



Clinical trial results:

A randomised, open-label, parallel-group, multi-centre trial comparing the efficacy and safety of 12 months treatment with one daily dose of ZOMACTON® to one daily dose of GENOTROPIN® in the treatment of children with idiopathic growth hormone deficiency

Summary

EudraCT number	2008-004849-28
Trial protocol	HU
Global end of trial date	25 June 2012

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	FE 999905 CS07
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	Kay Fiskers Plads 11, Copenhagen S , Denmark, 2300
Public contact	Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com
Scientific contact	Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.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	04 July 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that one daily dose of ZOMACTON (10 mg/mL) is equivalent to one daily dose of GENOTROPIN (12 mg/mL) in terms of growth measured as height velocity based on 12 months of treatment.

Protection of trial subjects:

The target trial population was children aged 3-11 years old, who was unable to provide legally binding consent. Therefore, informed consent had to be sought from the parent(s)/legal representatives on the child's behalf prior to enrolling the child in the trial.

Oral information was given to the children and the parent(s)/legal representatives by an experienced investigator, or adequately trained delegate site staff. The information was also provided in writing. The process of the assent from each child was carried out slowly with an age-appropriate language. The assent process was conducted with sufficient time and at the same time as the consent was obtained from the parent(s)/legal representatives, so that the informed consent reflected the presumed will of the child. Besides the oral information given to the child, information sheet and assent form were provided in an age-appropriate language with wording that corresponded to the child's psychological and intellectual maturity. Adequate time was given to the parent(s)/legal representative to discuss with their child with or without the presence of the Investigator, if required. The child's assent was not sufficient to allow participation in research unless supplemented by informed consent of the parent(s)/legal representatives.

The Investigator obtained freely given, written consent from each child's parent(s)/legal representatives as well as a signed or indicated assent from each child after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial relevant to the decision of the child and parent(s)/ legal representatives' decision to participate.

Background therapy: -

Evidence for comparator:

Growth hormone (GH) is essential for normal growth in children and acts by increasing growth, both via production of insulin-like growth factor (IGF), especially IGF-1, and via direct action on the growth plates. Lack of growth hormone in children leads to impairment of growth and eventually short stature. ZOMACTON is currently approved for treatment of children with growth hormone deficiency and for long-term treatment of growth retardation due to Turner's syndrome (gonadal dysgenesis) confirmed by chromosomal analysis. Other indications for other somatropin-products (e.g., GENOTROPIN) include children born small for gestational age, Prader-Willi's syndrome, patients with chronic renal insufficiency, and adults with growth hormone deficiency with adult or childhood onset. Biosimilarity would allow for expansion of the approved indications for ZOMACTON to include those approved for GENOTROPIN.

Actual start date of recruitment	22 November 2009
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	India: 24
Country: Number of subjects enrolled	Israel: 30

Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Ukraine: 41
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Hungary: 11
Worldwide total number of subjects	165
EEA total number of subjects	35

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)	165
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 259 subjects were screened in the trial of which 165 subjects were randomised: 82 in the ZOMACTON treatment group and 83 in the GENOTROPIN treatment group.

Pre-assignment

Screening details:

Trial was initiated with a pre-screening period during which time a confirmative standard GH stimulation test had to be performed. It took place up to 3 months (or 5 months in Israel) prior to the actual screening period. Pre-screening period was followed by a screening period which could be up to 21 days prior to actual 12-month treatment period.

Period 1

Period 1 title	Visit 2 (Day 0)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Zomacton

Arm description:

Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection).

Arm type	Experimental
Investigational medicinal product name	Zomacton
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomised to ZOMACTON treatment received a daily dose of 0.03 mg/kg/day ZOMACTON (10 mg/mL) for 12 months. ZOMACTON was administered as a subcutaneous transjection using ZomaJet®Vision X.

Arm title	Genotropin
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Arm description:

Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection)

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomised to GENOTROPIN treatment received a daily dose of 0.03 mg/kg/day GENOTROPIN (12 mg/mL) for 12 months. GENOTROPIN was administered as a subcutaneous injection using Genotropin Pen®12.

Number of subjects in period 1	Zomacton	Genotropin
Started	82	83
Completed	82	83

Period 2

Period 2 title	Treatment period (Day 0 - 12 Month)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Zomacton
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Zomacton
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomised to ZOMACTON treatment received a daily dose of 0.03 mg/kg/day ZOMACTON (10 mg/mL) for 12 months. ZOMACTON was administered as a subcutaneous transjection using ZomaJet®Vision X.

Arm title	Genotropin
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomised to GENOTROPIN treatment received a daily dose of 0.03 mg/kg/day GENOTROPIN (12 mg/mL) for 12 months. GENOTROPIN was administered as a subcutaneous injection using Genotropin Pen®12.

Number of subjects in period 2	Zomacton	Genotropin
Started	82	83
Completed	79	82
Not completed	3	1
Consent withdrawn by subject	1	-
Pre-treatment adverse event	1	-
Other	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Zomacton
Reporting group description:	
Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection).	
Reporting group title	Genotropin
Reporting group description:	
Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection)	

Reporting group values	Zomacton	Genotropin	Total
Number of subjects	82	83	165
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	82	83	165
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
All the subjects were paediatric.			
Units: years			
arithmetic mean	7.09	7.27	
standard deviation	± 2.29	± 2.2	-
Gender categorical			
At baseline (at Visit 0)			
Units: Subjects			
Female	27	28	55
Male	55	55	110
Race			
At baseline (at Visit 0)			
Units: Subjects			
Asian	12	13	25
Black or African American	1	0	1
White	69	70	139
Bone age			
At baseline (at Visit 0)			
Units: Years			
arithmetic mean	4.29	4.68	
standard deviation	± 2.21	± 2.09	-
Baseline height			
At baseline (at Visit 0)			
Units: cm			

arithmetic mean	104	106	
standard deviation	± 12.8	± 11.7	-
Peak GH stimulation test			
At baseline (at Visit 0)			
Units: µg/L			
arithmetic mean	3.25	2.95	
standard deviation	± 2.65	± 2.31	-
Baseline Body Mass Index (BMI)			
Units: kg/m/m			
arithmetic mean	16	16.3	
standard deviation	± 2.27	± 2.43	-

Subject analysis sets

Subject analysis set title	Full analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS comprised data from all randomised and treated subjects. If a subject received incorrect treatment (i.e., the actual treatment was not as randomised), he or she was included in the group reflecting the actual treatment received.

Subject analysis set title	Per Protocol (PP) Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in the FAS analysis set were excluded from the PP analysis set if they met any of the pre-specified criteria of protocol deviation or otherwise excluded due to any serious unforeseen violations deemed to invalidate the data and affect the conclusions of the trial.

Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The definition of the safety analysis set was identical to the FAS.

Reporting group values	Full analysis Set (FAS)	Per Protocol (PP) Analysis Set	Safety Analysis set
Number of subjects	165	153	165
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	165	153	165
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
All the subjects were paediatric.			
Units: years			
arithmetic mean	7.18	7.15	7.18
standard deviation	± 2.24	± 2.26	± 2.24

Gender categorical			
At baseline (at Visit 0)			
Units: Subjects			
Female	55	51	55
Male	110	102	110
Race			
At baseline (at Visit 0)			
Units: Subjects			
Asian	25	22	25
Black or African American	1	1	1
White	139	130	139
Bone age			
At baseline (at Visit 0)			
Units: Years			
arithmetic mean	4.48	4.44	4.48
standard deviation	± 2.16	± 2.17	± 2.16
Baseline height			
At baseline (at Visit 0)			
Units: cm			
arithmetic mean	105	105	105
standard deviation	± 12.3	± 12.4	± 12.3
Peak GH stimulation test			
At baseline (at Visit 0)			
Units: µg/L			
arithmetic mean	3.1	3.07	3.1
standard deviation	± 2.48	± 2.47	± 2.48
Baseline Body Mass Index (BMI)			
Units: kg/m/m			
arithmetic mean	16.1	16.2	16.1
standard deviation	± 2.35	± 2.35	± 2.35

End points

End points reporting groups

Reporting group title	Zomacton
Reporting group description: Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection).	
Reporting group title	Genotropin
Reporting group description: Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection)	
Reporting group title	Zomacton
Reporting group description: -	
Reporting group title	Genotropin
Reporting group description: -	
Subject analysis set title	Full analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS comprised data from all randomised and treated subjects. If a subject received incorrect treatment (i.e., the actual treatment was not as randomised), he or she was included in the group reflecting the actual treatment received.	
Subject analysis set title	Per Protocol (PP) Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: Subjects in the FAS analysis set were excluded from the PP analysis set if they met any of the pre-specified criteria of protocol deviation or otherwise excluded due to any serious unforeseen violations deemed to invalidate the data and affect the conclusions of the trial.	
Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The definition of the safety analysis set was identical to the FAS.	

Primary: Height velocity (HV) - Full analysis set

End point title	Height velocity (HV) - Full analysis set
End point description: The HV was defined as: (height at visit – height at baseline) / actual length of time between the two measurements.	
End point type	Primary
End point timeframe: 12 months treatment	

End point values	Zomacton	Genotropin	Full analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	82	162 ^[1]	
Units: cm/year				
arithmetic mean (standard deviation)	10.7 (± 3.07)	10.9 (± 3.42)	10.8 (± 3.25)	

Notes:

[1] - Total no. of subjects at month 12 ' End of trial' Visit.

Attachments (see zip file)	HV Last Observation Carried Forward (LOCF)/Height Velocity
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Statistical analyses

Statistical analysis title	ANCOVA of Height velocity at Month 12 (LOCF) - FAS
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Statistical analysis description:

Height velocity was analysed using an Analysis of Covariance (ANCOVA) model with baseline Chronological Age (CA), baseline HV, and log peak GH level after stimulation, as covariates and country, sex and treatment as factors.

Equivalence was declared since the 95% confidence interval (CI) for the difference in HV was with [-2.0 ; 2.0] for both FAS and PP.

Comparison groups	Zomacton v Genotropin
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.1

Primary: Height velocity - PP analysis set

End point title	Height velocity - PP analysis set
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End point description:

The HV was defined as: (height at visit – height at baseline) / actual length of time between the two measurements.

End point type	Primary
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End point timeframe:

12 months treatment

End point values	Zomacton	Genotropin	Per Protocol (PP) Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	74	74	148 ^[2]	
Units: cm/year				
arithmetic mean (standard deviation)	10.9 (± 3.07)	11.1 (± 3.23)	11 (± 3.15)	

Notes:

[2] - Total no. of subjects at month 12 ' End of trial' Visit.

Statistical analyses

Statistical analysis title	ANCOVA of Height velocity at Month 12 (LOCF) - PP
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Statistical analysis description:

Height velocity was analysed using an ANCOVA model with baseline CA, baseline HV, and log peak GH

level after stimulation, as covariates and country, sex and treatment as factors.

Equivalence was declared since the 95% CI for the difference in HV was with [-2.0 ; 2.0] for both FAS and PP.

Comparison groups	Zomacton v Genotropin
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were monitored continuously throughout the study from the time of obtaining informed consent until the end of trial.

Adverse event reporting additional description:

At each visit, AEs were elicited using a standard non-leading question. Adverse events could also be captured by symptoms spontaneously reported from the subject or as results of clinically significant changes and abnormalities observed by the Investigator. In addition, AEs were recorded in a booklet between the visits.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Zomacton
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Reporting group description:

Zomacton 10 mg/mL: It was administered with ZomaJet® Vision X (subcutaneous transjection).

Reporting group title	Genotropin
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Reporting group description:

Genotropin 12 mg/mL: It was administered with Genotropin Pen®12 (subcutaneous injection)

Serious adverse events	Zomacton	Genotropin	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 82 (6.10%)	0 / 83 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
abnormal behaviour			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Zomacton	Genotropin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 82 (43.90%)	31 / 83 (37.35%)	
Investigations			
Insulin-like growth factor decreased			
subjects affected / exposed	5 / 82 (6.10%)	6 / 83 (7.23%)	
occurrences (all)	6	9	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 82 (7.32%)	3 / 83 (3.61%)	
occurrences (all)	6	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 82 (3.66%)	5 / 83 (6.02%)	
occurrences (all)	3	6	
General disorders and administration site conditions			

Injection site haematoma subjects affected / exposed occurrences (all)	9 / 82 (10.98%) 10	4 / 83 (4.82%) 5	
Pyrexia subjects affected / exposed occurrences (all)	6 / 82 (7.32%) 10	7 / 83 (8.43%) 9	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 82 (8.54%) 8	7 / 83 (8.43%) 11	
Pharyngitis subjects affected / exposed occurrences (all)	7 / 82 (8.54%) 9	1 / 83 (1.20%) 1	
Viral infection subjects affected / exposed occurrences (all)	5 / 82 (6.10%) 5	3 / 83 (3.61%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2009	<p>The original protocol required an X-ray for determination of bone age (BA) at baseline (performed at the screening). However, at some sites, an X-ray had already been taken prior to the pre-screening visit. Therefore, to avoid repeated X-rays, the period for performing this X-ray was extended. An X-ray taken within 3 months prior to visit 2 was acceptable.</p> <p>"The difference between CA-BA ≥ 1" was an inclusion criterion in original protocol whereas "BA above 9 years in girls and above 10 years in boys" was an exclusion criterion. This was to reassure that the subject was at pre-pubertal stage upon enrolment of the trial and able to complete the 12-month treatment period prior to entering the puberty. However, the restriction of "CA-BA ≥ 1" was not relevant for younger children. Therefore, the inclusion criterion was changed to "BA/CA ≤ 0.9".</p> <p>The baseline GH level for inclusion was changed from "9 ng/mL" to "10 ng/mL" as this was the cut-point value for initiation of GH treatment.</p> <p>Any use of corticoid steroids and medications that could interfere with GH treatment was prohibited in the original protocol. However, some children may suffer from adrenocorticotrophic hormone deficiency and for these children glucocorticosteroid treatments are mandatory as physiological replacement. Hence, glucocorticosteroid treatment was allowed as long as it was at a stable dose level.</p> <p>As per exclusion criteria in the original protocol, children with any diagnosed or suspected severe chronic disease or clinical signs of dysmorphic features, malformations, or mental retardation were not allowed to be included in the trial. However, a child with minor dysmorphic features or malformation in stable condition could be enrolled into the trial as long as it doesn't place the child at excessive risk by participating in the trial, and therefore, the exclusion criteria were changed.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported