Clinical trial results:
Open-label, single-arm, Phase IV, multicenter trial to explore the immunogenicity of the liquid formulation of Saizen® in subjects with adult growth hormone deficiency (AGHD)

Summary

EudraCT number	2012-004263-47
Trial protocol	GB SE DE CZ
Global end of trial date	21 March 2016

Results information

Result version number	v1 (current)
This version publication date	03 March 2017
First version publication date	03 March 2017

Trial information

Trial identification

Sponsor protocol code	EMR200104-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01806298
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Center 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2016
Global end of trial reached?	Yes
Global end of trial date	21 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether the marketed Saizen solution for injection, administered according to the approved label for 9 months (39 weeks) in adults with GHD, induces the development of binding antibodies (BAbs).

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 June 2013
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	Australia: 31
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Sweden: 4
Worldwide total number of subjects	78
EEA total number of subjects	47

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	76
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First subject enrolled: 28 Jun 2013; Last subject visited on: 21 Mar 2016

Period 1

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

Arms

Arm title	Saizen®

Arm description:

Saizen® solution for injection was administered subcutaneously once daily for 39 weeks according to locally approved product labeling for the currently marketed formulation of Saizen®.

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

Dosage and administration details:

Saizen® solution for injection was administered subcutaneously once daily for 39 weeks.

Number of subjects in period 1	Saizen®
Started	78
Completed	68
Not completed	10
Consent withdrawn by subject	1
Adverse Event	3
Other	5
Protocol Non-compliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Saizen® solution for injection was administered subcutaneously once daily for 39 weeks according to locally approved product labeling for the currently marketed formulation of Saizen®. The safety analysis set included all treated subjects who had received at least 1 administration of Saizen®.

Reporting group values	Overall Study	Total	
Number of subjects	78	78	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 44.5 ± 12.61	 -	
Gender categorical Units: Subjects			
Female	30	30	
Male	48	48	

End points

End points reporting groups

Reporting group title	Saizen®

Reporting group description:

Saizen® solution for injection was administered subcutaneously once daily for 39 weeks according to locally approved product labeling for the currently marketed formulation of Saizen®.

Primary: Percentage of Subjects Developing Binding Antibodies (BAbs) to Saizen®

End point title	Percentage of Subjects Developing Binding Antibodies (BAbs) to Saizen®[1]

End point description:

Percentage of subjects developing BAbs = (Number of BAb positive subjects / Total number of subjects) x 100. The modified Intent-To-Treat (mITT) analysis set included all treated subjects who had received at least 1 administration of Saizen® and had at least 1 post-baseline BAbs assessment.

End point type	Primary

End point timeframe:

Baseline up to Week 39

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 4.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Binding Antibodies (BAbs) Who Became Positive for Neutralizing Antibodies (NAbs)

End point title	Percentage of Subjects With Binding Antibodies (BAbs) Who Became Positive for Neutralizing Antibodies (NAbs)

End point description:

Percentage of subjects with BAbs who become positive for NAbs = (Number of NAb positive subjects / Number of BAbs positive subjects) x 100.

End point type	Secondary

End point timeframe:

Baseline up to Week 39

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: percentage of subjects				

Notes:

[2] - Data could not be analysed as there were no subjects who were BAb positive.

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin-like Growth Factor-I (IGF-I) Levels

End point title	Insulin-like Growth Factor-I (IGF-I) Levels

End point description:

Growth Hormone (GH) biomarker levels were summarised by GH treatment status at study entry (that is subjects were classified as GH treatment-naïve subjects or subjects with prior GH treatment for adult growth hormone deficiency [AGHD]). The safety analysis set included all treated subjects who had received at least 1 administration of Saizen®. Here, "n" signifies those subjects who were evaluable for the specified category at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 8, 16, 29, 39 and 41

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: nanomoles per litre (nmol/L)				
arithmetic mean (standard deviation)				
GH Treatment-naive: Baseline (n = 64)	14.54 (± 7.219)			
Previously took GH treatment : Baseline (n = 14)	10.91 (± 4.744)			
GH Treatment-naive: Week 2 (n = 64)	21.15 (± 9.008)			
Previously took GH treatment: Week 2 (n = 14)	19.41 (± 5.804)			
GH Treatment-naive: Week 8 (n = 63)	23.41 (± 9.07)			
Previously took GH treatment: Week 8 (n = 13)	20.91 (± 5.437)			
GH Treatment-naive: Week 16 (n = 59)	22.34 (± 6.844)			
Previously took GH treatment: Week 16 (n = 13)	20.15 (± 7.381)			
GH Treatment-naive: Week 29 (n = 59)	25.07 (± 8.026)			
Previously took GH treatment: Week 29 (n = 13)	20.9 (± 6.81)			
GH Treatment-naive: Week 39 (n = 61)	23.82 (± 7.961)			
Previously took GH treatment: Week 39 (n = 14)	20.56 (± 8.486)			
GH Treatment-naive: Week 41 (n = 56)	15.28 (± 6.943)			

Previously took GH treatment: Week 41 (n = 12)	12.12 (± 4.91)			

Statistical analyses

No statistical analyses for this end point

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:

Growth Hormone (GH) biomarker levels were summarised by GH treatment status at study entry (that is subjects were classified as GH treatment-naïve subjects or subjects with prior GH treatment for adult growth hormone deficiency [AGHD]). The safety analysis set included all treated subjects who had received at least 1 administration of Saizen®. Here, "n" signifies those subjects who were evaluable for the specified category at each time point.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 8, 16, 29, 39 and 41

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: milligram/liter (mg/L)				
arithmetic mean (standard deviation)				
GH Treatment-naive: Baseline (n = 64)	2.62 (± 0.843)			
Previously took GH treatment : Baseline (n = 14)	2.2 (± 0.68)			
GH Treatment-naive: Week 2 (n = 64)	3.03 (± 0.872)			
Previously took GH treatment: Week 2 (n = 14)	2.85 (± 0.981)			
GH Treatment-naive: Week 8 (n = 63)	3.11 (± 0.831)			
Previously took GH treatment: Week 8 (n = 13)	2.77 (± 0.795)			
GH Treatment-naive: Week 16 (n = 59)	3.15 (± 0.746)			
Previously took GH treatment: Week 16 (n = 13)	2.93 (± 0.746)			
GH Treatment-naive: Week 29 (n = 59)	3.36 (± 0.737)			
Previously took GH treatment: Week 29 (n = 13)	3.22 (± 0.903)			
GH Treatment-naive: Week 39 (n = 61)	3.45 (± 0.938)			
Previously took GH treatment: Week 39 (n = 14)	3.03 (± 0.853)			
GH Treatment-naive: Week 41 (n= 56)	2.91 (± 0.758)			
Previously took GH treatment: Week 41 (n = 12)	2.63 (± 0.786)			

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin-like Growth Factor-I Standard Deviation Score (IGF-I SDS)

End point title	Insulin-like Growth Factor-I Standard Deviation Score (IGF-I SDS)

End point description:

Insulin-like Growth Factor-1 SDS was calculated based on the actual value of IGF-1 minus reference value of IGF-1 divided by reference standard deviation of IGF-1. SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) a subject's value was relative to the mean of the reference population. The scores were centered around zero. Negative score indicated that the IGF-I value was lower compared to the reference population. The safety analysis set included all treated subjects who had received at least 1 administration of Saizen®. Here, "n" signifies those subjects who were evaluable for the specified category at each time point.

End point type	Secondary

End point timeframe:

Baseline up to Week 41

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Standard deviation score				
arithmetic mean (standard deviation)				
GH Treatment-naive: Baseline (n = 64)	-3.27 (± 0.816)			
Previously took GH treatment : Baseline (n = 14)	-3.67 (± 1.223)			
GH Treatment-naive: Week 2 (n = 64)	-3.1 (± 0.775)			
Previously took GH treatment: Week 2 (n = 14)	-3.46 (± 1.14)			
GH Treatment-naive: Week 8 (n = 63)	-3.05 (± 0.769)			
Previously took GH treatment: Week 8 (n = 13)	-3.16 (± 0.697)			
GH Treatment-naive: Week 16 (n = 59)	-3.09 (± 0.799)			
Previously took GH treatment: Week 16 (n = 13)	-3.17 (± 0.652)			
GH Treatment-naive: Week 29 (n = 59)	-3.01 (± 0.773)			
Previously took GH treatment: Week 29 (n = 13)	-3.17 (± 0.713)			
GH Treatment-naive: Week 39 (n = 61)	-3.02 (± 0.78)			
Previously took GH treatment: Week 39 (n = 14)	-3.44 (± 1.29)			
GH Treatment-naive: Week 41 (n= 56)	-3.23 (± 0.83)			
Previously took GH treatment: Week 41 (n = 12)	-3.31 (± 0.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Adherence Rate as Documented Using EasypodTM Connect

End point title	Treatment Adherence Rate as Documented Using EasypodTM Connect

End point description:

Treatment adherence rate was measured by: (total dose received divided by total dose prescribed) multiplied by 100. Saizen solution for injection was administered using the easypod device and treatment adherence information was obtained from the device using the easypod connect software. The safety analysis set included all treated subjects who had received at least 1 administration of Saizen®.

End point type	Secondary

End point timeframe:

Week 2, 8, 16, 29 and 39

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: percentage of treatment adherence				
arithmetic mean (standard deviation)	89.3 (± 13.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events(TEAEs), Serious TEAEs, TEAEs Leading to Death, TEAEs Leading to Discontinuation

End point title	Number of Subjects With Treatment-emergent Adverse Events(TEAEs), Serious TEAEs, TEAEs Leading to Death, TEAEs Leading to Discontinuation

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the study drug. An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug or worsening of pre-existing medical condition, whether or not related to study drug. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. TEAEs include both Serious TEAEs and non-serious TEAEs. The safety analysis set.

End point type	Secondary

End point timeframe:

Baseline up to Week 41

End point values	Saizen®			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: subjects				
TEAEs	72			
Serious TEAEs	4			
TEAEs Leading to Death	0			
TEAEs Leading to Discontinuation	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 41

Adverse event reporting additional description:

Saizen® solution for injection was administered subcutaneously once daily for 39 weeks according to locally approved product labeling for the currently marketed formulation of Saizen®.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Saizen®

Reporting group description:

Saizen® solution for injection was administered subcutaneously once daily for 39 weeks according to locally approved product labeling for the currently marketed formulation of Saizen®.

Serious adverse events	Saizen®		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 78 (5.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Infection			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Saizen®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 78 (83.33%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	27 / 78 (34.62%)		
occurrences (all)	27		
Lethargy			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Migraine			

subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences (all)	4		
General disorders and administration site conditions			
Vomiting			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Chest discomfort			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Injection site bruising			
subjects affected / exposed	7 / 78 (8.97%)		
occurrences (all)	7		
Injection site pain			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Non-cardiac chest pain			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Vertigo			

subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	6 / 78 (7.69%)		
occurrences (all)	6		
Dry mouth			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	5 / 78 (6.41%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	7 / 78 (8.97%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Dyspnoea			

subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	5 / 78 (6.41%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 78 (16.67%)		
occurrences (all)	13		
Arthritis			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	10 / 78 (12.82%)		
occurrences (all)	10		
Joint swelling			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Musculoskeletal pain			

subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences (all)	4		
Infections and infestations			
Influenza			
subjects affected / exposed	6 / 78 (7.69%)		
occurrences (all)	6		
Lower respiratory tract infection			
subjects affected / exposed	5 / 78 (6.41%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	21 / 78 (26.92%)		
occurrences (all)	21		
Sinusitis			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	6 / 78 (7.69%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2013	Modified exclusion criterion 3 to allow inclusion of subjects with adequately treated basal cell or squamous cell skin cancer.
15 July 2014	1) Modified inclusion criterion 5 by increasing the maximum permitted BMI level measured at the Screening visit (Weight in kilograms / [Height in meters]^2) from less than or equal to (<=) 35 to <= 40 kg/m^ 2 . 2) Updated administrative information to reflect the change in the Sponsor's medical responsible, clinical trial leader and the principal statistician.
09 October 2014	1) Modified inclusion criterion 2 to allow recruitment of subjects with CO-AGHD as well as AO-AGHD. 2) Modified inclusion criterion 3 to allow enrollment of subjects who stopped prior GH treatment for AGHD 1 month prior to Screening as compared to at least 3 months prior to Screening previously. 3) Modified exclusion criterion 3 to ensure that the wording is in alignment with the Saizen label. Provided clarification that the presence of an active malignancy is a contraindication and that any pre-existing malignancy must be inactive with anti-tumor therapy completed prior to starting trial on Saizen therapy. 4) Updated administrative information to reflect the change in the Sponsor's principal statistician and the central laboratory.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported