Clinical trial results:
A phase IV open-label study of predictive markers in Growth Hormone Deficient and Turner Syndrome pre-pubertal children treated with SAIZEN®

Summary

EudraCT number	2004-005054-31
Trial protocol	GB FI ES DE AT SE IT
Global end of trial date	17 September 2007

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	24531

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merck Serono, a division of Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre merck KGaA, Merck KGaA, Merck Serono, a division of Merck KGaA, 49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre merck KGaA, Merck KGaA, Merck Serono, a division of 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	17 September 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify the most responsive serum biomarkers after one month of SAIZEN® therapy in growth hormone deficiency (GHD) and Turner syndrome (TS) children.

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	25 May 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	Argentina: 24
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Russian Federation: 73
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Korea, Republic of: 31
Worldwide total number of subjects	318
EEA total number of subjects	158

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)	3
Children (2-11 years)	249
Adolescents (12-17 years)	65
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Dec 2013/xxxxxxx. Clinical data cutoff: Oct 2007, Study completion date: Sep 2007.

Pre-assignment

Screening details:

A total of 319 subjects were screened for this trial. Only 1 subject withdrew from the study prior receiving the treatment due to personal reasons. Overall, 318 subjects were enrolled into the study.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Turner Syndrome (TS)

Arm description:

Subjects with TS were administered with SAIZEN® as subcutaneous injection at a dose of 0.050 milligram per kilogram (mg/kg) of body weight per day (within the recommended dosage 0.045-0.050 mg/kg body weight) for a period of 1 month.

Arm type	Experimental
Investigational medicinal product name	SAIZEN®
Investigational medicinal product code	
Other name	Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SAIZEN® was administered as subcutaneous injection at a dose of 0.050 mg/kg of body weight per day for a period of 1 month.

Arm title	Growth Hormone Deficiency (GHD)

Arm description:

Subjects with GHD were administered with SAIZEN® as subcutaneous injection at a dose of 0.035 mg/kg of body weight per day (within the recommended dosage 0.025-0.035 mg/kg body weight) for a period of 1 month.

Arm type	Experimental
Investigational medicinal product name	SAIZEN®
Investigational medicinal product code	
Other name	Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SAIZEN® was administered as subcutaneous injection at a dose of 0.035 mg/kg of body weight per day for a period of 1 month.

Number of subjects in period 1	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)
Started	149	169
Completed	147	167
Not completed	2	2
Adverse event	1	-
Unspecified	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Turner Syndrome (TS)
Reporting group description:	
Subjects with TS were administered with SAIZEN® as subcutaneous injection at a dose of 0.050 milligram per kilogram (mg/kg) of body weight per day (within the recommended dosage 0.045-0.050 mg/kg body weight) for a period of 1 month.	
Reporting group title	Growth Hormone Deficiency (GHD)
Reporting group description:	
Subjects with GHD were administered with SAIZEN® as subcutaneous injection at a dose of 0.035 mg/kg of body weight per day (within the recommended dosage 0.025-0.035 mg/kg body weight) for a period of 1 month.	

Reporting group values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)	Total
Number of subjects	149	169	318
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	9.3	8.94	
standard deviation	± 4.08	± 3.17	-
Gender, Male/Female Units: participants			
Female	149	63	212
Male	0	106	106

End points

End points reporting groups

Reporting group title	Turner Syndrome (TS)

Reporting group description:

Subjects with TS were administered with SAIZEN® as subcutaneous injection at a dose of 0.050 milligram per kilogram (mg/kg) of body weight per day (within the recommended dosage 0.045-0.050 mg/kg body weight) for a period of 1 month.

Reporting group title	Growth Hormone Deficiency (GHD)

Reporting group description:

Subjects with GHD were administered with SAIZEN® as subcutaneous injection at a dose of 0.035 mg/kg of body weight per day (within the recommended dosage 0.025-0.035 mg/kg body weight) for a period of 1 month.

Primary: Change from baseline in insulin like growth factor-1 standard deviation score (IGF-1 SDS) levels at month 1

End point title	Change from baseline in insulin like growth factor-1 standard deviation score (IGF-1 SDS) levels at month 1[1]

End point description:

IGF-1 SDS was calculated using the Elmlinger reference method. This endpoint was assessed within-subject change in IGF-1 levels (standard deviation scores) at month 1 from baseline. Descriptive statistics were determined for the baseline and month 1 assessments, and also for the level of change between these two assessments. If either the baseline or month 1 IGF-1 level was missing, then the within-subject change in IGF-1 was assumed to be missing. This endpoint was assessed in Intention to Treat (ITT) population with evaluable subjects. The ITT population included all subjects who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Month 1

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: Statistical analysis are presented in a separate attachment "hange from baseline in insulin like growth factor-1 standard deviation score (IGF-1 SDS) levels at month 1".

End point values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	162		
Units: Standard deviation score (SDS)				
arithmetic mean (standard deviation)	1.7692 (± 1.1889)	1.4007 (± 0.9811)		

Attachments (see zip file)	Statistical Analysis/Change from baseline in insulin like growth

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in insulin-like growth factor binding protein - 3 (IGFBP-3) level at month 1

End point title	Change from baseline in insulin-like growth factor binding protein - 3 (IGFBP-3) level at month 1

End point description:

This endpoint was assessed in ITT population with evaluable subjects.

End point type	Secondary

End point timeframe:

Month 1

End point values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	162		
Units: milligram per liter (mg/L)				
arithmetic mean (standard deviation)	0.86 (± 0.96)	0.69 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting glucose levels at month 1

End point title	Change from baseline in fasting glucose levels at month 1

End point description:

This endpoint was assessed in ITT population with evaluable subjects.

End point type	Secondary

End point timeframe:

Month 1

End point values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	142		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	0.22 (± 0.8)	0.13 (± 0.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting insulin levels at month 1

End point title	Change from baseline in fasting insulin levels at month 1

End point description:

This endpoint was assessed in ITT population with evaluable subjects.

End point type	Secondary

End point timeframe:

Month 1

End point values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	160		
Units: picomole per liter (pmol/L)				
arithmetic mean (standard deviation)	47.7 (± 177.2)	26.9 (± 79.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at month 1

End point title	Change from baseline in Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at month 1

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. This endpoint was assessed in ITT population with evaluable subjects. This endpoint was assessed in ITT popuation with evaluable subjects.

End point type	Secondary

End point timeframe:

Month 1

End point values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	136		
Units: picomole per liter *millimole per liter				
arithmetic mean (standard deviation)	2.132 (± 10.296)	1.061 (± 3.885)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bone alkaline phosphatase levels at month 1

End point title	Change from baseline in bone alkaline phosphatase levels at month 1

End point description:

This endpoint was assessed in ITT population with evaluable subjects.

End point type	Secondary

End point timeframe:

Month 1

End point values	Turner Syndrome (TS)	Growth Hormone Deficiency (GHD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	162		
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)	21.13 (± 80.68)	14.78 (± 25.23)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were captured from the date of informed consent until at least 4 weeks following the last SAIZEN® administration or the post-treatment visit, whichever represented the longer period.

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as those events having an onset date greater than or equal to the first dose date of the study medication and less than or equal to the last dose date plus 28 days.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Turner Syndrome

Reporting group description:

Subjects with Turner Syndrome were administered with SAIZEN® as subcutaneous injection at a dose of 0.050 mg/kg of body weight (within the recommended dosage 0.045-0.050 mg/kg body weight) for a period of 1 month.

Reporting group title	Growth Hormone Deficiency

Reporting group description:

Growth hormone deficiency subjects were administered with SAIZEN® as subcutaneous injection at a dose of 0.035 mg/kg of body weight (within the recommended dosage 0.025-0.035 mg/kg body weight) for a period of 1 month.

Serious adverse events	Turner Syndrome	Growth Hormone Deficiency	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Tonsillitis streptococcal			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
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	Turner Syndrome	Growth Hormone Deficiency	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 149 (24.16%)	51 / 169 (30.18%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 149 (4.03%)	9 / 169 (5.33%)	
occurrences (all)	7	9	
Injection site haemorrhage			
subjects affected / exposed	1 / 149 (0.67%)	1 / 169 (0.59%)	
occurrences (all)	1	1	
Injection site irritation			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 149 (0.67%)	0 / 169 (0.00%)	
occurrences (all)	1	0	
Injection site anaesthesia			
subjects affected / exposed	1 / 149 (0.67%)	0 / 169 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 149 (3.36%)	2 / 169 (1.18%)	
occurrences (all)	7	2	
Productive cough			
subjects affected / exposed	3 / 149 (2.01%)	0 / 169 (0.00%)	
occurrences (all)	5	0	
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 149 (0.67%)	1 / 169 (0.59%)	
occurrences (all)	1	1	

Epistaxis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 149 (0.67%)	0 / 169 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	1 / 149 (0.67%)	0 / 169 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 149 (0.67%)	0 / 169 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 149 (5.37%)	12 / 169 (7.10%)	
occurrences (all)	10	18	
Dizziness			
subjects affected / exposed	2 / 149 (1.34%)	1 / 169 (0.59%)	
occurrences (all)	3	2	
Somnolence			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 149 (0.67%)	1 / 169 (0.59%)	
occurrences (all)	1	1	
Ear pain			

subjects affected / exposed	1 / 149 (0.67%)	0 / 169 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 149 (2.01%)	4 / 169 (2.37%)	
occurrences (all)	3	4	
Diarrhoea			
subjects affected / exposed	1 / 149 (0.67%)	3 / 169 (1.78%)	
occurrences (all)	1	3	
Abdominal pain			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Enteritis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Dermatitis atopic			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Endocrine disorders			

Precocious puberty			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 149 (2.68%)	2 / 169 (1.18%)	
occurrences (all)	4	2	
Upper respiratory tract infection			
subjects affected / exposed	3 / 149 (2.01%)	2 / 169 (1.18%)	
occurrences (all)	4	2	
Gastroenteritis			
subjects affected / exposed	1 / 149 (0.67%)	2 / 169 (1.18%)	
occurrences (all)	2	2	
Ear infection			
subjects affected / exposed	2 / 149 (1.34%)	0 / 169 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	1 / 149 (0.67%)	1 / 169 (0.59%)	
occurrences (all)	1	1	
Pharyngitis			

subjects affected / exposed	0 / 149 (0.00%)	2 / 169 (1.18%)	
occurrences (all)	0	2	
Tonsillitis			
subjects affected / exposed	1 / 149 (0.67%)	1 / 169 (0.59%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Bronchitis acute			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Conjunctivitis viral			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Enterocolitis infectious			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Otitis externa			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 169 (0.59%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2007	The purpose of this amendment was to modify the primary endpoint from "change from baseline in IGF-1" levels at month 1 to "Change from baseline in IGF-1 SDS" levels at month 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Limitations of the trial were short duration of the study treatment, and relatively small sample size

Notes: