



## Clinical trial results:

### **Efficacy and Safety of Somatropin in Combination With Leuporelin Compared to Somatropin Alone in Pubertal Children With Idiopathic Short Stature (Phoenix)**

#### **Summary**

EudraCT number	2005-001750-25
Trial protocol	NL
Global end of trial date	07 July 2015

#### **Results information**

Result version number	v1 (current)
This version publication date	26 August 2016
First version publication date	26 August 2016

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	9861
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00266656
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number : 9861, Trial Alias: B9R-FP-GDGI

Notes:

##### **Sponsors**

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-285-4559,

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	07 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 July 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The present randomized trial was initially intended to study the benefits of a combined treatment with growth hormone (GH) and a gonadotropin-releasing hormone (GnRH) agonist for pubertal children with idiopathic short stature. However, treatments were stopped in January 2012 at the request of the French drug agency. Therefore, a protocol amendment divided the study in two study periods.

Study Period 1 involved combined treatment with somatropin and leuporelin or treatment with somatropin alone. Participants from France who participated in this Period 1 of the study were asked to participate in a long term safety follow up defined as a Period 2 of the study. Participants from the Netherlands were offered participation in Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS, clinicaltrials.gov Identifier: NCT01088412) for long term safety follow up independent of this study.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	42 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	France: 77
Worldwide total number of subjects	88
EEA total number of subjects	88

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	42
Adolescents (12-17 years)	46
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

No Text Entered

### Pre-assignment

Screening details:

No Text Entered

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Somatropin and Leuporelin: Experimental Arm 1
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Arm description:

0.05 milligram (mg) per kilogram (kg) per day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuporelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	LY137998, Humatrope
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

Investigational medicinal product name	Leuporelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

11.25 mg every 3 months

<b>Arm title</b>	Somatropin: Experimental Arm 2
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Arm description:

0.05mg/kg/day subcutaneous somatropin only.

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

Arm type	Experimental
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Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	LY137998, Humatrope
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

<b>Number of subjects in period 1</b>	<b>Somatropin and Leuporelin: Experimental Arm 1</b>	<b>Somatropin: Experimental Arm 2</b>
Started	45	43
Received At Least One Dose of Study Drug	45	43
Reached Final Height	1 <sup>[1]</sup>	1 <sup>[2]</sup>
Did Not Reach Final Height	44	42
Completed	20	19
Not completed	25	24
See justification section	25	24

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to system limitations, the participants listed as completed/not completed are the participants who participated/did not participate in study period 2. The actual completed/not completed participants are 1/44 for arm 1.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to system limitations, the participants listed as completed/not completed are the participants who participated/did not participate in study period 2. The actual completed/not completed participants are 1/43 for arm 2.

## Period 2

Period 2 title	Study Period 2 Long Term Follow-Up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Somatropin and Leuporelin: Experimental Arm 1

Arm description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuporelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

Arm type	Experimental
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Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	LY137998, Humatrope
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

Investigational medicinal product name	Leuprorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

11.25 mg every 3 months

<b>Arm title</b>	Somatropin: Experimental Arm 2
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Arm description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin only.

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	LY137998, Humatrope
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.05 milligram (mg) per kilogram (kg) per day

<b>Number of subjects in period 2</b>	Somatropin and Leuprorelin: Experimental Arm 1	Somatropin: Experimental Arm 2
Started	20	19
Completed	19	17
Not completed	1	2
Consent withdrawn by subject	1	1
Lost to follow-up	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Somatropin and Leuporelin: Experimental Arm 1
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Reporting group description:

0.05 milligram (mg) per kilogram (kg) per day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuporelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

Reporting group title	Somatropin: Experimental Arm 2
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Reporting group description:

0.05mg/kg/day subcutaneous somatropin only.

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

Reporting group values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2	Total
Number of subjects	45	43	88
Age categorical			
Units: Subjects			
Children (2-11 years)	20	22	42
Adolescents (12-17 years)	25	21	46
Age Continuous			
Units: years			
arithmetic mean	12.1	12.1	
standard deviation	± 1.41	± 1.33	-
Gender, Male/Female			
Units: participants			
Female	26	20	46
Male	19	23	42
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	38	40	78
More than one race	0	0	0
Unknown or Not Reported	2	1	3
Region of Enrollment			
Units: Subjects			
Netherlands	6	5	11
France	39	38	77

Standing Height SDS Units: Standard Deviation Score arithmetic mean standard deviation	-2.5 ± 0.45	-2.5 ± 0.46	-
Standing Height Units: centimeters arithmetic mean standard deviation	131.6 ± 6.72	131.6 ± 5.78	-



## End points

### End points reporting groups

Reporting group title	Somatropin and Leuprorelin: Experimental Arm 1
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Reporting group description:

0.05 milligram (mg) per kilogram (kg) per day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuprorelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

Reporting group title	Somatropin: Experimental Arm 2
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Reporting group description:

0.05mg/kg/day subcutaneous somatropin only.

One participant reached final height and completed the study. All participants from France were eligible to participate in the safety follow up period (study period 2 below).

Participants from the Netherlands exited the study after Study Period 1.

Reporting group title	Somatropin and Leuprorelin: Experimental Arm 1
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Reporting group description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin and 3-month formulation, subcutaneous or intramuscular injection of 11.25mg leuprorelin for three years (or for a minimum of 2 years until a chronological age of 13 years for girls and 15 years for boys, whichever occurs first).

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

Reporting group title	Somatropin: Experimental Arm 2
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Reporting group description:

No treatment was administered during the follow up period. Participants received the following during the treatment period: 0.05mg/kg/day subcutaneous somatropin only.

Participants from the Netherlands exited the study after Study Period 1. Participants from France were given the option to re-consent for Study Period 2.

Subject analysis set title	Arm: Somatropin and Leuprorelin: Experimental Arm 1
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All participants that started the study in addition to participants from previous control group who were ineligible to participate in the study were given somatropin and are included for AE assessment.

Subject analysis set title	Arm: Somatropin: Experimental Arm 2
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All participants that started the study in addition to participants from previous control group who were ineligible to participate in the study were given somatropin and are included for AE assessment.

### Primary: Number of Participants With One Or More Drug-related Adverse Events

End point title	Number of Participants With One Or More Drug-related Adverse Events <sup>[1]</sup>
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End point description:

A drug-related AE was an AE that occurred postdose or was present predose and became more severe postdose and was considered to be related to study treatment. A summary of other nonserious AEs, and all SAE's, regardless of causality, is located in the Reported Adverse Events section.

Population description: All participants who received at least one dose of study drug in Period 1 and all participants who entered Period 2 (safety population).

End point type	Primary
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End point timeframe:

Baseline through End of Study (up to 9 years)

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 analyses was planned after the discontinuation of treatments. Only descriptive statistics performed as participants were only followed up for safety.

End point values	Arm: Somatropin and Leuporelin: Experimental Arm 1	Arm: Somatropin: Experimental Arm 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	45		
Units: participants				
number (not applicable)				
Study Period 1 (n=46, 45)	42	38		
Study Period 2 (n=20, 19)	11	9		

## Statistical analyses

No statistical analyses for this end point

## Primary: Adult Height Standard Deviation Score (SDS)

End point title	Adult Height Standard Deviation Score (SDS) <sup>[2]</sup>
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End point description:

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received at least one dose of study drug with at least one follow up visit.

End point type	Primary
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End point timeframe:

Baseline through End of Study (up to 9 years)

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: The analysis for the primary efficacy objective on adult height SDS was not performed due to the early termination of study treatment. However, the height of patients was still monitored up to adult height in both treatment groups.

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: standard deviation score				
arithmetic mean (standard deviation)	-1.8 (± 0.53)	-1.9 (± 0.77)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Height Velocity

End point title	Height Velocity
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End point description:

Height velocity is the difference between 2 height measurements, divided by years elapsed between measurements.

Population description: All participants who received at least one dose of study drug with at least one follow up visit. The safety follow up participants did not reach final height at end of Period 1 unless final height is noted for participants that reached final height at the end of Period 1.

End point type	Secondary
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End point timeframe:

Baseline through End of Study (up to 9 years)

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: centimeter per year				
arithmetic mean (standard deviation)				
Randomization (n=45, 43)	7.8 (± 6.92)	7.4 (± 6.03)		
Month 3 (n=45, 43)	9.9 (± 3.94)	10.6 (± 3.53)		
Month 6 (n=45, 42)	8.1 (± 2.31)	9.7 (± 2.8)		
Month 12 (n=44, 42)	7 (± 1.64)	8.8 (± 2.33)		
Month 18 (n=42, 42)	6.6 (± 1.68)	8.4 (± 2.64)		
Month 24 (n=37, 41)	4.9 (± 1.33)	7.8 (± 3.36)		
Month 30 (n=25, 25)	6.2 (± 2.09)	5.8 (± 2.93)		
Month 36 (n=18, 19)	6.6 (± 3.25)	3.5 (± 2.71)		
Month 42 (n=13, 14)	5.7 (± 1.94)	3.7 (± 2.17)		
Month 48 (n=7, 8)	5.4 (± 2.27)	2.9 (± 2.73)		
Month 54 (n=1, 1)	6.3 (± 0)	7.1 (± 0)		
Safety follow up 6 months (n=16, 9)	4.6 (± 2.08)	4.5 (± 2.45)		
Safety follow up 12 months(n=15, 8)	2.9 (± 2.37)	2.3 (± 1.43)		
Safety follow up 18 months (n=12, 4)	3.3 (± 1.69)	1.2 (± 1.2)		
Safety follow up 24 months (n=9, 1)	2 (± 1.32)	2.5 (± 0)		
Safety follow up 36 months (n=5, 0)	1.3 (± 0.53)	0 (± 0)		
Safety follow up 42 months (n=2, 0)	2.1 (± 2.45)	0 (± 0)		
Safety follow up 12 months (final height)(n=18,14)	0.5 (± 0.86)	0.8 (± 1.59)		

Safety follow up 24 months (final height) (n=7,10)	0.3 ( $\pm$ 0.77)	0.3 ( $\pm$ 0.97)		
Safety follow up 36 months (final height) (n=3,7)	0.9 ( $\pm$ 0.78)	0.3 ( $\pm$ 0.6)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Height SDS

End point title	Height SDS
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End point description:

SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received at least one dose of study drug with at least one follow up visit. The safety follow up participants did not reach final height at end of Period 1 unless final height is noted for participants that reached final height at the end of Period 1.

End point type	Secondary
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End point timeframe:

Baseline through End of Study (up to 9 years)

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: standard deviation score				
arithmetic mean (standard deviation)				
Randomization (n=45, 43)	-2.5 ( $\pm$ 0.45)	-2.5 ( $\pm$ 0.46)		
Month 3 (n=45, 43)	-2.4 ( $\pm$ 0.42)	-2.4 ( $\pm$ 0.47)		
Month 6 (n=45, 42)	-2.3 ( $\pm$ 0.48)	-2.2 ( $\pm$ 0.52)		
Month 12 (n=44, 42)	-2.2 ( $\pm$ 0.5)	-2 ( $\pm$ 0.57)		
Month 18 (n=42, 42)	-2.2 ( $\pm$ 0.53)	-1.9 ( $\pm$ 0.63)		
Month 24 (n=37, 41)	-2.3 ( $\pm$ 0.58)	-1.8 ( $\pm$ 0.67)		
Month 30 (n=25, 25)	-2.2 ( $\pm$ 0.63)	-2 ( $\pm$ 0.58)		
Month 36 (n=18, 19)	-2 ( $\pm$ 0.65)	-2 ( $\pm$ 0.68)		
Month 42 (n=13, 14)	-1.8 ( $\pm$ 0.68)	-1.9 ( $\pm$ 0.66)		
Month 48 (n=7, 8)	-1.6 ( $\pm$ 0.52)	-1.9 ( $\pm$ 0.65)		
Month 54 (n=1, 1)	-1 ( $\pm$ 0)	-1.7 ( $\pm$ 0)		
Safety follow up 6 months (n=16, 9)	-2.1 ( $\pm$ 0.65)	-1.7 ( $\pm$ 0.77)		
Safety follow up 12 months (n=15, 8)	-1.9 ( $\pm$ 0.55)	-1.7 ( $\pm$ 0.77)		
Safety follow up 18 months (n=12, 4)	-1.9 ( $\pm$ 0.63)	-1.9 ( $\pm$ 0.78)		
Safety follow up 24 months (n=9, 1)	-1.9 ( $\pm$ 0.46)	-1.2 ( $\pm$ 0)		
Safety follow up 36 months (n=5, 0)	-1.9 ( $\pm$ 0.67)	0 ( $\pm$ 0)		
Safety follow up 42 months (n=2, 0)	-2.4 ( $\pm$ 0.18)	0 ( $\pm$ 0)		

Safety follow up 12 months (final height)(n=18,14)	-1.9 ( $\pm$ 0.46)	-1.8 ( $\pm$ 0.71)		
Safety follow up 24 months (final height) (n=7,10)	-1.6 ( $\pm$ 0.56)	-2 ( $\pm$ 0.79)		
Safety follow up 36 months (final height) (n=3,7)	-1.2 ( $\pm$ 0.9)	-2.2 ( $\pm$ 0.94)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Difference Between Adult Height SDS And Target Height SDS

End point title	Difference Between Adult Height SDS And Target Height SDS
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End point description:

This is the difference between the gender, age and country matched standard deviation score of adult height and standard deviation score of target height [calculated as (mother's height (SDS) + father's height (SDS))/2] for particular participant.

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received who reached final height.

End point type	Secondary
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End point timeframe:

Baseline through End of Study (up to 9 years)

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: standard deviation score				
arithmetic mean (standard deviation)	-0.6 ( $\pm$ 0.89)	-1.2 ( $\pm$ 0.8)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Difference Between Adult Height SDS And Baseline Predicted Height SDS

End point title	Difference Between Adult Height SDS And Baseline Predicted Height SDS
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End point description:

This is the difference between the gender, age and country matched standard deviation score of adult height and standard deviation score of baseline predicted height [calculated using the Bayley-Pinneau

method based on height and bone age] for particular participant.

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received who reached final height.

End point type	Secondary
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End point timeframe:

Baseline through End up Study (up to 9 years)

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: standard deviation score				
arithmetic mean (standard deviation)	1.1 (± 0.96)	1.2 (± 0.7)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Difference Between Adult Height SDS And Baseline Height SDS

End point title	Difference Between Adult Height SDS And Baseline Height SDS
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End point description:

This is the difference between the gender, age and country matched standard deviation score of adult height and standard deviation score of baseline height for particular participant.

The height of the participants were measured barefoot using a standard wall-mounted Harpenden stadiometer. SDS report the number of standard deviations from the mean for age and sex for an individual measurement (normal range: -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.

Population description: All participants who received who reached final height.

End point type	Secondary
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End point timeframe:

Baseline through End up Study (up to 9 years)

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: standard deviation score				
arithmetic mean (standard deviation)	0.6 (± 0.59)	0.6 (± 0.67)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Of Children With Normal Adult Height SDS

End point title	Percentage Of Children With Normal Adult Height SDS
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End point description:

Percentage of children with normal adult height SDS (greater than -2 SDS and less than +2 SDS).

Population description: All participants who received at least one dose of study drug with at least one follow up visit.

End point type	Secondary
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End point timeframe:

Baseline through End of Study (up to 9 years)

End point values	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: percentage of participants				
number (not applicable)	26.7	25.6		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Bone Age

End point title	Bone Age
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End point description:

Bone age measured using the X-Ray of left hand and wrist.

Population description: All participants who received at least one dose of study drug with at least one follow up visit. The safety follow up participants did not reach final height at end of Period 1 unless final height is noted for participants that reached final height at the end of Period 1.

End point type	Secondary
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End point timeframe:

Baseline through End of Study (up to 9 years)

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<b>End point values</b>	Somatropin and Leuporelin: Experimental Arm 1	Somatropin: Experimental Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: years				
arithmetic mean (standard deviation)				
Randomization (n=45, 43)	10.8 (± 1.58)	11 (± 1.45)		
Month 12 (n=40, 41)	11.7 (± 1.59)	12.1 (± 1.12)		
Month 24 (n=34, 37)	12.4 (± 1.32)	13.4 (± 1.09)		
Month 36 (n=18, 18)	13.3 (± 1.49)	14.5 (± 1.64)		
Month 48 (n=7, 8)	14.8 (± 1.33)	15.4 (± 1.27)		
Safety follow up 6 months (n=16, 7)	14.1 (± 1.11)	14.9 (± 0.81)		
Safety follow up 18 months (n=12, 3)	15.2 (± 1.25)	17 (± 1)		
Safety follow up 36 months (n=5, 0)	15.7 (± 1.04)	0 (± 0)		
Safety follow up 12 months (final height)(n=18,14)	19.6 (± 14.53)	16.3 (± 1.27)		

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

All participants that started the study in addition to 3 participants from previous control group who were ineligible to participate in the study were given somatropin and are included in somatropin arm for AE assessment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Somatropin: Experimental Arm 2
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Reporting group description: -

Reporting group title	Somatropin and Leuprorelin: Experimental Arm 1
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Reporting group description: -

Serious adverse events	Somatropin: Experimental Arm 2	Somatropin and Leuprorelin: Experimental Arm 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 45 (15.56%)	12 / 46 (26.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
histiocytosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
fall			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fracture			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
joint dislocation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
radius fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
road traffic accident			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper limb fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
wrist fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
congenital genital malformation			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thyroglossal cyst			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
migraine			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
complication of device removal			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
agitation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intentional self-injury			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mental disorder			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicidal ideation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
nephrolithiasis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal colic			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
appendiceal abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
appendicitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 45 (4.44%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
viral infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Somatropin: Experimental Arm 2	Somatropin and Leuporelin: Experimental Arm 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 45 (80.00%)	41 / 46 (89.13%)	
Injury, poisoning and procedural complications			
ligament sprain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 45 (2.22%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	16 / 45 (35.56%)	21 / 46 (45.65%)	
occurrences (all)	37	51	
General disorders and administration site conditions			
injection site pain			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed occurrences (all)  pyrexia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0  5 / 45 (11.11%) 6	8 / 46 (17.39%) 22  4 / 46 (8.70%) 4	
Ear and labyrinth disorders ear pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4	1 / 46 (2.17%) 5	
Immune system disorders hypersensitivity alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 46 (6.52%) 3	
Gastrointestinal disorders abdominal pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)  abdominal pain upper alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)  diarrhoea alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)  nausea alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)  toothache alternative dictionary used: MedDRA 18.0	7 / 45 (15.56%) 18  4 / 45 (8.89%) 10  3 / 45 (6.67%) 3  2 / 45 (4.44%) 3	4 / 46 (8.70%) 4  3 / 46 (6.52%) 11  3 / 46 (6.52%) 14  3 / 46 (6.52%) 7	

<p>subjects affected / exposed</p> <p>0 / 45 (0.00%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>0</p> <p>7</p> <p>vomiting</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>3 / 45 (6.67%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>5</p> <p>5</p>			
<p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>6 / 45 (13.33%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>15</p> <p>4</p> <p>epistaxis</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>2 / 45 (4.44%)</p> <p>3 / 46 (6.52%)</p> <p>occurrences (all)</p> <p>2</p> <p>4</p> <p>oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>4 / 45 (8.89%)</p> <p>5 / 46 (10.87%)</p> <p>occurrences (all)</p> <p>6</p> <p>6</p>			
<p>Skin and subcutaneous tissue disorders</p> <p>acne</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>5 / 45 (11.11%)</p> <p>2 / 46 (4.35%)</p> <p>occurrences (all)</p> <p>7</p> <p>2</p>			
<p>Endocrine disorders</p> <p>hypothyroidism</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>3 / 45 (6.67%)</p> <p>1 / 46 (2.17%)</p> <p>occurrences (all)</p> <p>3</p> <p>1</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>4 / 45 (8.89%)</p> <p>7 / 46 (15.22%)</p> <p>occurrences (all)</p> <p>6</p> <p>11</p> <p>pain in extremity</p>			

alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	4 / 46 (8.70%) 4	
scoliosis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	4 / 46 (8.70%) 4	
Infections and infestations bronchitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	3 / 46 (6.52%) 4	
cystitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 46 (6.52%) 3	
ear infection alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 8	4 / 46 (8.70%) 4	
gastroenteritis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 9	11 / 46 (23.91%) 15	
influenza alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 16	15 / 46 (32.61%) 17	
nasopharyngitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 10	19 / 46 (41.30%) 36	
rhinitis alternative dictionary used: MedDRA 18.0			



subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 11	5 / 46 (10.87%) 5	
tonsillitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 12	6 / 46 (13.04%) 9	
tracheitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	2 / 46 (4.35%) 2	
Metabolism and nutrition disorders vitamin d deficiency alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 46 (6.52%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2008	Study Period 1 treatment with Humatrope was suspended for all active participants. Participants from the Netherlands exited the study after Study Period 1 and participants from France were given the option to re-consent for Study Period 2.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No statistical analyses was performed after the early treatment termination. All data represented is descriptive statistics only and no confirmatory conclusions can be drawn from this study.

Notes: