



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 |
|-----------------------|---------|

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 |
| Arm title | 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

| | |
|------------------|---------------------|
| Arm title | Vosoritide 15 µg/kg |
|------------------|---------------------|

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

| Number of subjects in period 1 | 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 |
|-----------------|--|

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

| | |
|---|--|
| Statistical analysis title | 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 ^[1] |
|-----------------|---|

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 |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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 ^[2] |
|-----------------|---|

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 |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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 ^[3] |
|-----------------|--|

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 |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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_{0-∞}) of vosoritide at week 52

| | |
|-----------------|--|
| End point title | Area under the concentration-time curve from time zero to infinity (AUC _{0-∞}) of vosoritide at week 52 ^[4] |
|-----------------|--|

End point description:

Pharmacokinetics (PK) Parameter Area Under the Concentration-time Curve From Time 0 to Infinity (AUC_{0-∞}).

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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 ^[5] |
|-----------------|---|

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 |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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_z/F) of vosoritide at week 52

| | |
|-----------------|---|
| End point title | Apparent volume of distribution (V _z /F) of vosoritide at week |
|-----------------|---|

End point description:

Pharmacokinetics (PK) Parameter Apparent Volume of Distribution (V_z/F)

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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_{1/2}) of vosoritide at week 52

| | |
|-----------------|--|
| End point title | Plasma half life (t _{1/2}) of vosoritide at week 52 ^[7] |
|-----------------|--|

End point description:

Pharmacokinetics (PK) Parameter Plasma Half Life (t_{1/2}).

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | 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) |
|-----------------|---|

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 |
|----------------|-----------|

End point timeframe:

Up to Week 56

| | | | | |
|---|-----------------|---------------------|--|--|
| End point values | 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

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 56

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|---------------------|
| Reporting group title | Vosoritide 15 µg/kg |
|-----------------------|---------------------|

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 %

| Non-serious adverse events | 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">- Upper limit of age range increased from less than 15 years old to less than 18 years old.- Stratification /randomization to be conducted by Tanner stage rather than by age group.- 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.- ISR photo language has been revised.- 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.- Inclusion criteria #4 revised to elaborate on requirements for entering Study 111-301 from 111-901.- New section, Procedures due to Achondroplasia added.- Pregnancy Testing, language added stating that start date of menses is captured.- New section, Events of Special Interest, added.- Statistical Methods and Determination of Sample Size, has been substantially revised. |
| 05 January 2018 | <ul style="list-style-type: none">- Evaluation of change from baseline in bone metabolism biomarkers moved from exploratory to secondary objectives.- Exclusion criterion #6 revised to include evidence of decreased growth velocity (AGV < 1.5 cm/year) as assessed over a period of at least 6 months.- 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.- Salivary cortisol, serum prolactin, FSH/LH, and cognitive assessment with the CBCL added as safety assessments.- Use of Birth Control During and After Study Participation, progestogen-only hormonal contraception removed.- DXA scans to no longer include tibia scans.- 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. |
| 01 February 2019 | <ul style="list-style-type: none">- The following exploratory objectives moved to secondary:<ul style="list-style-type: none">a. Change from baseline in body proportion ratios of the extremities.b. Effect of vosoritide on bone morphology/quality by X-ray and DXA.c. Changes in HRQoL and functional independence.- Contraception in inclusion criteria and birth control during and after the study updated.- Duration of subject participation updated to account for 4-week safety follow-up after Week 52.- Primary and secondary efficacy variables separated so that new secondary variables are incorporated.- Replaced "18 years of age" with "age of majority".- Inserted "In Japan, subject enrollment was staggered initially, with a minimum of a 2-week window between the first 4 subjects enrolled". |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported