Clinical trial results:
A Phase I/II, open-label, dose escalating with 48 week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of PRO053 in subjects with Duchenne muscular dystrophy

Summary

EudraCT number	2011-005042-35
Trial protocol	GB BE IT NL FR
Global end of trial date	31 August 2016

Results information

Result version number	v1 (current)
This version publication date	23 March 2017
First version publication date	23 March 2017

Trial information

Trial identification

Sponsor protocol code	PRO053-CLIN-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01957059
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, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com
Scientific contact	Clinical Trials, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001374-PIP01-12
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	10 October 2016
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of PRO053 after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 July 2013
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: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	8
Adolescents (12-17 years)	1
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:

Visit S1 will include confirmation of consent and evaluation of the full DNA diagnostic report and the inclusion and exclusion criteria. Visit S2 should not be conducted until enrolment into any given dose group is agreed. S2 will be conducted within 2 weeks prior to first dose. S2 will include evaluation of the inclusion and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Cohort 1

Arm description:

BMN 053

Arm type	Experimental
Investigational medicinal product name	BMN053
Investigational medicinal product code	BMN053
Other name	PRO053
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

In the dose-escalation phase, two cohorts of three subjects each receive two single doses of BMN 053 in two study periods (i.e., four single doses in total per subject). In each study period they will receive BMN 053 by IV infusion and by SC injection (separated by one week).
Cohort 1:
1 mg/kg SC followed by 1 mg/kg IV
And then 6 mg/kg SC followed by 6 mg/kg IV

Arm title	Cohort 2

Arm description:

BMN 053

Arm type	Experimental
Investigational medicinal product name	BMN053
Investigational medicinal product code	BMN053
Other name	PRO053
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

In the dose-escalation phase, two cohorts of three subjects each receive two single doses of BMN 053 in two study periods (i.e., four single doses in total per subject). In each study period they will receive BMN 053 by IV infusion and by SC injection (separated by one week).
Cohort 2:
3 mg/kg SC followed by 3 mg/kg IV
And then 9 mg/kg SC followed by 9 mg/kg IV

Number of subjects in period 1	Cohort 1	Cohort 2
Started	9	3
Completed	0	3
Not completed	9	0
Study Subject Withdrawal by Parent or Guardian	2	-
Study Terminated by Sponsor	7	-

Baseline characteristics

Reporting groups	
Reporting group title	dose escalation

Reporting group description: -

Reporting group values	dose escalation	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
6 - 14	9	9	
Age continuous Units: Years			
arithmetic mean	8.6		
standard deviation	± 2.83	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	9	9	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
BMN 053	
Reporting group title	Cohort 2
Reporting group description:	
BMN 053	

Primary: Efficacy

End point title	Efficacy[1]
End point description:	
To assess the efficacy of BMN 053 at recommended dosing regimen after 48 weeks of dosing in ambulant subjects with Duchenne muscular dystrophy.	
End point type	Primary
End point timeframe:	
48 weeks	

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 the early termination of this study, the treatment phase of the study was not initiated. For the dose escalation/regimen selection phase no formal statistical analysis was performed.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: meter				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - Due to the early termination of this study, the treatment phase of the study was not initiated.

[3] - Due to the early termination of this study, the treatment phase of the study was not initiated.

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	18.1/19

Reporting groups	
Reporting group title	BMN 053

Reporting group description: -

Serious adverse events	BMN 053		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Myoclonus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BMN 053		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Haematoma			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			

Influenza like illness subjects affected / exposed occurrences (all) Inflammation subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2 1 / 9 (11.11%) 1 2 / 9 (22.22%) 2 2 / 9 (22.22%) 4 1 / 9 (11.11%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 3 / 9 (33.33%) 3 3 / 9 (33.33%) 4 1 / 9 (11.11%) 1		
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) Activated partial thromboplastin time shortened subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1 1 / 9 (11.11%) 4		

Alpha 1 microglobulin increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Complement factor c3 decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Glutamate dehydrogenase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
International normalised ratio increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	16		
Protein urine			
subjects affected / exposed	7 / 9 (77.78%)		
occurrences (all)	54		
Urine protein/creatinine ratio increased			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Fall subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 4		
Infusion related reaction subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Joint injury subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Post procedural haematoma subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Procedural pain subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Wound subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Nervous system disorders Myoclonus subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Headache subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 26		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Eye disorders Conjunctival hyperaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Eye inflammation			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Anal fissure			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	9		
Dental caries			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	8		

Mouth ulceration subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Erythema subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Granuloma skin subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Pigmentation disorder subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Renal and urinary disorders			
Chromaturia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Haematuria subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3		

Pain in extremity			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Laryngitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	11		
Onychomycosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Post procedural infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Upper respiratory tract infection			

subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	6		
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2013	Prot Amt 1
17 April 2014	Prot Amt 2
11 May 2015	Prot Amt 3
13 January 2016	Prot Amt 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported