Clinical trial results:
Optimization of the dosage regimen with growth hormone therapy in children born small for gestational age. An open label, randomized pilot study, comparing in children treated for 3 years, the efficacy of a Saizen® treatment at the same dose versus a lower maintenance dose prolonged during 1 additional year (SGA OPTIMIS)

Summary

EudraCT number	2015-001696-51
Trial protocol	Outside EU/EEA
Global end of trial date	12 September 2007

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	25735

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00249821
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?	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	12 September 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2007
Global end of trial reached?	Yes
Global end of trial date	12 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluating the benefit in terms of height gain of a fourth year of an recombinant human growth hormone (r-hGH) induction regimen with a daily dose of 0.057 milligram /kilogram/day (mg/kg/day) in comparison to a maintenance regimen at a lower daily dose of 0.035 mg/kg/day, after an initial 3-year period at the induction dose of 0.057mg/kg/day in subjects born Small for gestational age (SGA).

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	28 February 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	France: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
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:

First subject signed informed consent form: February 28, 2005. Clinical data cutoff: September 12, 2007, Study completion date: September 12, 2007.

Pre-assignment

Screening details:

A total of 22 subjects were included in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Saizen® 0.035 mg/kg/day

Arm description:

Saizen® (r-hGH) subcutaneously administered at the daily dose of 0.035 mg/kg or 0.24 mg/kg/week for duration of 12 months.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	Saizen
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Saizen® (r-hGH) subcutaneously administered at the daily dose of 0.035 mg/kg or 0.24 mg/kg/week for duration of 12 months.

Arm title	Saizen® 0.057 mg/kg/day

Arm description:

Saizen® r-hGH subcutaneously administered at the daily dose of 0.057 milligram/kilogram (mg/kg) or 0.40 mg/kg/week for duration of 12 months.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	Saizen
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Saizen® (recombinant human growth hormone, r-hGH) subcutaneously administered at the daily dose of 0.057 milligram/kilogram (mg/kg) or 0.40 mg/kg/week for duration of 12 months.

Number of subjects in period 1	Saizen® 0.035 mg/kg/day	Saizen® 0.057 mg/kg/day
Started	12	10
Completed	11	10
Not completed	1	0
Technical problem	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Saizen® 0.057 mg/kg/day
Reporting group description:	
Saizen® r-hGH subcutaneously administered at the daily dose of 0.057 milligram/kilogram (mg/kg) or 0.40 mg/kg/week for duration of 12 months.	
Reporting group title	Saizen® 0.035 mg/kg/day
Reporting group description:	
Saizen® (r-hGH) subcutaneously administered at the daily dose of 0.035 mg/kg or 0.24 mg/kg/week for duration of 12 months.	

Reporting group values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day	Total
Number of subjects	10	12	22
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	7.9	8	
standard deviation	± 0.9	± 1.49	-
Gender, Male/Female			
Units: participants			
Female	4	4	8
Male	6	8	14

End points

End points reporting groups

Reporting group title	Saizen® 0.035 mg/kg/day
Reporting group description:	
Saizen® (r-hGH) subcutaneously administered at the daily dose of 0.035 mg/kg or 0.24 mg/kg/week for duration of 12 months.	
Reporting group title	Saizen® 0.057 mg/kg/day
Reporting group description:	
Saizen® r-hGH subcutaneously administered at the daily dose of 0.057 milligram/kilogram (mg/kg) or 0.40 mg/kg/week for duration of 12 months.	

Primary: Height Velocity

End point title	Height Velocity
End point description:	
Height Velocity (HV) is the change in height since the previous year´s measurement and more precisely: HV = {(h-hp)/(d-dp)} * 365.25 [centimeter (cm)/year] where h is current height in cm, hp is previous height in cm, closest to 1 year previous, d is the current date and dp is the date of measurement of previous height, closest to 1 year previous. Additionally, d and dp have to be within 0.6 years and 1.5 years. HV is the mean height velocity over the interval between d and dp but is displayed as HV at d. Full Analysis (FA) set included all the subjects who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. Last observation carried forward (LOCF) was used to impute missing values.	
End point type	Primary
End point timeframe:	
Month 12	

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: centimeter (cm)/year				
arithmetic mean (standard deviation)	6.4 (± 1.35)	4.4 (± 1.15)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Height Velocity
Statistical analysis description:	
Month 12: Analysis of co-variance (ANCOVA) method with covariates “height” and “age” at baseline was used to calculate presented p-value.	
Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	ANCOVA

Secondary: Change from baseline in Height-Standard Deviation Score (H-SDS) at Month 6 and Month 12

End point title	Change from baseline in Height-Standard Deviation Score (H-SDS) at Month 6 and Month 12

End point description:

Height-Standard Deviation Score (H-SDS) was calculated as height minus mean (age-and sex-matched reference) divided by standard deviation (SD) [age and sex-matched reference]. Greater H-SDS indicates greater height. FA set included all the subjects who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. LOCF was used to impute missing values.

End point type	Secondary

End point timeframe:

Baseline (randomization), Month 6 and Month 12

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: standard deviation score				
arithmetic mean (standard deviation)				
Baseline (randomization)	-1.3 (± 0.42)	-1.5 (± 0.37)		
Change at Month 6	0.3 (± 0.22)	0.1 (± 0.1)		
Change at Month 12	0.3 (± 0.3)	-0.1 (± 0.24)		

Statistical analyses

Statistical analysis title	Statistical analysis H-SDS: Month 6

Statistical analysis description:

Change at Month 6: ANCOVA method with covariates “height” and “age” at baseline was used to calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.012
Method	ANCOVA

Statistical analysis title	Statistical analysis H-SDS: Month 12
Statistical analysis description:	
Change at Month 12: ANCOVA method with covariates “height” and “age” at baseline was used to calculate presented p-value.	
Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	ANCOVA

Secondary: Height velocity-Standard deviation score (HV-SDS)

End point title	Height velocity-Standard deviation score (HV-SDS)
End point description:	
Height Velocity-Standard Deviation Score (HV-SDS) was calculated as height velocity minus reference mean height velocity divided by SD of the reference mean height velocity. Greater HV-SDS indicates greater height velocity. FA set included all the subjects who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. Here "n" signifies number of subjects analyzed at that particular time point for each arm group respectively. LOCF was used to impute missing values.	
End point type	Secondary
End point timeframe:	
Month 6 and Month 12	

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: standard deviation score				
arithmetic mean (standard deviation)				
Month 6 (n= 10,11)	0.6 (± 0.44)	0.1 (± 0.22)		
Month 12 (n=10,12)	0.3 (± 0.29)	-0.1 (± 0.24)		

Statistical analyses

Statistical analysis title	Statistical analysis HV-SDS: Month 6
Statistical analysis description:	
Month 6: ANCOVA method with covariates “height” and “age” at baseline was used to calculate presented p-value.	
Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	ANCOVA

Statistical analysis title	Statistical analysis HV-SDS: Month 12

Statistical analysis description:

Month 12: ANCOVA method with covariates "height" and "age" at baseline was used to calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	ANCOVA

Secondary: Change from baseline in height at Month 6

End point title	Change from baseline in height at Month 6

End point description:

FA set included all the subjects who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. LOCF was used to impute missing values.

End point type	Secondary

End point timeframe:

Baseline (randomization) and Month 6

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (randomization)	121.1 (± 7.99)	119.2 (± 5.29)		
Change at Month 6	3.6 (± 1.31)	2.5 (± 0.99)		

Statistical analyses

Statistical analysis title	Statistical Analysis:change from baseline height

Statistical analysis description:

Change at Month 6: ANCOVA method with covariates "height" and "age" at baseline was used to

calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.029
Method	ANCOVA

Secondary: Change from baseline in bone age at Month 12

End point title	Change from baseline in bone age at Month 12

End point description:

Bone age was assessed by a left wrist X-Ray and evaluated by the investigator according to the Greulich and Pyle method.FA set included all participants who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. 'N' (Number of subjects analyzed) signified those participants who were evaluable for this measure and "n" = number of subjects analyzed at that particular time point for each arm group respectively.

End point type	Secondary

End point timeframe:

Baseline (randomization) and Month 12

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: years				
arithmetic mean (standard deviation)				
Baseline (randomization) (n = 9,10)	7.5 (± 0.82)	7 (± 1.85)		
Change at Month 12 (n=9,7)	1.4 (± 0.79)	1.4 (± 0.89)		

Statistical analyses

Statistical analysis title	Statistical Analysis:change from baseline: height

Statistical analysis description:

Change at Month 12: ANCOVA method with covariates "height" and "age" at baseline was used to calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.972
Method	ANCOVA

Secondary: Insulin Like Growth Factor-1 (IGF-1) Levels

End point title	Insulin Like Growth Factor-1 (IGF-1) Levels

End point description:

FA set included all subjects who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. 'N' (Number of subjects analyzed) signified those participants who were evaluable for this measure and "n" = number of subjects analyzed at that particular time point for each arm group respectively.

End point type	Secondary

End point timeframe:

Baseline (randomization), Month 6 and Month 12

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: microgram/liter (mcg/L)				
arithmetic mean (standard deviation)				
Baseline (randomization) (n= 10,11)	319.6 (± 146.27)	275.4 (± 98.82)		
Month 6 (n= 9,7)	369.3 (± 120.13)	262.4 (± 65.52)		
Month 12 (n=10,10)	414.3 (± 176.7)	263 (± 120.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis:IGF-1 Month 6

Statistical analysis description:

Month 6: ANCOVA method with covariates "height" and "age" at baseline was used to calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.058
Method	ANCOVA
Confidence interval	
level	95 %

Statistical analysis title	Statistical Analysis:IGF-1 Month 12

Statistical analysis description:

Month 12: ANCOVA method with covariates "height" and "age" at baseline was used to calculate

presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	ANCOVA

Secondary: Insulin Like Growth Factor Binding Protein-3 (IGFBP-3) Levels

End point title	Insulin Like Growth Factor Binding Protein-3 (IGFBP-3) Levels

End point description:

FA set included all subjects who received at least 1 dose of study medication and had at least 1 height evaluation post randomization. 'N' (Number of subjects analyzed) signified those subjects who were evaluable for this measure and "n" = number of subjects analyzed at that particular time point for each arm group respectively.

End point type	Secondary

End point timeframe:

Baseline (randomization), Month 6 and Month 12

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: milligram/L (mg/L)				
arithmetic mean (standard deviation)				
Baseline (randomization) (n= 10,10)	3.4 (± 0.7)	3.4 (± 0.6)		
Month 6 (n= 9,7)	3 (± 0.84)	3.3 (± 0.81)		
Month 12 (n= 9,10)	3.6 (± 1.02)	3.5 (± 0.77)		

Statistical analyses

Statistical analysis title	Statistical Analysis:IGBP-3: Month 6

Statistical analysis description:

Month 6: ANCOVA method with covariates "height" and "age" at baseline was used to calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.793
Method	ANCOVA

Statistical analysis title	Statistical Analysis:IGBP-3: Month 12

Statistical analysis description:

Month 12: ANCOVA method with covariates "height" and "age" at baseline was used to calculate presented p-value.

Comparison groups	Saizen® 0.057 mg/kg/day v Saizen® 0.035 mg/kg/day
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.055
Method	ANCOVA

Secondary: Number of subjectss with treatment emergent adverse events (TEAEs)

End point title	Number of subjectss with treatment emergent adverse events (TEAEs)

End point description:

Adverse Events (AEs): Any untoward medical occurrence in the form of signs, clinically significant abnormalities in laboratory findings, diseases, symptoms, or worsening of complications. TEAEs: AEs that occur during treatment with the Investigational Medicinal Product (IMP). The safety population included all the subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline (randomization) until Month 12

End point values	Saizen® 0.057 mg/kg/day	Saizen® 0.035 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Subjects				
number (not applicable)	2	1		

Statistical analyses

No statistical analyses for this end point

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	11.0

Reporting groups

Reporting group title	Saizen® 0.035 mg/kg/day

Reporting group description:

Saizen® (r-hGH) subcutaneously administered at the daily dose of 0.035 mg/kg or 0.24 mg/kg/week for duration of 12 months.

Reporting group title	Saizen® 0.057 mg/kg/day

Reporting group description:

Saizen® (recombinant human growth hormone, r-hGH) subcutaneously administered at the daily dose of 0.057 milligram/kilogram (mg/kg) or 0.40 mg/kg/week for duration of 12 months.

Serious adverse events	Saizen® 0.035 mg/kg/day	Saizen® 0.057 mg/kg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Saizen® 0.035 mg/kg/day	Saizen® 0.057 mg/kg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	2 / 10 (20.00%)	
Investigations			
Insulin-like growth factor increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Immune system disorders			

Asthma			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	

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

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

Subject's inclusion period was extended but due to remaining low recruitment rate, it was finally decided to stop enrollment even if only 22 subjects were enrolled.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22508151