Clinical trial results:
A Phase 2, Open-label, Sequential Cohort Dose-escalation Study of BMN 111 in Children with Achondroplasia

Summary

EudraCT number	2013-004137-32
Trial protocol	GB FR
Global end of trial date	02 October 2017

Results information

Result version number	v1 (current)
This version publication date	27 June 2019
First version publication date	27 June 2019

Trial information

Trial identification

Sponsor protocol code	111-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02055157
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, CA, United States, 94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., medinfo@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., medinfo@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002033-PIP01-16
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	12 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2017
Global end of trial reached?	Yes
Global end of trial date	02 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the initial 6-month phase is: To evaluate the safety and tolerability of daily Subcutaneous (SC) injections of BMN 111 administered for 6 months

The primary objective of the study extension is: To evaluate the safety and tolerability of daily Subcutaneous (SC) injections of BMN 111 administered for up to 24 months

Protection of trial subjects:

This clinical study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	35
EEA total number of subjects	6

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	0

months)	
Children (2-11 years)	35
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 9 study centers in United States, Australia, United Kingdom and France.

Pre-assignment

Screening details:

Of the 35 subjects enrolled to study, 32 subjects completed the initial six months and 30 completed the eighteen months extension.

Period 1

Period 1 title	Initial 6 months
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Cohorts 1

Arm description:

BMN 111 at 2.5 µg/kg daily subcutaneous injection, over a period of 6 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

BMN 111 at 2.5 µg/kg daily subcutaneous injection, over a period of 6 months.

Arm title	Cohorts 2

Arm description:

BMN 111 at 7.5 µg/kg daily subcutaneous injection, over a period of 6 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

BMN 111 at 7.5 µg/kg daily subcutaneous injection, over a period of 6 months.

Arm title	Cohorts 3

Arm description:

BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 6 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 6 months.

Arm title	Cohorts 4
Arm description:	
BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 6 months.	
Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 6 months.

Number of subjects in period 1	Cohorts 1	Cohorts 2	Cohorts 3
Started	8	8	10
Completed	7	7	10
Not completed	1	1	0
Consent withdrawn by subject	1	-	-
Subject D/C due to PI decision	-	1	-
Subject D/C due to AE	-	-	-

Number of subjects in period 1	Cohorts 4
Started	9
Completed	8
Not completed	1
Consent withdrawn by subject	-
Subject D/C due to PI decision	-
Subject D/C due to AE	1

Period 2

Period 2 title	18-month extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	Cohorts 1

Arm description:

BMN 111 at 2.5 µg/kg daily subcutaneous injection, dose determined to be suboptimal after the end of the initial 6 months, 7 subjects escalated to 7.5 µg/kg daily subcutaneous injection, discontinued 1 subject escalating 6 subjects to BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

BMN 111 at 7.5 µg/kg daily subcutaneous injection, dose determined to be suboptimal after the end of the initial 6 months, discontinued 1 subject escalating 6 subjects to BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm title	Cohorts 2

Arm description:

BMN 111 at 7.5 µg/kg daily subcutaneous injection, dose determined to be suboptimal after the end of the initial 6 months, discontinued 1 subject escalating 6 subjects to BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

BMN 111 at 7.5 µg/kg daily subcutaneous injection, dose determined to be suboptimal after the end of the initial 6 months, discontinued 1 subject escalating 6 subjects to BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm title	Cohorts 3

Arm description:

BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm title	Cohorts 4

Arm description:

BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Arm type	Experimental
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 18 months.

Number of subjects in period 2	Cohorts 1	Cohorts 2	Cohorts 3
Started	7	7	10
Completed	6	6	10
Not completed	1	1	0
Subject D/C due to growth plates closure	-	1	-
Consent withdrawn by subject	1	-	-

Number of subjects in period 2	Cohorts 4
Started	8
Completed	8
Not completed	0
Subject D/C due to growth plates closure	-
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohorts 1
Reporting group description:	
BMN 111 at 2.5 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 2
Reporting group description:	
BMN 111 at 7.5 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 3
Reporting group description:	
BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 4
Reporting group description:	
BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 6 months.	

Reporting group values	Cohorts 1	Cohorts 2	Cohorts 3
Number of subjects	8	8	10
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.3	8.3	8.0
standard deviation	± 1.58	± 2.19	± 1.63
Gender categorical Units: Subjects			
Female	5	3	6
Male	3	5	4
Ethnicity Units: Subjects			
Not Hispanic or Latino	8	8	9
Hispanic or Latino	0	0	1
Not Reported	0	0	0
Race Units: Subjects			
White	7	6	5
Asian	0	1	3
Black or African American	1	0	1
Other	0	1	1
Weight Units: kg			
arithmetic mean	18.58	22.50	25.13
standard deviation	± 2.223	± 4.099	± 5.736
Body Mass Index Units: kg/m2			
arithmetic mean	20.13	21.78	22.21
standard deviation	± 2.089	± 2.1	± 2.694

Reporting group values	Cohorts 4	Total	
Number of subjects	9	35	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	6.9		
standard deviation	± 1.17	-	
Gender categorical Units: Subjects			
Female	5	19	
Male	4	16	
Ethnicity Units: Subjects			
Not Hispanic or Latino	7	32	
Hispanic or Latino	1	2	
Not Reported	1	1	
Race Units: Subjects			
White	6	24	
Asian	3	7	
Black or African American	0	2	
Other	0	2	
Weight Units: kg			
arithmetic mean	19.59		
standard deviation	± 2.859	-	
Body Mass Index Units: kg/m2			
arithmetic mean	20.44		
standard deviation	± 1.038	-	

End points

End points reporting groups

Reporting group title	Cohorts 1
Reporting group description:	
BMN 111 at 2.5 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 2
Reporting group description:	
BMN 111 at 7.5 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 3
Reporting group description:	
BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 4
Reporting group description:	
BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 6 months.	
Reporting group title	Cohorts 1
Reporting group description:	
BMN 111 at 2.5 µg/kg daily subcutaneous injection, dose determined to be suboptimal after the end of the initial 6 months, 7 subjects escalated to 7.5 µg/kg daily subcutaneous injection, discontinued 1 subject escalating 6 subjects to BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.	
Reporting group title	Cohorts 2
Reporting group description:	
BMN 111 at 7.5 µg/kg daily subcutaneous injection, dose determined to be suboptimal after the end of the initial 6 months, discontinued 1 subject escalating 6 subjects to BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.	
Reporting group title	Cohorts 3
Reporting group description:	
BMN 111 at 15.0 µg/kg daily subcutaneous injection, over a period of 18 months.	
Reporting group title	Cohorts 4
Reporting group description:	
BMN 111 at 30.0 µg/kg daily subcutaneous injection, over a period of 18 months.	
Subject analysis set title	Cohort 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Population includes all subjects who received at least one dose of study treatment and were used for safety analysis in the initial 6-month period and entire study period.	
Subject analysis set title	Cohort 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Population includes all subjects who received at least one dose of study treatment and were used for safety analysis in the initial 6-month period and entire study period.	
Subject analysis set title	Cohort 3
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Population includes all subjects who received at least one dose of study treatment and were used for safety analysis in the initial 6-month period and entire study period.	
Subject analysis set title	Cohort 4
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Population includes all subjects who received at least one dose of study treatment and were used for safety analysis in the initial 6-month period and entire study period.	

Primary: Number of subjects with adverse events (AEs) by severity grade and study drug treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with adverse events (AEs) by severity grade and study drug treatment-emergent adverse events (TEAEs)[1]

End point description:

Safety Analysis Population includes all subjects who received at least one dose of study treatment and were used for safety analysis in the initial 6-month period and entire study period.

SAE (Serious Adverse Event). AE (CTCAE) Grade: 1=Mild, 2=Moderate, 3=Severe or Undesirable, 4=Life Threatening or Debilitating.

End point type	Primary

End point timeframe:

Up to Month 24 ± 14 Days

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: Statistical Results were summarized by dose cohort and for all cohorts combined.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	10	9
Units: Number of subjects analysed				
Any Study Drug-Related AE—Grade 1	7	7	9	9
Any Study Drug-Related AE—Grade 2	0	1	0	0
Any Study Drug-Related AE—Grade 3	0	0	0	0
Any Study Drug-Related AE—Grade 4	0	0	0	0
Subjects with at Least 1 Reported TEAE	8	8	10	9
At Least 1 Reported Study Drug-Related TEAE	7	8	9	9
Subjects with at Least 1 Reported SAE	1	0	1	1
At Least 1 Reported Study Drug-Related SAE	0	0	0	0
Permanently Discontinued Study Drug due to TEAE	0	0	0	1
Subjects Who Discontinued Study due to TEAE	0	0	0	0
Subjects Who Died	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Annualized Growth Velocity (AGV) during Initial 6-Month

End point title	Change From Baseline of Annualized Growth Velocity (AGV) during Initial 6-Month

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Annualized Growth Velocity assessed by anthropometric measurements and measurement ratios. Anthropometric measurements included standing height, sitting height, weight, head circumference,

upper and lower arm and leg, hand and foot. Ratios calculated of Upper arm to forearm length ratio, Upper leg to lower leg length ratio, Upper to lower body segment ratio. Weight was measured at Screening and at each in-clinic dosing visit.

End point type	Secondary

End point timeframe:

At 6 month (Day 183)

End point values	Cohorts 1	Cohorts 2	Cohorts 3	Cohorts 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	10	8
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline of Initial 6-Month Period (N = 8,8,10,8)	3.755 (± 1.1094)	2.891 (± 1.3920)	4.044 (± 2.2751)	4.492 (± 1.1889)
Change from Baseline to Day 183 (N = 7,8,10,8)	-0.371 (± 1.5920)	1.276 (± 1.4387)	2.014 (± 1.9990)	2.085 (± 2.1375)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Annualized Growth Velocity (AGV) during Entire Study Period Cohort 3 and 4

End point title	Change From Baseline of Annualized Growth Velocity (AGV) during Entire Study Period Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline (N= 10,8)	4.044 (± 2.2751)	4.492 (± 1.1889)		
Change from Baseline to Month 24 (N= 10,8)	1.744 (± 1.7974)	1.538 (± 1.3387)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Annualized Growth Velocity (AGV) during Entire Study Period - Cohort 1 and 2 Switchers

End point title	Change From Baseline of Annualized Growth Velocity (AGV) during Entire Study Period - Cohort 1 and 2 Switchers

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Mos (Months)

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 1	Cohorts 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline (N = 6,6)	3.629 (± 1.1586)	3.510 (± 0.8327)		
Change from Baseline at >=12 Mos on 15µg/kg(N=3,6)	1.846 (± 2.1466)	2.245 (± 0.9176)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Z-Scores Using CDC Reference Standard during 6-Months Post-Treatment

End point title	Change From Baseline of Z-Scores Using CDC Reference Standard during 6-Months Post-Treatment

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Height and Weight Z-Scores includes conversion of Height and weight to age-and sex-appropriate standard score (SDS), also referred to as Z-score by comparison with reference standards (non-ACH) derived from average-stature children from the Centers for Disease Control and Prevention (CDC) database.

End point type	Secondary

End point timeframe:

At month 6 (Day 183)

End point values	Cohorts 1	Cohorts 2	Cohorts 3	Cohorts 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	10	8
Units: z score				
arithmetic mean (standard deviation)				
Baseline (n = 7,8,10,8)	-6.056 (± 0.6331)	-5.145 (± 0.8530)	-4.613 (± 1.1355)	-5.193 (± 0.7486)
Change from Baseline to Day 183 (n = 7,8,10,8)	-0.008 (± 0.1788)	0.078 (± 0.1440)	0.229 (± 0.1505)	0.265 (± 0.1869)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Height Z-Scores Using CDC Reference Standard during Entire Study Period - Cohort 3 and 4

End point title	Change From Baseline of Height Z-Scores Using CDC Reference Standard during Entire Study Period - Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Height and Weight Z-Scores includes conversion of Height and weight to age-and sex-appropriate standard score (SDS), also referred to as Z-score by comparison with reference standards (non-ACH) derived from average-stature children from the Centers for Disease Control and Prevention (CDC) database.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: z score				
arithmetic mean (standard deviation)				
Baseline (n = 10, 8)	-4.613 (± 1.1355)	-5.193 (± 0.7486)		
Change from Baseline to Month 24 (n = 10, 8)	0.788 (± 0.2842)	0.896 (± 0.3010)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Height Z-Scores Using Non-ACH References during Entire Study Period - Cohort 1 and 2 Switchers

End point title	Change From Baseline of Height Z-Scores Using Non-ACH References during Entire Study Period - Cohort 1 and 2 Switchers

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Height and Weight Z-Scores includes conversion of Height and weight to age-and sex-appropriate standard score (SDS), also referred to as Z-score by comparison with reference standards (non-ACH) derived from average-stature children from the Centers for Disease Control and Prevention (CDC) database.

Mos (Months)

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 1	Cohorts 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: z score				
arithmetic mean (standard deviation)				
Baseline (n = 6,6)	-6.064 (± 0.6932)	-4.912 (± 0.7708)		
Change from Baseline to >=12 Mos on 15ug/kg(n=3,6)	0.520 (± 0.2950)	0.259 (± 0.1887)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Weight Z-Scores Using Non-ACH References during Entire Study Period - Cohort 1 and 2 Switchers

End point title	Change From Baseline of Weight Z-Scores Using Non-ACH References during Entire Study Period - Cohort 1 and 2 Switchers

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Height and Weight Z-Scores includes conversion of Height and weight to age-and sex-appropriate standard score (SDS), also referred to as Z-score by comparison with reference standards (non-ACH) derived from average-stature children from the Centers for Disease Control and Prevention (CDC) database.

Mos (Months)

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 1	Cohorts 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: z score				
arithmetic mean (standard deviation)				
Baseline (n = 6,6)	-2.615 (± 0.9648)	-1.436 (± 0.3942)		
Change from Baseline to >=12 Mos on 15ug/kg(n=3,6)	0.926 (± 0.2311)	0.173 (± 0.1287)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper to Lower Body Ratios during 6 Months Post Treatment

End point title	Change From Baseline of Upper to Lower Body Ratios during 6 Months Post Treatment

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 6 and month 24

End point values	Cohorts 1	Cohorts 2	Cohorts 3	Cohorts 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	10	8
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n = 7,8,10,8)	2.094 (± 0.0984)	2.027 (± 0.1793)	1.911 (± 0.2286)	1.962 (± 0.1822)
Change from Baseline to Day 183 (n = 7,8,10,8)	-0.021 (± 0.0626)	0.003 (± 0.0510)	-0.024 (± 0.0369)	-0.030 (± 0.0811)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper to Lower Body Ratios during Entire Study Period - Cohort 3 and 4

End point title	Change From Baseline of Upper to Lower Body Ratios during Entire Study Period - Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n= 10,8)	1.911 (± 0.2286)	1.962 (± 0.1822)		
Change from Baseline to Month 24 (n= 10,8)	-0.067 (± 0.0451)	-0.121 (± 0.1058)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper Arm to Lower Arm Length Ratio during 6 Months Post Treatment - Cohort 3 and 4

End point title	Change From Baseline of Upper Arm to Lower Arm Length Ratio during 6 Months Post Treatment - Cohort 3 and 4[2]

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 6 (Day 183) and 24

Notes:

[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: Statistical Results were summarized by dose cohort and for all cohorts combined.

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 10,8)	1.130 (± 0.1190)	1.106 (± 0.0816)		
Change from Baseline to Day 183 (n = 10,8)	-0.048 (± 0.1002)	0.003 (± 0.0869)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper Arm to Lower Arm Length Ratio during Entire Study Period - Cohort 3 and 4

End point title	Change From Baseline of Upper Arm to Lower Arm Length Ratio during Entire Study Period - Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 10,8)	1.130 (± 0.1190)	1.106 (± 0.0816)		
Change from Baseline to Month 24 (n = 10,8)	0.037 (± 0.0673)	-0.027 (± 0.0504)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper Leg to Knee to Heel Length Ratio during 6 Months Post Treatment - Cohort 3 and 4

End point title	Change From Baseline of Upper Leg to Knee to Heel Length Ratio during 6 Months Post Treatment - Cohort 3 and 4[3]

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 6 (Day 183)

Notes:

[3] - 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: Statistical Results were summarized by dose cohort and for all cohorts combined.

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 10,8)	0.687 (± 0.0268)	0.691 (± 0.0847)		
Change from Baseline to Day 183 (n = 10,8)	0.007 (± 0.0411)	-0.006 (± 0.0810)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper Leg to Knee to Heel Length Ratio during Entire Study Period - Cohort 3 and 4

End point title	Change From Baseline of Upper Leg to Knee to Heel Length Ratio during Entire Study Period - Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 10,8)	0.687 (± 0.0268)	0.691 (± 0.0847)		
Change from Baseline to Month 24 (n = 10, 8)	0.010 (± 0.0503)	-0.033 (± 0.1065)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper Leg Length to Tibial Length Ratio during 6 Months Post Treatment - Cohort 3 and 4

End point title	Change From Baseline of Upper Leg Length to Tibial Length Ratio during 6 Months Post Treatment - Cohort 3 and 4[4]

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 6 (Day 183)

Notes:

[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: Statistical Results were summarized by dose cohort and for all cohorts combined.

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n =10,8)	1.107 (± 0.0607)	1.061 (± 0.1341)		
Change from Baseline to Day 183 (n = 10,8)	0.034 (± 0.1048)	0.015 (± 0.1571)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Upper Leg Length to Tibial Length Ratio during Entire Study Period - Cohort 3 and 4

End point title	Change From Baseline of Upper Leg Length to Tibial Length Ratio during Entire Study Period - Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 10,8)	1.107 (± 0.0607)	1.061 (± 0.1341)		
Change from Baseline to Month 24 (n = 10,8)	0.014 (± 0.0888)	-0.012 (± 0.1477)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Arm Span to Height Ratio during 6 Months Post Treatment - Cohort 3 and 4

End point title	Change From Baseline of Arm Span to Height Ratio during 6 Months Post Treatment - Cohort 3 and 4[5]

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 6 (Day 183)

Notes:

[5] - 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: Statistical Results were summarized by dose cohort and for all cohorts combined.

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 4,7)	0.913 (± 0.0123)	0.893 (± 0.0284)		
Change from Baseline to Day 183 (n= 4,7)	0.007 (± 0.0063)	0.001 (± 0.0143)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Arm Span to Height Ratio during Entire Study Period - Cohort 3 and 4

End point title	Change From Baseline of Arm Span to Height Ratio during Entire Study Period - Cohort 3 and 4

End point description:

Efficacy Analysis Population includes all subjects who received at least one dose of study treatment and who had post treatment data for any efficacy endpoint in the corresponding period were included in the Efficacy Analysis and Extension Efficacy Analysis population.

Body Proportion ratios assessed includes Upper to Lower Body ratio: Sitting Height / (Standing Height – Sitting Height), Upper Arm Length to Lower Arm (Forearm) Length ratio: Upper Arm Length / Lower Arm (Forearm) Length, Upper to Lower Leg ratio: Upper Leg Length (Thigh) / Knee to Heel Length and Upper Leg Length (Thigh)/ Tibial Leg Length, Arm Span to Height ratio: Arm Span / Standing Height.

End point type	Secondary

End point timeframe:

At month 24

End point values	Cohorts 3	Cohorts 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 5,8)	0.911 (± 0.0119)	0.900 (± 0.0315)		
Change from Baseline to Month 24 (n = 5,8)	0.000 (± 0.0123)	-0.006 (± 0.0290)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of BMN 111 at month 24

End point title	Time to Maximum Observed Concentration (Tmax) of BMN 111 at month 24

End point description:

Pharmacokinetic Parameter Tmax is the time to reach Cmax (maximum observed plasma concentration)

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose for month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: min				
median (full range (min-max))	15.5 (6.00 to 32.0)	17.0 (15.0 to 30.0)	30.0 (15.0 to 88.0)	30.0 (15.0 to 60.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of BMN 111 at month 24

End point title	Maximum Observed Plasma Concentration (Cmax) of BMN 111 at month 24

End point description:

Pharmacokinetic Parameter Cmax is the maximum observed plasma concentration.

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose at month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: pg/mL				
arithmetic mean (standard deviation)	21800 (± 35500)	4450 (± 2330)	8730 (± 4800)	20500 (± 12700)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time 0 to the Last Measurable Concentration (AUC(0-t)) of BMN 111 at month 24

End point title	Area Under the Plasma Concentration-time Curve From Time 0 to the Last Measurable Concentration (AUC(0-t)) of BMN 111 at month 24

End point description:

Pharmacokinetic parameter (AUC(0-t)) is the Area under the plasma concentration-time curve from time 0 to the time of last measurable concentration.

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose at month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: pg-min/mL				
arithmetic mean (standard deviation)	602000 (± 526000)	180000 (± 104000)	609000 (± 457000)	1730000 (± 936000)

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) of BMN 111 at month 24

End point title	Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) of BMN 111 at month 24

End point description:

Pharmacokinetic parameter (AUC0-∞) is the Area under the plasma concentration-time curve from time 0 to infinity.

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information

in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose at month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: pg-min/mL				
arithmetic mean (standard deviation)	720000 (± 539000)	382000 (± 0.00)	643000 (± 470000)	1720000 (± 1000000)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance of BMN 111 (CL/F) at month 24

End point title	Apparent clearance of BMN 111 (CL/F) at month 24

End point description:

Pharmacokinetic parameter (CL/F) is the Apparent clearance of BMN 111.

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose at month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: mL/min/kg				
arithmetic mean (standard deviation)	33.0 (± 23.2)	39.3 (± 0.00)	31.9 (± 14.8)	26.7 (± 21.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution of BMN 111 (Vz/F) at month 24

End point title	Apparent volume of distribution of BMN 111 (Vz/F) at month 24

End point description:

Pharmacokinetic parameter (Vz/F) is the Apparent volume of BMN 111.

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose at month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: mL/kg				
arithmetic mean (standard deviation)	1060 (± 629)	1220 (± 0.00)	1210 (± 428)	1180 (± 472)

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life (t1/2) of BMN 111 at month 24

End point title	Elimination half-life (t1/2) of BMN 111 at month 24

End point description:

Pharmacokinetic parameter (t1/2) is the Elimination half-life

PK Analysis Population for each of initial 6-month period and the extension period, all subjects who received at least one dose of study treatment in this study and had any post-treatment PK information in the corresponding period were included in the analysis.

End point type	Secondary

End point timeframe:

At pre-dose, 5, 15, 30, 60, 90, 120 and 180 minutes post dose at month 24.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	10	8
Units: min				
arithmetic mean (standard deviation)	23.5 (± 2.56)	21.5 (± 0.00)	29.0 (± 8.05)	38.4 (± 14.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AbdominalUp to Month 24 ♦ 14 Days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	Entire Study Period - Cohort 1
Reporting group description: -	
Reporting group title	Entire Study Period - Cohort 2
Reporting group description: -	
Reporting group title	Entire Study Period - Cohort 3
Reporting group description: -	
Reporting group title	Entire Study Period - Cohort 4
Reporting group description: -	

Serious adverse events	Entire Study Period - Cohort 1	Entire Study Period - Cohort 2	Entire Study Period - Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (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
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Entire Study Period - Cohort 4		
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	0		
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Entire Study Period - Cohort 1	Entire Study Period - Cohort 2	Entire Study Period - Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	8 / 8 (100.00%)	9 / 10 (90.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 8 (62.50%)	5 / 8 (62.50%)	4 / 10 (40.00%)
occurrences (all)	8	13	4
Haematoma			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pallor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Ear tube insertion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Tooth extraction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	6 / 8 (75.00%)	7 / 8 (87.50%)	8 / 10 (80.00%)
occurrences (all)	1035	1051	1398
Injection site erythema			
subjects affected / exposed	5 / 8 (62.50%)	7 / 8 (87.50%)	9 / 10 (90.00%)
occurrences (all)	76	1231	465
Injection site swelling			
subjects affected / exposed	5 / 8 (62.50%)	4 / 8 (50.00%)	5 / 10 (50.00%)
occurrences (all)	32	4	431
Injection site urticaria			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	2 / 10 (20.00%)
occurrences (all)	105	3	145
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Pyrexia			

subjects affected / exposed	5 / 8 (62.50%)	3 / 8 (37.50%)	5 / 10 (50.00%)
occurrences (all)	5	3	7
Injection site bruising			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 10 (0.00%)
occurrences (all)	11	2	0
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	4	1	1
Injection site pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Injection site haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Application site erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cyst			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injection site discolouration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Medical device site reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 8 (62.50%)	2 / 8 (25.00%)	3 / 10 (30.00%)
occurrences (all)	8	2	5
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	3 / 10 (30.00%)
occurrences (all)	2	8	6
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	3 / 8 (37.50%)	0 / 10 (0.00%)
occurrences (all)	1	5	0
Rhinorrhoea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Sleep apnoea syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Sneezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tonsillar hypertrophy			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Asthma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasal dryness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Snoring			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Emotional disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Irritability			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Enuresis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Frustration tolerance decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Aggression			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eosinophil count increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	3
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Vitamin D decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Blood immunoglobulin E increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory rate increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sleep study abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	2 / 10 (20.00%)
occurrences (all)	1	5	6
Fall			
subjects affected / exposed	4 / 8 (50.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	4	0	2
Contusion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	4	2	1
Procedural anxiety			

subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Limb injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Excoriation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Meniscus injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Soft tissue injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sunburn			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 8 (50.00%)	2 / 8 (25.00%)	3 / 10 (30.00%)
occurrences (all)	15	8	13
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	4	1	2
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sinus headache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 8 (25.00%)	4 / 8 (50.00%)	1 / 10 (10.00%)
occurrences (all)	2	6	2
Ear swelling			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Otorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Middle ear effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Tympanic membrane hyperaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Eye discharge			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye irritation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypermetropia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	2 / 10 (20.00%)
occurrences (all)	6	5	6
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	1 / 10 (10.00%)
occurrences (all)	3	2	1
Abdominal pain upper			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	1	3
Dental caries			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Faeces discoloured			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Malpositioned teeth			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0

Aphthous ulcer			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Parotid gland enlargement			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	2 / 10 (20.00%)
occurrences (all)	1	4	2
Dermatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	2	3
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Rash generalised			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Rash pruritic			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Miliaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin striae			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Arthralgia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	2
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	3 / 8 (37.50%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	2
Groin pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	4 / 8 (50.00%)	5 / 10 (50.00%)
occurrences (all)	1	11	12
Ear infection			
subjects affected / exposed	2 / 8 (25.00%)	3 / 8 (37.50%)	2 / 10 (20.00%)
occurrences (all)	4	12	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	3 / 10 (30.00%)
occurrences (all)	1	4	7
Otitis media			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	2 / 10 (20.00%)
occurrences (all)	1	1	3
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	3 / 8 (37.50%)	0 / 10 (0.00%)
occurrences (all)	0	7	0
Gastroenteritis viral			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	0 / 10 (0.00%)
occurrences (all)	2	2	0

Viral infection			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	3	0	2
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Bronchitis			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Acute sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Atypical pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Croup infectious			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Eye abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Incision site infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Onychomycosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Scarlet fever			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Varicella			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Entire Study Period - Cohort 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Haematoma			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pallor			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Surgical and medical procedures			
Ear tube insertion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tooth extraction			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	9 / 9 (100.00%)		
occurrences (all)	1869		
Injection site erythema			
subjects affected / exposed	9 / 9 (100.00%)		
occurrences (all)	1935		
Injection site swelling			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	28		
Injection site urticaria			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	10		
Injection site pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	60		
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Injection site bruising			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Injection site pruritus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Injection site haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Application site erythema			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Cyst			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Injection site discolouration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injection site induration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Medical device site reaction			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Hypersensitivity			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Seasonal allergy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	10		
Oropharyngeal pain			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tonsillar hypertrophy			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nasal dryness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Snoring			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Emotional disorder				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Irritability				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Attention deficit/hyperactivity disorder				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Enuresis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Frustration tolerance decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Aggression				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Investigations				
Body temperature increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	3			
Eosinophil count increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Vitamin D decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood immunoglobulin E increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Respiratory rate increased				

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Sleep study abnormal			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Contusion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Procedural anxiety			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Thermal burn			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Excoriation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Joint injury			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Meniscus injury			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Post-traumatic pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Soft tissue injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	8		
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Sinus headache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Ear swelling			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Otorrhoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Middle ear effusion			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Eye discharge			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Eye inflammation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Eye irritation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypermetropia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Abdominal pain			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Faeces discoloured			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Malpositioned teeth			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Aphthous ulcer			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gingival bleeding			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Parotid gland enlargement			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rash generalised			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Miliaria			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin exfoliation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin striae			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Pollakiuria			

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	8		
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Joint range of motion decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Myalgia			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	9		
Ear infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Otitis media			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	5		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Influenza				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	2			
Otitis externa				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Acute sinusitis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Atypical pneumonia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Croup infectious				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Eye abscess				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Gastrointestinal viral infection				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Incision site infection				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Onychomycosis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			

Rash pustular subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Scarlet fever subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Tooth abscess subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Varicella subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2014	Amendment 1 established an optional, open-label extension phase of approximately 18 months to commence at the end of the initial phase of the study, making a total study duration of approximately 25 months, including a 1-month safety follow-up visit. The rationale for extending this Phase 2 study was to assess the long-term safety and tolerability of BMN 111 in children with ACH; and to assess longer-term effects of BMN 111 on the growth in these children.
08 May 2015	Amendment 2 established higher doses in 2 additional cohorts in the initial 6 months of the study. Cohort 4 and 5 daily doses of 30 µg/kg and up to 60 µg/kg BMN 111, respectively, were selected with the intent to achieve exposures expected to result in further increases in growth velocity in children with ACH with an acceptable safety profile. In addition, baseline hip assessments and hip monitoring to screen for effects on hip joints and/or mobility were added for all cohorts.
26 October 2015	Amendment 3 added a thyroid function test at the Month 24 visit to assess any changes over the course of the open-label extension phase of 111-202. This amendment also specified that the assessment at Month 24 would serve as the baseline/screening assessments for entry into 111-205 and waived the safety follow-up visit at Month 25 if a subject enrolled in 111-205 at the Month 24/Study Completion Visit. These changes ensured uninterrupted transition of subjects who complete 111-202 into 111-205.
22 August 2016	Amendment 4 removed Cohort 5 based on the 6-month data from Cohort 4. Preliminary PK data from Cohort 4 (30 µg/kg daily) showed a greater than dose proportional increase in BMN 111 exposure, with mean plasma maximum observed plasma concentration (Cmax) and area under the time-concentration curve from zero to the last quantifiable concentration (AUC0-t) values at the target exposure previously expected to require daily doses up to 60 µg/kg. A marginal improvement was observed in both absolute AGV and change from baseline AGV in Cohort 4 (BMN 111 daily at 30 µg/kg) after 6 months of BMN 111 treatment when compared with Cohort 3 (BMN 111 daily at 15 µg/kg). Given this observation, higher doses of BMN 111 were not expected to demonstrate an improved benefit/risk profile. Thus, Cohort 5 (with daily dosing up to 60 µg/kg) was not pursued.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported