Clinical trial results:
Comparison of Somavaratan (VRS-317), a Long-acting Human Growth Hormone, to Daily rhGH in a Phase 3, Randomized, One-year, Open-label, Multi-center, Non-inferiority Trial in Pre-pubertal Children With Growth Hormone Deficiency

Summary

EudraCT number	2014-004525-41
Trial protocol	SE BE NL PL
Global end of trial date	23 August 2017

Results information

Result version number	v1 (current)
This version publication date	14 December 2022
First version publication date	14 December 2022

Trial information

Trial identification

Sponsor protocol code	0014VR4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02339090
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Versartis, Inc.
Sponsor organisation address	3730 Kirby Drive, Suite 1200, Houston, Texas, United States, 77098
Public contact	Chief Operating Officer, Versartis, Inc., +1 (936) 355-1910, clinicaltrials@aravive.com
Scientific contact	Chief Operating Officer, Versartis, Inc., +1 (936) 355-1910, clinicaltrials@aravive.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2017
Global end of trial reached?	Yes
Global end of trial date	23 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the safety and efficacy of subcutaneous somavaratan and daily recombinant human growth hormone (rhGH) during 12 months of treatment.

Protection of trial subjects:

The study was performed in compliance the Food & Drug Administration Code of Federal Regulations for Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) Regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	United States: 88
Worldwide total number of subjects	136
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	136
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:

34 participants randomized in rhGH group, out of which 32 participants received treatment.

Pre-assignment

Screening details:

Participants were stratified by region (North America and Europe), age (above and below anticipated median age of 7.5 years) and baseline Insulin-like growth factor-I (IGF-I) standard deviation score (SDS) (above and below anticipated median of -1.7) and randomized in a 3:1 ratio to receive either somavaratan or rhGH.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Somavaratan

Arm description:

Participants received somavaratan 3.5 milligrams (mg)/kilogram (kg) subcutaneous (SC) bolus injection twice monthly for 12 months.

Arm type	Experimental
Investigational medicinal product name	Somavaratan
Investigational medicinal product code	VRS-317
Other name	Long-acting recombinant human growth hormone
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Somavaratan was administered per dose and schedule specified in the arm description.

Arm title	rhGH

Arm description:

Participants received commercially available rhGH (genotropin) 34 micrograms (µg)/kg once daily SC bolus injection for 12 months.

Arm type	Active comparator
Investigational medicinal product name	rhGH
Investigational medicinal product code	
Other name	daily growth hormone, recombinant growth hormone therapy
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

rhGH was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Somavaratan	rhGH
Started	104	32
Received a Least 1 Dose of Study Drug	104	32
Completed	98	29
Not completed	6	3
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	-
Non-compliance With Study Drug	-	1
Poor Growth	3	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Somavaratan
Reporting group description:	
Participants received somavaratan 3.5 milligrams (mg)/kilogram (kg) subcutaneous (SC) bolus injection twice monthly for 12 months.	
Reporting group title	rhGH
Reporting group description:	
Participants received commercially available rhGH (genotropin) 34 micrograms (µg)/kg once daily SC bolus injection for 12 months.	

Reporting group values	Somavaratan	rhGH	Total
Number of subjects	104	32	136
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.0	6.9	
standard deviation	± 2.03	± 2.38	-
Gender categorical Units: Subjects			
Female	46	10	56
Male	58	22	80
Ethnicity Units: Subjects			
Hispanic or Latino	8	3	11
Not Hispanic or Latino	96	29	125
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	5	0	5
Black or African American	1	0	1
White	91	31	122
Unknown or Not Reported	6	1	7

End points

End points reporting groups

Reporting group title	Somavaratan
Reporting group description:	
Participants received somavaratan 3.5 milligrams (mg)/kilogram (kg) subcutaneous (SC) bolus injection twice monthly for 12 months.	
Reporting group title	rhGH
Reporting group description:	
Participants received commercially available rhGH (genotropin) 34 micrograms (µg)/kg once daily SC bolus injection for 12 months.	
Subject analysis set title	rhGH
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received commercially available rhGH (genotropin) 34 µg/kg once daily SC bolus injection for 12 months.	

Primary: Annual Height Velocity

End point title	Annual Height Velocity[1]
End point description:	
Height measured without shoes in triplicate by stadiometer. Annual height velocity was calculated as (height at Month 12 - height at Baseline)/(Month 12 Date - Baseline Date) * 365.25, where height was expressed as centimetres (cm) so that height velocity is expressed as centimetres per year (cm/yr). Annual height velocity after 12 months continuous treatment with either somavaratan or daily rhGH has been reported. Missing data was imputed using last observation carried forward. Least square (LS) mean was calculated using analysis of covariance (ANCOVA) model. ITT population included all randomized participants.	
End point type	Primary
End point timeframe:	
12 months	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting statistics for specified arms only.

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	104	34		
Units: cm/year				
least squares mean (standard error)	9.43 (± 0.28)	10.70 (± 0.48)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
An ANCOVA model will be used to determine the adjusted (least squares) means and standard error (SE) to determine the confidence interval (CI) of the difference. ANCOVA model included treatment group, region, and gender as fixed effects; with baseline age and baseline IGF-I SDS as covariates.	
Comparison groups	Somavaratan v rhGH

Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	LS Mean Difference
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.32
upper limit	-0.24

Notes:

[2] - Threshold for significance: annualized height velocity between somavaratan and daily rhGH ≤ -2.0 cm/year

Secondary: Change From Baseline in Height Standard Deviation Score (SDS) at Month 12

End point title	Change From Baseline in Height Standard Deviation Score (SDS) at Month 12

End point description:

Height SDS was determined using the Center for Disease Control (CDC) Clinical Growth Charts; 2000. The SD score was calculated as the participant's height value minus the mean divided by the standard deviation (SD). The mean and the SD vary depending on the age and sex of the participant. Mean change from baseline in height SDS at Month 12 is presented. ITT population included all randomized participants. Here, 'overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	30		
Units: SD score				
arithmetic mean (standard deviation)	0.8 (± 0.53)	1.0 (± 0.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age Relative to Chronological Age at Month 12, as Assessed by Central Reader

End point title	Change From Baseline in Bone Age Relative to Chronological Age at Month 12, as Assessed by Central Reader

End point description:

Bone age was assessed from a radiograph of the left hand and wrist by central reader. ITT population included all randomized participants. Here, 'overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	29		
Units: months				
arithmetic mean (standard deviation)	1.1 (± 0.47)	1.3 (± 0.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI) at Month 12

End point title	Change From Baseline in Body Mass Index (BMI) at Month 12

End point description:

The BMI is a person’s weight in kilograms divided by the square of height in meters. ITT population included all randomized participants. Here, ‘overall number of participants analyzed’ signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	30		
Units: kilograms (kg)/square meter (m^2)				
arithmetic mean (standard deviation)	1.1 (± 0.86)	-0.1 (± 0.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight at Month 12

End point title	Change From Baseline in Body Weight at Month 12

End point description:

Body weight measured in light clothing and without shoes. ITT population included all randomized participants. Here, ‘overall number of participants analyzed’ signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	30		
Units: kg				
arithmetic mean (standard deviation)	4.9 (± 1.87)	3.8 (± 1.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insulin-like Growth Factor 1 (IGF-I) SDS at Month 12

End point title	Change From Baseline in Insulin-like Growth Factor 1 (IGF-I) SDS at Month 12

End point description:

The SD score was calculated as the actual value of IGF-I minus mean reference value of IGF-I divided by reference standard deviation of IGF-I. The mean and the SD vary depending on the age and sex of the participant. Change in IGF-I level (SD score) at Month 12 from Baseline was assessed. A higher score reflects a better outcome. ITT population included all randomized participants. Here, 'overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	28		
Units: SD score				
arithmetic mean (standard deviation)	0.9 (± 0.99)	1.8 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insulin-like Growth Factor Binding Protein 3 (IGFBP-3) at Month 12

End point title	Change From Baseline in Insulin-like Growth Factor Binding Protein 3 (IGFBP-3) at Month 12

End point description:

ITT population included all randomized participants. Here, 'overall number of participants analyzed' signifies participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	26		
Units: nanomoles (nmol)/milliliter (mL)				
arithmetic mean (standard deviation)	32.2 (± 30.2)	49.8 (± 19.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. SAEs included death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent 1 of the outcomes listed in this definition. A summary of serious and non-serious AEs regardless of causality is located in 'Reported Adverse Events module'. Safety population included all participants who received any amount of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Month 12

End point values	Somavaratan	rhGH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	32		
Units: participants	80	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Month 12	
Adverse event reporting additional description:	
Safety population included all participants who received any amount of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Somavaratan
Reporting group description:	
Participants received somavaratan 3.5 mg/kg SC bolus injection twice monthly for 12 months.	
Reporting group title	rhGH
Reporting group description:	
Participants received commercially available rhGH (genotropin) 34 µg/kg once daily SC bolus injection for 12 months.	

Serious adverse events	Somavaratan	rhGH	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 104 (5.77%)	0 / 32 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	2 / 104 (1.92%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syringomyelia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis			

subjects affected / exposed	1 / 104 (0.96%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 104 (0.96%)	0 / 32 (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			
Otitis media			
subjects affected / exposed	1 / 104 (0.96%)	0 / 32 (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	Somavaratan	rhGH	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 104 (56.73%)	16 / 32 (50.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 104 (15.38%)	4 / 32 (12.50%)	
occurrences (all)	58	15	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	18 / 104 (17.31%)	4 / 32 (12.50%)	
occurrences (all)	28	6	
Injection site pain			
subjects affected / exposed	18 / 104 (17.31%)	3 / 32 (9.38%)	
occurrences (all)	25	5	
Injection site haematoma			
subjects affected / exposed	6 / 104 (5.77%)	1 / 32 (3.13%)	
occurrences (all)	6	1	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	12 / 104 (11.54%)	5 / 32 (15.63%)	
occurrences (all)	19	8	
Diarrhoea			
subjects affected / exposed	7 / 104 (6.73%)	1 / 32 (3.13%)	
occurrences (all)	7	1	
Nausea			
subjects affected / exposed	5 / 104 (4.81%)	3 / 32 (9.38%)	
occurrences (all)	8	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 104 (14.42%)	2 / 32 (6.25%)	
occurrences (all)	18	2	
Oropharyngeal pain			
subjects affected / exposed	7 / 104 (6.73%)	1 / 32 (3.13%)	
occurrences (all)	10	1	
Nasal congestion			
subjects affected / exposed	2 / 104 (1.92%)	2 / 32 (6.25%)	
occurrences (all)	2	3	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 104 (1.92%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 104 (10.58%)	3 / 32 (9.38%)	
occurrences (all)	17	4	
Pain in extremity			
subjects affected / exposed	12 / 104 (11.54%)	1 / 32 (3.13%)	
occurrences (all)	20	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 104 (11.54%)	3 / 32 (9.38%)	
occurrences (all)	17	6	
Nasopharyngitis			

subjects affected / exposed	7 / 104 (6.73%)	2 / 32 (6.25%)	
occurrences (all)	12	3	
Otitis media			
subjects affected / exposed	7 / 104 (6.73%)	0 / 32 (0.00%)	
occurrences (all)	7	0	
Ear infection			
subjects affected / exposed	6 / 104 (5.77%)	0 / 32 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2014	The protocol was revised to modify the protocol-specified criteria for routine funduscopy in sites located outside of North America.
17 July 2015	- A new stopping criteria was added: Individual participants with confirmed positive neutralizing antibody and a change in height standard deviation score (HT-SDS) ≤ 0 in the past 6 months may be withdrawn from treatment at the discretion of the Principal Investigator and Medical Monitor. - A new activity 12-lead electrocardiogram (ECG) (triplicate tracings) was added.
05 April 2017	Changes were made to align this protocol with other somavaratan pediatric growth hormone deficiency (GHD) study protocols, all of which were intended to enhance safety of participants. The primary change was the removal of an interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 February 2015	Enrollment paused on 17 Feb 2015 for FDA Partial Clinical Hold. All issues resolved and enrollment resumed on 23 June 2015.	23 June 2015

Notes:

Limitations and caveats

None reported