Clinical trial results:
A phase II, open label, extension study to assess the effect of PRO044 in patients with Duchenne muscular dystrophy

Summary

EudraCT number	2013-003605-26
Trial protocol	IT SE NL BE
Global end of trial date	10 August 2016

Results information

Result version number	v1 (current)
This version publication date	08 March 2017
First version publication date	08 March 2017

Trial information

Trial identification

Sponsor protocol code	PRO044-CLIN-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02329769
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, CA 94949
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	30 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, tolerability and efficacy of two different doses of intravenous (IV) PRO044 and one dose of subcutaneous (SC) PRO044 in subjects with DMD after 48 weeks treatment.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2014
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: 4
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	5
Adolescents (12-17 years)	8
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening visit will include confirmation of subject consent, an interview and evaluation of the inclusion and exclusion criteria and the assessments as described in the schedule of assessments. All results from assessments conducted at the screening visit must be available for review prior to the first PRO044 dose in this study.

Period 1

Period 1 title	BMN044 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	6 mg/kg/week IV

Arm description:

6 mg/kg/week IV

Arm type	Experimental
Investigational medicinal product name	BMN-044
Investigational medicinal product code	BMN-044
Other name	PRO-044, PS188
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Product: Active ingredient is PS188 which is the sodium salt of a 20-mer 2’-O-methyl-phosphorothioate oligoribonucleotide with a sequence optimised to skip exon 44 in the human dystrophin pre-mRNA.
Formulation: Solution of the active ingredient PS188 in 20 mM phosphate buffer, pH 7 solution for injection.
Strength: 200 mg/mL.
Vial content: 0.7 mL or 1.0 mL in a 3 mL glass type I vial.
Subject will receive 6 mg/kg weekly through IV administration.

Arm title	9 mg/kg/week IV

Arm description:

9 mg/kg/week IV

Arm type	Experimental
Investigational medicinal product name	BMN-044
Investigational medicinal product code	BMN-044
Other name	PRO-044, PS188
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Product: Active ingredient is PS188 which is the sodium salt of a 20-mer 2’-O-methyl-phosphorothioate oligoribonucleotide with a sequence optimised to skip exon 44 in the human dystrophin pre-mRNA.
Formulation: Solution of the active ingredient PS188 in 20 mM phosphate buffer, pH 7 solution for injection.
Strength: 200 mg/mL.
Vial content: 0.7 mL or 1.0 mL in a 3 mL glass type I vial.
Subject will receive 9 mg/kg weekly through IV administration.

Arm title	6 mg/kg/week SC

Arm description:

6 mg/kg/week SC

Arm type	Experimental
Investigational medicinal product name	BMN-044
Investigational medicinal product code	BMN-044
Other name	PRO-044, PS188
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Product: Active ingredient is PS188 which is the sodium salt of a 20-mer 2’-O-methyl-phosphorothioate oligoribonucleotide with a sequence optimised to skip exon 44 in the human dystrophin pre-mRNA.
Formulation: Solution of the active ingredient PS188 in 20 mM phosphate buffer, pH 7 solution for injection.
Strength: 200 mg/mL.
Vial content: 0.7 mL or 1.0 mL in a 3 mL glass type I vial.
Subject will receive 6 mg/kg weekly through SC administration.

Number of subjects in period 1	6 mg/kg/week IV	9 mg/kg/week IV	6 mg/kg/week SC
Started	6	5	4
Completed	3	2	2
Not completed	3	3	2
Study Terminated by Sponsor	3	3	2

Baseline characteristics

Reporting groups	
Reporting group title	6 mg/kg/week IV
Reporting group description: 6 mg/kg/week IV	
Reporting group title	9 mg/kg/week IV
Reporting group description: 9 mg/kg/week IV	
Reporting group title	6 mg/kg/week SC
Reporting group description: 6 mg/kg/week SC	

Reporting group values	6 mg/kg/week IV	9 mg/kg/week IV	6 mg/kg/week SC
Number of subjects	6	5	4
Age categorical Units: Subjects			
9-19	6	5	4
Age continuous Units: Years			
arithmetic mean	13	12.4	12.8
standard deviation	± 3.63	± 1.82	± 3.77
Gender categorical Units: Subjects			
Female	0	0	0
Male	6	5	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	5	5	4
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	6	5	4
Other	0	0	0
Weight Units: kg			
arithmetic mean	52	52.1	35.7
standard deviation	± 20.94	± 13.43	± 17.37
Length Units: cm			
arithmetic mean	145.5	140.6	131.9
standard deviation	± 13.52	± 19.33	± 19

Reporting group values	Total		
Number of subjects	15		
Age categorical Units: Subjects			
9-19	15		
Age continuous Units: Years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female Male	0 15		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported	1 14 0		
Race Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White Other	0 0 0 0 15 0		
Weight Units: kg arithmetic mean standard deviation	 -		
Length Units: cm arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	6 mg/kg/week IV
Reporting group description: 6 mg/kg/week IV	
Reporting group title	9 mg/kg/week IV
Reporting group description: 9 mg/kg/week IV	
Reporting group title	6 mg/kg/week SC
Reporting group description: 6 mg/kg/week SC	

Primary: Not applicable

End point title	Not applicable[1]

End point description:

Due to a company decision to stop development of exon-skipping DMD therapy, efficacy data were not summarised.

End point type	Primary

End point timeframe:

Not applicable

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: Due to a company decision to stop development of exon-skipping DMD therapy, efficacy data were not summarised.

End point values	6 mg/kg/week IV	9 mg/kg/week IV	6 mg/kg/week SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: not applicable				
number (not applicable)				

Notes:

[2] - Not applicable

[3] - Not applicable

[4] - Not applicable

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Study Period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	6 mg/kg/week IV
Reporting group description: -	
Reporting group title	6 mg/kg/week SC
Reporting group description: -	
Reporting group title	9 mg/kg/week IV
Reporting group description: -	

Serious adverse events	6 mg/kg/week IV	6 mg/kg/week SC	9 mg/kg/week IV
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	6 mg/kg/week IV	6 mg/kg/week SC	9 mg/kg/week IV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	4 / 4 (100.00%)	5 / 5 (100.00%)
Surgical and medical procedures			

Suture insertion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	6
Infusion site pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Vaccination site erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Xerosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 6 (50.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Epistaxis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	3 / 6 (50.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Alpha 1 microglobulin increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	3
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Complement factor C3 decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	1	1	5
Crystal urine present			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cystatin C increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Inflammatory marker increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Investigation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Protein urine present			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Red blood cells urine			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Laceration			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Thermal burn			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	4 / 5 (80.00%)
occurrences (all)	3	0	17
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	4	0	3
Constipation			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	2	1	1
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Gastritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	4	0	1
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ecchymosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Keloid scar			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Rash pruritic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	2
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Groin pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Impetigo			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 6 (66.67%)	3 / 4 (75.00%)	0 / 5 (0.00%)
occurrences (all)	7	6	0
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tinea versicolour			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Wound infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2014	Amendment 1
12 October 2015	Amendment 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported