



## Clinical trial results:

**Multicentre study to evaluate the efficacy and safety of a liquid formulation of recombinant growth hormone, Omnitrope® 3.3mg/mL, in the treatment of pre-pubertal children of small stature suffering from somatotropin deficiency (GH) – phase IIIb**

### Summary

EudraCT number	2015-002802-34
Trial protocol	Outside EU/EEA
Global end of trial date	31 July 2008

### Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

### Trial information

#### Trial identification

Sponsor protocol code	Sandoz/OMNI/F/01/03
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Sandoz S.A.S
Sponsor organisation address	49, avenue Georges Pompidou, Levallois-Perret Cedex, France, 92300
Public contact	Strategic Planning Biopharma Clinical Development, Sandoz, 0049 80244760, biopharma.clinicaltrials@sandoz.com
Scientific contact	Strategic Planning Biopharma Clinical Development, Sandoz, 0049 80244760, biopharma.clinicaltrials@sandoz.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	08 November 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 July 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy and tolerance of Omnitrope® 3.3 mg/ml injection, administered at a dose of 0.23 mg/kg/week, in terms of clinical and immunological parameters, and laboratory test results.

Protection of trial subjects:

Before the patient embarked on the study, the Investigator was obliged to explain clearly to every Patient/Family/Legal Representative the nature and objectives of the clinical trial, its benefits and risks, their rights and the confidentiality of the data, before providing a copy of the Information Sheet to read and keep.

At the Pre-Inclusion Visit, after the Patient/Family/Legal Representative had familiarised themselves with the information provided, the Investigator asked them to give their agreement in writing by dating page and signing the Informed Consent Form.

For the Amendments that entailed changes to the Information Sheet and Informed Consent Form, the Investigator had to get new Forms signed and dated by every Patient/Family/Legal Representative.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2003
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	France: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	53
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 100 patients should have been recruited in 41 French sites, due to slow recruitment 51 patients were enrolled in 23 sites  
first patient first visit 20 Oct 2003  
last patient first visit 13 Nov 2006  
last patient last visit 31 Jul 2008.

### Pre-assignment

Screening details:

53 patients were screened, 2 patients didn't meet the screening criteria and were therefore not included in the study due to either violation of inclusion criteria or growth hormone test not showing deficiency

### Pre-assignment period milestones

Number of subjects started	53
Number of subjects completed	51

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2
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### Period 1

Period 1 title	Treatment Phase up to Month 12
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	All patients
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Omnitrope®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Omnitrope® 3.3 mg/mL injection administered subcutaneously using an injector pen with ready-to-use 1.5 ml cartridges. Included patients were given a dosage of 0.23 mg/kg/week, i.e. 0.033 mg/kg/day injected once daily for 12 months.

<b>Number of subjects in period 1<sup>[1]</sup></b>	All patients
Started	51
Completed	51

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 2 patients were screened but not enrolled into the trial

## Period 2

Period 2 title	Treatment Phase Month 12 - 24
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NAP

## Arms

Arm title	All patients
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Arm description:

This study phase was already voluntary for the patients. Therefore 51 started and only 41 ended it.

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

Dosage and administration details:

Omnitrope® 3.3 mg/mL injection administered subcutaneously using an injector pen with ready-to-use 1.5 ml cartridges. Included patients were given a dosage of 0.23 mg/kg/week, i.e. 0.033 mg/kg/day injected once daily for 12 months.

Number of subjects in period 2	All patients
Started	51
Completed	41
Not completed	10
Consent withdrawn by subject	1
Unknown but no AE	5
Switch to commercialised product	3
Lack of efficacy	1

## Period 3

Period 3 title	Treatment Phase Month 24 - 36
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NAP

## Arms

<b>Arm title</b>	All patients
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Omnitrope®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

Omnitrope® 3.3 mg/mL injection administered subcutaneously using an injector pen with ready-to-use 1.5 ml cartridges. Included patients were given a dosage of 0.23 mg/kg/week, i.e. 0.033 mg/kg/day injected once daily for 12 months.

<b>Number of subjects in period 3</b>	All patients
Started	41
Completed	24
Not completed	17
Unknown but no AE	8
Lost to follow-up	2
Switch to commercialised product	4
Lack of efficacy	1
Protocol deviation	2

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment Phase up to Month 12
Reporting group description: -	

Reporting group values	Treatment Phase up to Month 12	Total	
Number of subjects	51	51	
Age categorical			
Patients where divided into 3 agegroup			
Units: Subjects			
< 4 years	7	7	
[4-8) years	27	27	
>= 8 years	17	17	
Age continuous			
children with the age of 1.19 to 11.62 years were included into the study			
Units: years			
arithmetic mean	6.87		
full range (min-max)	1.33 to 11.82	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	42	42	
Scan of brain			
MR examination of the brain, with centralised reading for the results			
Units: Subjects			
Normal	1	1	
Not done	50	50	
MRI brain			
Units: Subjects			
Normal	20	20	
Abnormal	16	16	
Not done	15	15	
Gestational Age [weeks]			
Units: weeks			
arithmetic mean	39.22		
full range (min-max)	34 to 46	-	
Birth height			
Units: cm			
arithmetic mean	47.96		
full range (min-max)	42 to 51	-	
Birth weight			
Units: gram(s)			
arithmetic mean	3110		
full range (min-max)	1420 to 4760	-	
Cranial perimeter			
Units: cm			
arithmetic mean	34.53		

full range (min-max)	31 to 38.5	-	
Father's height			
Units: cm			
arithmetic mean	171.7		
full range (min-max)	155 to 193.5	-	
Age of father's puberty			
Units: years			
arithmetic mean	14.11		
full range (min-max)	12.6 to 17	-	
Mother's height			
Units: cm			
arithmetic mean	158.12		
full range (min-max)	139.5 to 174	-	
Age of mother's first menstruation			
Units: years			
arithmetic mean	13.21		
full range (min-max)	10.6 to 17	-	
Weight			
Units: kg			
arithmetic mean	17.91		
full range (min-max)	8.3 to 34.5	-	
BMI			
Units: kg/cm2			
arithmetic mean	15.35		
full range (min-max)	12.12 to 25.38	-	
Height			
Units: cm			
arithmetic mean	106.49		
full range (min-max)	73 to 134	-	
Height SDS			
height minus standard height of the respective age divided by standard deviation for the respective age of the standard population			
Units: SDS			
arithmetic mean	-2.39		
full range (min-max)	-4.03 to -1.47	-	



## End points

### End points reporting groups

Reporting group title	All patients
Reporting group description: -	
Reporting group title	All patients
Reporting group description: This study phase was already voluntary for the patients. Therefore 51 started and only 41 ended it.	
Reporting group title	All patients
Reporting group description: -	

### Primary: Height velocity after 12 months

End point title	Height velocity after 12 months <sup>[1]</sup>
End point description: Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25. To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.	
End point type	Primary
End point timeframe: 12 months	

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: The whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: cm/year				
arithmetic mean (standard deviation)				
Height velocity month 12	9.66 (± 2.14)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Height velocity after 24 months

End point title	Height velocity after 24 months <sup>[2]</sup>
End point description: Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25. To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.	
End point type	Primary

End point timeframe:

Month 12 to month 24

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 whole study was performed only with descriptive analysis.

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: cm/year				
arithmetic mean (standard deviation)				
Height velocity month 24	8.65 (± 1.42)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height velocity after 36 months

End point title	Height velocity after 36 months <sup>[3]</sup>
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End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25. To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

End point type	Primary
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End point timeframe:

Month 24 to 36

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: The whole study was performed only with descriptive analysis.

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: cm/year				
arithmetic mean (standard deviation)				
Height velocity month 36	8.2 (± 1)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height velocity SDS after 12 months

End point title	Height velocity SDS after 12 months <sup>[4]</sup>
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**End point description:**

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25.

Increase in height velocity SDS (related to chronological age and gender)

SDS values are calculated for height velocity using the following equation:  $SDS = X1 - X2 / SD$  in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

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End point type	Primary
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End point timeframe:

Baseline to month 12

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**Notes:**

[4] - 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 whole study was performed only with descriptive analysis.

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: SDS/year				
arithmetic mean (standard deviation)				
Height velocity SDS month 12	4.66 (± 3.07)			

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**Statistical analyses**

No statistical analyses for this end point

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**Primary: Height velocity SDS after 24 months**

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End point title	Height velocity SDS after 24 months <sup>[5]</sup>
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End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25.

Increase in height velocity SDS (related to chronological age and gender)

SDS values are calculated for height velocity using the following equation:  $SDS = X1 - X2 / SD$  in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

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End point type	Primary
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End point timeframe:

month 12 to 24

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**Notes:**

[5] - 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 whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: SDS/year				
arithmetic mean (standard deviation)				
Height velocity SDS month 24	3.45 (± 2.2)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height velocity SDS after 36 months

End point title	Height velocity SDS after 36 months <sup>[6]</sup>
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End point description:

Height velocity is calculated in cm/year by dividing the difference in two height readings by the interval of time between the measurements and multiplying by 365.25.

Increase in height velocity SDS (related to chronological age and gender)

SDS values are calculated for height velocity using the following equation:  $SDS = X1 - X2 / SD$  in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

To ensure accurate estimation of height and growth rate, each patient was measured three times at each Visit by the same Investigator using the same graduated height gauge. The height recorded represents the mean of these three measurements.

End point type	Primary
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End point timeframe:

month 24 to 36

Notes:

[6] - 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 whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: SDS/year				
arithmetic mean (standard deviation)				
Height velocity SDS month 36	2.55 (± 2.01)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height gain after 12 months

End point title	Height gain after 12 months <sup>[7]</sup>
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End point description:

Height gain expressed in cm

End point type	Primary
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End point timeframe:

Baseline to month 12

Notes:

[7] - 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 whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: cm				
arithmetic mean (standard deviation)				
Height gain month 12	9.67 (± 1.84)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Height gain after 24 months

End point title	Height gain after 24 months <sup>[8]</sup>
End point description:	height gain expressed in cm
End point type	Primary
End point timeframe:	Month 12 to 24

Notes:

[8] - 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 whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: cm				
arithmetic mean (standard deviation)				
Height gain month 24	17.04 (± 2.75)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Height gain after 36 months

End point title	Height gain after 36 months <sup>[9]</sup>
End point description:	height gain expressed in cm
End point type	Primary

End point timeframe:

Month 24 to 36

Notes:

[9] - 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 whole study was performed only with descriptive analysis.

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: cm				
arithmetic mean (standard deviation)				
Height gain month 36	24.6 (± 3.21)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height gain SDS

End point title	Height gain SDS <sup>[10]</sup>
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End point description:

Standard Deviation Score (SDS) which is based on the difference between the mean value for normal children of the same gender at that chronological age. SDS values are calculated for height using the following equation:  $SDS = (X1 - X2) / SD$  in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

End point type	Primary
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End point timeframe:

Baseline to month 12

Notes:

[10] - 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 whole study was performed only with descriptive analysis.

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: SDS				
arithmetic mean (standard deviation)				
Height gain SDS month 12	-1.48 (± 0.65)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height gain SDS after 24 months

End point title	Height gain SDS after 24 months <sup>[11]</sup>
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End point description:

Standard Deviation Score (SDS) which is based on the difference between the mean value for normal children of the same gender at that chronological age. SDS values are calculated for height using the following equation:  $SDS = X1 - X2 / SD$  in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

End point type	Primary
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End point timeframe:

Month 12 to 24

Notes:

[11] - 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 whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: SDS				
arithmetic mean (standard deviation)				
Height gain SDS month 24	-0.97 (± 0.61)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Height gain SDS after 36 months

End point title	Height gain SDS after 36 months <sup>[12]</sup>
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End point description:

Standard Deviation Score (SDS) which is based on the difference between the mean value for normal children of the same gender at that chronological age. SDS values are calculated for height using the following equation:  $SDS = X1 - X2 / SD$  in which X1 is the actual measurement, X2 is the norm for that chronological age (CA) (or bone age, if appropriate) and SD is the standard deviation at that age.

End point type	Primary
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End point timeframe:

Month 24 to 36

Notes:

[12] - 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 whole study was performed only with descriptive analysis.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: cm				
arithmetic mean (standard deviation)				
Height gain SDS month 36	-0.71 (± 0.71)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: IGF-1 baseline to month 12

End point title IGF-1 baseline to month 12

End point description:

Increases in IGF-1 levels were calculated every six months. Changes in IGF-1 levels were evaluated for each individual patient and for all subjects.

End point type Secondary

End point timeframe:

Baseline to month 12

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	64.88 ( $\pm$ 54.18)			
Month 6	172.4 ( $\pm$ 127)			
Month 12	193.5 ( $\pm$ 103.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: IGF-1 month 12 to month 24

End point title IGF-1 month 12 to month 24

End point description:

Increases in IGF-1 levels were calculated every six months. Changes in IGF-1 levels were evaluated for each individual patient and for all subjects.

End point type Secondary

End point timeframe:

Month 12 to 24

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 18	208.5 ( $\pm$ 79.12)			
Month 24	241.2 ( $\pm$ 113)			



## Statistical analyses

No statistical analyses for this end point

### Secondary: IGF-1 month 24 to month 36

End point title	IGF-1 month 24 to month 36
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End point description:

Increases in IGF-1 levels were calculated every six months. Changes in IGF-1 levels were evaluated for each individual patient and for all subjects.

End point type	Secondary
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End point timeframe:

Month 24 to 36

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 36	234.5 (± 169.8)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: IGF-1 SDS baseline to month 12

End point title	IGF-1 SDS baseline to month 12
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to month 12

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline	-1.28 (± 1.26)			
Month 6	0.58 (± 1.77)			
Month 12	0.6 (± 1.48)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: IGF-1 SDS month 12 to month 24

End point title	IGF-1 SDS month 12 to month 24
End point description:	
End point type	Secondary
End point timeframe:	
Month 12 to 24	

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: SDS				
arithmetic mean (standard deviation)				
Month 18	0.91 (± 1.5)			
Month 24	0.6 (± 1.55)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: IGF-1 SDS month 36

End point title	IGF-1 SDS month 36
End point description:	
End point type	Secondary
End point timeframe:	
Month 24 to 36	

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: SDS				
arithmetic mean (standard deviation)				
Month 36	0.44 (± 2.01)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Antibodies against GH - Baseline and Month 12

End point title	Antibodies against GH - Baseline and Month 12
End point description: Immunological safety was assessed by assaying for antibodies against GH at a central laboratory. This endpoint was analysed even for patients that dropped out of the study.	
End point type	Secondary
End point timeframe: 24 Months - assessments where done at baseline, at month 12 and at month 24	

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Negative / positive				
Negative - Baseline	44			
Missing - Baseline	6			
Negative - Month 12	42			
Missing - Month 12	8			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Antibodies against GH - Month 24

End point title	Antibodies against GH - Month 24
End point description: Immunological safety was assessed by assaying for antibodies against GH at a central laboratory. This endpoint was analysed even for patients that dropped out of the study.	
End point type	Secondary

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End point timeframe:

24 Months - assessments where done at baseline, at month 12 and at month 24

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<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Negative / Positive				
Negative - Month 24	25			
Missing - Month 24	16			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

51 subjects were exposed to the treatment for 12 months, 43 for 18 months, 41 for 24 months and 24 for 36 months, representing about 1400 subject\*months

Adverse event reporting additional description:

The following assessments were made at each Visit:

- Local tolerance at the injection site.
- Systemic tolerance through the recording of Adverse Events and concomitant treatments

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	All patients
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Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 51 (3.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Surgical and medical procedures			
Appendectomy	Additional description: Appendectomy was performed on 7 May and his hospital stay lasted from 7 - 14 May 2005. During this time, the treatment was interrupted. The Investigator judged the relationship between the event and the Study Treatment as Improbable.		
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation	Additional description: Constipation was diagnosed; he was given an enema and put on Fortax and Spasfon. He completely recovered and was discharged on 17 March 2006. The Investigator judged that no related to study treatment		
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

<b>Non-serious adverse events</b>	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 51 (82.35%)		
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 51 (19.61%)		
occurrences (all)	10		
Gastrointestinal disorders			
Pharyngitis			
subjects affected / exposed	8 / 51 (15.69%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Rhinitis			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	9		
Cough			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		
Infections and infestations			
Ear infection			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	9		
Acute tonsillitis			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	6		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2004	Methodological change: increased dose for non-responders in the second year of treatment; change to the Information Sheet; and updating of the list of Investigating Centres
14 December 2004	Methodological change: change in the central laboratory for anti-GH antibody assays; change in the volumes of blood to be drawn; change of the injector-pen and to the related Questionnaire; date of the preliminary statistical analysis put back (from 30 April 2005 to a later, as yet unfixed date, due to the low inclusion rate); change to the Information Sheet; updating of the list of Investigating Centres; and modification of the Sponsor's legal status.
10 January 2006	Extension of the inclusion period by one year, through 31 December 2006; changes in the section on SAEs; updating of the Investigator's Brochure (N° 11 of 25 May 2005); and updating of the list of Investigating Centres

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported