EU Clinical Trials Register

Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children with Achondroplasia, Age 0 to < 60 Months

Summary

EudraCT number	2016-003826-18
Trial protocol	GB
Global end of trial date	26 January 2022

Results information

Result version number	v1 (current)
This version publication date	28 March 2023
First version publication date	28 March 2023
Summary attachment (see zip file)	Secondary Endpoints_ITQOL Tables (BMN 111-206_Secondary Endpoints_ITQOL Tables.pdf)
	PK parameter Endpoints tables (BMN 111-206_PK parameter screenshot.pdf)

Trial information

Trial identification

Sponsor protocol code	BMN 111-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03583697
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., clinicaltrials@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2022
Global end of trial reached?	Yes
Global end of trial date	26 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were to:
- Evaluate the safety and tolerability of Vosoritide in children aged 0 to < 60 months with ACH
- Evaluate the effect of Vosoritide on change from baseline in length/height Z-score

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the protocol and also with the following:

• European Clinical Trial Directive 2001/20/EC and Good Clinical Practice (GCP) Directive 2005/28/EC, for studies conducted within any European country
• United States (US) Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable
• International Council on Harmonisation, Harmonised Tripartite Guideline: Guideline for GCP E6 (ICH E6)
• The ethical principles established by the Declaration of Helsinki

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	19 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	Australia: 18
Worldwide total number of subjects	75
EEA total number of subjects	0

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)	40
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 was a multi-center study conducted by 16 principal investigators at 16 study centers in four countries (United States, Australia, United Kingdom and Japan).

Pre-assignment

Screening details:

A total of 75 participants (full analysis set [FAS]) were enrolled into the study, of which 11 participants were enrolled to receive vosoritide (sentinel participants). 64 participants were randomized to receive vosoritide or placebo (32 randomized for vosoritide and 32 for placebo), which constituted the FAS (randomized).

Period 1

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

Blinding implementation details:

Participants & site members were blinded to study treatment. The investigator and staff involved with the study also remained blinded to the treatment randomization code. In an emergency medical situation where participant management would be determined or significantly altered by knowing the treatment assignment, the investigator could be unblinded without prior written approval from the Medical Monitor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sentinel

Arm description:

Cohort 1 Sentinel: Participants stratified by age >= 24 to < 60 months, received vosoritide 15 μg/kg/day (n=4)
Cohort 2 Sentinel: Participants stratified by age >= 6 to < 24 months, received vosoritide 15 μg/kg/day & 30 μg/kg/day (n=4)
Cohort 3 Sentinel: Participants stratified by age 0 to < 6 months, received vosoritide 30 μg/kg/day (n=3)

Arm type	Active comparator
Investigational medicinal product name	BMN 111
Investigational medicinal product code	
Other name	Vosoritide
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 1 Sentinel participants received a 15 μg/kg vosoritide single daily subcutaneous injection for 52 weeks.

Cohort 2 Sentinel participants Initially dosed with single daily subcutaneous injection of vosoritide 15 μg/kg/day and were adjusted to 30 μg/kg/day following the review of safety and PK data then adjusted to 15 μg/kg/day during the visit immediately preceding the 2-year birthday.

Cohort 3 Sentinel participants received a 30 μg/kg vosoritide single daily subcutaneous injection for 52 weeks.

Arm title	Randomized Vosoritide

Arm description:

Cohort 1: Vosoritide 15 μg/kg/day (n=15)
Cohort 2: Vosoritide 15 μg/kg/day & 30 μg/kg/day (n=8)
Cohort 3: Vosoritide 30 μg/kg/day (n=9)

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

Dosage and administration details:

Cohort 1: Participants received a vosoritide 15 µg/kg daily subcutaneous injection for 52 weeks.

Cohort 2: Participants received vosoritide 15 µg/kg to 30 µg/kg daily subcutaneous injection for 52 weeks.

Cohort 3: Participants received vosoritide 30 µg/kg daily subcutaneous injection for 52 weeks.

Arm title	Randomized Placebo

Arm description:

Cohort 1: Placebo (n=16)
Cohort 2: Placebo (n=8)
Cohort 3: Placebo (n=8)

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:

Participants received a placebo single daily subcutaneous injection for 52 weeks.

Number of subjects in period 1	Sentinel	Randomized Vosoritide	Randomized Placebo
Started	11	32	32
Completed	11	31	31
Not completed	0	1	1
Consent withdrawn by subject	-	-	1
AE of sudden infant death syndrome, not related	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Sentinel
Reporting group description:	

Cohort 1 Sentinel: Participants stratified by age >= 24 to < 60 months, received vosoritide 15 µg/kg/day (n=4)
Cohort 2 Sentinel: Participants stratified by age >= 6 to < 24 months, received vosoritide 15 µg/kg/day & 30 µg/kg/day (n=4)
Cohort 3 Sentinel: Participants stratified by age 0 to < 6 months, received vosoritide 30 µg/kg/day (n=3)

Reporting group title	Randomized Vosoritide
Reporting group description:	

Cohort 1: Vosoritide 15 µg/kg/day (n=15)
Cohort 2: Vosoritide 15 µg/kg/day & 30 µg/kg/day (n=8)
Cohort 3: Vosoritide 30 µg/kg/day (n=9)

Reporting group title	Randomized Placebo
Reporting group description:	

Cohort 1: Placebo (n=16)
Cohort 2: Placebo (n=8)
Cohort 3: Placebo (n=8)

Reporting group values	Sentinel	Randomized Vosoritide	Randomized Placebo
Number of subjects	11	32	32
Age categorical			
Units: Subjects			
Age continuous			
Age at Screening, months Full analysis population (FAS).			
Units: months			
arithmetic mean	23.4	23.0	26.5
standard deviation	± 21.0	± 16.9	± 19.3
Gender categorical			
Full analysis population (FAS).			
Units: Subjects			
Female	3	15	19
Male	8	17	13
Race			
Full analysis population (FAS).			
Units: Subjects			
White	8	21	25
Asian-Other	1	6	2
Asian-Japanese	0	4	4
Multiple	2	1	0
Native Hawaiian or Other Pacific Islander	0	0	1
Ethnicity			
Full analysis population (FAS).			
Units: Subjects			
Not Hispanic or Latino	11	29	29
Hispanic or Latino	0	3	3

Age continuous			
Age on Day 1, months. Full analysis population (FAS).			
Units: Months			
arithmetic mean	24.71	24.39	27.82
standard deviation	± 20.79	± 16.83	± 19.25
Weight			
Full analysis population (FAS).			
Units: Kg			
arithmetic mean	10.12	10.20	10.55
standard deviation	± 3.70	± 3.83	± 4.31
Weight Z-Score			
Full analysis population (FAS).			
Units: Z-Score			
arithmetic mean	-1.41	-1.49	-1.59
standard deviation	± 0.73	± 1.26	± 1.44
BMI			
Body Mass Index (BMI) Full analysis population (FAS).			
Units: kg/m^2			
arithmetic mean	20.06	19.48	20.14
standard deviation	± 1.87	± 2.45	± 2.39
BMI Z-Score			
Baseline is defined as Day 1 or screening if a Day 1 assessment is not available. Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention. For height used for BMI calculation, participants aged < 24 months, body length takes precedence over standing height. Participants aged < 24 months at baseline and >= 24 months at Week 52, body length takes precedence. BMI Z-Scores were derived only for participants aged 24 months or older. BMI Z-Score: (n=Sentinel 4, Vosoritide 15, Placebo 16)			
Units: Z-Score			
arithmetic mean	2.79	2.52	2.77
standard deviation	± 0.98	± 1.15	± 0.75

Reporting group values	Total		
Number of subjects	75		
Age categorical Units: Subjects			

Age continuous			
Age at Screening, months Full analysis population (FAS).			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Full analysis population (FAS).			
Units: Subjects			
Female	37		
Male	38		

Race			
Full analysis population (FAS).			
Units: Subjects			
White	54		
Asian-Other	9		
Asian-Japanese	8		
Multiple	3		
Native Hawaiian or Other Pacific Islander	1		
Ethnicity			
Full analysis population (FAS).			
Units: Subjects			
Not Hispanic or Latino	69		
Hispanic or Latino	6		
Age continuous			
Age on Day 1, months. Full analysis population (FAS).			
Units: Months			
arithmetic mean			
standard deviation	-		
Weight			
Full analysis population (FAS).			
Units: Kg			
arithmetic mean			
standard deviation	-		
Weight Z-Score			
Full analysis population (FAS).			
Units: Z-Score			
arithmetic mean			
standard deviation	-		
BMI			
Body Mass Index (BMI) Full analysis population (FAS).			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		
BMI Z-Score			
Baseline is defined as Day 1 or screening if a Day 1 assessment is not available. Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention. For height used for BMI calculation, participants aged < 24 months, body length takes precedence over standing height. Participants aged < 24 months at baseline and >= 24 months at Week 52, body length takes precedence. BMI Z-Scores were derived only for participants aged 24 months or older. BMI Z-Score: (n=Sentinel 4, Vosoritide 15, Placebo 16)			
Units: Z-Score			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Sentinel
Reporting group description:	
Cohort 1 Sentinel: Participants stratified by age >= 24 to < 60 months, received vosoritide 15 µg/kg/day (n=4) Cohort 2 Sentinel: Participants stratified by age >= 6 to < 24 months, received vosoritide 15 µg/kg/day & 30 µg/kg/day (n=4) Cohort 3 Sentinel: Participants stratified by age 0 to < 6 months, received vosoritide 30 µg/kg/day (n=3)	
Reporting group title	Randomized Vosoritide
Reporting group description:	
Cohort 1: Vosoritide 15 µg/kg/day (n=15) Cohort 2: Vosoritide 15 µg/kg/day & 30 µg/kg/day (n=8) Cohort 3: Vosoritide 30 µg/kg/day (n=9)	
Reporting group title	Randomized Placebo
Reporting group description:	
Cohort 1: Placebo (n=16) Cohort 2: Placebo (n=8) Cohort 3: Placebo (n=8)	
Subject analysis set title	Cohort 1: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort 1 included participants stratified by age >=24 to <36 months and >=36 to <60 months. The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent	
Subject analysis set title	Cohort 1: Vosoritide
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort 1 included participants stratified by age >=24 to <36 months and >=36 to <60 months. Vosoritide 15 µg/kg/day The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent.	
Subject analysis set title	Cohort 2: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort 2 included participants stratified by age >=6 to <15 months and >=15 months to <24 months). The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent	
Subject analysis set title	Cohort 2: Vosoritide
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort 2 included participants stratified by age >=6 to <15 months and >=15 months to <24 months). Vosoritide 15 µg/kg/day & 30 µg/kg/day The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent	
Subject analysis set title	Cohort 3: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort 3 included participants stratified by age 0 to < 6 months. The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent	
Subject analysis set title	Cohort 3: Vosoritide
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort 3 included participants stratified by age 0 to < 6 months. Vosoritide 30 µg/kg/day	

The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent

Subject analysis set title	All Vosoritide
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent.

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

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

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. A severity grade was defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. As per CTCAE, Grade 1 scales as Mild; Grade 2 scales as Moderate; Grade 3 scales as severe or medically significant but not immediately life threatening; Grade 4 scales as life-threatening consequences; and Grade 5 scales as death related to AE. Safety Population includes all sentinel and randomized participants in the FAS who received at least one dose of vosoritide or placebo in this study.

Serious adverse event (SAE)

End point type	Primary

End point timeframe:

Up to Week 56 (Safety Follow-Up +/-7d)

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: Only descriptive data was analyzed for this endpoint.

End point values	Sentinel	Randomized Vosoritide	Randomized Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	32	32	
Units: Numbers				
Participants with any AE	11	32	32	
Participants with any SAE	0	3	6	
Participants with any treatment-related AE	8	29	17	
Participants with any treatment-related SAEs	0	0	0	
Participants with any AE of CTCAE grade >=3	0	2	3	
Participants who died	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in height Z-score at Week 52

End point title	Change from baseline in height Z-score at Week 52[2]

End point description:

Standing Height/body length was 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).

The primary efficacy analysis population was the subset of randomized participants in the FAS. The Full Analysis Set (FAS) was defined according to the intent-to-treat principle and included all enrolled sentinel and randomized participants with a signed informed consent.

FAS Randomized population includes randomized vosoritide (32 participants) and randomized placebo (32 participants).
FAS analysis population includes All vosoritide (43 participants) and Placebo (32 participants).

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis for FAS (All Vosoritide and Placebo) includes Sentinel participants.

End point values	Randomized Vosoritide	Randomized Placebo	All Vosoritide	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	32	32	43	32
Units: Z-score				
least squares mean (confidence interval 95%)	-0.06 (-0.26 to 0.15)	-0.31 (-0.48 to -0.13)	0.01 (-0.15 to 0.17)	-0.30 (-0.47 to -0.13)

Statistical analyses

Statistical analysis title	Height Z-Score-Placebo Vs Vosoritide(FAS Random)

Statistical analysis description:

Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.
Participants aged < 24 months, body length takes precedence over standing height. Participants aged < 24 months at baseline and >= 24 months at Week 52, body length takes precedence.

Difference in LS means were obtained from an analysis of covariance model.

Comparison groups	Randomized Vosoritide v Randomized Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Mean difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.53

Notes:

[3] - Covariance model

Statistical analysis title	Height Z-Score - Placebo Vs Vosoritide (FAS)

Statistical analysis description:

Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

Participants aged < 24 months, body length takes precedence over standing height. Participants aged < 24 months at baseline and >= 24 months at Week 52, body length takes precedence.

Difference in LS means were obtained from an analysis of covariance model.

Comparison groups	All Vosoritide v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.54

Notes:

[4] - Covariance model

Secondary: Change from baseline in height at Week 52

End point title	Change from baseline in height at Week 52[5]

End point description:

FAS Randomized population includes randomized vosoritide (32 participants) and randomized placebo (32 participants).

FAS analysis population includes All vosoritide (43 participants) and Placebo (32 participants).

End point type	Secondary

End point timeframe:

Baseline to 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: Statistical analysis for FAS (All Vosoritide and Placebo) includes Sentinel participants.

End point values	Randomized Vosoritide	Randomized Placebo	All Vosoritide	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	32	32	43	32
Units: cm				
least squares mean (confidence interval 95%)	8.15 (7.55 to 8.75)	7.38 (6.87 to 7.89)	8.41 (7.93 to 8.89)	7.45 (6.95 to 7.95)

Statistical analyses

Statistical analysis title	Height-Placebo Vs Vosoritide(FAS Randomized)

Statistical analysis description:

Difference in LS means were obtained from an analysis of covariance model.

Comparison groups	Randomized Vosoritide v Randomized Placebo

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Mean difference (final values)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	1.56

Notes:

[6] - Covariance model.

Statistical analysis title	Height - Placebo Vs Vosoritide (FAS)

Statistical analysis description:

Difference in LS means were obtained from an analysis of covariance model.

Comparison groups	All Vosoritide v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Mean difference (final values)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.66

Notes:

[7] - Covariance model.

Secondary: Change from baseline in annualized growth velocity (AGV) at Week 52

End point title	Change from baseline in annualized growth velocity (AGV) at Week 52[8]

End point description:

AGV was derived over 12-month intervals starting from the baseline visit. Annualized growth velocity (AGV) = Standing Height at Date 2 - Standing Height at Date 1/Interval Lenght (Days) x 365.25.

FAS Randomized population includes randomized vosoritide (32 participants) and randomized placebo (32 participants).

FAS analysis population includes All vosoritide (43 participants) and Placebo (32 participants).

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[8] - 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 analysis for FAS (All Vosoritide and Placebo) includes Sentinel participants.

End point values	Randomized Vosoritide	Randomized Placebo	All Vosoritide	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	32	32	43	32
Units: cm/year				
least squares mean (confidence interval 95%)	-2.17 (-2.76 to -1.58)	-2.95 (-3.45 to -2.45)	-2.41 (-2.88 to -1.94)	-3.32 (-3.81 to -2.84)

Statistical analyses

Statistical analysis title	AGV - Placebo Vs Vosoritide(FAS Randomized)
Statistical analysis description:	
Difference in LS means were obtained from an analysis of covariance model.	
Comparison groups	Randomized Vosoritide v Randomized Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Mean difference (final values)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	1.54

Notes:

[9] - Covariance model.

Statistical analysis title	AGV - Placebo Vs Vosoritide (FAS)
Statistical analysis description:	
Difference in LS means were obtained from an analysis of covariance model.	
Comparison groups	All Vosoritide v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.59

Secondary: Change from baseline in upper to lower body segment ratio at Week 52

End point title	Change from baseline in upper to lower body segment ratio at Week 52[10]

End point description:

Upper to Lower Body ratio=Sitting Height / (Standing Height – Sitting Height). The ratio of derived

sitting height and derived standing height was also calculated.

FAS Randomized population includes randomized vosoritide (32 participants) and randomized placebo (32 participants).

FAS analysis population includes All vosoritide (43 participants) and Placebo (32 participants).

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

Notes:

[10] - 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 analysis for FAS (All Vosoritide and Placebo) includes Sentinel participants.

End point values	Randomized Vosoritide	Randomized Placebo	All Vosoritide	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	32	32	43	32
Units: Ratio				
least squares mean (confidence interval 95%)	-0.20 (-0.28 to -0.13)	-0.13 (-0.21 to -0.06)	-0.19 (-0.25 to -0.13)	-0.13 (-0.20 to -0.06)

Statistical analyses

Statistical analysis title	Upper-Lower Body Placebo Vs Vosoritide (FAS Rand)

Statistical analysis description:

Upper to lower body segment ratio.

Difference in LS means were obtained from an analysis of covariance model.

Comparison groups	Randomized Vosoritide v Randomized Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.04

Notes:

[11] - Covariance model.

Statistical analysis title	Upper-Lower Body Ratio Placebo Vs Vosoritide (FAS)

Statistical analysis description:

Upper to lower body segment ratio.

Difference in LS means were obtained from an analysis of covariance model.

Comparison groups	All Vosoritide v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.03

Notes:

[12] - Covariance model.

Secondary: Change from baseline in other growth measures (upper body length, head circumference, arm span, upper arm length, lower arm length, Lower Body Length, upper leg length, knee to heel length, and tibial length) at Week 52

End point title	Change from baseline in other growth measures (upper body length, head circumference, arm span, upper arm length, lower arm length, Lower Body Length, upper leg length, knee to heel length, and tibial length) at Week 52

End point description:

Change from baseline in other growth measures (upper body length, head circumference, arm span, upper arm length, lower arm (Forearm) length, Lower Body Length, Upper Leg Length (Thigh), knee to heel length, and tibial length) at Week 52.

The number of participants analyzed is reported in sequence: (n=Cohort 1 Placebo, Cohort 1 Vosoritide, Cohort 2 Placebo, Cohort 2 Vosoritide, Cohort 3 Placebo, Cohort 3 Vosoritide) vosoritide including sentinel and randomized participants for each category.

Upper body length: (n=16, 19, 7, 12, 8, 11)
Head Circumference: (n=16, 19, 7, 11, 8, 11)
Arm Span: (n=16, 19, 7, 10, 8, 10)
Upper Arm Length: (n=16, 19, 7, 11, 8, 11)
Lower Arm (Forearm) Length : (n=16, 19, 7, 10, 8, 11)
Lower Body Length: (n=16, 19, 7, 12, 8, 11)
Upper Leg Length (Thigh): (n=16, 19, 7, 10, 8, 11)
Knee to Heel Length: (n=16, 19, 7, 11, 8, 11)
Tibial Length: (n=16, 19, 7, 11, 8, 11)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	8	12
Units: cm				
arithmetic mean (standard deviation)				
Upper body length	3.04 (± 1.52)	3.54 (± 1.81)	5.45 (± 1.75)	5.20 (± 1.50)
Head Circumference	0.68 (± 0.66)	0.74 (± 0.49)	2.29 (± 1.28)	3.10 (± 1.45)
Arm Span	4.86 (± 1.99)	5.82 (± 3.65)	7.13 (± 1.59)	7.22 (± 1.45)
Upper Arm Length	1.02 (± 1.13)	0.77 (± 0.96)	1.08 (± 0.93)	1.44 (± 1.26)
Lower Arm (Forearm) Length	0.49 (± 0.96)	0.79 (± 0.90)	1.78 (± 0.44)	1.57 (± 0.98)
Lower Body Length	2.41 (± 1.31)	2.89 (± 1.99)	2.39 (± 1.27)	3.79 (± 1.56)

Upper Leg Length (Thigh)	0.82 (± 1.75)	1.55 (± 1.46)	0.38 (± 1.71)	1.10 (± 1.42)
Knee to Heel Length	1.52 (± 0.76)	2.21 (± 0.67)	2.70 (± 0.75)	2.29 (± 1.91)
Tibial Length	0.85 (± 0.69)	1.16 (± 1.35)	1.97 (± 1.49)	1.99 (± 0.80)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	12		
Units: cm				
arithmetic mean (standard deviation)				
Upper body length	6.58 (± 0.99)	6.75 (± 0.86)		
Head Circumference	5.35 (± 0.71)	6.29 (± 0.81)		
Arm Span	8.22 (± 1.93)	8.99 (± 4.77)		
Upper Arm Length	1.95 (± 1.23)	1.44 (± 1.33)		
Lower Arm (Forearm) Length	1.66 (± 0.82)	1.49 (± 0.79)		
Lower Body Length	3.86 (± 1.55)	4.41 (± 1.53)		
Upper Leg Length (Thigh)	1.98 (± 2.21)	1.93 (± 1.65)		
Knee to Heel Length	2.93 (± 0.68)	3.12 (± 0.85)		
Tibial Length	1.83 (± 0.88)	1.39 (± 0.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in other body proportion ratios (arm span to height ratio, upper arm length to lower arm [forearm] length ratio, upper leg length [thigh] to knee to heel length ratio, and upper leg length (thigh) to tibial length ratio) at Week 52

End point title	Change from baseline in other body proportion ratios (arm span to height ratio, upper arm length to lower arm [forearm] length ratio, upper leg length [thigh] to knee to heel length ratio, and upper leg length (thigh) to tibial length ratio) at Week 52

End point description:

The number of participant analyzed is reported in sequence: (n=Cohort 1 Placebo, Cohort 1 Vosoritide, Cohort 2 Placebo, Cohort 2 Vosoritide, Cohort 3 Placebo, Cohort 3 Vosoritide) vosoritide including sentinel and randomized participants for each category.

Upper Arm Length to Lower Arm (Forearm) Length Ratio: (n=16, 19, 7, 10, 8, 11)
Upper Leg Length(Thigh)-Knee to Heel Length Ratio: (n=16, 19, 7, 10, 8, 11)
Upper Leg Length (Thigh) to Tibial Length Ratio: (n=16, 19, 7, 10, 8, 11)
Arm Span to Standing Height Ratio: (n=16,19, 7, 10, 8, 10)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	7	10
Units: Ratio				
arithmetic mean (standard deviation)				
Upper Arm Length to Lower Arm(Forearm)Length Ratio	0.05 (± 0.15)	0.00 (± 0.12)	-0.09 (± 0.06)	0.01 (± 0.10)
Upper Leg Length(Thigh)-Knee to Heel Length Ratio	-0.01 (± 0.08)	0.01 (± 0.07)	-0.09 (± 0.10)	-0.03 (± 0.08)
Upper Leg Length (Thigh) to Tibial Length Ratio	0.00 (± 0.12)	0.02 (± 0.17)	-0.16 (± 0.24)	-0.10 (± 0.07)
Arm Span to Standing Height Ratio	0.00 (± 0.02)	0.00 (± 0.06)	0.00 (± 0.02)	-0.01 (± 0.02)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	12		
Units: Ratio				
arithmetic mean (standard deviation)				
Upper Arm Length to Lower Arm(Forearm)Length Ratio	0.02 (± 0.11)	-0.01 (± 0.12)		
Upper Leg Length(Thigh)-Knee to Heel Length Ratio	0.01 (± 0.16)	-0.02 (± 0.11)		
Upper Leg Length (Thigh) to Tibial Length Ratio	0.00 (± 0.29)	0.04 (± 0.22)		
Arm Span to Standing Height Ratio	-0.01 (± 0.04)	-0.02 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body mass index (BMI) at Week 52

End point title	Change from baseline in body mass index (BMI) at Week 52

End point description:

Body Mass Index (BMI): For height used for BMI calculation, participants aged < 24 months, body length takes precedence over standing height. Participants aged < 24 months at baseline and >= 24 months at Week 52, body length takes precedence.
There were no meaningful differences in BMI between treatment groups from baseline to Week 52 (change of <1 BMI score at Week 52 across all cohorts).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	8	12
Units: kg/m^2				
arithmetic mean (standard deviation)	0.20 (± 1.34)	-0.45 (± 0.94)	0.55 (± 1.17)	0.08 (± 0.75)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	12		
Units: kg/m^2				
arithmetic mean (standard deviation)	0.74 (± 1.70)	0.94 (± 1.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in BMI Z-score at Week 52

End point title	Change from baseline in BMI Z-score at Week 52

End point description:

BMI Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention. BMI Z-scores are derived only for participants aged 24 months or older, the change from baseline to Week 52 in BMI Z-score is summarized for Cohort 1 only as no participants in Cohort 2 or Cohort 3 were 24 months at baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	19		
Units: Z-Score				
arithmetic mean (standard deviation)	-0.12 (± 0.48)	-0.18 (± 0.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in weight Z-score at Week 52

End point title	Change from baseline in weight Z-score at Week 52

End point description:

Z-Scores were derived using age-sex specific reference data (means and SDs) for average stature children per the Centers for Disease Control and Prevention.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	7	12
Units: Z-score				
arithmetic mean (standard deviation)	0.14 (± 0.44)	0.14 (± 0.42)	0.74 (± 0.82)	0.70 (± 0.64)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.81 (± 0.49)	-0.66 (± 0.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Infant Toddler Quality of Life (ITQoL) scores at Week 52

End point title	Change from baseline in Infant Toddler Quality of Life (ITQoL) scores at Week 52

End point description:

# of participants analyzed reported in sequence:(n=C1 Placebo,C1 Vosoritide,C2 Placebo,C2 Vosoritide,C3 Placebo,C3 Vosoritide)incl sentinel for each category.

Overall Health Score:(n=12, 15, 5,10, 6, 10)
Physical Abilities Score:(n=14, 17, 7, 12, 7, 6)
Growth and Development Scores:(n=14, 17, 7, 12, 8, 10)
Pain Score:(n=14, 17, 7,12, 8, 10)
Temperament and mood Score:(n=14, 17, 7,12, 8, 10)
Behavior score:(n=13, 17, 5, 8, 0, 1) Ref PDF
Global behavior score:(n=13, 17, 5, 9, 0, 1) Ref PDF
Getting on with others score:(n=12, 17, 5, 8, 0,0) Ref PDF
Global health perceptions score:(n=13, 17, 7, 12, 8, 9)
Change in health score:(n=13, 16, 5, 6, 0, 1) Ref PDF
Parental impact emotional score:(n=14, 17, 7, 12, 8, 10)
Parental Impact Time Score:(n=14, 17, 7, 12, 8, 10)
Family Cohesion Score:(n=14, 16, 7, 12, 8, 10)

97(ITQOL) item full-length version was used. For each concept, item responses are scored, summed, & transformed on a scale from 0(worst health) to 100(best health)

End point type	Secondary

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	8	12
Units: Score on a scale				
arithmetic mean (standard deviation)				
Overall Health Score	3.75 (± 17.60)	4.33 (± 15.10)	-5.00 (± 15.41)	-3.50 (± 14.15)
Physical Abilities Score	-6.01 (± 9.83)	8.82 (± 23.06)	3.36 (± 8.62)	1.30 (± 16.05)
Growth and Development Scores	4.82 (± 11.62)	4.34 (± 9.40)	-0.71 (± 8.75)	1.46 (± 26.01)
Pain Score	-1.19 (± 20.37)	-1.47 (± 18.22)	-1.19 (± 18.90)	-7.64 (± 27.63)
Temperament and mood Score	4.79 (± 9.60)	0.54 (± 5.40)	0.66 (± 7.18)	-0.49 (± 9.78)
Global health perceptions score	-1.07 (± 15.43)	2.24 (± 12.37)	-2.73 (± 11.29)	-4.55 (± 12.18)
Parental impact emotional score	2.04 (± 23.13)	-0.84 (± 8.89)	0.51 (± 14.64)	-6.85 (± 11.94)
Parental Impact Time Score	9.52 (± 29.06)	4.76 (± 10.78)	-8.05 (± 19.70)	-2.38 (± 35.61)
Family Cohesion Score	1.79 (± 13.53)	-1.25 (± 10.72)	0.00 (± 15.00)	-7.08 (± 28.08)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	12		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Overall Health Score	-5.00 (± 7.75)	0.50 (± 13.01)		
Physical Abilities Score	2.35 (± 29.29)	-15.91 (± 22.74)		
Growth and Development Scores	3.57 (± 6.35)	-3.50 (± 13.19)		
Pain Score	-4.69 (± 27.77)	2.50 (± 22.58)		
Temperament and mood Score	-2.43 (± 6.76)	4.62 (± 10.48)		
Global health perceptions score	-2.84 (± 13.62)	0.50 (± 17.11)		
Parental impact emotional score	9.82 (± 20.89)	-2.50 (± 19.05)		
Parental Impact Time Score	-10.7 (± 17.59)	2.38 (± 14.93)		
Family Cohesion Score	-3.13 (± 8.84)	-4.50 (± 15.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in functional independence measure for children (WeeFIM-II) Score at Week 52

End point title	Change from Baseline in functional independence measure for children (WeeFIM-II) Score at Week 52

End point description:

The Pediatric Functional Independence Measure-II (WeeFIM®-II) is designed to measure the functional independence of children between the ages of 6 months and 18 years who have physical or general developmental limitations (Msall 1994b). The WeeFIM-II is comprised of 3 domains that are rated by clinicians based on information obtained from parents/caregivers (self-care [score range 8 to 56], mobility [score range 8 to 35], and cognition [score range 8 to 35]) and provides a total score between 18 (worst) and 126 (Best).
The Wee-FIM-II is only validated in children ages 6 months to 18 years. Therefore results for Cohort 3 is not summarized.

The number of participants analyzed is reported in sequence: (n=Cohort 1 Placebo, Cohort 1 Vosoritide, Cohort 2 Placebo, Cohort 2 Vosoritide) incl sentinel for each category.
WeeFIM-II Total Score: (n=14, 19, 6,11)
WeeFIM : Self-Care Score: (n=14, 19, 6, 11)
WeeFIM: Mobility Score: (n=14, 19, 6, 11)
WeeFIM: Cognitive Score: (n=14, 19, 6, 11)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	8	12
Units: Score on a scale				
arithmetic mean (standard deviation)				
WeeFIM-II Total Score	11.2 (± 11.1)	14.7 (± 17.3)	16.2 (± 14.6)	16.5 (± 28.1)
WeeFIM : Self-Care Score	6.4 (± 6.0)	6.6 (± 7.2)	3.7 (± 2.3)	5.6 (± 14.1)
WeeFIM: Mobility Score	2.2 (± 3.4)	4.5 (± 5.6)	7.0 (± 7.5)	6.7 (± 9.4)
WeeFIM: Cognitive Score	2.6 (± 4.0)	3.6 (± 6.0)	5.5 (± 7.6)	4.2 (± 8.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) scores at Week 52

End point title	Change from baseline in Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) scores at Week 52

End point description:

The number of participants analyzed is reported in sequence: (n=Cohort 1 Placebo, Cohort 1 Vosoritide, Cohort 2 Placebo, Cohort 2 Vosoritide, Cohort 3 Placebo, Cohort 3 Vosoritide) for each category.
Motor Composite Score: (n=2, 4, 4, 9, 5,8)
Cognitive scaled score: (n=2, 4, 3, 8, 6,9)
Cognitive composite score: (n=2, 4, 3, 8, 6, 9)

Receptive communication language scaled score: (n=2, 4, 3, 9, 5,9)
Expressive communication language scaled score: (n=2, 4, 4, 8, 5, 8)
Language sum of scaled score: (n=2, 4, 4, 9, 6,9)
Language composite score: (n=2, 4, 4, 9, 5, 9)
Fine motor scaled score: (n=2, 4, 4, 9, 5, 8)
Gross motor scaled score: (n=2, 4, 4, 9, 5, 9)
BSID-III is performance-based clinician-reported outcome assessment for use in children from 1 to 42 months (1 month to 3.5 years). individually administered by the trained clinician to the participant/child. Each (sub)scale yields a total raw score, standardized according to the participant's chronological age (scaled scores)

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	8	12
Units: Score on a scale				
arithmetic mean (standard deviation)				
Motor Composite Score	-2.0 (± 5.7)	4.8 (± 11.5)	12.0 (± 17.5)	-2.3 (± 12.3)
Cognitive scaled score	-1.0 (± 2.8)	-0.5 (± 1.7)	3.3 (± 4.9)	0.6 (± 3.2)
Cognitive composite score	-5.0 (± 14.1)	-2.5 (± 8.7)	16.7 (± 24.7)	3.1 (± 16.0)
Receptive communication language scaled score	-1.0 (± 0.0)	-1.8 (± 2.5)	3.3 (± 4.0)	1.0 (± 1.2)
Expressive communication language scaled score	2.5 (± 0.7)	0.3 (± 1.3)	2.8 (± 2.9)	-0.1 (± 2.2)
Language sum of scaled score	1.5 (± 0.7)	-1.5 (± 3.3)	6.0 (± 5.2)	1.8 (± 4.0)
Language composite score	4.5 (± 2.1)	-4.5 (± 9.9)	17.8 (± 15.2)	5.3 (± 12.1)
Fine motor scaled score	-0.5 (± 3.5)	0.0 (± 2.9)	1.5 (± 3.3)	-2.1 (± 2.5)
Gross motor scaled score	0.0 (± 5.7)	1.0 (± 0.8)	2.8 (± 3.2)	1.3 (± 2.8)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	12		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Motor Composite Score	5.4 (± 22.2)	11.1 (± 18.1)		
Cognitive scaled score	1.5 (± 1.9)	2.1 (± 4.4)		
Cognitive composite score	7.5 (± 9.4)	10.6 (± 22.1)		
Receptive communication language scaled score	-3.0 (± 2.1)	0.7 (± 5.2)		
Expressive communication language scaled score	-1.8 (± 1.6)	-0.1 (± 3.3)		
Language sum of scaled score	-7.3 (± 6.4)	-0.3 (± 6.6)		
Language composite score	-13.4 (± 5.8)	-0.9 (± 19.5)		
Fine motor scaled score	2.2 (± 4.8)	2.6 (± 2.7)		
Gross motor scaled score	-0.2 (± 3.1)	0.1 (± 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Child Behaviour Checklist (CBCL) at Week 52

End point title	Change from Baseline in Child Behaviour Checklist (CBCL) at Week 52

End point description:

The number of participants analyzed is reported in sequence: (n=Cohort 1 Placebo, Cohort 1 Vosoritide, Cohort 2 Placebo, Cohort 2 Vosoritide) vosoritide including sentinel and randomized participants for each category.
Emotionally Reactive Total: (n=15, 18, 4, 5)
Anxious/Depressed Total: (n=15, 18, 4, 5)
Withdrawn Total: (n=15, 18, 4, 5)
Somatic Complaints Total: (n=15, 18, 4, 5)
Sleep Problems Total: (n=15, 18, 4, 5)
Attention Problems Total: (n=15, 18, 4, 5)
Aggressive Behavior Total: (n=15, 18, 4, 5)
Total Problems Total: (n=15, 18, 4, 5)
The CBCL 1.5-5 years old consists of 100 questions, scored on a three-point Likert scale (0=Not True (as far as you know), 1= Somewhat or Sometimes True, 2=Very True or Often True). The time frame for item responses was the past 2 months. Raw scores, t-scores, and percentiles are calculated for all subscales and syndromes, with higher scores indicating higher problems.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	19	8	12
Units: Score on a scale				
arithmetic mean (standard deviation)				
CBCL Pre-School : Emotionally Reactive Total	-0.2 (± 1.5)	0.1 (± 1.4)	1.0 (± 2.0)	1.0 (± 3.9)
CBCL Pre-School : Anxious/Depressed Total	0.3 (± 1.7)	0.2 (± 1.4)	0.0 (± 2.2)	0.8 (± 3.1)
CBCL Pre-School : Withdrawn Total	-0.6 (± 1.7)	0.6 (± 1.5)	0.8 (± 2.2)	-0.2 (± 1.6)
CBCL Pre-School : Somatic Complaints Total	0.1 (± 1.7)	0.3 (± 1.0)	0.5 (± 1.0)	1.8 (± 4.1)
CBCL Pre-School : Sleep Problems Total	-0.3 (± 3.2)	0.1 (± 1.9)	-0.3 (± 1.7)	1.4 (± 4.3)
CBCL Pre-School : Attention Problems Total	-0.1 (± 1.9)	-0.1 (± 1.6)	-0.3 (± 1.0)	-0.2 (± 2.0)
CBCL Pre-School : Aggressive Behavior Total	-1.1 (± 2.4)	0.3 (± 4.1)	-0.8 (± 1.5)	-0.4 (± 2.7)
CBCL Pre-School : Total Problems Total	-3.0 (± 13.0)	2.8 (± 11.7)	-2.3 (± 6.0)	3.6 (± 23.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bilateral X-rays of lower extremities at Wee 52

End point title	Change from baseline in bilateral X-rays of lower extremities at Wee 52

End point description:

The number of participants analyzed is reported in sequence: (n= All Vosoritide, Placebo) for each category.
Left Femur Length: (n= 17, 14)
Right Femur Length: (n= 17, 14)
Left Fibula Length: (n= 40,,27)
Right Fibula Length: (n= 39, 27)
Left Tibia Length: (n= 40, 27)
Right Tibia Length: (n= 39, 27)
Left Distance Between Ankle Joint and Distal Growth Plate of Fibula: (n= 38, 26)
Right Distance Between Ankle Joint and Distal Growth Plate of Fibula: (n= 37, 26)
Left Lower Extremity: (n= 18, 14)
Right Lower Extremity: (n= 18, 14)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: cm				
arithmetic mean (standard deviation)				
Left Femur Length	2.29 (± 0.58)	2.01 (± 0.62)		
Right Femur Length	2.35 (± 0.49)	2.20 (± 0.73)		
Left Fibula Length	2.00 (± 0.61)	1.97 (± 0.69)		
Right Fibula Length	2.00 (± 0.64)	1.89 (± 0.75)		
Left Tibia Length	1.92 (± 0.55)	1.69 (± 0.70)		
Right Tibia Length	1.96 (± 0.57)	1.68 (± 0.77)		
Lt Dis btw Ankle Joint&Distal Growth Plate Fibula	-0.02 (± 0.23)	0.07 (± 0.23)		
Rt Dis btw Ankle Joint&Distal Growth Plate Fibula	-0.05 (± 0.23)	0.05 (± 0.22)		
Left Lower Extremity	6.02 (± 6.67)	3.87 (± 1.56)		
Right Lower Extremity	6.08 (± 6.54)	4.26 (± 1.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bilateral X-rays of Left/Right Tibia bowing angle at Week 52

End point title	Change from baseline in bilateral X-rays of Left/Right Tibia bowing angle at Week 52

End point description:

The number of participants analyzed is reported in sequence: (n=All vosoritide , Placebo) for each category.
Left Tibia Bowing Angle : (n= 39, 27)
Right Tibia Bowing Angle : (n=38, 27)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Degrees				
arithmetic mean (standard deviation)				
Left Tibia Bowing Angle	-0.97 (± 5.88)	1.07 (± 5.38)		
Right Tibia Bowing Angle	-2.34 (± 5.37)	-0.93 (± 5.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bilateral X-rays of Left Femur Length (cm) to Tibia Length (cm) Ratio and Right Femur Length (cm) to Tibia Length (cm) Ratio & Right Femur Length (cm) to Tibia Length (cm) Ratio at Week 52

End point title	Change from baseline in bilateral X-rays of Left Femur Length (cm) to Tibia Length (cm) Ratio and Right Femur Length (cm) to Tibia Length (cm) Ratio & Right Femur Length (cm) to Tibia Length (cm) Ratio at Week 52

End point description:

The number of participants analyzed is reported in sequence: (n= All Vosoritide, Placebo)
Left Femur Length (cm) to Tibia Length (cm) Ratio : (n= 17, 14)
Right Femur Length (cm) to Tibia Length (cm) Ratio: (n= 17, 14)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Ratio				
arithmetic mean (standard deviation)				
Left Femur Length (cm) to Tibia Length (cm) Ratio	-0.03 (± 0.06)	-0.05 (± 0.05)		
Right Femur Length (cm) to Tibia Length (cm) Ratio	-0.05 (± 0.06)	-0.02 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bilateral X-rays of Left Tibia Length (cm) to Fibula Length (cm) Ratio & Right Tibia Length (cm) to Fibula Length (cm) Ratio at Week 52

End point title	Change from baseline in bilateral X-rays of Left Tibia Length (cm) to Fibula Length (cm) Ratio & Right Tibia Length (cm) to Fibula Length (cm) Ratio at Week 52

End point description:

The number of participants analyzed is reported in sequence: (n= All vosoritide, Placebo)
Left Tibia Length (cm) to Fibula Length (cm) Ratio: (n=40, 27)
Right Tibia Length (cm) to Fibula Length (cm) Ratio: (n=39, 27)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Ratio				
arithmetic mean (standard deviation)				
Left Tibia Length (cm) to Fibula Length (cm) Ratio	-0.02 (± 0.04)	-0.04 (± 0.04)		
Right Tibia Length (cm) to Fibula Length(cm) Ratio	-0.02 (± 0.05)	-0.03 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in X-ray of Lumbar spine vertebral ratios at Week 52

End point title	Change from baseline in X-ray of Lumbar spine vertebral ratios at Week 52

End point description:

The number of participants analyzed is reported in sequence: (n= All Vosoritide, Placebo) for each category.
Anterior Height to Medial Height Ratio (L1): (n= 30, 23)
Anterior Height to Medial Height Ratio (L2): (n= 23, 13)
Anterior Height to Medial Height Ratio (L3): (n= 19, 11)
Anterior Height to Medial Height Ratio (L4): (n=26, 15)
Anterior Height to Medial Height Ratio (L5): (n=27, 12)
Anterior Height to Posterior Height Ratio (L1): (n= 40, 27)
Anterior Height to Posterior Height Ratio (L2): (n= 40, 27)
Anterior Height to Posterior Height Ratio (L3): (n= 40, 27)
Anterior Height to Posterior Height Ratio (L4): (n= 40, 27)
Anterior Height to Posterior Height Ratio (L5): (n= 40, 27)
Medial Height to Posterior Height Ratio (L1): (n= 30, 23)
Medial Height to Posterior Height Ratio (L2): (n= 23, 13)
Medial Height to Posterior Height Ratio (L3): (n= 19, 11)
Medial Height to Posterior Height Ratio (L4): (n= 26, 15)
Medial Height to Posterior Height Ratio (L5):(n= 27,12)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Ratio				
arithmetic mean (standard deviation)				
Anterior Height to Medial Height Ratio (L1)	-0.04 (± 0.16)	-0.04 (± 0.20)		
Anterior Height to Medial Height Ratio (L2)	-0.06 (± 0.16)	-0.07 (± 0.16)		
Anterior Height to Medial Height Ratio (L3)	-0.02 (± 0.19)	0.04 (± 0.09)		
Anterior Height to Medial Height Ratio (L4)	0.02 (± 0.12)	-0.01 (± 0.11)		
Anterior Height to Medial Height Ratio (L5)	-0.02 (± 0.15)	0.04 (± 0.17)		
Anterior Height to Posterior Height Ratio (L1)	-0.03 (± 0.13)	-0.08 (± 0.17)		
Anterior Height to Posterior Height Ratio (L2)	-0.02 (± 0.13)	-0.03 (± 0.12)		
Anterior Height to Posterior Height Ratio (L3)	-0.01 (± 0.16)	0.04 (± 0.12)		
Anterior Height to Posterior Height Ratio (L4)	0.03 (± 0.11)	0.02 (± 0.13)		
Anterior Height to Posterior Height Ratio (L5)	0.01 (± 0.13)	0.02 (± 0.15)		
Medial Height to Posterior Height Ratio (L1)	-0.01 (± 0.15)	-0.04 (± 0.12)		
Medial Height to Posterior Height Ratio (L2)	0.05 (± 0.11)	0.03 (± 0.09)		
Medial Height to Posterior Height Ratio (L3)	-0.02 (± 0.10)	-0.02 (± 0.10)		
Medial Height to Posterior Height Ratio (L4)	-0.03 (± 0.13)	0.04 (± 0.10)		
Medial Height to Posterior Height Ratio (L5)	0.02 (± 0.16)	-0.04 (± 0.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in X-ray of Lumbar Spine Transverse Diameter at Week 52

End point title	Change from baseline in X-ray of Lumbar Spine Transverse Diameter at Week 52
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	27		
Units: cm				
arithmetic mean (standard deviation)				
Transverse Diameter (L1)	0.12 (± 0.17)	0.12 (± 0.11)		
Transverse Diameter (L2)	0.12 (± 0.16)	0.09 (± 0.13)		
Transverse Diameter (L3)	0.08 (± 0.15)	0.09 (± 0.12)		
Transverse Diameter (L4)	0.09 (± 0.13)	0.06 (± 0.11)		
Transverse Diameter (L5)	0.10 (± 0.13)	0.05 (± 0.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in X-ray of Lumbar Spine Sagittal Width and Week 52

End point title	Change from baseline in X-ray of Lumbar Spine Sagittal Width and Week 52
End point description:	

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
Sagittal Width (L1): (n=34, 26)
Sagittal Width (L2): (n=34, 26)
Sagittal Width (L3): (n=34, 26)
Sagittal Width (L4): (n=34, 26)
Sagittal Width (L5): (n=31, 25)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: cm				
arithmetic mean (standard deviation)				
Sagittal Width (L1)	0.07 (± 0.26)	0.00 (± 0.22)		
Sagittal Width (L2)	0.05 (± 0.18)	0.01 (± 0.18)		
Sagittal Width (L3)	0.08 (± 0.20)	0.04 (± 0.19)		
Sagittal Width (L4)	0.16 (± 0.24)	0.03 (± 0.16)		
Sagittal Width (L5)	0.13 (± 0.34)	0.06 (± 0.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in X-ray of Lumbar Spine Angles at Week 52

End point title	Change from baseline in X-ray of Lumbar Spine Angles at Week 52
End point description:	

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo)
Sacral Tilt: (n= 40, 27)
Lordosis Angle: (n= 40, 27)
Kyphosis Angle: (n= 39, 27)

End point type	Secondary
End point timeframe:	

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Degree				
arithmetic mean (standard deviation)				
Sacral Tilt	10.6 (± 13.2)	5.7 (± 15.9)		
Lordosis Angle	12.5 (± 17.4)	8.4 (± 14.2)		
Kyphosis Angle	-2.2 (± 13.9)	-2.1 (± 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from Baseline in X-ray of lumbar spine angle changes: Number of participants with an increase in Lumbar Spine Angle at Week 52

End point title	Changes from Baseline in X-ray of lumbar spine angle changes: Number of participants with an increase in Lumbar Spine Angle at Week 52
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Number of participants				
Increase in sacral tilt (deg) >=5 to <10	3	6		
Increase in sacral tilt (deg) >=10	24	10		
Increase in lordosis angle (deg) >=5 to <10	5	1		
Increase in lordosis angle (deg) >=10	19	14		
Increase in kyphosis angle (deg) >=5 to <10	3	2		
Increase in kyphosis angle (deg) >=10	9	4		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI Parameter: Change from baseline to Week 52 for Volume of Face, Sinus, Calvarium, Whole Brain Total Volume, Ventricles Total Volume.

End point title	MRI Parameter: Change from baseline to Week 52 for Volume of Face, Sinus, Calvarium, Whole Brain Total Volume, Ventricles Total Volume.
End point description:	

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
Volume of Face: (n=30, 21)
Volume of Sinus: (n=35, 24)
Volume of Calvarium: (n=34, 24)
Whole Brain Total Volume: (n=34, 24)
Ventricles Total Volume: (n=34, 25)

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: cm^3				
arithmetic mean (standard deviation)				
Volume of Face	80.527 (± 59.211)	78.107 (± 33.369)		
Volume of Sinus	2.362 (± 3.578)	1.195 (± 3.769)		
Volume of Calvarium	213.075 (± 202.415)	183.427 (± 183.210)		
Whole Brain Total Volume	175.399 (± 158.088)	146.247 (± 115.274)		
Ventricles Total Volume	11.394 (± 20.416)	8.515 (± 16.325)		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI Parameter: Change from baseline to Week 52 for area of Area of Foramen Magnum & Area of Spinal Cord at the Foramen Magnum Level

End point title	MRI Parameter: Change from baseline to Week 52 for area of Area of Foramen Magnum & Area of Spinal Cord at the Foramen Magnum Level
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: cm^2				
arithmetic mean (standard deviation)				
Area of Foramen Magnum	0.002 (± 0.034)	0.006 (± 0.020)		
Area of Spinal Cord at the Foramen Magnum Level	0.001 (± 0.020)	0.007 (± 0.016)		

Statistical analyses

No statistical analyses for this end point

Secondary: MRI Parameter: Change from baseline to Week 52 for Ratio of Face Volume to Calvarium, Ratio of Area of Spinal Cord to Foramen Magnum, Ratio of Face Volume to Sinus

End point title	MRI Parameter: Change from baseline to Week 52 for Ratio of Face Volume to Calvarium, Ratio of Area of Spinal Cord to Foramen Magnum, Ratio of Face Volume to Sinus

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo)
Ratio of face volume to calvarium: (n=29, 20)
Ratio of area of spinal cord to foramen magnum: (n=35, 25)
Ratio of face volume to sinus: (n=30, 21)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Ratio				
arithmetic mean (standard deviation)				
Ratio of face volume to calvarium	0.002 (± 0.031)	0.003 (± 0.033)		
Ratio of area of spinal cord to foramen magnum	0.005 (± 0.120)	0.037 (± 0.100)		
Ratio of face volume to sinus	-6.798 (± 175.646)	14.505 (± 284.950)		

Statistical analyses

No statistical analyses for this end point

Secondary: DEXA parameter: Change from baseline to Week 52 for Whole Body Less Head bone mineral content (BMC)

End point title	DEXA parameter: Change from baseline to Week 52 for Whole Body Less Head bone mineral content (BMC)

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
GE - Lunar Prodigy: Whole Body Less Head BMC: (n=8, 12)
Hologic - Discovery Horizon Whole Body Less Head BMC: (n=18, 8)
Dual Energy X-Ray Absorptiometry (DEXA)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: gm				
arithmetic mean (standard deviation)				
GE - Lunar Prodigy: Whole Body Less Head BMC	55.87 (± 14.68)	50.26 (± 17.44)		
Hologic Discovery Horizon Whole Body Less Head BMC	44.61 (± 12.62)	47.19 (± 12.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: DEXA parameter: Change from baseline to Week 52 of Whole Body Less Head bone mineral density (BMD)

End point title	DEXA parameter: Change from baseline to Week 52 of Whole Body Less Head bone mineral density (BMD)
End point description:	
GE - Lunar Prodigy Whole Body Less Head BMD: (n=8,12) Hologic - Discovery Horizon Whole Body Less Head BMD: (18, 8)	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: g/cm^2				
arithmetic mean (standard deviation)				
GE - Lunar Prodigy Whole Body Less Head BMD	0.04 (± 0.02)	0.05 (± 0.03)		
Hologic Discovery Horizon Whole Body Less Head BMD	0.03 (± 0.01)	0.04 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: DEXA parameter: Change from baseline to Week 52 of Whole Body BMC

End point title	DEXA parameter: Change from baseline to Week 52 of Whole Body BMC

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
GE - Lunar Prodigy Whole Body BMC: (n=8, 12)
Hologic - Discovery Horizon Whole Body BMC: (n=18, 8)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: gm				
arithmetic mean (standard deviation)				
GE - Lunar Prodigy Whole Body BMC	96.85 (± 39.82)	98.99 (± 32.45)		
Hologic - Discovery Horizon Whole Body BMC	87.97 (± 32.35)	101.33 (± 33.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: DEXA parameter: Change from baseline to Week 52 of Whole Body BMD

End point title	DEXA parameter: Change from baseline to Week 52 of Whole Body BMD

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
GE - Lunar Prodigy Whole Body BMD: (n=8, 12)
 Hologic - Discovery Horizon Whole Body BMD: (n=18, 8)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: g/cm^2				
arithmetic mean (standard deviation)				
GE - Lunar Prodigy Whole Body BMD	0.06 (± 0.06)	0.07 (± 0.04)		
Hologic - Discovery Horizon Whole Body BMD	0.05 (± 0.02)	0.07 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: DEXA parameter: Change from baseline to Week 52 of Lumbar Spine BMC

End point title	DEXA parameter: Change from baseline to Week 52 of Lumbar Spine BMC

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
GE - Lunar Prodigy Lumbar Spine BMC: (n=9, 10)
Hologic - Discovery Horizon Lumbar Spine BMC: (n=27, 13)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: gm				
arithmetic mean (standard deviation)				
GE - Lunar Prodigy Lumbar Spine BMC	2.73 (± 0.83)	2.09 (± 0.97)		
Hologic - Discovery Horizon Lumbar Spine BMC	2.19 (± 0.68)	1.94 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: DEXA parameter: Change from baseline to Week 52 of Lumbar Spine BMD

End point title	DEXA parameter: Change from baseline to Week 52 of Lumbar Spine BMD

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
GE - Lunar Prodigy Lumbar Spine BMD: (n=9, 10)
Hologic - Discovery Horizon Lumbar Spine BMD: (27, 13)

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: g/cm^2				
arithmetic mean (standard deviation)				
GE - Lunar Prodigy Lumbar Spine BMD	0.07 (± 0.04)	0.05 (± 0.03)		
Hologic - Discovery Horizon Lumbar Spine BMD	0.05 (± 0.03)	0.06 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 52 in whole body BMD Z-score

End point title	Change from baseline to Week 52 in whole body BMD Z-score
End point description:	
Hologic - Discovery Horizon Whole Body BMD Z-Score	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	4		
Units: Z-score				
arithmetic mean (standard deviation)				
Hologic - Discovery Horizon Whole Body BMD Z-Score	-0.20 (± 0.35)	0.30 (± 0.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 52 in Lumbar Spine BMD Z-Score

End point title	Change from baseline to Week 52 in Lumbar Spine BMD Z-Score
End point description:	
Hologic - Discovery Horizon Lumbar Spine BMD Z-Score	
End point type	Secondary

End point timeframe:
Baseline to Week 52

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	4		
Units: Z-score				
arithmetic mean (standard deviation)	0.17 (± 0.24)	0.03 (± 0.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of participants with Incidence of Antibody Positivity at Scheduled Visits

End point title	Immunogenicity: Number of participants with Incidence of Antibody Positivity at Scheduled Visits

End point description:

Number of participants with Incidence of Antibody Positivity at Scheduled Visits for : total antibody (TAb), Neutralizing antibodies (NAb), atrial natriuretic peptide (ANP), B-type Natriuretic Peptide (BNP) & C-type natriuretic peptide (CNP).

TAb Titer Positive, NAb Titer Positive, ANP Reactivity Positive, BNP Reactivity Positive & CNP Reactivity Positive.
Day 1 is the baseline assessment result taken prior to first dose of study drug.
Ever Positive = the number of participants with at least one positive sample result.

End point type	Secondary

End point timeframe:
At Day 1, Week 3, Week 13, Week 26, Week 52, & Ever Positive.

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: Number of participants				
TAb Titer Positive: Day 1	0	0		
TAb Titer Positive: Week 3	0	0		
TAb Titer Positive: Week 13	0	0		
TAb Titer Positive: Week 26	2	0		
TAb Titer Positive: Week 52	8	0		
TAb Titer Ever Positive	8	0		
NAb Titer Positive: Day 1	0	0		
NAb Titer Positive: Week 3	0	0		
NAb Titer Positive: Week 13	0	0		
NAb Titer Positive: Week 26	0	0		
NAb Titer Positive: Week 52	0	0		

NAb Titer Ever Positive	0	0		
ANP Reactivity Positive: Day 1	3	5		
ANP Reactivity Positive: Week 3	0	0		
ANP Reactivity Positive: Week 13	1	0		
ANP Reactivity Positive: Week 26	6	0		
ANP Reactivity Positive: Week 52	11	0		
ANP Reactivity Ever Positive	12	0		
BNP Reactivity Positive: Day 1	0	3		
BNP Reactivity Positive: Week 3	0	0		
BNP Reactivity Positive: Week 13	2	0		
BNP Reactivity Positive: Week 26	3	0		
BNP Reactivity Positive: Week 52	2	0		
BNP Reactivity Ever Positive	3	0		
CNP Reactivity Positive: Day 1	0	1		
CNP Reactivity Positive: Week 3	0	0		
CNP Reactivity Positive: Week 13	1	0		
CNP Reactivity Positive: Week 26	2	0		
CNP Reactivity Positive: Week 52	4	0		
CNP Reactivity Ever Positive	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker: Bone Specific Alkaline Phosphatase (BSAP) overtime

End point title	Biomarker: Bone Specific Alkaline Phosphatase (BSAP) overtime

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
Baseline: (n= 43, 32)
Day 8: (n=42, 27)
Change from baseline to Day 8: (n=42, 27)
Week 6: (n=41, 29)
Change from baseline to Week 6: (n=41, 29)
Week 20: (n=40, 28)
Change from baseline to Week 20: (n=40, 28)
Week 39: (n=34, 24)
Change from baseline to Week 39 : (n=34, 24)

End point type	Secondary

End point timeframe:

At Baseline, Day 8, Week 6, Week 20, & Week 39.

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: U/L				
arithmetic mean (standard deviation)				
BSAP: Baseline	140.28 (± 183.23)	113.43 (± 33.56)		
BSAP: Day 8	122.32 (± 99.09)	104.12 (± 29.12)		
BSAP: Change from baseline to Day 8	-19.39 (± 202.90)	-7.67 (± 17.53)		
BSAP: Week 6	130.38 (± 140.08)	109.46 (± 29.04)		
BSAP: Change from baseline to Week 6	2.63 (± 218.60)	-6.17 (± 24.32)		
BSAP: Week 20	109.67 (± 30.88)	104.46 (± 29.69)		
BSAP: Change from baseline to Week 20	-7.21 (± 96.94)	-11.32 (± 18.19)		
BSAP: Week 39	108.49 (± 32.02)	208.13 (± 363.56)		
BSAP: Change from baseline to Week 39	-12.21 (± 105.04)	95.41 (± 352.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker: Type II Collagen C-Telopeptides Normalized for Creatinine (CTX-II)

End point title	Biomarker: Type II Collagen C-Telopeptides Normalized for Creatinine (CTX-II)
End point description:	
End point type	Secondary
End point timeframe:	

Baseline to Week 52.

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	24		
Units: ng/ mmol Cr				
arithmetic mean (standard deviation)	-9364.7 (± 65244.1)	-7607.6 (± 54614.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker: Plasma cGMP Change from Pre-Dose to Maximum Post-Dose at Week 52

End point title	Biomarker: Plasma cGMP Change from Pre-Dose to Maximum Post-Dose at Week 52
End point description:	

End point type	Secondary

End point timeframe:

Week 52 Pre-Dose to Week 52 Maximum Post-Dose.

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	21		
Units: nM				
arithmetic mean (standard deviation)	39.079 (± 25.706)	9.460 (± 26.307)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Sleep Study Indices at Week 52

End point title	Change in Sleep Study Indices at Week 52

End point description:

A sleep study was performed in a limited number of qualified sleep centers. A sleep-testing device was used to assess the presence and severity of sleep-disordered breathing by measurement of blood oxygen saturation, pulse rate, and airflow during overnight monitoring. Assessment of episodes of sleep apnea included but were not limited to the number of episodes of apnea and hypopnea per hour (Apnea/Hypopnea Index).

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Cohort 1: Placebo	Cohort 1: Vosoritide	Cohort 2: Placebo	Cohort 2: Vosoritide
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	16	5	9
Units: Number per Hour				
arithmetic mean (standard deviation)				
Apnea Hypopnea Index	-0.54 (± 2.70)	-1.45 (± 4.63)	1.06 (± 4.80)	-0.72 (± 1.41)
Apnea Index	-1.07 (± 2.12)	-0.83 (± 1.93)	0.40 (± 2.34)	-0.71 (± 1.61)
Central Apnea Index	-1.26 (± 2.66)	-0.74 (± 1.86)	-0.28 (± 0.89)	-0.71 (± 1.61)
Hypopnea Index	0.52 (± 1.35)	-0.61 (± 3.63)	0.66 (± 2.53)	-0.01 (± 1.32)

Desaturation per Hour >=3%	-0.41 (± 1.51)	-1.24 (± 3.98)	0.98 (± 3.60)	-0.69 (± 1.30)
Obstructive Index	0.19 (± 0.73)	-0.09 (± 0.45)	0.68 (± 1.52)	-0.01 (± 0.08)

End point values	Cohort 3: Placebo	Cohort 3: Vosoritide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	10		
Units: Number per Hour				
arithmetic mean (standard deviation)				
Apnea Hypopnea Index	1.89 (± 6.31)	-0.94 (± 2.78)		
Apnea Index	-1.09 (± 1.22)	-0.36 (± 2.54)		
Central Apnea Index	-1.00 (± 0.97)	0.50 (± 0.92)		
Hypopnea Index	2.97 (± 5.45)	-0.56 (± 0.54)		
Desaturation per Hour >=3%	1.71 (± 6.63)	-0.93 (± 2.60)		
Obstructive Index	-0.07 (± 0.64)	-0.86 (± 2.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) at Day1, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) at Day1, Week 13, Week 26, Week 39, & Week 52

End point description:

Vosoritide concentrations at 5-, 15- and 30-minute post-dose for one participant on Day 1 were not available, hence PK parameters for this participant were excluded from summary statistics.
PK parameters for another participant on Day 1 obtained from extrapolation. AUC0-∞ excluded from summary statistics. PK parameters are not available for this participant at Week 13 due to unsuccessful venipuncture, and Week 26 as post-dose PK samples were not collected.

The number of participants analyzed are reported in sequence (n = Day 01, Week 13, Week 26, Week 39, Week 52)

Cohort 1 15 µg/kg/day: (n=16, 15, 16, 16, 15)
Cohort 2 15 µg/kg/day: (n=1, 1, 4, 4, 3) Refer PDF
Cohort 2 30 µg/kg/day: (n=7, 6, 3, 2, 3)
Cohort 3 30 µg/kg/day: (n=8, 6, 6, 3,7)

End point type	Secondary

End point timeframe:

At Day1, Week 13, Week 26, Week 39, & Week 52.

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: min*pg/ml				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	149000 (± 98000)			
Cohort 1 15 µg/kg/day: Week 13	197000 (± 144000)			
Cohort 1 15 µg/kg/day: Week 26	306000 (± 252000)			
Cohort 1 15 µg/kg/day: Week 39	284000 (± 137000)			
Cohort 1 15 µg/kg/day: Week 52	303000 (± 208000)			
Cohort 2 15 µg/kg/day: Week 26	233000 (± 132000)			
Cohort 2 15 µg/kg/day: Week 39	204000 (± 39700)			
Cohort 2 15 µg/kg/day: Week 52	137000 (± 48900)			
Cohort 2 30 µg/kg/day: Day 01	557000 (± 278000)			
Cohort 2 30 µg/kg/day: Week 13	670000 (± 312000)			
Cohort 2 30 µg/kg/day: Week 26	429000 (± 163000)			
Cohort 2 30 µg/kg/day: Week 39	387000 (± 53800)			
Cohort 2 30 µg/kg/day: Week 52	768000 (± 391000)			
Cohort 3 30 µg/kg/day: Day 01	353000 (± 133000)			
Cohort 3 30 µg/kg/day: Week 13	382000 (± 268000)			
Cohort 3 30 µg/kg/day: Week 26	305000 (± 82100)			
Cohort 3 30 µg/kg/day: Week 39	575000 (± 455000)			
Cohort 3 30 µg/kg/day: Week 52	622000 (± 455000)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Area under the plasma concentration-time curve from time 0 to nominal 120 minutes postdose (AUC 0- 120 min) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Area under the plasma concentration-time curve from time 0 to nominal 120 minutes postdose (AUC 0- 120 min) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

The number of participants analyzed in Cohort 1 is reported in Cohort 1 Day 01, Week 13, Week 26, Week 39, Week 52) in sequence (n=18, 16, 17, 19, 16), Cohort 2 15 µg/kg/day: (n=3, 2, 5, 5, 5), Cohort 2 30 µg/kg/day: (n=7, 8, 3, 2, 3), & Cohort 3 30 µg/kg/day: (n=11, 7, 6, 4, 8)

End point type	Secondary
End point timeframe:	
At Day 01, Week 13, Week 26, Week 39, & Week 52	

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: min*pg/ml				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	134000 (± 96500)			
Cohort 1 15 µg/kg/day: Week 13	183000 (± 126000)			
Cohort 1 15 µg/kg/day: Week 26	283000 (± 222000)			
Cohort 1 15 µg/kg/day: Week 39	257000 (± 132000)			
Cohort 1 15 µg/kg/day: Week 52	260000 (± 172000)			
Cohort 2 15 µg/kg/day: Day 01	83100 (± 48300)			
Cohort 2 15 µg/kg/day: Week 13	115000 (± 59300)			
Cohort 2 15 µg/kg/day: Week 26	197000 (± 121000)			
Cohort 2 15 µg/kg/day: Week 39	166000 (± 81000)			
Cohort 2 15 µg/kg/day: Week 52	125000 (± 76700)			
Cohort 2 30 µg/kg/day: Day 01	525000 (± 251000)			
Cohort 2 30 µg/kg/day: Week 13	642000 (± 353000)			
Cohort 2 30 µg/kg/day: Week 26	408000 (± 148000)			
Cohort 2 30 µg/kg/day: Week 39	365000 (± 44700)			
Cohort 2 30 µg/kg/day: Week 52	670000 (± 335000)			
Cohort 3 30 µg/kg/day: Day 01	312000 (± 119000)			
Cohort 3 30 µg/kg/day: Week 13	342000 (± 245000)			
Cohort 3 30 µg/kg/day: Week 26	300000 (± 79100)			
Cohort 3 30 µg/kg/day: Week 39	591000 (± 359000)			
Cohort 3 30 µg/kg/day: Week 52	558000 (± 400000)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Area under the plasma concentration-time curve from time 0 to the time of last measurable concentration (AUC0-t) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Area under the plasma concentration-time curve from time 0 to the time of last measurable concentration (AUC0-t) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

The number of participants analyzed in Cohort 1 is reported in Cohort 1 Day 01, Week 13, Week 26, Week 39, Week 52) in sequence (n=18, 16, 17, 19, 16), Cohort 2 15 µg/kg/day: (n=3, 2, 5, 5, 5) Cohort 2 30 µg/kg/day: (n=7, 8, 3, 2, 3), & Cohort 3 30 µg/kg/day: (n=11, 7, 6, 4, 8)

End point type	Secondary

End point timeframe:

At Day 01, Week 13, Week 26, Week 39, & Week 52

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: min*pg/ml				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	132000 (± 97300)			
Cohort 1 15 µg/kg/day: Week 13	182000 (± 127000)			
Cohort 1 15 µg/kg/day: Week 26	282000 (± 222000)			
Cohort 1 15 µg/kg/day: Week 39	256000 (± 132000)			
Cohort 1 15 µg/kg/day: Week 52	258000 (± 169000)			
Cohort 2 15 µg/kg/day: Day 01	65900 (± 33600)			
Cohort 2 15 µg/kg/day: Week 13	112000 (± 62900)			
Cohort 2 15 µg/kg/day: Week 26	196000 (± 121000)			
Cohort 2 15 µg/kg/day: Week 39	165000 (± 82400)			
Cohort 2 15 µg/kg/day: Week 52	122000 (± 75700)			
Cohort 2 30 µg/kg/day: Day 01	547000 (± 279000)			
Cohort 2 30 µg/kg/day: Week 13	645000 (± 357000)			
Cohort 2 30 µg/kg/day: Week 26	407000 (± 148000)			
Cohort 2 30 µg/kg/day: Week 39	365000 (± 44300)			
Cohort 2 30 µg/kg/day: Week 52	672000 (± 334000)			
Cohort 3 30 µg/kg/day: Day 01	323000 (± 129000)			
Cohort 3 30 µg/kg/day: Week 13	340000 (± 244000)			

Cohort 3 30 µg/kg/day: Week 26	297000 (± 80700)			
Cohort 3 30 µg/kg/day: Week 39	567000 (± 361000)			
Cohort 3 30 µg/kg/day: Week 52	557000 (± 401000)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Maximum observed plasma concentration (Cmax) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Maximum observed plasma concentration (Cmax) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

The number of participant analyzed in Cohort 1 is reported in Cohort 1 Day 01, Week 13, Week 26, Week 39, Week 52) in sequence (n=18, 16, 17, 19, 16) Cohort 2 15 µg/kg/day: (n=3, 2, 5, 5, 5) Cohort 2 30 µg/kg/day: (n=7, 8, 3, 2, 3), & Cohort 3 30 µg/kg/day: (n=11, 7, 6, 4, 8).

End point type	Secondary

End point timeframe:

At Day 01, Week 13, Week 26, Week 39, & Week 52

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: pg/ml				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	4430 (± 3670)			
Cohort 1 15 µg/kg/day: Week 13	4350 (± 1670)			
Cohort 1 15 µg/kg/day: Week 26	5850 (± 3260)			
Cohort 1 15 µg/kg/day: Week 39	5600 (± 2200)			
Cohort 1 15 µg/kg/day: Week 52	5640 (± 2740)			
Cohort 2 15 µg/kg/day: Day 01	2840 (± 1230)			
Cohort 2 15 µg/kg/day: Week 13	5970 (± 2390)			
Cohort 2 15 µg/kg/day: Week 26	6800 (± 3360)			
Cohort 2 15 µg/kg/day: Week 39	4600 (± 2150)			
Cohort 2 15 µg/kg/day: Week 52	3870 (± 2120)			
Cohort 2 30 µg/kg/day: Day 01	14500 (± 5950)			
Cohort 2 30 µg/kg/day: Week 13	13400 (± 6070)			
Cohort 2 30 µg/kg/day: Week 26	10100 (± 2970)			
Cohort 2 30 µg/kg/day: Week 39	6980 (± 1140)			
Cohort 2 30 µg/kg/day: Week 52	12900 (± 6260)			
Cohort 3 30 µg/kg/day: Day 01	13400 (± 5710)			

Cohort 3 30 µg/kg/day: Week 13	10500 (± 6850)			
Cohort 3 30 µg/kg/day: Week 26	11500 (± 4290)			
Cohort 3 30 µg/kg/day: Week 39	18400 (± 11900)			
Cohort 3 30 µg/kg/day: Week 52	13500 (± 6770)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Time to reach maximum concentration (Tmax) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Time to reach maximum concentration (Tmax) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

The number of participants analyzed in Cohort 1 is reported in Cohort 1 Day 01, Week 13, Week 26, Week 39, Week 52) in sequence (n=18, 16, 17, 19, 16), Cohort 2 15 µg/kg/day: (n=3, 2, 5, 5, 5) Cohort 2 30 µg/kg/day: (n=7, 8, 3, 2, 3), & Cohort 3 30 µg/kg/day: (n=11, 7, 6, 4, 8).

End point type	Secondary

End point timeframe:

At Day 01, Week 13, Week 26, Week 39, & Week 52.

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: min				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	13.1 (± 6.33)			
Cohort 1 15 µg/kg/day: Week 13	14.3 (± 5.5)			
Cohort 1 15 µg/kg/day: Week 26	16.1 (± 8.69)			
Cohort 1 15 µg/kg/day: Week 39	17.4 (± 11.9)			
Cohort 1 15 µg/kg/day: Week 52	16.1 (± 6.27)			
Cohort 2 15 µg/kg/day: Day 01	11.3 (± 6.35)			
Cohort 2 15 µg/kg/day: Week 13	6 (± 1.41)			
Cohort 2 15 µg/kg/day: Week 26	10.8 (± 5.5)			
Cohort 2 15 µg/kg/day: Week 39	15.4 (± 11.6)			
Cohort 2 15 µg/kg/day: Week 52	14.2 (± 5.76)			
Cohort 2 30 µg/kg/day: Day 01	12.9 (± 9.1)			
Cohort 2 30 µg/kg/day: Week 13	14 (± 8.42)			
Cohort 2 30 µg/kg/day: Week 26	12 (± 5.2)			
Cohort 2 30 µg/kg/day: Week 39	15 (± 0)			
Cohort 2 30 µg/kg/day: Week 52	14.3 (± 1.53)			
Cohort 3 30 µg/kg/day: Day 01	7.36 (± 3.53)			
Cohort 3 30 µg/kg/day: Week 13	9.43 (± 5.22)			
Cohort 3 30 µg/kg/day: Week 26	9 (± 4.69)			

| Cohort 3 30 µg/kg/day: Week 39 | 11.3 (± 3.59) | | | |
| Cohort 3 30 µg/kg/day: Week 52 | 14.5 (± 3.51) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Apparent clearance (CL/F) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Apparent clearance (CL/F) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

Vosoritide concentrations at 5-, 15- and 30-minute post-dose for one participant on Day 1 were not available, hence PK parameters for this participant were excluded from summary statistics.
PK parameters for another participant on Day 1 obtained from extrapolation. AUC0-∞, CL/F, V/F and t1/2 excluded from summary statistics. PK parameters are not available for this participant at Week 13 due to unsuccessful venipuncture, and Week 26 as post-dose PK samples were not collected.

The number of participants analyzed are reported in sequence (n = Day 01, Week 13, Week 26, Week 39, Week 52)

Cohort 1 15 µg/kg/day: (n=16, 15, 16, 16, 15)
Cohort 2 15 µg/kg/day: (n=1, 1, 4, 4, 3) Refer PDF
Cohort 2 30 µg/kg/day: (n=7, 6, 3, 2, 3)
Cohort 3 30 µg/kg/day: (n=8, 6, 6, 3, 7)

End point type	Secondary

End point timeframe:

At Day 01, Week 13, Week 26, Week 39, & Week 52.

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: ml/min/kg				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	134 (± 59.8)			
Cohort 1 15 µg/kg/day: Week 13	111 (± 58.5)			
Cohort 1 15 µg/kg/day: Week 26	79.8 (± 48.3)			
Cohort 1 15 µg/kg/day: Week 39	65.3 (± 32.7)			
Cohort 1 15 µg/kg/day: Week 52	69 (± 41.2)			
Cohort 2 15 µg/kg/day: Week 26	79.5 (± 38.4)			
Cohort 2 15 µg/kg/day: Week 39	75.5 (± 14.8)			
Cohort 2 15 µg/kg/day: Week 52	122 (± 52.5)			
Cohort 2 30 µg/kg/day: Day 01	65.9 (± 31.6)			
Cohort 2 30 µg/kg/day: Week 13	58.7 (± 40.4)			
Cohort 2 30 µg/kg/day: Week 26	79.4 (± 37.7)			
Cohort 2 30 µg/kg/day: Week 39	78.3 (± 10.9)			
Cohort 2 30 µg/kg/day: Week 52	49.7 (± 32)			
Cohort 3 30 µg/kg/day: Day 01	95.9 (± 34)			
Cohort 3 30 µg/kg/day: Week 13	115 (± 78.1)			

Cohort 3 30 µg/kg/day: Week 26	104 (± 23.2)			
Cohort 3 30 µg/kg/day: Week 39	73.6 (± 41.6)			
Cohort 3 30 µg/kg/day: Week 52	76.5 (± 49.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Apparent volume of distribution (Vz/F) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Apparent volume of distribution (Vz/F) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

Vosoritide concentrations at 5-, 15- and 30-minute post-dose for one participant on Day 1 were not available, hence PK parameters for this participant were excluded from summary statistics.
PK parameters for another participant on Day 1 obtained from extrapolation. V/F excluded from summary statistics. PK parameters are not available for this participant at Week 13 due to unsuccessful venipuncture, and Week 26 as post-dose PK samples were not collected.

The number of participants analyzed are reported in sequence (n = Day 01, Week 13, Week 26, Week 39, Week 52)

Cohort 1 15 µg/kg/day: (n=16, 15, 16, 16, 15)
Cohort 2 15 µg/kg/day: (n=1, 1, 4, 4, 3) Refer PDF
Cohort 2 30 µg/kg/day: (n=7, 6, 3, 2, 3)
Cohort 3 30 µg/kg/day: (n=8, 6, 6, 3, 7)

End point type	Secondary

End point timeframe:

At Day 01, Week 13, Week 26, Week 39, & Week 52.

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: ml/kg				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	4070 (± 2310)			
Cohort 1 15 µg/kg/day: Week 13	3990 (± 2960)			
Cohort 1 15 µg/kg/day: Week 26	3400 (± 2520)			
Cohort 1 15 µg/kg/day: Week 39	2330 (± 1150)			
Cohort 1 15 µg/kg/day: Week 52	2660 (± 1420)			
Cohort 2 15 µg/kg/day: Week 26	3890 (± 2880)			
Cohort 2 15 µg/kg/day: Week 39	2250 (± 284)			
Cohort 2 15 µg/kg/day: Week 52	3770 (± 1410)			
Cohort 2 30 µg/kg/day: Day 01	3190 (± 1790)			
Cohort 2 30 µg/kg/day: Week 13	2090 (± 1360)			
Cohort 2 30 µg/kg/day: Week 26	1960 (± 829)			
Cohort 2 30 µg/kg/day: Week 39	2920 (± 205)			
Cohort 2 30 µg/kg/day: Week 52	3040 (± 2630)			
Cohort 3 30 µg/kg/day: Day 01	5240 (± 1890)			
Cohort 3 30 µg/kg/day: Week 13	4260 (± 2960)			

Cohort 3 30 µg/kg/day: Week 26	2750 (± 710)			
Cohort 3 30 µg/kg/day: Week 39	2200 (± 951)			
Cohort 3 30 µg/kg/day: Week 52	2620 (± 1950)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Elimination half-life (t1/2) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point title	PK parameter: Elimination half-life (t1/2) at Day 01, Week 13, Week 26, Week 39, & Week 52

End point description:

Vosoritide concentrations at 5-, 15- and 30-minute post-dose for one participant on Day 1 were not available, hence PK parameters for this participant were excluded from summary statistics.
PK parameters for another participant on Day 1 obtained from extrapolation. AUC0-∞, CL/F, V/F and t1/2 excluded from summary statistics. PK parameters are not available for this participant at Week 13 due to unsuccessful venipuncture, and Week 26 as post-dose PK samples were not collected.

The number of participants analyzed are reported in sequence (n = Day 01, Week 13, Week 26, Week 39, Week 52)

Cohort 1 15 µg/kg/day: (n=16, 15, 16, 16, 15)
Cohort 2 15 µg/kg/day: (n=1, 1, 4, 4, 3) Refer PDF
Cohort 2 30 µg/kg/day: (n=7, 6, 3, 2, 3)
Cohort 3 30 µg/kg/day: (n=8, 6, 6, 3, 7)

End point type	Secondary

End point timeframe:

At Day 01, Week 13, Week 26, Week 39, & Week 52.

End point values	All Vosoritide			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: min				
arithmetic mean (standard deviation)				
Cohort 1 15 µg/kg/day: Day 01	21.7 (± 7.99)			
Cohort 1 15 µg/kg/day: Week 13	25.4 (± 10.7)			
Cohort 1 15 µg/kg/day: Week 26	29.2 (± 7.06)			
Cohort 1 15 µg/kg/day: Week 39	25.7 (± 7.82)			
Cohort 1 15 µg/kg/day: Week 52	29 (± 9.12)			
Cohort 2 15 µg/kg/day: Week 26	32.7 (± 9.62)			
Cohort 2 15 µg/kg/day: Week 39	20.9 (± 2.18)			
Cohort 2 15 µg/kg/day: Week 52	24 (± 12.8)			
Cohort 2 30 µg/kg/day: Day 01	33.3 (± 8.41)			
Cohort 2 30 µg/kg/day: Week 13	25.6 (± 3.59)			
Cohort 2 30 µg/kg/day: Week 26	21 (± 13.1)			
Cohort 2 30 µg/kg/day: Week 39	26.2 (± 5.46)			
Cohort 2 30 µg/kg/day: Week 52	40.1 (± 15.2)			
Cohort 3 30 µg/kg/day: Day 01	41.1 (± 18.8)			
Cohort 3 30 µg/kg/day: Week 13	26.2 (± 7.1)			

Cohort 3 30 µg/kg/day: Week 26	19.2 (± 6.14)		
Cohort 3 30 µg/kg/day: Week 39	22.7 (± 5.36)		
Cohort 3 30 µg/kg/day: Week 52	24.3 (± 6.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker: Bone and Collagen Metabolism Biomarker Over Time-CNP Col X BM

End point title	Biomarker: Bone and Collagen Metabolism Biomarker Over Time-CNP Col X BM

End point description:

The number of participants analyzed is reported in sequence: (n=All Vosoritide, Placebo) for each category.
Baseline: (n= 42, 32)
Day 8: (n=42, 24)
Change from baseline to Day 8: (n=41, 24)
Week 6: (n=41, 29)
Change from baseline to Week 6: (n=40, 29)
Week 20: (n=42, 29)
Change from baseline to Week 20: (n=41, 29)
Week 39: (n=33, 22)
Change from baseline to Week 39 : (n=32, 22)

End point type	Secondary

End point timeframe:

At Baseline, Day 8, Week 6, Week 20, & Week 39.

End point values	All Vosoritide	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	32		
Units: pg/mL				
arithmetic mean (standard deviation)				
CNP Col X BM: Baseline	9833.8 (± 3444.7)	9555.0 (± 4016.7)		
CNP Col X BM: Day 8	12093.8 (± 4443.8)	10017.5 (± 3831.2)		
CNP Col X BM: Change from baseline to Day 8	2139.5 (± 3871.9)	1391.3 (± 3354.2)		
CNP Col X BM: Week 6	13456.3 (± 4763.3)	9464.8 (± 4243.3)		
CNP Col X BM: Change from baseline to Week 6	3400.3 (± 4554.6)	200.3 (± 3867.5)		
CNP Col X BM: Week 20	12833.3 (± 4581.9)	12064.8 (± 5277.3)		
CNP Col X BM: Change from baseline to Week 20	2928.0 (± 4385.9)	2435.5 (± 4666.9)		
CNP Col X BM: Week 39	12249.7 (± 5056.5)	9932.7 (± 4004.4)		
CNP Col X BM: Change from baseline to Week 39	2362.8 (± 5752.9)	946.4 (± 3490.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 56 Safety Follow-Up.

Adverse event reporting additional description:

The Safety Population was a subset of the FAS who received at least one dose of vosoritide or placebo in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Vosoritide

Reporting group description: -

Serious adverse events	Placebo	Vosoritide	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)	3 / 43 (6.98%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions				
Sudden infant death syndrome				
subjects affected / exposed	0 / 32 (0.00%)	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (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				
Respiratory distress				
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychiatric disorders				
Autism spectrum disorder				
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (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				
Pneumonia				
subjects affected / exposed	0 / 32 (0.00%)	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory syncytial virus bronchiolitis				
subjects affected / exposed	0 / 32 (0.00%)	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastroenteritis				
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Otitis media				

subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Parainfluenzae virus infection		
subjects affected / exposed	1 / 32 (3.13%)	0 / 43 (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	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	43 / 43 (100.00%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 32 (9.38%)	7 / 43 (16.28%)	
occurrences (all)	5	9	
Arthropod bite			
subjects affected / exposed	2 / 32 (6.25%)	6 / 43 (13.95%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	13 / 32 (40.63%)	34 / 43 (79.07%)	
occurrences (all)	154	3057	
Injection site erythema			
subjects affected / exposed	13 / 32 (40.63%)	33 / 43 (76.74%)	
occurrences (all)	1738	5100	
Injection site swelling			
subjects affected / exposed	2 / 32 (6.25%)	8 / 43 (18.60%)	
occurrences (all)	3	36	
Injection site urticaria			
subjects affected / exposed	1 / 32 (3.13%)	6 / 43 (13.95%)	
occurrences (all)	1	22	
Injection site induration			

subjects affected / exposed	0 / 32 (0.00%)	5 / 43 (11.63%)	
occurrences (all)	0	14	

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 32 (6.25%)	5 / 43 (11.63%)	
occurrences (all)	4	7	

Respiratory, thoracic and mediastinal disorders			
Sleep apnea syndrome			
subjects affected / exposed	0 / 32 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Epistaxis			
subjects affected / exposed	0 / 32 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

Skin and subcutaneous tissue disorders			
Dermatitis Diaper			
subjects affected / exposed	1 / 32 (3.13%)	4 / 43 (9.30%)	
occurrences (all)	1	5	

Infections and infestations			
Viral Infection			
subjects affected / exposed	4 / 32 (12.50%)	8 / 43 (18.60%)	
occurrences (all)	8	28	
Lower respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	4 / 43 (9.30%)	
occurrences (all)	3	4	
Rhinitis			
subjects affected / exposed	0 / 32 (0.00%)	4 / 43 (9.30%)	
occurrences (all)	0	8	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2018	• The lower age range of participating participants who have a >= 6-month period of pretreatment growth assessment in 111-901 immediately before study entry was revised from >= 3 months to >= 6 months. • Language updated to state that no two sentinel participants would be dosed on the same day for any cohort. • Echocardiogram would be performed at the Week 56Safety Follow-up and Early Termination visits • Use of residual plasma samples for cGMP PD biomarker assessment in all age groups was added to procedures. • An anti-vosoritide immunogenicity assessment was added at Week 3. • Bone metabolism urine biomarkers, vosoritide pharmacodynamic urine biomarkers, and urine chemistry assessments were added at Week 39. • The sleep study scheduled at the Week 26 visit was removed. • DXA scans would no longer include tibia scans. • If the 111-901 visit at which the participant entered 111-206 and the 111-206 Screening visit were on the same day, the procedures common to both visits were performed one time only. • On days when PK samples were being drawn, ECG would be performed within a 5-minute window prior to the 30-minute PK assessment. • Exclusion criterion #6 was revised from "…as determined by the Investigator based on the following assessments…) to (…as determined by theInvestigator and informed by the following assessments…). The determination about whether presence of cervicomedullary compression is likely to require surgical intervention will be informed by physical exam, polysomnography, and MRI. • Exclusion criterion #15 was revised to include cervicomedullary decompression surgery (Cohorts 2 and 3 only). • Inclusion/exclusion criteria was added for Cohort 3 participants enrolling in the observational period. • A table of restricted medications, including growth hormone, was added. For participants enrolled in Cohort 3 (0 to < 6 months old), the collection period for all AEs was to begin after informed consent is obtained.
08 February 2019	The following exploratory objectives were revised to secondary objectives. • Evaluate the effect of vosoritide on growth parameters and body proportions, including change from baseline in upper:lower segment ratio • Evaluate the effect of vosoritide on sleep apnea • Evaluate the effect of vosoritide on skull and brain morphology, including foramen magnum, ventricular and brain parenchymal dimensions • Describe the incidence of surgical interventions, including cervical decompression, adenotonsellectomy, and typanostomy The secondary imaging assessment procedures, excluding the MRI assessment, were moved to the secondary safety variables section. The hip imaging assessment was removed, the X-ray assessment was modified to include long bone growth, and the DXA assessment would no longer include the forearm. Also, the paragraph discussing the possibility of non-radiological methods of assessment for participants in Cohort 3 was deleted. The screening baseline hip assessment with pelvis X-ray was removed from the Schedule of Events. Footnotes were changed to modify procedures and to add early termination visits (ETV) for anthropomorphic measurements, DXA, and X-rays.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported