



## Clinical trial results:

### A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of BMN 111 in Children with Achondroplasia.

#### Summary

EudraCT number	2015-003836-11
Trial protocol	GB ES DE
Global end of trial date	30 October 2019

#### Results information

Result version number	v1 (current)
This version publication date	24 September 2020
First version publication date	24 September 2020

#### Trial information

##### Trial identification

Sponsor protocol code	111-301
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03197766
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc
Sponsor organisation address	105 Digital Drive, Novato, 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)	EMA-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	21 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2019
Global end of trial reached?	Yes
Global end of trial date	30 October 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Evaluate change from baseline in annualized growth velocity at 52 weeks in subjects treated with BMN 111 compared with control subjects in the placebo group

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	12 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United States: 53
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	121
EEA total number of subjects	36

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	96
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at 24 study centers in 7 countries.

### Pre-assignment

Screening details:

A total of 121 subjects were enrolled into the study; 61 subjects were randomized to receive placebo and 60 subjects to receive vosoritide.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Subjects received a placebo single daily subcutaneous injection for 52 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a placebo single daily subcutaneous injection for 52 weeks

<b>Arm title</b>	Vosoritide 15 µg/kg
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Arm description:

Subjects received a 15 µg/kg vosoritide single daily subcutaneous injection for 52 weeks

Arm type	Active comparator
Investigational medicinal product name	Vosoritide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a 15 µg/kg vosoritide single daily subcutaneous injection for 52 weeks

<b>Number of subjects in period 1</b>	Placebo	Vosoritide 15 µg/kg
Started	61	60
Completed	61	58
Not completed	0	2
Consent withdrawn by subject	-	1
Adverse Event	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received a placebo single daily subcutaneous injection for 52 weeks	
Reporting group title	Vosoritide 15 µg/kg
Reporting group description:	
Subjects received a 15 µg/kg vosoritide single daily subcutaneous injection for 52 weeks	

Reporting group values	Placebo	Vosoritide 15 µg/kg	Total
Number of subjects	61	60	121
Age categorical			
Units: Subjects			
≥ 5 to < 8 years	24	31	55
≥ 8 to < 11 years	24	17	41
≥ 11 to < 15 years	13	12	25
Age continuous			
Units: years			
arithmetic mean	9.06	8.35	
standard deviation	± 2.47	± 2.43	-
Gender categorical			
Units: Subjects			
Female	28	29	57
Male	33	31	64
Race			
Units: Subjects			
White	41	45	86
Asian - Other	9	7	16
Asian - Japanese	4	3	7
Multiple	5	2	7
Black or African American	2	3	5
Ethnicity			
Units: Subjects			
Not Hispanic Or Latino	55	59	114
Hispanic Or Latino	6	1	7

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received a placebo single daily subcutaneous injection for 52 weeks	
Reporting group title	Vosoritide 15 µg/kg
Reporting group description:	
Subjects received a 15 µg/kg vosoritide single daily subcutaneous injection for 52 weeks	

### Primary: Change from baseline of annualized growth velocity (AGV)

End point title	Change from baseline of annualized growth velocity (AGV)
End point description:	
Annualized growth velocity (AGV) = Standing Height at Date 2 - Standing Height at Date 1/Interval Length (Days) x 365.25	
The Full Analysis Set (FAS) was defined according to the intention to treat and included all randomized consented subjects. The FAS use to present the baseline characteristics and efficacy data by randomized treatment group.	
Two subjects in the vosoritide group discontinued from the study before Week 52. The values for these 2 subjects were imputed for this analysis. The type I error was controlled using hierarchical testing.	
End point type	Primary
End point timeframe:	
At Baseline and Week 52	

End point values	Placebo	Vosoritide 15 µg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline (n = 61, 60)	4.06 (± 1.20)	4.26 (± 1.53)		
Change from Baseline to Week 52 (n = 60, 58)	-0.12 (± 1.74)	1.35 (± 1.71)		

### Statistical analyses

Statistical analysis title	Annualized Growth Velocity - Placebo Vs Vosoritide
Comparison groups	Placebo v Vosoritide 15 µg/kg

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

### Secondary: Change from baseline of height Z-score

End point title	Change from baseline of height Z-score
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End point description:

Standing Height converted to an age-and sex-appropriate standard deviation score (SDS), also referred to as a Z-score, by comparison with reference data available for average stature children from the Centers for Disease Control and Prevention(CDC).

Full Analysis Set(FAS) population

Two subjects in the vosoritide group discontinued from the study before Week 52. The values for these 2 subjects were imputed for this analysis. The type I error was controlled using hierarchical testing.

End point type	Secondary
End point timeframe:	
At Baseline and Week 52	

End point values	Placebo	Vosoritide 15 µg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Z-score				
arithmetic mean (standard deviation)				
Baseline (n = 61, 60)	-5.14 (± 1.07)	-5.13 (± 1.11)		
Change from Baseline to Week 52 (n = 61, 60)	0.00 (± 0.28)	0.24 (± 0.32)		

### Statistical analyses

<b>Statistical analysis title</b>	Height Z-Score - Placebo Vs Vosoritide
Comparison groups	Placebo v Vosoritide 15 µg/kg
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

### Secondary: Change from baseline of upper to lower body segment ratio

End point title	Change from baseline of upper to lower body segment ratio
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End point description:

Full Analysis Set (FAS) population.

Two subjects in the vosoritide group discontinued from the study before Week 52. The values for these 2 subjects were imputed for this analysis. The type I error was controlled using hierarchical testing.

End point type	Secondary
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End point timeframe:

At Baseline and Week 52

End point values	Placebo	Vosoritide 15 µg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Ratio				
arithmetic mean (standard deviation)				
Baseline (n = 61, 60)	2.01 (± 0.21)	1.98 (± 0.20)		
Change from Baseline to Week 52 (n = 60, 58)	-0.03 (± 0.09)	-0.03 (± 0.11)		

## Statistical analyses

Statistical analysis title	Upper to Lower Body Ratio - Placebo Vs Vosoritide
Comparison groups	Placebo v Vosoritide 15 µg/kg
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.506
Method	ANCOVA

## Secondary: Time taken to reach peak concentration (Tmax) of vosoritide at week 52

End point title	Time taken to reach peak concentration (Tmax) of vosoritide at week 52 <sup>[1]</sup>
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End point description:

Pharmacokinetics (PK) Parameter Time taken to reach Peak Concentration (Tmax)

At week 52: number of PK parameters used in the calculation of the statistics = 56

End point type	Secondary
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End point timeframe:

At week 52.

Notes:

[1] - 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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: min				
arithmetic mean (standard deviation)	16.8 (± 11.7)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum plasma concentration (Cmax) of vosoritide at week 52

End point title	Maximum plasma concentration (Cmax) of vosoritide at week 52 <sup>[2]</sup>
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End point description:

Pharmacokinetics (PK) Parameter Maximum Plasma Concentration (Cmax).

At week 52: number of PK parameters used in the calculation of the statistics = 56

End point type	Secondary
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End point timeframe:

At Week 52.

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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: pg/mL				
arithmetic mean (standard deviation)	5800 (± 3680)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area under the concentration-time curve from time zero to time of last measurable concentration (AUC0-t) of vosoritide at week 52

End point title	Area under the concentration-time curve from time zero to time of last measurable concentration (AUC0-t) of vosoritide at week 52 <sup>[3]</sup>
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End point description:

Pharmacokinetics (PK) Parameter Area under the concentration-time curve from time zero to time of last measurable concentration (AUC0-t).

At week 52: number of PK parameters used in the calculation of the statistics = 56

End point type	Secondary
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End point timeframe:

At week 52.

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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: pg-min/mL				
arithmetic mean (standard deviation)	290000 (± 235000)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area under the concentration-time curve from time zero to infinity (AUC<sub>0-∞</sub>) of vosoritide at week 52

End point title	Area under the concentration-time curve from time zero to infinity (AUC <sub>0-∞</sub> ) of vosoritide at week 52 <sup>[4]</sup>
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End point description:

Pharmacokinetics (PK) Parameter Area Under the Concentration-time Curve From Time 0 to Infinity (AUC<sub>0-∞</sub>).

At week 52: number of PK parameters used in the calculation of the statistics = 48

End point type	Secondary
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End point timeframe:

At week 52.

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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: pg-min/mL				
arithmetic mean (standard deviation)	276000 (± 187000)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Apparent clearance (CL/F) of vosoritide at week 52

End point title	Apparent clearance (CL/F) of vosoritide at week 52 <sup>[5]</sup>
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End point description:

Pharmacokinetics(PK) Parameter Apparent Clearance (CL/F)

At week 52: number of PK parameters used in the calculation of the statistics = 48

End point type	Secondary
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End point timeframe:

At week 52.

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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: mL/min/kg				
arithmetic mean (standard deviation)	79.4 (± 53.0)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent volume of distribution (V<sub>z</sub>/F) of vosoritide at week 52

End point title	Apparent volume of distribution (V <sub>z</sub> /F) of vosoritide at week
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End point description:

Pharmacokinetics (PK) Parameter Apparent Volume of Distribution (V<sub>z</sub>/F)

At week 52: number of PK parameters used in the calculation of the statistics = 48

End point type	Secondary
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End point timeframe:

At week 52.

Notes:

[6] - 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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: mL/kg				
arithmetic mean (standard deviation)	2910 (± 1660)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma half life (t<sub>1/2</sub>) of vosoritide at week 52

End point title	Plasma half life (t <sub>1/2</sub> ) of vosoritide at week 52 <sup>[7]</sup>
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End point description:

Pharmacokinetics (PK) Parameter Plasma Half Life (t<sub>1/2</sub>).

At week 52: number of PK parameters used in the calculation of the statistics = 48

End point type	Secondary
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End point timeframe:

At week 52.

Notes:

[7] - 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: Results summarised using descriptive statistics only

<b>End point values</b>	Vosoritide 15 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: min				
arithmetic mean (standard deviation)	27.9 (± 9.91)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with treatment emergent adverse events (TEAEs)

End point title	Number of subjects with treatment emergent adverse events (TEAEs)
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End point description:

A treatment-emergent Adverse Events (TEAE) is any Adverse Events that newly appeared, increased in frequency or worsened in severity following initiation of study drug administration.

Safety Population are those all subjects in the FAS who received at least one dose of double-blind vosoritide or placebo in this study. Safety Population used to present the safety summaries by actual treatment received.

End point type	Secondary
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End point timeframe:

Up to Week 56

<b>End point values</b>	Placebo	Vosoritide 15 µg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: participants				
Subjects with any Adverse Event	60	59		
Subjects with any Serious Adverse Event	4	3		
Subjects with any treatment-related Adverse Event	51	53		
Any treatment-related Serious Adverse Event	0	0		
Death	0	0		

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 56

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Vosoritide 15 µg/kg
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Reporting group description: -

Serious adverse events	Placebo	Vosoritide 15 µg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 61 (6.56%)	3 / 60 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			

subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	Vosoritide 15 µg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 61 (98.36%)	59 / 60 (98.33%)	
Investigations			
Blood pressure decreased			
subjects affected / exposed	3 / 61 (4.92%)	7 / 60 (11.67%)	
occurrences (all)	3	10	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 61 (6.56%)	4 / 60 (6.67%)	
occurrences (all)	5	5	
Nervous system disorders			



Headache			
subjects affected / exposed	16 / 61 (26.23%)	14 / 60 (23.33%)	
occurrences (all)	30	23	
Dizziness			
subjects affected / exposed	1 / 61 (1.64%)	4 / 60 (6.67%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	29 / 61 (47.54%)	44 / 60 (73.33%)	
occurrences (all)	229	2280	
Injection site erythema			
subjects affected / exposed	40 / 61 (65.57%)	41 / 60 (68.33%)	
occurrences (all)	1215	3987	
Injection site swelling			
subjects affected / exposed	6 / 61 (9.84%)	23 / 60 (38.33%)	
occurrences (all)	53	322	
Pyrexia			
subjects affected / exposed	13 / 61 (21.31%)	10 / 60 (16.67%)	
occurrences (all)	22	11	
Injection site urticaria			
subjects affected / exposed	2 / 61 (3.28%)	8 / 60 (13.33%)	
occurrences (all)	5	71	
Injection site bruising			
subjects affected / exposed	8 / 61 (13.11%)	5 / 60 (8.33%)	
occurrences (all)	16	19	
Fatigue			
subjects affected / exposed	0 / 61 (0.00%)	4 / 60 (6.67%)	
occurrences (all)	0	4	
Injection site mass			
subjects affected / exposed	1 / 61 (1.64%)	4 / 60 (6.67%)	
occurrences (all)	1	34	
Injection site haemorrhage			
subjects affected / exposed	7 / 61 (11.48%)	2 / 60 (3.33%)	
occurrences (all)	15	4	
Injection site pruritus			

subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 102	1 / 60 (1.67%) 220	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	6 / 60 (10.00%) 11	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	4 / 60 (6.67%) 4	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	12 / 61 (19.67%) 16  2 / 61 (3.28%) 2  4 / 61 (6.56%) 6	16 / 60 (26.67%) 25  6 / 60 (10.00%) 8  3 / 60 (5.00%) 3	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)  Nasal congestion subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 10  4 / 61 (6.56%) 4  4 / 61 (6.56%) 5	7 / 60 (11.67%) 8  6 / 60 (10.00%) 13  3 / 60 (5.00%) 3	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Pain in extremity	4 / 61 (6.56%) 7	9 / 60 (15.00%) 11	

subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4	5 / 60 (8.33%) 8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 61 (29.51%)	16 / 60 (26.67%)	
occurrences (all)	29	26	
Upper respiratory tract infection			
subjects affected / exposed	10 / 61 (16.39%)	8 / 60 (13.33%)	
occurrences (all)	12	8	
Ear infection			
subjects affected / exposed	6 / 61 (9.84%)	6 / 60 (10.00%)	
occurrences (all)	6	8	
Influenza			
subjects affected / exposed	3 / 61 (4.92%)	6 / 60 (10.00%)	
occurrences (all)	3	8	
Otitis media			
subjects affected / exposed	6 / 61 (9.84%)	6 / 60 (10.00%)	
occurrences (all)	9	7	
Viral infection			
subjects affected / exposed	3 / 61 (4.92%)	5 / 60 (8.33%)	
occurrences (all)	5	11	
Gastroenteritis			
subjects affected / exposed	3 / 61 (4.92%)	4 / 60 (6.67%)	
occurrences (all)	3	4	
Gastroenteritis viral			
subjects affected / exposed	1 / 61 (1.64%)	4 / 60 (6.67%)	
occurrences (all)	1	4	
Pharyngitis			
subjects affected / exposed	4 / 61 (6.56%)	1 / 60 (1.67%)	
occurrences (all)	7	1	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	7 / 61 (11.48%)	3 / 60 (5.00%)	
occurrences (all)	7	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2016	Use of Birth Control During and After Study Participation
27 April 2017	<ul style="list-style-type: none"><li>- Upper limit of age range increased from less than 15 years old to less than 18 years old.</li><li>- Stratification /randomization to be conducted by Tanner stage rather than by age group.</li><li>- Criterion for removing subjects from treatment or assessment, "Subject has reached near adult height in the judgment of the investigator" revised to be more specific.</li><li>- ISR photo language has been revised.</li><li>- Inclusion criterion #1, regarding informed consent, revised to state the subjects who reach age of 18 years while study is ongoing are asked to provide their own written consent.</li><li>- Inclusion criteria #4 revised to elaborate on requirements for entering Study 111-301 from 111-901.</li><li>- New section, Procedures due to Achondroplasia added.</li><li>- Pregnancy Testing, language added stating that start date of menses is captured.</li><li>- New section, Events of Special Interest, added.</li><li>- Statistical Methods and Determination of Sample Size, has been substantially revised.</li></ul>
05 January 2018	<ul style="list-style-type: none"><li>- Evaluation of change from baseline in bone metabolism biomarkers moved from exploratory to secondary objectives.</li><li>- Exclusion criterion #6 revised to include evidence of decreased growth velocity (AGV &lt; 1.5 cm/year) as assessed over a period of at least 6 months.</li><li>- Exclusion criterion #15 revised to state that subjects with previous bone-related surgery may enroll if surgery occurred at least 6 months prior to screening, rather than 12 months, excluding tooth extraction.</li><li>- Salivary cortisol, serum prolactin, FSH/LH, and cognitive assessment with the CBCL added as safety assessments.</li><li>- Use of Birth Control During and After Study Participation, progestogen-only hormonal contraception removed.</li><li>- DXA scans to no longer include tibia scans.</li><li>- Hip Clinical Assessment, requirement to be completed by a physician, i.e., the investigator or sub-investigator changed to assessment by an appropriately qualified health care professional.</li></ul>
01 February 2019	<ul style="list-style-type: none"><li>- The following exploratory objectives moved to secondary:<ul style="list-style-type: none"><li>a. Change from baseline in body proportion ratios of the extremities.</li><li>b. Effect of vosoritide on bone morphology/quality by X-ray and DXA.</li><li>c. Changes in HRQoL and functional independence.</li></ul></li><li>- Contraception in inclusion criteria and birth control during and after the study updated.</li><li>- Duration of subject participation updated to account for 4-week safety follow-up after Week 52.</li><li>- Primary and secondary efficacy variables separated so that new secondary variables are incorporated.</li><li>- Replaced "18 years of age" with "age of majority".</li><li>- Inserted "In Japan, subject enrollment was staggered initially, with a minimum of a 2-week window between the first 4 subjects enrolled".</li></ul>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported