Clinical trial results:
A phase IV open-label study of predictive markers in growth hormone deficient pre-pubertal children treated with Saizen®

Summary

EudraCT number	2015-001569-20
Trial protocol	Outside EU/EEA
Global end of trial date	20 April 2009

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	27709

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01187550
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the response between GHD children born appropriate for gestational age (AGA) and those born small for gestation age (SGA) after 4 weeks of Saizen® therapy

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2007
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	China: 214
Worldwide total number of subjects	214
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)	214
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: -

Pre-assignment

Screening details:

Out of 214 subjects enrolled in the study, 1 subject could not be categorized as appropriate for gestational age (AGA) or small for gestational age (SGA) since weight and height at birth was not available.

Period 1

Period 1 title	Overall Study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Appropriate for gestational age (AGA)

Arm description:

Subjects in AGA group received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (sc) at the daily dose of 0.033 milligram/kilogram (mg/kg) body weight for 4 weeks.

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

Dosage and administration details:

Saizen (r-hGH) was administered subcutaneously at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Arm title	Small for gestational age (SGA)

Arm description:

Subjects in SGA group received Saizen (r-hGH) sc at the daily dose of 0.033 mg/kg body weight for 4 weeks.

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

Dosage and administration details:

Saizen (r-hGH) was administered subcutaneously at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Number of subjects in period 1	Appropriate for gestational age (AGA)	Small for gestational age (SGA)
Started	183	30
Treated	175	30
Completed	169	29
Not completed	14	1
Randomized but not treated	8	-
Unspecified	3	-
Protocol deviation	3	1

Period 2

Period 2 title	Baseline period
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Appropriate for gestational age (AGA)

Arm description:

Subjects in AGA group received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (sc) at the daily dose of 0.033 milligram/kilogram (mg/kg) body weight for 4 weeks.

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

Dosage and administration details:

Saizen (r-hGH) was administered subcutaneously at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Saizen (r-hGH) was administered subcutaneously at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Arm title	Small for gestational age (SGA)

Arm description:

Subjects in SGA group received Saizen (r-hGH) sc at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Arm type	Experimental

Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Saizen (r-hGH) was administered subcutaneously at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Out of a total of 213 subjects, data for baseline measure (age) was available for only 205 subjects who were treated. Hence, a separate period is created to add baseline data only.

Number of subjects in period 2[2]	Appropriate for gestational age (AGA)	Small for gestational age (SGA)
Started	175	30
Completed	169	29
Not completed	6	1
Adverse event	2	-
Unspecified	4	-
Lost to follow-up	-	1

Notes:

[2] - 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: Out of 214 subjects enrolled in the study, 1 subject could not be categorized as appropriate for gestational age (AGA) or small for gestational age (SGA) since weight and height at birth was not available.

Baseline characteristics

Reporting groups	
Reporting group title	Appropriate for gestational age (AGA)
Reporting group description:	
Subjects in AGA group received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (sc) at the daily dose of 0.033 milligram/kilogram (mg/kg) body weight for 4 weeks.	
Reporting group title	Small for gestational age (SGA)
Reporting group description:	
Subjects in SGA group received Saizen (r-hGH) sc at the daily dose of 0.033 mg/kg body weight for 4 weeks.	

Reporting group values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)	Total
Number of subjects	175	30	205
Age categorical Units: Subjects			
Age Continuous			
Out of a total of 213 subjects data for baseline measure (age) was available for only 205 subjects who were treated.			
Units: years			
arithmetic mean	10.52	9.39	
standard deviation	± 3.844	± 4.349	-
Gender, Male/Female			
Out of a total of 213 subjects, data for baseline measure (gender) was available for only 205 subjects who were treated.			
Units: participants			
Female	46	6	52
Male	129	24	153

End points

End points reporting groups

Reporting group title	Appropriate for gestational age (AGA)
Reporting group description:	
Subjects in AGA group received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (sc) at the daily dose of 0.033 milligram/kilogram (mg/kg) body weight for 4 weeks.	
Reporting group title	Small for gestational age (SGA)
Reporting group description:	
Subjects in SGA group received Saizen (r-hGH) sc at the daily dose of 0.033 mg/kg body weight for 4 weeks.	
Reporting group title	Appropriate for gestational age (AGA)
Reporting group description:	
Subjects in AGA group received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (sc) at the daily dose of 0.033 milligram/kilogram (mg/kg) body weight for 4 weeks.	
Reporting group title	Small for gestational age (SGA)
Reporting group description:	
Subjects in SGA group received Saizen (r-hGH) sc at the daily dose of 0.033 mg/kg body weight for 4 weeks.	

Primary: Change from baseline in Serum Insulin Like Growth Factor-1 Standard Deviation Score (IGF-1 SDS) Levels at Week 4

End point title	Change from baseline in Serum Insulin Like Growth Factor-1 Standard Deviation Score (IGF-1 SDS) Levels at Week 4
End point description:	
Insulin Like Growth Factor-1 Standard Deviation Score (IGF-1 SDS) was calculated as logarithm (log) 10 actual value of IGF-1 - log 10 (mean reference value of IGF-1) divided by log10 reference standard deviation of IGF-1. The intent-to-treat (ITT) population set included all the subjects who received at least 1 dose of study medication.	
End point type	Primary
End point timeframe:	
Baseline and Week 4	

End point values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	30		
Units: nanogram/millilter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline	-2.04 (± 2.341)	-2.22 (± 2.39)		
Change at Week 4	1.38 (± 1.358)	0.85 (± 1.257)		

Statistical analyses

Statistical analysis title	Statistical analysis: IGF-1SDS
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.194
Method	Wilcoxon rank sum test

Secondary: Change from Baseline in Insulin Like Growth Factor Binding Protein-3 (IGFBP-3) levels at Week 4

End point title	Change from Baseline in Insulin Like Growth Factor Binding Protein-3 (IGFBP-3) levels at Week 4
End point description:	
ITT population set included all the subjects who received at least 1 dose of study medication.	
End point type	Secondary
End point timeframe:	
Baseline and Week 4	

End point values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	30		
Units: microgram/mL (mcg/mL)				
arithmetic mean (standard deviation)				
Baseline	3.16 (± 1.386)	2.57 (± 1.525)		
Change at Week 4	0.58 (± 0.869)	0.51 (± 0.805)		

Statistical analyses

Statistical analysis title	Statistical Analysis :IGFBP-3
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.752
Method	Wilcoxon rank sum test
Confidence interval	
level	95 %

Secondary: Change from baseline in fasting glucose at Week 4

End point title	Change from baseline in fasting glucose at Week 4

End point description:

ITT population set included all the subjects who received at least 1 dose of study medication. Here 'N' (Number of subjects analyzed) signified those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	30		
Units: millimole/liter (mmol/L)				
arithmetic mean (standard deviation)				
Baseline	4.83 (± 0.471)	4.46 (± 1.106)		
Change at Week 4	0.17 (± 0.578)	0.22 (± 0.886)		

Statistical analyses

Statistical analysis title	Statistical Analysis :Fasting Glucose
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.71
Method	Wilcoxon rank sum test

Secondary: Change from baseline in fasting insulin at Week 4

End point title	Change from baseline in fasting insulin at Week 4

End point description:

ITT population set included all the participants who received at least 1 dose of study medication. Here 'N' (Number of participants analyzed) signified those participants who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	26		
Units: picomole/L (pmol/L)				
arithmetic mean (standard deviation)				
Baseline	36.17 (± 74.575)	23.58 (± 14.892)		
Change at Week 4	10.08 (± 81.674)	12.04 (± 32.389)		

Statistical analyses

Statistical analysis title	Statistical Analysis: Fasting Insulin
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.265
Method	Wilcoxon rank sum test
Confidence interval	
level	95 %

Secondary: Change from baseline in homeostasis model assessment of insulin resistance (HOMA-IR) test at Week 4

End point title	Change from baseline in homeostasis model assessment of insulin resistance (HOMA-IR) test at Week 4

End point description:

HOMA-IR is used to assess insulin resistance and calculated by an empirical mathematical formula based on fasting plasma glucose and fasting plasma insulin levels. HOMA-IR = fasting plasma insulin (picomole/liter [pmol/L]) * fasting plasma glucose (millimole/liter [mmol/L]) divided by 22.5. ITT population set included all the subjects who received at least 1 dose of study medication. Here 'N' (Number of subjects analyzed) signified those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	26		
Units: pmol/L*mmol/L				
arithmetic mean (standard deviation)				

Baseline	7.91 (± 15.662)	5.06 (± 3.29)		
Change at Week 4	2.96 (± 18.458)	2.48 (± 6.527)		

Statistical analyses

Statistical analysis title	Statistical Analysis: HOMA -IR
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.308
Method	Wilcoxon rank sum test
Confidence interval	
level	95 %

Secondary: Change from baseline in lipid profile at Week 4

End point title	Change from baseline in lipid profile at Week 4

End point description:

Total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides levels were evaluated. ITT population set included all the subjects who received at least 1 dose of study medication. Here 'N' (Number of subjects analyzed) signified those subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Appropriate for gestational age (AGA)	Small for gestational age (SGA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	30		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (Total Cholesterol)	4.16 (± 0.752)	4.22 (± 0.833)		
Baseline (HDL-Cholesterol)	1.56 (± 0.452)	1.59 (± 0.443)		
Baseline (LDL-Cholesterol)	2.18 (± 0.672)	2.19 (± 0.709)		
Baseline (Triglycerides)	0.99 (± 0.527)	1.02 (± 0.638)		
Change at Week 4 (Total Cholesterol)	-0.28 (± 0.601)	-0.03 (± 0.612)		
Change at Week 4 (HDL-Cholesterol)	-0.1 (± 0.317)	0.02 (± 0.329)		
Change at Week 4 (LDL-Cholesterol)	-0.24 (± 0.546)	0.02 (± 0.502)		
Change at Week 4 (Triglycerides)	0.12 (± 0.551)	-0.09 (± 0.831)		

Statistical analyses

Statistical analysis title	Statistical Analysis :total cholesterol
Statistical analysis description: For total cholesterol: Wilcoxon rank sum test was used to calculate p-value.	
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.078
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis :HDL-cholesterol
Statistical analysis description: For HDL-cholesterol: Wilcoxon rank sum test was used to calculate p-value.	
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis:LDL-cholesterol
Statistical analysis description: For LDL-cholesterol: Wilcoxon rank sum test was used to calculate p-value.	
Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis:triglycerides
Statistical analysis description: For triglycerides: Wilcoxon rank sum test was used to calculate p-value.	

Comparison groups	Appropriate for gestational age (AGA) v Small for gestational age (SGA)
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.091
Method	Wilcoxon rank sum test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are collected on an ongoing basis from day of written informed consent. All new AEs must be recorded until 4 weeks post drug administration. AEs are classified as pre-treatment, treatment-emergent and post-treatment.

Adverse event reporting additional description:

Pre-Treatment:Medical conditions present at initial study visit that did not worsen in severity or frequency during study;Treatment-Emergent: If onset date of AE was on or after the first dose date of the study medication; Post-Treatment: If the onset date of AE was post 4 weeks after drug administration for subjects who completed the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Small for gestational age (SGA)

Reporting group description:

Subjects in SGA group received Saizen (r-hGH) sc at the daily dose of 0.033 mg/kg body weight for 4 weeks.

Reporting group title	Appropriate for gestational age (AGA)

Reporting group description:

Subjects in AGA group received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (sc) at the daily dose of 0.033 milligram/kilogram (mg/kg) body weight for 4 weeks.

Serious adverse events	Small for gestational age (SGA)	Appropriate for gestational age (AGA)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Small for gestational age (SGA)	Appropriate for gestational age (AGA)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	27 / 175 (15.43%)	
Investigations			
Liver Function Test Abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	3 / 175 (1.71%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Hyperhidrosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 175 (0.00%)	
occurrences (all)	1	0	
Injection Site Dermatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Injection Site Reaction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)	5 / 175 (2.86%)	
occurrences (all)	1	5	
Eye disorders			
Conjunctivitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	

Eye Oedema			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Ocular Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	2 / 175 (1.14%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal Pain Upper			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	2 / 175 (1.14%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	2 / 175 (1.14%)	
occurrences (all)	0	2	
Rhinorrhoea			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	2 / 175 (1.14%)	
occurrences (all)	0	2	
Tonsillitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	4 / 175 (2.29%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Skin Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 175 (0.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)	1 / 175 (0.57%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Anorexia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 175 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported