Clinical trial results:
RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-1 (rhIGF-1) TREATMENT OF CHILDREN AND ADOLESCENTS WITH GROWTH FAILURE ASSOCIATED WITH PRIMARY IGF-1 DEFICIENCY: AN OPEN-LABEL, MULTI-CENTER, EXTENSION STUDY

Summary

EudraCT number	2019-000844-81
Trial protocol	Outside EU/EEA
Global end of trial date	19 January 2010

Results information

Result version number	v1 (current)
This version publication date	22 September 2019
First version publication date	22 September 2019

Trial information

Trial identification

Sponsor protocol code	MS306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00330668
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 Quai Georges Gorse, Boulogne Billancourt, France, 92100
Public contact	Medical Director, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Pharma, clinical.trials@ipsen.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	01 December 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this extension study (following on from Study MS301) was to collect safety and efficacy data on the continued use of recombinant human insulin-like growth factor-1 (rhIGF-1) in children and adolescents treated for primary IGF-1 deficiency (IGFD) (height Standard Deviation [SD] score and IGF-1 SD Score <–2 and normal stimulated growth hormone [GH]).

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice as set out in the International Conference on Harmonization E6 document and the United States Code of Federal Regulations, the ethical principles that have their origins in the Declaration of Helsinki, and all applicable local and national regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 October 2005
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	United States: 114
Worldwide total number of subjects	114
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	104
Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 3b, open-label, multi-centre, extension study in prepubertal and pubertal male and female subjects with growth failure associated with primary IGFD. All subjects that completed study MS301 (EudraCT 2019-001020-36) were eligible to enter this study, MS306. The study was terminated early by the sponsor on 01 December 2009.

Pre-assignment

Screening details:

As subjects entered MS306 whilst MS301 was continuing, dosages were adjusted in MS306 after MS301 data became available. Baseline study data for MS306 were taken from the data collected for Visit 9 (Month 12) of study MS301.

Period 1

Period 1 title	Twice a Day (BID) Dosing Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All rhIGF-1 BID Subjects

Arm description:

All subjects entering MS306 began rhIGF-1 BID treatment. Each subject treated in MS301 had an MS306 starting dose that was based on their dose at the completion of MS301 (i.e. 40, 80 or 120 micrograms [µg]/ kilogram [kg] rhIGF-1 BID). MS301 untreated control subjects were randomised in MS306 in a 1:1 ratio to a dose of either 80 or 120 µg/kg rhIGF-1 BID.

Following Protocol Amendment 1 all subjects received either 80 or 120 µg/kg rhIGF-1 BID until the implementation of Protocol Amendment 2.

Arm type	Experimental
Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	Mecasermin, Increlex®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhIGF-1 at 40, 80, or 120 µg/kg BID.

Number of subjects in period 1	All rhIGF-1 BID Subjects
Started	114
Completed	78
Not completed	36
Non-Compliance	5
Consent withdrawn by subject	19
Adverse event, non-fatal	1
Other reason	3
Sponsor Decision	1

Lost to follow-up	7

Period 2

Period 2 title	Once a Day (QD) Dosing Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All rhIGF-1 QD Subjects

Arm description:

Following Protocol Amendment 2, all subjects were first switched to receive 160 µg/kg rhIGF-1 QD, followed by individual dose-escalation first to 200 µg/kg rhIGF-1 QD and subsequently to a targeted maximum dose of 240 µg/kg rhIGF-1 QD. Subjects were treated QD until the early termination of the study.

Arm type	Experimental
Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	Mecasermin, Increlex®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of 160 µg/kg rhIGF-1 QD, followed by individual dose-escalation to 200 µg/kg rhIGF-1 QD and then to a targeted maximum dose of 240 µg/kg rhIGF-1 QD.

Number of subjects in period 2	All rhIGF-1 QD Subjects
Started	78
Completed	0
Not completed	78
Consent withdrawn by subject	1
Sponsor decision to terminate study early	74
Other reason	1
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Twice a Day (BID) Dosing Period

Reporting group description: -

Reporting group values	Twice a Day (BID) Dosing Period	Total	
Number of subjects	114	114	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	104	104	
Adolescents (12-17 years)	10	10	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	8.5		
standard deviation	± 2.4	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	82	82	
Race/Ethnicity Units: Subjects			
Hispanic	6	6	
White	100	100	
Black	1	1	
Asian	4	4	
Native Hawaiian	1	1	
Other	2	2	

End points

End points reporting groups

Reporting group title	All rhIGF-1 BID Subjects

Reporting group description:

All subjects entering MS306 began rhIGF-1 BID treatment. Each subject treated in MS301 had an MS306 starting dose that was based on their dose at the completion of MS301 (i.e. 40, 80 or 120 micrograms [µg]/ kilogram [kg] rhIGF-1 BID). MS301 untreated control subjects were randomised in MS306 in a 1:1 ratio to a dose of either 80 or 120 µg/kg rhIGF-1 BID.

Following Protocol Amendment 1 all subjects received either 80 or 120 µg/kg rhIGF-1 BID until the implementation of Protocol Amendment 2.

Reporting group title	All rhIGF-1 QD Subjects

Reporting group description:

Following Protocol Amendment 2, all subjects were first switched to receive 160 µg/kg rhIGF-1 QD, followed by individual dose-escalation first to 200 µg/kg rhIGF-1 QD and subsequently to a targeted maximum dose of 240 µg/kg rhIGF-1 QD. Subjects were treated QD until the early termination of the study.

Subject analysis set title	Modified Intent-To-Treat (MITT) Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects in the Intent-To-Treat (ITT) population (i.e. treated subjects having at least one baseline and at least 1 post baseline assessment of the primary efficacy endpoint of the original protocol before amendments) and who were randomised to receive 120 µg/kg rhIGF-1 BID in either MS301 or MS306, were included in the MITT population.

Primary: Height Velocity During BID Dosing Period

End point title	Height Velocity During BID Dosing Period[1]

End point description:

Height was measured standing, without shoes, as the average of 3 measurements by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer at baseline and each study visit up to 3 years. Height velocity (during any interval of time (annualised) is computed as (height on date 2 – height on date 1)/(age on date 2 – age on date 1) where height is expressed as centimetres so that height velocity is expressed as centimetres per year (cm/yr). Height Velocity is presented for subjects completing each year of BID treatment (i.e. Year 1 [0-1 years], Year 2 [1-2 years], Year 3 [2-3 years]).

End point type	Primary

End point timeframe:

At Years 1, 2 and 3 in BID dosing period.

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 comparative analyses were planned for this endpoint.

End point values	Modified Intent-To-Treat (MITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	55[2]			
Units: cm/year				
arithmetic mean (standard deviation)				
Year 1	7.7 (± 1.5)			
Year 2	6.1 (± 1.4)			
Year 3	5.9 (± 1.1)			

Notes:

[2] - Year 1: n=54, Year 2: n=44, Year 3: n=16

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Height SD Score During BID Dosing Period

End point title	Mean Change From Baseline in Height SD Score During BID Dosing Period

End point description:

Height was measured standing, without shoes, as the average of 3 measurements by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer at baseline and each study visit up to 3 years. Height SD score was calculated using the National Center for Health Statistics 2000 data as provided by the Center for Disease Control. Mean change from baseline in height SD score is presented for all subjects completing each year of BID treatment (i.e. Year 1 [0-1 years], Year 2 [1-2 years], Year 3 [2-3 years]).

End point type	Secondary

End point timeframe:

At baseline and Years 1, 2 and 3 in BID dosing period.

End point values	Modified Intent-To-Treat (MITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	55[3]			
Units: SD score/year				
arithmetic mean (standard deviation)				
Year 1	0.5 (± 0.3)			
Year 2	0.7 (± 0.4)			
Year 3	0.9 (± 0.6)			

Notes:

[3] - Year 1: n=54, Year 2: n=44, Year 3: n=16

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Body Mass Index (BMI) SD Score During BID Dosing Period

End point title	Mean Change From Baseline in Body Mass Index (BMI) SD Score During BID Dosing Period

End point description:

BMI SD score was calculated using the National Center for Health Statistics 2000 data as provided by the Center for Disease Control. Mean change from baseline in BMI SD score is presented for all subjects completing each year of BID treatment (i.e. Year 1 [0-1 years], Year 2 [1-2 years], Year 3 [2-3 years]).

End point type	Secondary

End point timeframe:

At baseline and Years 1, 2 and 3 in BID dosing period.

End point values	Modified Intent-To-Treat (MITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	55[4]			
Units: SD score/year				
arithmetic mean (standard deviation)				
Year 1	0.3 (± 0.5)			
Year 2	0.2 (± 0.5)			
Year 3	0.4 (± 0.5)			

Notes:

[4] - Year 1: n=54, Year 2: n=44, Year 3: n=16

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Bone Age During BID Dosing Period

End point title	Mean Change From Baseline in Bone Age During BID Dosing Period

End point description:

Radiographs of the left hand and wrist were taken on an approximately annual basis for determination of bone (skeletal) age. The films were sent to a central facility for standardised evaluation. Mean change from baseline in bone age is presented for all subjects completing each year of BID treatment (i.e. Year 1 [0-1 years], Year 2 [1-2 years], Year 3 [2-3 years]).

End point type	Secondary

End point timeframe:

At baseline and Years 1, 2 and 3 in BID dosing period.

End point values	Modified Intent-To-Treat (MITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	55[5]			
Units: Years				
arithmetic mean (standard deviation)				
Year 1	1.2 (± 0.5)			
Year 2	2.3 (± 0.6)			
Year 3	3.4 (± 0.7)			

Notes:

[5] - Year 1: n=53, Year 2: n=38, Year 3: n=12

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Predicted Adult Height During BID Dosing Period

End point title	Mean Change From Baseline in Predicted Adult Height During BID Dosing Period

End point description:

Predicted adult heights were estimated using the Roche-Wainer-Theissen method which takes into account changes in age, height and bone age. Mean change from baseline in predicted adult height is presented for all subjects completing each year of BID treatment (i.e. Year 1 [0-1 years], Year 2 [1-2 years], Year 3 [2-3 years]).

End point type	Secondary

End point timeframe:

At baseline and Years 1, 2 and 3 in BID dosing period.

End point values	Modified Intent-To-Treat (MITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	55[6]			
Units: cm				
arithmetic mean (standard deviation)				
Year 1	2.7 (± 2.0)			
Year 2	3.9 (± 3.2)			
Year 3	3.7 (± 3.4)			

Notes:

[6] - Year 1: n=53, Year 2: n=38, Year 3: n=12

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for the overall study (including both the BID and QD dosing periods) from Day 1 until early termination of the study (up to 4 years, 3 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Safety Population

Reporting group description:

The safety population included all subjects who received at least one dose of study medication.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 114 (5.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Externa			

subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 114 (0.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 114 (93.86%)		
Investigations			
Blood Glucose Decreased			
subjects affected / exposed	7 / 114 (6.14%)		
occurrences (all)	8		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	7 / 114 (6.14%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	35 / 114 (30.70%)		
occurrences (all)	86		
Dizziness			
subjects affected / exposed	6 / 114 (5.26%)		
occurrences (all)	7		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all) Injection Site Hypertrophy subjects affected / exposed occurrences (all) Injection Site Bruising subjects affected / exposed occurrences (all) Influenza Like Illness subjects affected / exposed occurrences (all)	28 / 114 (24.56%) 43 16 / 114 (14.04%) 30 9 / 114 (7.89%) 10 9 / 114 (7.89%) 18		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	8 / 114 (7.02%) 8		
Immune system disorders Seasonal Allergy subjects affected / exposed occurrences (all)	6 / 114 (5.26%) 6		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	7 / 114 (6.14%) 9		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Abdominal Pain Upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	23 / 114 (20.18%) 44 20 / 114 (17.54%) 27 13 / 114 (11.40%) 13		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	21 / 114 (18.42%) 27		
Pharyngolaryngeal Pain subjects affected / exposed occurrences (all)	14 / 114 (12.28%) 21		
Tonsillar Hypertrophy subjects affected / exposed occurrences (all)	8 / 114 (7.02%) 11		
Nasal Congestion subjects affected / exposed occurrences (all)	7 / 114 (6.14%) 13		
Rhinitis Allergic subjects affected / exposed occurrences (all)	6 / 114 (5.26%) 6		
Musculoskeletal and connective tissue disorders			
Pain In Extremity subjects affected / exposed occurrences (all)	10 / 114 (8.77%) 13		
Arthralgia subjects affected / exposed occurrences (all)	9 / 114 (7.89%) 15		
Infections and infestations			
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	38 / 114 (33.33%) 79		
Pharyngitis Streptococcal subjects affected / exposed occurrences (all)	23 / 114 (20.18%) 32		
Influenza subjects affected / exposed occurrences (all)	22 / 114 (19.30%) 31		
Nasopharyngitis subjects affected / exposed occurrences (all)	22 / 114 (19.30%) 34		
Gastroenteritis Viral			

subjects affected / exposed occurrences (all)	20 / 114 (17.54%) 23		
Otitis Media subjects affected / exposed occurrences (all)	20 / 114 (17.54%) 28		
Sinusitis subjects affected / exposed occurrences (all)	12 / 114 (10.53%) 24		
Otitis Externa subjects affected / exposed occurrences (all)	11 / 114 (9.65%) 16		
Ear Infection subjects affected / exposed occurrences (all)	10 / 114 (8.77%) 13		
Gastroenteritis subjects affected / exposed occurrences (all)	9 / 114 (7.89%) 14		
Bronchitis subjects affected / exposed occurrences (all)	8 / 114 (7.02%) 9		
Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	8 / 114 (7.02%) 10		
Molluscum Contagiosum subjects affected / exposed occurrences (all)	7 / 114 (6.14%) 7		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	46 / 114 (40.35%) 72		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2005	Provision was made for subjects completing MS301 on 120 µg/kg rhIGF-1 BID to continue at this dose during MS306. Subjects randomised to receive 40 µg/kg rhIGF-1 BID during MS301 would commence MS306 on 80 µg/kg rhIGF-1, followed by a dose escalation to 120 µg/kg rhIGF-1 BID at Week 3. Subjects in the untreated cohort of MS301 would commence at 80 or 120 µg/kg rhIGF-1 BID. Subjects originally randomised to 80 or 120 µg/kg rhIGF-1 BID during MS301 but who then completed that study on <80 µg/kg rhIGF-1 BID following a dose-reduction, were considered by the Investigator and Medical Monitor on an individual basis and assigned to a MS306 dose accordingly. Pregnancy testing was introduced for female subjects with Tanner Stage 2 breast development. Additional covariates were added to the primary analysis (pre-treatment height velocity, age at the beginning of the second year of treatment and sex). Fundoscopic examinations were introduced at all visits. Anti-IGF-1 antibody evaluation (previously planned only at Visit 1 and End of Study) would take place annually.
08 May 2009	All subjects were switched from BID to QD dosing, using a dose escalation procedure with a targeted maximum dose of 240 µg/kg rhIGF-1 QD. Subjects underwent mandatory dose reduction if their IGF-1 SDS for estimated 24 hour mean IGF-1 concentration was >+3 on two occasions. The urinalysis test, thyroid function test and fasting blood tests for lipids, glucose and insulin were all discontinued. Non-fasting capillary blood glucose was conducted at each and every visit. All clinical visits were to occur in the morning. The maximum duration of QD treatment was limited to 1 year.

Notes:

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.

The study was terminated by the sponsor due to an unacceptably high incidence of hypoglycaemia observed in approximately 50% of the subjects receiving 200 µg/kg rhIGF-1 or greater QD.

Notes: