Clinical trial results:
A Phase 3, Randomised, Multicenter, Open-Label, Crossover Study Assessing Subject Perception of Treatment Burden With Use of Weekly Growth Hormone (Somatrogon) Versus Daily Growth Hormone (Genotropin) Injections in Children With Growth Hormone Deficiency

Summary

EudraCT number	2018-000918-38
Trial protocol	GB SK CZ BG
Global end of trial date	28 August 2020

Results information

Result version number	v1 (current)
This version publication date	04 March 2021
First version publication date	04 March 2021

Trial information

Trial identification

Sponsor protocol code	C0311002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03831880
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the treatment burden of a weekly Somatrogon injection schedule and a daily Genotropin injection schedule.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	87
EEA total number of subjects	31

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)	46
Adolescents (12-17 years)	41
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 107 subjects were enrolled and 87 subjects aged 3 to less than (<) 18 years, with growth hormone deficiency (GHD) who were stable on treatment with daily Genotropin were randomised in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Daily Genotropin Then Weekly Somatrogon

Arm description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

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

Dosage and administration details:

Subjects received Genotropin, daily subcutaneous at the same dose as their daily hGH which they were receiving at the time of enrollment.

Arm title	Weekly Somatrogon Then Daily Genotropin

Arm description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

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

Dosage and administration details:

Subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week.

Number of subjects in period 1	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin
Started	43	44
Completed	43	44

Period 2

Period 2 title	Period 1 (12 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Daily Genotropin Then Weekly Somatrogon

Arm description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

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

Dosage and administration details:

Subjects received Genotropin, daily subcutaneous at the same dose as their daily hGH which they were receiving at the time of enrollment.

Arm title	Weekly Somatrogon Then Daily Genotropin

Arm description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

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

Dosage and administration details:

Subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week.

Number of subjects in period 2	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin
Started	43	44
Completed	43	43
Not completed	0	1
Adverse event, not serious	-	1

Period 3

Period 3 title	Period 2 (12 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Daily Genotropin Then Weekly Somatrogon

Arm description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

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

Dosage and administration details:

Subjects received Genotropin, daily subcutaneous at the same dose as their daily hGH which they were receiving at the time of enrollment.

Arm title	Weekly Somatrogon Then Daily Genotropin

Arm description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

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

Dosage and administration details:

Subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week.

Number of subjects in period 3	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin
Started	43	43
Completed	43	42
Not completed	0	1
Protocol Deviation	-	1

Period 4

Period 4 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Daily Genotropin Then Weekly Somatrogon

Arm description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Weekly Somatrogon Then Daily Genotropin

Arm description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin
Started	43	42
Completed	43	43

Joined	0	1
Continued Follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Daily Genotropin Then Weekly Somatrogon

Reporting group description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Reporting group title	Weekly Somatrogon Then Daily Genotropin

Reporting group description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Reporting group values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin	Total
Number of subjects	43	44	87
Age categorical Units: Subjects			
In Utero	0	0	0
Pre-term newborn - gestational age < 37 wk	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	21	25	46
Adolescents (12-17 years)	22	19	41
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	10.8	10.7	
standard deviation	± 3.4	± 3.7	-
Sex: Female, Male Units: Subjects			
Female	9	6	15
Male	34	38	72
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	1	4
White	39	42	81
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	39	42	81
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Daily Genotropin Then Weekly Somatrogon

Reporting group description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Reporting group title	Weekly Somatrogon Then Daily Genotropin

Reporting group description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Reporting group title	Daily Genotropin Then Weekly Somatrogon

Reporting group description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Reporting group title	Weekly Somatrogon Then Daily Genotropin

Reporting group description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Reporting group title	Daily Genotropin Then Weekly Somatrogon

Reporting group description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Reporting group title	Weekly Somatrogon Then Daily Genotropin

Reporting group description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Reporting group title	Daily Genotropin Then Weekly Somatrogon

Reporting group description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Reporting group title	Weekly Somatrogon Then Daily Genotropin

Reporting group description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Reporting group title	Daily Genotropin Then Weekly Somatrogon

Reporting group description:

Subjects were randomised to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects received Somatrogon, weekly subcutaneously at a dose of 0.66 milligram per kilogram per week (mg/kg/week) for 12 weeks. Subjects were followed up maximum for 35 days (5 weeks) after last dose of study drug.

Reporting group title	Weekly Somatrogon Then Daily Genotropin

Reporting group description:

Subjects were randomised to receive Somatrogon, weekly subcutaneously at a dose of 0.66 mg/kg/week, for 12 weeks in Period 1. Period 1 was followed by Period 2, where subjects continued to receive Genotropin, daily subcutaneously at the same dose which they were receiving at the time of enrollment, for 12 weeks. Subjects were followed up maximum for 35 days after last dose of study drug.

Subject analysis set title	Genotropin
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received Genotropin, daily subcutaneously, in overall study (either in Period 1 or in Period 2).

Subject analysis set title	Somatrogon
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received Somatrogon, weekly subcutaneously, at a dose of 0.66 mg/kg/week, in overall study (either in Period 1 or in Period 2).

Primary: Total Score Related to Overall Life Interference Assessed at Baseline, Using Dyad Clinical Outcomes Assessment 1 (DCOA 1) Questionnaire

End point title	Total Score Related to Overall Life Interference Assessed at Baseline, Using Dyad Clinical Outcomes Assessment 1 (DCOA 1) Questionnaire[1]

End point description:

Subjects were assessed for their treatment burden using DCOA 1 questionnaire completed by subject/caregiver dyads. The subject life interference questionnaire component of the DCOA 1 had 7 questions (life interference [5 questions]: a measure of life interference [daily activities/social activities/leisure/night away from home/travel]; life interference-changes to life routine [1 question]: a measure of how often changes are made to life routine; and life interference-bother of growth hormone [GH] injections [1 question]: a measure of how often the growth hormone injections cause bother) and all questions used a 5-point scale: 1= never, 2= rarely, 3= sometimes, 4= often, 5= always. The overall life interference total score was sum of all 7 questions, scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant less life interference (better outcome). FAS was analysed. 'Number of Subjects Analysed' = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline

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: No statistical analysis was planned for this endpoint

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: units on a scale				
arithmetic mean (standard deviation)	29.5 (± 18.0)	27.1 (± 19.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Total Score Related to Overall Life Interference Assessed at Week 12, Using DCOA 1 Questionnaire

End point title	Total Score Related to Overall Life Interference Assessed at Week 12, Using DCOA 1 Questionnaire[2]

End point description:

Subjects were assessed for their treatment burden using DCOA 1 questionnaire completed by subject/caregiver dyads. The subject life interference questionnaire component of the DCOA 1 had 7 questions (life interference [5 questions]: a measure of life interference [daily activities/social activities/leisure/night away from home/travel]; life interference-changes to life routine [1 question]: a measure of how often changes are made to life routine; and life interference-bother of growth hormone [GH] injections [1 question]: a measure of how often the growth hormone injections cause bother) and

all questions used a 5-point scale: 1= never, 2= rarely, 3= sometimes, 4= often, 5= always. The overall life interference total score was sum of all 7 questions, scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant less life interference (better outcome). FAS was analysed. 'Number of Subjects Analysed' = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Week 12

Notes:

[2] - 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: No statistical analysis was planned for this endpoint

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: units on a scale				
arithmetic mean (standard deviation)	25.2 (± 17.3)	7.1 (± 7.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Total Score Related to Overall Life Interference Assessed at Week 24, Using DCOA 1 Questionnaire

End point title	Total Score Related to Overall Life Interference Assessed at Week 24, Using DCOA 1 Questionnaire[3]

End point description:

Subjects were assessed for their treatment burden using DCOA 1 questionnaire completed by subject/caregiver dyads. The subject life interference questionnaire component of the DCOA 1 had 7 questions (life interference [5 questions]: a measure of life interference [daily activities/social activities/leisure/night away from home/travel]; life interference-changes to life routine [1 question]: a measure of how often changes are made to life routine; and life interference-bother of growth hormone [GH] injections [1 question]: a measure of how often the growth hormone injections cause bother) and all questions used a 5-point scale: 1= never, 2= rarely, 3= sometimes, 4= often, 5= always. The overall life interference total score was sum of all 7 questions, scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant less life interference (better outcome). FAS was analysed. 'Number of Subjects Analysed' = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Week 24

Notes:

[3] - 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: No statistical analysis was planned for this endpoint

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: units on a scale				

arithmetic mean (standard deviation)	9.5 (± 13.3)	23.0 (± 22.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Total Score Related to Overall Life Interference by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Score Related to Overall Life Interference by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment burden using DCOA 1 questionnaire completed by subject/caregiver dyads. The subject life interference questionnaire component of the DCOA 1 had 7 questions (life interference [5 questions]: a measure of life interference [daily activities/social activities/leisure/night away from home/travel]; life interference-changes to life routine [1 question]: a measure of how often changes are made to life routine; and life interference-bother of growth hormone [GH] injections [1 question]: a measure of how often the growth hormone injections cause bother) and all questions used a 5-point scale: 1= never, 2= rarely, 3= sometimes, 4= often, 5= always. The overall life interference total score was sum of all 7 questions, scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant less life interference (better outcome). FAS was analysed. 'Number of Subjects Analysed' = subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	24.13 (20.61 to 27.65)	8.63 (5.05 to 12.22)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.71
upper limit	-11.27

Notes:

[4] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Score Related to Pen Ease of Use Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Score Related to Pen Ease of Use Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked 5 questions from Section I of the Injection Pen Assessment Questionnaire (IPAQ) patient-reported outcome (PRO) tool related to pen ease of use and used a 5-point scale: 1= very easy, 2= somewhat easy, 3= neither easy nor difficult, 4= somewhat difficult, 5= very difficult. The total score related to pen ease of use was sum of all 5 questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 42, 40)	10.6 (± 11.3)	11.6 (± 12.8)		
Week 12 (n= 43, 40)	12.0 (± 13.8)	5.1 (± 7.6)		
Week 24 (n= 42, 42)	5.5 (± 9.3)	9.4 (± 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Score Related to Pen Ease of Use by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Score Related to Pen Ease of Use by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked 5 questions from Section I of the IPAQ PRO tool related to pen ease of use and used a 5-point scale: 1= very easy, 2= somewhat easy, 3= neither easy nor difficult, 4= somewhat difficult, 5= very difficult. The total score related to pen ease of use was sum of all 5 questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower

score meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline up to Week 24	

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	10.71 (8.27 to 13.14)	5.32 (2.84 to 7.80)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.69
upper limit	-2.09

Notes:

[5] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Score Related to Ease of the Injection Schedule Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Score Related to Ease of the Injection Schedule Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to ease of injection schedule and used a 5-point scale: 1= very easy, 2= somewhat easy, 3= neither easy nor difficult, 4= somewhat difficult, 5= very difficult. The total score related to ease of the injection schedule ranged from 1 to 5; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary
End point timeframe:	
Baseline, Week 12, Week 24	

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 42, 40)	18.5 (± 20.0)	16.3 (± 17.5)		
Week 12 (n= 43, 40)	23.3 (± 25.2)	4.4 (± 11.2)		
Week 24 (n= 42, 42)	9.5 (± 18.3)	17.9 (± 22.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Score Related to Ease of the Injection Schedule by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Score Related to Ease of the Injection Schedule by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to ease of injection schedule and used a 5-point scale: 1= very easy, 2= somewhat easy, 3= neither easy nor difficult, 4= somewhat difficult, 5= very difficult. The total score related to ease of the injection schedule ranged from 1 to 5; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	20.56 (16.22 to 24.89)	6.96 (2.54 to 11.37)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.74
upper limit	-7.45

Notes:

[6] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Score Related to Convenience of the Injection Schedule Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Score Related to Convenience of the Injection Schedule Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to ease of injection schedule and used a 7-point scale: 1=extremely convenient to 7=extremely inconvenient. The total score related to convenience of injection schedule ranged from 1 to 7; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 42, 40)	34.5 (± 21.0)	32.5 (± 21.3)		
Week 12 (n= 43, 40)	35.3 (± 23.9)	7.9 (± 10.7)		
Week 24 (n= 42, 42)	11.9 (± 14.4)	33.3 (± 24.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Score Related to Convenience of the Injection Schedule by

Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Score Related to Convenience of the Injection Schedule by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to ease of injection schedule and used a 7-point scale: 1=extremely convenient to 7=extremely inconvenient. The total score related to convenience of injection schedule ranged from 1 to 7; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	34.30 (30.13 to 38.47)	9.96 (5.71 to 14.21)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-24.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.1
upper limit	-18.57

Notes:

[7] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Score Related to Satisfaction With Overall Treatment Experience Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Score Related to Satisfaction With Overall Treatment Experience Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by

subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to subject satisfaction with treatment and used a 5-point scale: 1=very satisfied to 5=very dissatisfied. The total score related to satisfaction with overall treatment ranged from 1 to 5; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 42, 40)	28.0 (± 21.5)	29.4 (± 23.3)		
Week 12 (n= 43, 40)	27.3 (± 27.2)	20.0 (± 31.1)		
Week 24 (n= 42, 42)	22.0 (± 32.3)	30.4 (± 27.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Score Related to Satisfaction With Overall Treatment Experience by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Score Related to Satisfaction With Overall Treatment Experience by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to subject satisfaction with treatment and used a 5-point scale: 1=very satisfied to 5=very dissatisfied. The total score related to satisfaction with overall treatment ranged from 1 to 5; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	28.95 (22.55 to 35.36)	21.13 (14.61 to 27.65)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0739 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.42
upper limit	0.77

Notes:

[8] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Scores Related to Willingness to Continue Injection Schedule Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Willingness to Continue Injection Schedule Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to subject willingness to continue treatment and used a 5-point scale: 1=extremely willing to 5=not at all willing. The total score related to willingness to continue injection schedule ranged from 1 to 5; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 42, 40)	18.5 (± 20.0)	22.5 (± 23.9)		

Week 12 (n= 43, 40)	28.5 (± 27.6)	10.6 (± 21.1)		
Week 24 (n= 42, 42)	13.1 (± 24.8)	30.4 (± 29.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Scores Related to Willingness to Continue Injection Schedule by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Willingness to Continue Injection Schedule by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to subject willingness to continue treatment and used a 5-point scale: 1=extremely willing to 5=not at all willing. The total score related to willingness to continue injection schedule ranged from 1 to 5; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	29.54 (23.95 to 35.12)	11.93 (6.24 to 17.62)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-17.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.15
upper limit	-10.06

Notes:

[9] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Scores Related to Injection Signs and Symptoms for Subjects Aged 8 Years and Above Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Injection Signs and Symptoms for Subjects Aged 8 Years and Above Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subjects (8-17 years old). Subjects were asked 4 questions from Section I of the IPAQ PRO tool related to subject's injection signs and symptoms and used a 11-point scale: 0=no pain to 10=worst possible pain; 0=no stinging to 10=worst possible stinging; 0=no bruising to 10=worst possible bruising; and 0=no bleeding to 10=worst possible bleeding, respectively. The total score was sum of all questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score for injection signs and symptoms meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 35, 29)	15.0 (± 10.4)	13.8 (± 11.9)		
Week 12 (n= 34, 25)	16.2 (± 12.2)	13.7 (± 10.3)		
Week 24 (n= 32, 32)	13.6 (± 12.2)	10.9 (± 9.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Scores Related to Injection Signs and Symptoms for Subjects Aged 8 Years and Above by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Injection Signs and Symptoms for Subjects Aged 8 Years and Above by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by

subjects (8-17 years old). Subjects were asked 4 questions from Section I of the IPAQ PRO tool related to subject's injection signs and symptoms and used a 11-point scale: 0=no pain to 10=worst possible pain; 0=no stinging to 10=worst possible stinging; 0=no bruising to 10=worst possible bruising; and 0=no bleeding to 10=worst possible bleeding, respectively. The total score was sum of all questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score for injection signs and symptoms meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	57		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	13.56 (10.78 to 16.34)	14.27 (11.32 to 17.21)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6137 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	3.51

Notes:

[10] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Scores Related to Assessment of Signs, Completed by Caregiver for Children Aged <8 Years Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Assessment of Signs, Completed by Caregiver for Children Aged <8 Years Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by caregiver for children under 8 years. Subjects were asked 2 questions from Section I of the IPAQ PRO tool related to subject's assessment of signs and used a 11-point scale: 0=no bruising to 10=worst possible bruising and 0=no bleeding to 10=worst possible bleeding, respectively. The total score was sum of all questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a

lower score for assessment of signs meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 6, 10)	14.2 (± 14.6)	13.5 (± 11.3)		
Week 12 (n= 7, 10)	9.3 (± 10.6)	13.0 (± 15.8)		
Week 24 (n= 8, 9)	5.6 (± 7.8)	9.4 (± 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Scores Related to Assessment of Signs, Completed by Caregiver for Children Aged <8 Years by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Assessment of Signs, Completed by Caregiver for Children Aged <8 Years by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by caregiver for children under 8 years. Subjects were asked 2 questions from Section I of the IPAQ PRO tool related to subject's assessment of signs and used a 11-point scale: 0=no bruising to 10=worst possible bruising and 0=no bleeding to 10=worst possible bleeding, respectively. The total score was sum of all questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score for assessment of signs meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	18		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	8.75 (2.65 to 14.86)	9.31 (3.47 to 15.16)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8404 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.29
upper limit	6.41

Notes:

[11] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Scores Related to Caregiver Life Interference, Including Family Life Interference Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Caregiver Life Interference, Including Family Life Interference Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by caregiver. Subjects were asked 13 questions from Section I of the IPAQ PRO tool related to caregiver life interference and used a 5-point scale: 1= never to 5= always. The total score ranged was sum of scores from all questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score for caregiver and family life interference meant less life interference (a better outcome). FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				

Baseline (n= 41, 40)	17.8 (± 17.5)	20.0 (± 20.1)		
Week 12 (n= 43, 40)	15.9 (± 16.7)	3.1 (± 5.5)		
Week 24 (n= 42, 42)	3.8 (± 6.0)	18.1 (± 23.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Scores Related to Caregiver Life Interference, Including Family Life Interference by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Caregiver Life Interference, Including Family Life Interference by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by caregiver. Subjects were asked 13 questions from Section I of the IPAQ PRO tool related to caregiver life interference and used a 5-point scale: 1= never to 5= always. The total score ranged was sum of scores from all questions; scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score for caregiver and family life interference meant less life interference (a better outcome). FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	17.01 (13.77 to 20.25)	3.54 (0.24 to 6.84)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-13.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.59
upper limit	-9.35

Notes:

[12] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Total Scores Related to Missed Injections Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Missed Injections Assessed at Baseline, Week 12 and Week 24, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to number of missed injections (daily or weekly administration) during past 4 weeks. The total scores ranged from 0 to 31 for daily administration (Genotropin) and from 0 to 5 for weekly administration (Somatrogon). All scores were transformed from raw scores and converted to a 0 to 100 scale; a lower score for missed injections meant a better outcome. FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 41, 40)	7.8 (± 15.1)	7.3 (± 16.1)		
Week 12 (n= 43, 40)	4.3 (± 8.2)	0.0 (± 0.0)		
Week 24 (n= 42, 42)	1.9 (± 7.4)	3.1 (± 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Scores Related to Missed Injections by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point title	Total Scores Related to Missed Injections by Treatment in Overall Study, Using DCOA 1 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 1 questionnaire completed by subject/caregiver dyads. Subjects were asked a question from Section I of the IPAQ PRO tool related to number of missed injections (daily or weekly administration) during past 4 weeks. The total scores ranged from 0 to 31 for daily administration (Genotropin) and from 0 to 5 for weekly administration (Somatrogon). All scores were transformed from raw scores and converted to a 0 to 100 scale; a lower

score for missed injections meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	3.71 (2.03 to 5.39)	0.95 (-0.76 to 2.66)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0245 [13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.16
upper limit	-0.36

Notes:

[13] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Secondary: Number of Subjects as per Responses to Choice of Injection Pen Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Choice of Injection Pen Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/caregivers responded to question from Section II of the IPAQ PRO tool "If you were given the choice between the daily growth hormone injection pen and the weekly growth hormone injection pen, which pen would you choose?" Response was: 1) the daily injection pen (Genotropin) or 2) the weekly injection pen (Somatrogon). FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Somatrogon	38	36		
Genotropin	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Preferred Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Preferred Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/caregivers responded to question from Section II of the IPAQ PRO tool "Which growth hormone injection schedule do you prefer overall?" by choosing from any 1 option from: 1) prefer the daily injection schedule; 2) prefer the weekly injection schedule; 3) no preference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Somatrogon	40	37		
Genotropin	2	4		
No Preference	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Convenience of the Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Convenience of the Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/caregivers responded to question from Section II of the IPAQ PRO tool "Which growth hormone injection schedule was more convenient overall?" by choosing from any 1 option from: 1) daily injection schedule was more convenient; 2) weekly injection schedule was more convenient; 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Somatrogon	40	40		
Genotropin	2	2		
No Difference	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Ease of Following Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Ease of Following Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/caregivers responded to question from Section II of the IPAQ PRO tool "Which growth hormone injection schedule was easier to follow overall?" by choosing from any 1 option from: 1) easier to follow daily injection schedule; 2) easier to follow weekly injection schedule; 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Somatrogon	38	34		
Genotropin	4	4		
No Difference	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Pen Ease of Use Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Pen Ease of Use Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/caregiver were asked a question "Which pen was easier to use?" from Section II of the IPAQ PRO tool. Question had 4 parts: preparing the injection pen (Part I), setting the dose (Part II), injecting the medicine (Part III) and storing the pen (Part IV). Subjects/caregiver expressed their preference by choosing from any 1 option for each activity from: 1) daily pen easier to use; 2) weekly pen easier to use; 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Part I: Somatrogon	29	25		
Part I: Genotropin	3	4		
Part I: No difference	10	13		
Part II: Somatrogon	21	17		
Part II: Genotropin	6	8		
Part II: No Difference	15	17		
Part III: Somatrogon	13	18		
Part III: Genotropin	16	12		
Part III: No Difference	13	12		
Part IV: Somatrogon	12	14		
Part IV: Genotropin	2	2		
Part IV: No Difference	28	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Subject Life Interference Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Subject Life Interference Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/caregiver were asked a question "Which injection schedule interfered less?" from Section II of the IPAQ PRO tool related to subject life interference. Subjects were assessed for 5 activities: daily activities (Activity 1), social activities (Activity 2), recreation/leisure activities (Activity 3), spending night away from home (Activity 4) and travel (Activity 5). The subjects expressed their preference by choosing from any 1 option for each activity from: 1) daily injection schedule interfered less; 2) weekly injection schedule interfered less; 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Activity 1: Somatrogon	35	31		
Activity 1: Genotropin	2	1		
Activity 1: No Difference	5	10		
Activity 2: Somatrogon	34	34		
Activity 2: Genotropin	2	0		
Activity 2: No Difference	6	8		
Activity 3: Somatrogon	34	33		
Activity 3: Genotropin	2	1		
Activity 3: No Difference	6	8		
Activity 4: Somatrogon	36	37		
Activity 4: Genotropin	2	1		
Activity 4: No Difference	4	4		
Activity 5: Somatrogon	33	37		
Activity 5: Genotropin	3	0		
Activity 5: No Difference	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Caregiver Life Interference Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Caregiver Life Interference Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Caregivers of subjects were asked a question "Which injection schedule interfered less?" from Section II of the IPAQ PRO tool related to caregiver life interference and were assessed for 5 activities: daily activities (Activity 1), social activities (Activity 2), recreation/leisure activities (Activity 3), spending night away from home (Activity 4) and travel (Activity 5). Preference was expressed by choosing from any 1 option for each activity from: 1) daily injection schedule interfered less; 2) weekly injection schedule interfered less; 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Activity 1: Somatrogon	36	31		
Activity 1: Genotropin	2	0		
Activity 1: No Difference	4	11		
Activity 2: Somatrogon	36	32		
Activity 2: Genotropin	2	0		
Activity 2: No Difference	4	10		
Activity 3: Somatrogon	35	34		
Activity 3: Genotropin	2	0		
Activity 3: No Difference	5	8		
Activity 4: Somatrogon	35	37		
Activity 4: Genotropin	1	0		
Activity 4: No Difference	6	5		
Activity 5: Somatrogon	35	37		
Activity 5: Genotropin	2	0		
Activity 5: No Difference	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Family Life Interference Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Family Life Interference Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/ caregiver were asked a question "Which injection schedule interfered less?" from Section II of the IPAQ PRO tool related to family life interference and assessed for 5 activities: daily activities (Activity 1), social activities (Activity 2), recreation/leisure activities (Activity 3), spending night away from home (Activity 4) and travel (Activity 5). Preference was expressed by choosing from any 1 option for each activity from: 1) daily injection schedule interfered less; 2) weekly injection schedule interfered less; 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Activity 1: Somatrogon	32	29		
Activity 1: Genotropin	1	0		
Activity 1: No Difference	9	13		
Activity 2: Somatrogon	32	30		
Activity 2: Genotropin	1	0		
Activity 2: No Difference	9	12		
Activity 3: Somatrogon	32	32		
Activity 3: Genotropin	1	0		
Activity 3: No Difference	9	10		
Activity 4: Somatrogon	31	34		
Activity 4: Genotropin	1	0		
Activity 4: No Difference	10	8		
Activity 5: Somatrogon	31	36		
Activity 5: Genotropin	1	0		
Activity 5: No Difference	10	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Response to Benefit Relating to the Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Response to Benefit Relating to the Injection Schedule Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects were assessed for their treatment experience using DCOA 2 questionnaire completed by subject/caregiver dyads. Subjects/ caregiver were asked a question "How beneficial was to take injections less often?" from Section II of the IPAQ PRO tool pertaining to benefit relating to the Injection schedule and used a 5-point scale: 1= extremely beneficial, 2= very beneficial, 3= moderately beneficial, 4= slightly beneficial and 5= not at all beneficial. Lower score of benefit relating to injection schedule meant a better outcome. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Extremely Beneficial	28	20		
Very Beneficial	11	14		
Moderately Beneficial	1	3		
Slightly Beneficial	0	3		
Not At All Beneficial	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects as per Responses to Intention to Comply Assessed at Week 24, Using DCOA 2 Questionnaire

End point title	Number of Subjects as per Responses to Intention to Comply Assessed at Week 24, Using DCOA 2 Questionnaire

End point description:

Subjects/caregiver dyads were asked 4 questions "Which schedule would be better able to follow?" (Question 1), "Which schedule would be more likely to follow for a longer time?" (Question 2), "Which schedule would be better able to follow for a longer time?" (Question 3) and "Which schedule would be more likely to follow?" (Question 4) from Section II of the IPAQ PRO tool related to subject intention to comply with treatment. Options for each question were: 1) daily injection (Genotropin), 2) weekly injection (Somatrogon) or 3) no difference. FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
Question 1: Somatrogon	33	31		
Question 1: Genotropin	2	2		
Question 1: No Difference	7	9		
Question 2: Somatrogon	29	32		
Question 2: Genotropin	1	2		
Question 2: No Difference	12	8		
Question 3: Somatrogon	34	35		
Question 3: Genotropin	1	1		
Question 3: No Difference	7	6		
Question 4: Somatrogon	26	31		
Question 4: Genotropin	3	2		
Question 4: No Difference	13	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA) Score Assessed at Baseline, Week 12 and Week 24

End point title	Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA) Score Assessed at Baseline, Week 12 and Week 24

End point description:

The PGIS-IDA rated the severity of the impact on daily activities due to the treatment administration during the past 4 weeks on a 7-point scale (1= not present to 7= extremely severe). Scores were transformed from raw scores to a 0 to 100 scale. Lower scores meant less impact on daily activities (better outcome). FAS was analysed. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 41, 40)	15.0 (± 14.8)	16.3 (± 16.2)		
Week 12 (n= 43, 40)	19.0 (± 19.4)	4.6 (± 7.5)		
Week 24 (n= 42, 42)	7.1 (± 9.8)	22.2 (± 20.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA) Score by Treatment in Overall Study

End point title	Patient Global Impression Severity-Impact on Daily Activities (PGIS-IDA) Score by Treatment in Overall Study

End point description:

The PGIS-IDA rated the severity of the impact on daily activities due to the treatment administration during the past 4 weeks on a 7-point scale (1= not present to 7= extremely severe). Scores were transformed from raw scores to a 0 to 100 scale. Lower scores meant less impact on daily activities (better outcome). FAS was analysed. Here 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	82		
Units: units on a scale				
arithmetic mean (confidence interval 95%)	20.64 (17.30 to 23.99)	6.06 (2.66 to 9.46)		

Statistical analyses

Statistical analysis title	Genotropin versus Somatrogon
Comparison groups	Genotropin v Somatrogon

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-14.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.72
upper limit	-10.44

Notes:

[14] - 95% CI: Model-based difference in means. Results were based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment-Emergent Treatment Related AEs and SAEs

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment-Emergent Treatment Related AEs and SAEs

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was any untoward medical occurrence at any dose that: resulted in death, was life threatening (immediate risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions), resulted in congenital anomaly/birth defect. Treatment-emergent AEs (TEAEs) were defined as events that occurred between first dose of study drug up to 35 days after last dose of study drug. Related TEAEs were those AEs who had relation to the study treatment and was judged by investigator. The safety analysis set was analysed, included all randomised subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to 29 Weeks

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	87		
Units: subjects				
Treatment-Emergent AEs	38	47		
Treatment-Emergent SAEs	0	0		
Treatment-Emergent Treatment Related AEs	14	21		
Treatment-Emergent Treatment Related SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Adverse Events per Severity

End point title	Number of Subjects With Adverse Events per Severity

End point description:

AE was assessed according to severity; mild (did not interfered with subject's usual function), moderate (interfered to some extent with subject's usual function) and severe (interfered significantly with subject's usual function). The safety analysis set was analysed, included all randomised subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to 29 Weeks

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	87		
Units: subjects				
Mild	34	41		
Moderate	4	6		
Severe	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Discontinuations due to Adverse Events (AEs)

End point title	Number of Subjects With Discontinuations due to Adverse Events (AEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. The discontinuations due to adverse events was defined for subjects. The safety analysis set was analysed, included all randomised subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to 29 Weeks

End point values	Genotropin	Somatrogon		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	87		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Abnormalities

End point title	Number of Subjects With Laboratory Abnormalities

End point description:

The laboratory abnormality parameters included Hematology: erythrocyte (ery.) mean corpuscular volume, ery. mean corpuscular hemoglobin:<0.9*lower limit normal (LLN), leukocytes:<0.6*LLN, lymphocytes:<0.8*LLN, neutrophils:<0.8*LLN greater than (>) 1.2*upper limit normal (ULN), eosinophils, monocytes:>1.2*ULN. Clinical chemistry: bilirubin, direct bilirubin, indirect bilirubin:>1.5*ULN, gamma glutamyl transferase:>3.0*ULN, albumin:>1.2*ULN, blood urea nitrogen:>1.3*ULN, urate:>1.2*ULN, high-density lipoprotein (HDL) cholesterol:<0.8*LLN, potassium, magnesium:>1.1*ULN, phosphate:>1.2*ULN, bicarbonate:<0.9*LLN, creatine kinase:>2.0*ULN. Urinalysis: specific gravity:>1.030, ketones, urine protein, urine hemoglobin, nitrite, leukocyte esterase:>=1. The safety analysis set was analysed, included all randomised subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects evaluable for specified time points.

End point type	Other pre-specified

End point timeframe:

Week 1 to Week 12, Week 13 to Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: subjects				
Week 1 to Week 12 (n= 41, 36)	19	19		
Week 13 to Week 24 (n= 42, 43)	24	21		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Positive Anti-Recombinant Human Growth Hormone (rhGH) Antibodies and Neutralising Antibodies (NAb)

End point title	Number of Subjects With Positive Anti-Recombinant Human Growth Hormone (rhGH) Antibodies and Neutralising Antibodies (NAb)

End point description:

Blood samples were collected for determination of rhGH and NAb. The subjects who tested positive for antibodies were reported. The safety analysis set was analysed, included all randomised subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: subjects				
Baseline: Non-neutralising	5	0		
Baseline: Neutralising	0	0		
Week 12: Non-neutralising	3	3		
Week 12: Neutralising	0	0		
Week 24: Non-neutralising	4	6		
Week 24: Neutralising	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Positive Anti-Somatrogon Antibodies and Neutralising Antibodies (NAb)

End point title	Number of Subjects With Positive Anti-Somatrogon Antibodies and Neutralising Antibodies (NAb)

End point description:

Blood samples were collected for determination of anti-somatrogon antibodies and NAb. The subjects who tested positive for antibodies were reported. The safety analysis set was analysed, included all randomised subjects who received at least 1 dose of study drug. Here, "99999" signifies subjects were not tested for anti-somatrogon antibodies.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12, Week 24

End point values	Daily Genotropin Then Weekly Somatrogon	Weekly Somatrogon Then Daily Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: subjects				
Baseline: Non-neutralising	0	0		
Baseline: Neutralising	0	0		
Week 12: Non-neutralising	99999	4		
Week 12: Neutralising	99999	0		
Week 24: Non-neutralising	0	99999		

Week 24: Neutralising	0	99999		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 35 days after last dose (up to 29 weeks)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Genotropin
Reporting group description:	
Subjects received Genotropin, daily subcutaneously, in overall study (either in Period 1 or in Period 2).	
Reporting group title	Somatrogon
Reporting group description:	
Subjects received Somatrogon, weekly subcutaneously, at a dose of 0.66 mg/kg/week, in overall study (either in Period 1 or in Period 2).	

Serious adverse events	Genotropin	Somatrogon	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 86 (0.00%)	0 / 87 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Genotropin	Somatrogon	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 86 (44.19%)	47 / 87 (54.02%)	
General disorders and administration site conditions			
Administration site oedema			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Administration site pain			
subjects affected / exposed	0 / 86 (0.00%)	2 / 87 (2.30%)	
occurrences (all)	0	2	
Application site pruritus			

subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Fat tissue increased			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 86 (1.16%)	1 / 87 (1.15%)	
occurrences (all)	1	1	
Injection site bruising			
subjects affected / exposed	2 / 86 (2.33%)	1 / 87 (1.15%)	
occurrences (all)	3	3	
Injection site erythema			
subjects affected / exposed	1 / 86 (1.16%)	1 / 87 (1.15%)	
occurrences (all)	1	1	
Injection site haematoma			
subjects affected / exposed	8 / 86 (9.30%)	4 / 87 (4.60%)	
occurrences (all)	10	5	
Injection site haemorrhage			
subjects affected / exposed	2 / 86 (2.33%)	0 / 87 (0.00%)	
occurrences (all)	3	0	
Injection site pain			
subjects affected / exposed	11 / 86 (12.79%)	13 / 87 (14.94%)	
occurrences (all)	23	19	
Injection site reaction			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Injection site swelling			
subjects affected / exposed	2 / 86 (2.33%)	2 / 87 (2.30%)	
occurrences (all)	2	2	
Pyrexia			
subjects affected / exposed	4 / 86 (4.65%)	2 / 87 (2.30%)	
occurrences (all)	4	2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	

Social circumstances			
Excessive exercise			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 86 (2.33%)	4 / 87 (4.60%)	
occurrences (all)	3	4	
Nasal congestion			
subjects affected / exposed	1 / 86 (1.16%)	2 / 87 (2.30%)	
occurrences (all)	1	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Respiratory tract congestion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 86 (1.16%)	1 / 87 (1.15%)	
occurrences (all)	1	1	
Psychiatric disorders			
Emotional distress			
subjects affected / exposed	1 / 86 (1.16%)	1 / 87 (1.15%)	
occurrences (all)	1	4	
Insomnia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Investigations			
Body temperature increased			

subjects affected / exposed	1 / 86 (1.16%)	3 / 87 (3.45%)	
occurrences (all)	2	3	
Insulin-like growth factor increased			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 86 (5.81%)	6 / 87 (6.90%)	
occurrences (all)	6	6	
Lethargy			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Hyperacusis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Eye disorders			

Eye pruritus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Tongue ulceration			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 86 (0.00%)	2 / 87 (2.30%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 86 (0.00%)	3 / 87 (3.45%)	
occurrences (all)	0	3	
Muscle twitching			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Neck pain			

subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 86 (1.16%)	2 / 87 (2.30%)	
occurrences (all)	1	3	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Conjunctivitis viral			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	2 / 86 (2.33%)	3 / 87 (3.45%)	
occurrences (all)	2	3	
Gastroenteritis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Laryngitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	5 / 86 (5.81%)	6 / 87 (6.90%)	
occurrences (all)	5	6	
Otitis media			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	

Pharyngitis streptococcal			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 86 (1.16%)	1 / 87 (1.15%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)	4 / 87 (4.60%)	
occurrences (all)	2	4	
Urinary tract infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	3 / 86 (3.49%)	1 / 87 (1.15%)	
occurrences (all)	3	1	
Viral rash			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 86 (2.33%)	0 / 87 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2018	(A) Schedule of Activities. Medication dispensation added for Genotropin at Visits 3 and 6. (B) Schedule of Activities. DYAD Questionnaire (completed by Clinical Site Staff) added at Visits 1, 4 and 7. (C) Section 4.1. Inclusion criterion #2 (Currently on treatment with either Genotropin Pen®, Genotropin GoQuick Pen®, HumatroPen® [United States of America {USA} only], or Omnitrope® Pen [USA only]) >=3 months and had been compliant on a stable dose (+/-10%) for at least 3 months prior to screening), was modified to allow for GHD subjects on a wider range of doses to enroll in the study. (D) Section 4.2. Exclusion criterion #5 (Other causes of short stature such as uncontrolled primary hypothyroidism and rickets), was modified to remove celiac disease as exclusionary. As this is not an efficacy study assessing linear growth, children with celiac disease (which can impact growth) need not be excluded. (E) Section 5. Clarification added regarding which body weight measurement is to be used for dosing of somatrogon at Visits 1 and 4. (F) Sections 6.2.3 and 6.2.6. Genotropin drug dispensation added.
28 August 2018	(A) Schedule of Activities. Anti-rhGH antibodies (and neutralising antibodies) added at Screening, and Visits 4 and 7 at the request of the FDA. (B) Section 2 and Protocol Summary. Detection of anti-rhGH antibodies (and neutralising antibodies) added to align with FDA request. (C) Section 5.4. Arm included as an allowable injection site for Genotropin; its prior omission was in error.
08 November 2018	(A) Added free thyroxine (FT4) testing at Screening and at Visits 4 and 7 at the request of the MHRA. (B) Modified Section 13, definition of end of trial to be last subject last visit (LSLV) at the request of the MHRA.
03 May 2019	(A) Section 4.2. Addition of children with closed epiphyses to the Exclusion Criteria to address the request of EU Health Authorities. (B) Section 4.2. Exclusion criteria regarding allowable injectable medications clarified. (C) Sections 5.5, 6.1.1, 6.2.3, & 6.2.4. Dosing windows expanded for Genotropin (36 hours +/- 24 hours) and somatrogon (7 days +/- 72 hours) prior to Visits 1 and 4 providing increased flexibility in dosing for subjects/caregivers prior to visits. (D) Section 5.8.1. Allowable injectable concomitant medications clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported