



## Clinical trial results:

**A multi center, multi national, open label, extension study to evaluate the long-term efficacy and safety of BMN 044 (PRO044) in subjects with Duchenne muscular dystrophy**

### Summary

EudraCT number	2015-003681-87
Trial protocol	BE IT
Global end of trial date	12 September 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	BMN-044-201
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02958202
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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	03 November 2016
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	12 September 2016
Was the trial ended prematurely?	Yes

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Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the long-term safety of BMN 044 in subjects with DMD correctable by BMN 044 induced DMD exon 44 skipping who have previously participated in an eligible study with BMN 044

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Protection of trial subjects:

Not applicable.

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Background therapy: -

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Evidence for comparator: -

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Actual start date of recruitment	19 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	7
EEA total number of subjects	7

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Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	3
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

For subjects enrolling directly after completion of an existing BMN044 study, assessments from their last visit will be used as the baseline assessment. For subjects who have not received any BMN044 treatment for more than 28 days, these assessments will be performed: Physical examination, ECG, echocardiography, urinalysis hematology/biochemistry.

### Period 1

Period 1 title	044201 (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	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
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive 6 mg/kg weekly through IV administration.

BMN 044 is presented in a 2R glass vial (Type 1) containing a solution of the active ingredient dissolved in 20 mM aqueous phosphate buffer, pH 7 solution for injection, 100 and 200 mg/mL. Each vial of BMN 044 contains 1.0 mL (0.8 mL extractable amount) of active ingredient. The solution is colorless to slightly yellow in appearance.

<b>Arm title</b>	9 mg/kg/week IV
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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
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive 9 mg/kg weekly through IV administration.

BMN 044 is presented in a 2R glass vial (Type 1) containing a solution of the active ingredient dissolved in 20 mM aqueous phosphate buffer, pH 7 solution for injection, 100 and 200 mg/mL. Each vial of BMN 044 contains 1.0 mL (0.8 mL extractable amount) of active ingredient. The solution is colorless to slightly yellow in appearance.

<b>Arm title</b>	6 mg/kg/week SC
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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
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects will receive 6 mg/kg weekly through SC administration.

BMN 044 is presented in a 2R glass vial (Type 1) containing a solution of the active ingredient dissolved in 20 mM aqueous phosphate buffer, pH 7 solution for injection, 100 and 200 mg/mL. Each vial of BMN 044 contains 1.0 mL (0.8 mL extractable amount) of active ingredient. The solution is colorless to slightly yellow in appearance.

<b>Number of subjects in period 1</b>	6 mg/kg/week IV	9 mg/kg/week IV	6 mg/kg/week SC
Started	3	2	2
Completed	0	0	0
Not completed	3	2	2
Consent withdrawn by subject	1	-	-
Study Terminated by Sponsor	2	2	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	3	2	2
Age categorical			
Units: Subjects			
10 - 21	3	2	2
Age continuous			
Units: Years			
arithmetic mean	14.7	13.5	15
standard deviation	± 5.69	± 0.71	± 5.66
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	3	2	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	2	2
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	3	2	2
Other	0	0	0

Reporting group values	Total		
Number of subjects	7		
Age categorical			
Units: Subjects			
10 - 21	7		

Age continuous Units: Years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	0		
Male	7		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	7		
Unknown or Not Reported	0		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	7		
Other	0		

## 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: Safety

End point title	Safety <sup>[1]</sup>
End point description: The primary (safety) analysis will be conducted on final completion of the study and will include the entirety of available safety data from both the source studies and this study.	
End point type	Primary
End point timeframe: Long term extension	

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: Safety data presented elsewhere

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	3	2	2	
Units: Totality of safety data	3	2	2	

### 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	19.0
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### Reporting groups

Reporting group title	6 mg/kg/week IV
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Reporting group description: -

Reporting group title	9 mg/kg/week IV
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Reporting group description: -

Reporting group title	6 mg/kg/week SC
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Reporting group description: -

Serious adverse events	6 mg/kg/week IV	9 mg/kg/week IV	6 mg/kg/week SC
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	6 mg/kg/week IV	9 mg/kg/week IV	6 mg/kg/week SC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 2 (100.00%)	2 / 2 (100.00%)
Investigations			
Complement factor C3 decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Sunburn			



subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	2
Traumatic haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Injection site atrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Injection site discolouration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	8
Injection site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	4
Injection site haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 2 (100.00%)
occurrences (all)	0	0	9
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 2 (0.00%) 0	1 / 2 (50.00%) 1
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 2 (50.00%) 2	0 / 2 (0.00%) 0
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all)  Pain in extremity subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1  1 / 3 (33.33%) 2	0 / 2 (0.00%) 0  0 / 2 (0.00%) 0	0 / 2 (0.00%) 0  1 / 2 (50.00%) 1
Infections and infestations Gastroenteritis viral subjects affected / exposed occurrences (all)  Streptococcal infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0  1 / 3 (33.33%) 1	1 / 2 (50.00%) 1  0 / 2 (0.00%) 0	0 / 2 (0.00%) 0  0 / 2 (0.00%) 0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2016	<p>The rationale for this amendment is to improve the understanding of the required assessments to be completed and to address feedback from Regulatory and Ethics Groups.</p> <ol style="list-style-type: none"><li>1. Clarification of how subjects will transition from parent studies to this study depending on whether they are still taking BMN 044 or have been off treatment for more than 28 days.</li><li>2. Clarification of assessments required during the 2 phases of the study, including revising the schedule of assessment tables.</li><li>3. Confirm monitoring requirements for intravenous infusions.</li><li>4. Making the laboratory stopping criteria consistent with the BioMarin AON programme.</li><li>5. Amending the statistical section to account for handling transitioning subjects and their data.</li><li>6. Administrative changes to improve the readability of the document and ensure consistency throughout.</li></ol>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

BioMarin terminated the study early due to a company decision to stop the development of exon-skipping DMD therapies. This decision was based on the marketing authorisation filing in the US and EU for a related compound, drisapersen, for which regula

Notes: