and the assessments described in the schedule of assessment.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Received IV Dose
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Arm description:

Received IV Dose

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	Intravenous use, Subcutaneous use

Dosage and administration details:

This was an open-label study in which all study subjects received active treatment. All subjects initially received the same dose of drisapersen (6 mg/kg/week) either S.C. or I.V. in the Continued Treatment phase.

<b>Arm title</b>	Received SC Dose
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Arm description:

Received SC Dose

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	Intravenous use, Subcutaneous use

Dosage and administration details:

This was an open-label study in which all study subjects received active treatment. All subjects initially received the same dose of drisapersen (6 mg/kg/week) either S.C. or I.V. in the Continued Treatment phase.

<b>Number of subjects in period 1</b>	Received IV Dose	Received SC Dose
Started	10	12
Completed	0	0
Not completed	10	12
Consent withdrawn by subject	-	1
Other	10	11

## Baseline characteristics

### Reporting groups

Reporting group title	Received IV Dose
Reporting group description: Received IV Dose	
Reporting group title	Received SC Dose
Reporting group description: Received SC Dose	

Reporting group values	Received IV Dose	Received SC Dose	Total
Number of subjects	10	12	12
Age categorical Units: Subjects			
Age ≤ 7 years	0	0	0
Age > 7 and ≤ 12 years	4	4	4
Age > 12 years	6	8	8
Age continuous Units: Years			
arithmetic mean	13.3	13.3	
standard deviation	± 2.36	± 2.14	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	10	12	12
Weight Units: kg			
arithmetic mean	35.5	36.2	
standard deviation	± 14.17	± 12.96	-
Length Units: cm			
arithmetic mean	130.5	130.8	
standard deviation	± 11.88	± 11.1	-

## End points

### End points reporting groups

Reporting group title	Received IV Dose
Reporting group description: Received IV Dose	
Reporting group title	Received SC Dose
Reporting group description: Received SC Dose	

### Primary: 6 MWD

End point title	6 MWD <sup>[1]</sup>
End point description: The safety data provided for this study is split per route of administration, IV or SC. This gives the appearance of there having been 2 arms, but in this study, all subjects could have received both SC and IV administrations. Therefore the efficacy information should be represented as a single arm.  Counts of 0 have been inserted for 2 arms for the primary efficacy endpoint, as a value is required by the system.  The total distance walked in 6 minutes throughout the extension phase is represented for each subject in the attached chart.	

End point type	Primary
End point timeframe: Long term extension study	
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: Summary statistics have been presented by visit where applicable.	

End point values	Received IV Dose	Received SC Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Meter	0	0		

Attachments (see zip file)	6MWD data 673/6mwd figure_673.pdf
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Study Period

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Received IV Dose
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Reporting group description: -

Reporting group title	Received SC Dose
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Reporting group description: -

Serious adverse events	Received IV Dose	Received SC Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			



subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Received IV Dose	Received SC Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	12 / 12 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Wisdom teeth removal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Atrophy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Chills			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Device occlusion		
subjects affected / exposed	1 / 10 (10.00%)	2 / 12 (16.67%)
occurrences (all)	1	2
Discomfort		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Extravasation		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Fatigue		
subjects affected / exposed	1 / 10 (10.00%)	3 / 12 (25.00%)
occurrences (all)	1	3
Fibrosis		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Gait disturbance		
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Inflammation		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Influenza like illness		
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)
occurrences (all)	2	2
Injection site atrophy		
subjects affected / exposed	5 / 10 (50.00%)	6 / 12 (50.00%)
occurrences (all)	8	18
Injection site bruising		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Injection site calcification		
subjects affected / exposed	4 / 10 (40.00%)	7 / 12 (58.33%)
occurrences (all)	5	15
Injection site discolouration		

subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	7
Injection site erythema		
subjects affected / exposed	5 / 10 (50.00%)	5 / 12 (41.67%)
occurrences (all)	6	8
Injection site haematoma		
subjects affected / exposed	2 / 10 (20.00%)	4 / 12 (33.33%)
occurrences (all)	2	15
Injection site induration		
subjects affected / exposed	4 / 10 (40.00%)	8 / 12 (66.67%)
occurrences (all)	5	22
Injection site inflammation		
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Injection site irritation		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Injection site pain		
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	4
Injection site pruritus		
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Injection site rash		
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	1
Injection site reaction		
subjects affected / exposed	1 / 10 (10.00%)	4 / 12 (33.33%)
occurrences (all)	1	5
Injection site swelling		
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Injection site ulcer		
subjects affected / exposed	2 / 10 (20.00%)	2 / 12 (16.67%)
occurrences (all)	3	2
Injection site vesicles		

subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	3	
Local swelling			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Mass			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 10 (40.00%)	1 / 12 (8.33%)	
occurrences (all)	6	1	
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	2	3	
Oropharyngeal pain			
subjects affected / exposed	2 / 10 (20.00%)	5 / 12 (41.67%)	
occurrences (all)	4	5	
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			

Anger			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Insomnia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Albumin urine present			
subjects affected / exposed	4 / 10 (40.00%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood albumin decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood creatinine decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood fibrinogen increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Blood iron decreased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
C-reactive protein increased		
subjects affected / exposed	5 / 10 (50.00%)	6 / 12 (50.00%)
occurrences (all)	13	8
Complement factor C3 decreased		
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)
occurrences (all)	3	0
Complement factor decreased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Cystatin C abnormal		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Cystatin C increased		
subjects affected / exposed	8 / 10 (80.00%)	2 / 12 (16.67%)
occurrences (all)	11	2
Gamma-glutamyltransferase increased		
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)
occurrences (all)	4	0
Globulin urine present		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Glutamate dehydrogenase increased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Haematocrit decreased		
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)
occurrences (all)	3	0
Haemoglobin decreased		
subjects affected / exposed	6 / 10 (60.00%)	1 / 12 (8.33%)
occurrences (all)	11	1
Haptoglobin increased		
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)
occurrences (all)	3	0

Light chain analysis increased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Mean cell haemoglobin concentration decreased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Mean cell haemoglobin decreased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	0
Monocyte count increased		
subjects affected / exposed	4 / 10 (40.00%)	1 / 12 (8.33%)
occurrences (all)	5	1
Platelet count decreased		
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)
occurrences (all)	2	1
Protein urine present		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Red blood cell count decreased		
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)
occurrences (all)	4	0
Red blood cells urine		
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)
occurrences (all)	4	0
Red blood cells urine positive		
subjects affected / exposed	4 / 10 (40.00%)	0 / 12 (0.00%)
occurrences (all)	6	0
Transferrin decreased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Transferrin saturation decreased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Urine albumin/creatinine ratio increased		

subjects affected / exposed	4 / 10 (40.00%)	0 / 12 (0.00%)	
occurrences (all)	6	0	
Urine protein/creatinine ratio increased			
subjects affected / exposed	6 / 10 (60.00%)	1 / 12 (8.33%)	
occurrences (all)	18	1	
Vitamin B6 abnormal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
White blood cells urine positive			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	3 / 10 (30.00%)	2 / 12 (16.67%)	
occurrences (all)	5	2	
Femur fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Foot fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Heat stroke			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Joint dislocation			



subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Limb injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Lower limb fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nail injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Ulna fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	4 / 10 (40.00%)	2 / 12 (16.67%)	
occurrences (all)	7	2	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Left ventricular failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
Ventricular tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	2 / 12 (16.67%) 3	
Headache subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 17	3 / 12 (25.00%) 8	
Hypokinesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
Migraine subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 4	0 / 12 (0.00%) 0	
Migraine with aura subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3	0 / 12 (0.00%) 0	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 12 (8.33%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 6	1 / 12 (8.33%) 2	
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Vertigo			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Panophthalmitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	3 / 10 (30.00%)	3 / 12 (25.00%)	
occurrences (all)	6	3	
Constipation			
subjects affected / exposed	4 / 10 (40.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	3 / 12 (25.00%)	
occurrences (all)	2	4	
Epigastric discomfort			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Gastritis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Gingival pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Inguinal hernia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 10 (30.00%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Oesophageal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)	4 / 12 (33.33%)	
occurrences (all)	7	8	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 12 (25.00%)	
occurrences (all)	1	3	
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Eczema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	3 / 10 (30.00%)	1 / 12 (8.33%)	
occurrences (all)	4	2	

Hair texture abnormal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 12 (16.67%) 2	
Ingrowing nail subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	1 / 12 (8.33%) 1	
Keratosis pilaris subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Madarosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 12 (16.67%) 3	
Pruritus subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 12 (16.67%) 3	
Rash subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	2 / 12 (16.67%) 3	
Skin discolouration subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 12 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	
Skin mass subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Skin ulcer subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 12 (8.33%) 1	
Renal and urinary disorders Albuminuria subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 12	6 / 12 (50.00%) 6	
Microalbuminuria			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Proteinuria			
subjects affected / exposed	10 / 10 (100.00%)	7 / 12 (58.33%)	
occurrences (all)	41	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 10 (50.00%)	1 / 12 (8.33%)	
occurrences (all)	8	1	
Back pain			
subjects affected / exposed	4 / 10 (40.00%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Clubbing			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Muscle spasms			
subjects affected / exposed	1 / 10 (10.00%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Muscle tightness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 10 (10.00%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	4 / 10 (40.00%)	3 / 12 (25.00%)	
occurrences (all)	8	5	
Tendon pain			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Fungal infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Fungal skin infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	7 / 12 (58.33%)	
occurrences (all)	2	8	
Gastrointestinal infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Injection site abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Injection site infection			
subjects affected / exposed	3 / 10 (30.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Injection site pustule			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	

Localised infection		
subjects affected / exposed	3 / 10 (30.00%)	2 / 12 (16.67%)
occurrences (all)	3	2
Nail infection		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	6 / 10 (60.00%)	4 / 12 (33.33%)
occurrences (all)	11	5
Onychomycosis		
subjects affected / exposed	2 / 10 (20.00%)	4 / 12 (33.33%)
occurrences (all)	2	4
Oral fungal infection		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Respiratory tract infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	2
Rhinitis		
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	2
Sinusitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	1
Skin infection		
subjects affected / exposed	2 / 10 (20.00%)	2 / 12 (16.67%)
occurrences (all)	2	2
Tinea versicolour		
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	3 / 10 (30.00%)	5 / 12 (41.67%)
occurrences (all)	6	13
Wound infection		
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	1



Wound infection staphylococcal subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2009	<p>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.</p> <p>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.</p> <p>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.</p>
16 July 2010	<ul style="list-style-type: none"><li>• Enhanced safety monitoring.</li><li>• Addition of stopping criteria.</li><li>• Addition of alternative injection sites for drug administration.</li><li>• Addition of DEXA scans.</li><li>• Additional muscle biopsy at 12 months.</li><li>• Dose capping according to weight.</li><li>• Allowance for intermittent dosing for any subject reaching any of the study stopping criteria.</li><li>• Addition of a parent questionnaire.</li><li>• Change in Clinical Research Manager.</li><li>• Other minor clarification and corrections.</li></ul> <p>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.</p>

15 November 2010	<p>Further additions to the enhanced safety monitoring implemented in Amendment 6.</p> <ul style="list-style-type: none"> <li>•Additional detail for stopping criteria.</li> <li>•Change in dosing regimen for all subjects.</li> <li>•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.</li> <li>•Additional instructions on the assessment of local injection site reactions.</li> <li>•Change in blood volumes.</li> <li>•Additions to safety monitoring.</li> <li>•Muscle function (adjustment in visit schedule)</li> <li>•Other minor clarifications and corrections.</li> </ul> <p>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.</p> <p>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.</p>
09 March 2011	<ul style="list-style-type: none"> <li>• Extension of the study until 2013.</li> <li>• Change in frequency of efficacy measured in order to reduce the burden on the subjects.</li> <li>• Change in visit schedule in order to reduce the travel burden on the families.</li> <li>• Change in blood volumes.</li> <li>• Other minor clarifications and corrections.</li> </ul> <p>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.</p>
14 April 2011	<ul style="list-style-type: none"> <li>•Change in legal sponsorship from Prosensa Therapeutics B.V. to GlaxoSmithKline (implemented on 21 July 2011).</li> <li>•Change in supply of drisapersen.</li> <li>•Change in frequency of cystatin C measurements to enhance safety monitoring (every 4 weeks rather than every 12 weeks).</li> <li>•Other minor clarifications and corrections.</li> </ul>
10 August 2011	<ul style="list-style-type: none"> <li>•Enhanced safety monitoring and stopping criteria.</li> <li>•Enhanced monitoring and stopping criteria for inflammation.</li> <li>•Modified stopping criteria for coagulation.</li> <li>•Modified stopping criteria for hepatic toxicity.</li> <li>•Change in primary medical contact.</li> <li>•Change in definition of serious adverse events (SAEs).</li> <li>•Other minor clarifications</li> </ul>
17 May 2012	<ul style="list-style-type: none"> <li>•Enhanced safety monitoring and stopping criteria</li> <li>•Enhanced renal monitoring</li> <li>•Modified renal stopping criteria</li> <li>•Clarification to the Disseminated Intravascular Coagulation criteria</li> <li>•Update sponsor signature page</li> <li>•Change in Definition of AEs</li> <li>•Change in study schedule for taking subject height and weight / Parent questionnaire added to flowchart</li> <li>•Option to return to weekly dosing at 6 mg/kg drisapersen</li> </ul>

01 December 2012	<ol style="list-style-type: none"> <li>Updated protocol title to include intravenous dosing as an alternative route of administration.</li> <li>Inclusion of intravenous dose escalation (0.5 mg/kg, 2.0 mg/kg and 6 mg/kg) over a 4 hour infusion period <ul style="list-style-type: none"> <li>Reduction of infusion time to 2 hours</li> <li>Reduction of infusion time to 1 hour.</li> </ul> </li> <li>Added text to better describe the treatment beyond study period <ul style="list-style-type: none"> <li>Added text for intravenous administration.</li> </ul> </li> <li>Laboratory Safety Parameter Stopping and Follow-up Criteria <ul style="list-style-type: none"> <li>Added text for ECG</li> </ul> </li> <li>Other minor clarifications and corrections.</li> </ol>
12 July 2013	<p>The amendment will assess the potential for intravenous dosing of PRO051 as an alternative route of administration.</p> <p>A summary of the changes is provided below.</p> <ol style="list-style-type: none"> <li>Update sponsor signatory details</li> <li>Increased length of study</li> <li>Adjustment of blood volumes</li> <li>Addition of informed consent for subjects 18 years of age</li> <li>Update to Safety Laboratory: <ol style="list-style-type: none"> <li>removal of several biomarker tests (- exploratory biomarkers not used in clinical practice which have not provided an additional positive effect with respect to safety monitoring)</li> <li>renal criteria timing</li> <li>removal of echocardiography (acknowledgement that this continues to be part of the subjects' clinical standard of care)</li> <li>removal of DEXA (has been less informative than hoped)</li> <li>removal of antibody to dystrophin determination (subjects have now had long term exposure without positive antibodies to dystrophin, so extended monitoring not required)</li> </ol> </li> <li>Addition of a second central laboratory</li> <li>Other minor clarifications and corrections</li> </ol>
09 October 2013	Instructions for investigators for subject management during the time period while dosing is on hold per drisapersen Dear Investigator Letter dated 20 September 2013

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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24 September 2013	<p>This substantial amendment is to request a temporary halt of study PRO051-02. This is due to data recently obtained from study DMD114044 (a double-blind, placebo-controlled, Phase III study) in which a total of 186 boys were randomised to drisapersen at a dose of 6mg/kg/week (N=125) or placebo (N=61) via subcutaneous injection over 48 weeks. The difference in the primary endpoint of 6 minute walking distance between drisapersen and placebo groups did not reach statistical significance. There was no treatment difference in key secondary assessments. In addition, a greater proportion of subjects in the drisapersen treatment group reported injection site and renal adverse events compared to placebo. In other studies, severe thrombocytopenia has been reported in drisapersen-treated subjects. GSK are committed to fully analyzing the data in order to determine whether there may be a favourable benefit to risk profile for a subgroup of subjects. Full evaluation of the benefit-to-risk profile of drisapersen treatment across all studies is anticipated to be completed by the end of 2013. Until then, all dosing in ongoing drisapersen studies including PRO051-02 has been halted.</p>	-
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Notes:

## Limitations and caveats

None reported