



## Clinical trial results:

**An open, multicenter, randomized, controlled trial to evaluate the correlation between spontaneous catch-up growth, clinical response to Saizen® (recombinant human growth hormone, r-hGH) and gene expression profiling in children small for gestational age (SGA)**

### Summary

EudraCT number	2015-001681-25
Trial protocol	Outside EU/EEA
Global end of trial date	10 July 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	23681
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01067352
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	10 July 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 July 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the correlation between gene expression and catch-up growth (either spontaneous or drug-induced after one year of treatment) in SGA children.

A secondary objective was to evaluate the percentage of patients who were not treated, but who showed a spontaneous catch-up growth during two years of observation.

Safety objectives included the safety and tolerability of Saizen (recombinant human growth hormone, r-hGH) in SGA 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	20 February 2004
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	Italy: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	25
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited in 12 study centers in Italy from 20 Feb 2004 to 10 Jul 2009.

### Pre-assignment

Screening details:

in total, 25 subject enrolled in this study

### 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
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<b>Arm title</b>	Group A, less than third percentile (Saizen)
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Arm description:

Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (s.c) at the daily dose of 0.035 milligram(mg)/kilogram(kg) for 2 years.

Arm type	Experimental
Investigational medicinal product name	Recombinant human growth hormone (r-hGH)
Investigational medicinal product code	
Other name	Saizen
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Recombinant human GH were administered subcutaneously at the daily dose of 0.067 mg/kg of body weight to Group A1.

<b>Arm title</b>	Group A2, less than third percentile (No treatment)
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Arm description:

Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Arm title</b>	Group B, more than third percentile (No treatment)
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Arm description:

Subjects with more than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)
Started	9	6	10
Completed	8	3	9
Not completed	1	3	1
Consent withdrawn by subject	1	2	1
Physician decision	-	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Group A, less than third percentile (Saizen)
Reporting group description: Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (s.c) at the daily dose of 0.035 milligram(mg)/kilogram(kg) for 2 years.	
Reporting group title	Group A2, less than third percentile (No treatment)
Reporting group description: Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.	
Reporting group title	Group B, more than third percentile (No treatment)
Reporting group description: Subjects with more than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.	

Reporting group values	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)
Number of subjects	9	6	10
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	5.7 ± 1.2	5 ± 0.7	5.2 ± 0.4
Gender, Male/Female Units: participants			
Female	4	4	5
Male	5	2	5

Reporting group values	Total		
Number of subjects	25		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: participants			
Female	13		
Male	12		

## End points

### End points reporting groups

Reporting group title	Group A, less than third percentile (Saizen)
Reporting group description: Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (s.c) at the daily dose of 0.035 milligram(mg)/kilogram(kg) for 2 years.	
Reporting group title	Group A2, less than third percentile (No treatment)
Reporting group description: Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.	
Reporting group title	Group B, more than third percentile (No treatment)
Reporting group description: Subjects with more than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.	

### Primary: Correlation between gene expression profiling and catch-up growth in small for gestational age (SGA) children

End point title	Correlation between gene expression profiling and catch-up growth in small for gestational age (SGA) children <sup>[1]</sup>
End point description: Gene expression profiling:analysis of ribonucleic acid (RNA) extracted from body tissue or fluids using Clontech Atlas Human Array to study level of activation of genes in tissue analyzed. Analysis was performed to identify possible correlation between catch-up growth (either spontaneous or drug-induced after Week 48) and therapeutic response to rhGH. Spontaneous catch up growth:shown by SGA subjects having length more than third percentile at Week 96 without any treatment;drug induced growth was by SGA subjects having length more than third percentile at Week 96 with drug treatment. Gene expression profiling was not performed due to RNA degradation in nearly all of the blood samples and hence no comparison between gene expression and growth was made.	
End point type	Primary
End point timeframe: Baseline and Week 48	

#### 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: Gene expression profiling was not performed due to RNA degradation in nearly all of the blood samples and hence no comparison between gene expression and growth was made.

End point values	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[2]</sup>	0 <sup>[3]</sup>	0 <sup>[4]</sup>	
Units: correlation factor				
arithmetic mean (standard deviation)	( )	( )	( )	

#### Notes:

[2] - Comparison between gene expression and growth could not be done as gene profiling could not be done.

[3] - Comparison between gene expression and growth could not be done as gene profiling could not be done.

[4] - Comparison between gene expression and growth could not be done as gene profiling could not be

done.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of untreated subjects who showed a spontaneous catch-up growth

End point title	Percentage of untreated subjects who showed a spontaneous catch-up growth
End point description: Spontaneous catch up growth was the growth shown by SGA subjects having length more than third percentile at Week 96 without any study drug treatment. Data was not analyzed due to small number of evaluable participants.	
End point type	Secondary
End point timeframe: Baseline through Week 96	

End point values	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[5]</sup>	0 <sup>[6]</sup>	0 <sup>[7]</sup>	
Units: Percentage of subjects				
number (not applicable)				

Notes:

[5] - Data was not analyzed due to small number of evaluable subjects.

[6] - Data was not analyzed due to small number of evaluable subjects.

[7] - Data was not analyzed due to small number of evaluable subjects.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs) and AEs leading to study drug discontinuation

End point title	Number of subjects with adverse events (AEs), serious adverse events (SAEs) and AEs leading to study drug discontinuation
End point description: AEs: any new untoward medical occurrences/worsening of pre-existing medical condition, whether or not related to study drug , SAE: any AE that resulted in death; was life threatening; resulted in persistent/significant disability/incapacity; resulted in/prolonged an existing in-patient hospitalization; was a congenital anomaly/birth defect; or was an overdose. Subjects who discontinued from the study due to AE were also recorded. This endpoint was assessed in safety analysis population which included all randomized subjectss with at least 1 post-baseline assessment.	
End point type	Secondary



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End point timeframe:  
Baseline through Week 96

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<b>End point values</b>	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	10	
Units: subjects				
number (not applicable)				
AEs	6	4	9	
SAEs	0	0	0	
Discontinuation due to AEs	0	0	0	

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were collected on an ongoing basis from day of written informed consent. All new AEs were recorded until the post-treatment safety, on Day 30 post-drug administration.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	MedDRA (U)
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### Reporting groups

Reporting group title	Group A, less than third percentile (Saizen)
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Reporting group description:

Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received Saizen (recombinant human growth hormone, r-hGH) subcutaneously (s.c) at the daily dose of 0.035 milligram(mg)/kilogram(kg) for 2 years.

Reporting group title	Group A2, less than third percentile (No treatment)
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Reporting group description:

Subjects with less than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.

Reporting group title	Group B, more than third percentile (No treatment)
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Reporting group description:

Subjects with more than third percentile for height (according to the Tanner reference table) at the age of 4-6 years received no drug treatment for 2 years.

Serious adverse events	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Group A, less than third percentile (Saizen)	Group A2, less than third percentile (No treatment)	Group B, more than third percentile (No treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	4 / 4 (100.00%)	9 / 10 (90.00%)
General disorders and administration site conditions			
Cyst			

subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	6 / 8 (75.00%)	2 / 4 (50.00%)	4 / 10 (40.00%)
occurrences (all)	15	6	6
Immune system disorders			
Milk allergy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	2 / 10 (20.00%)
occurrences (all)	4	0	2
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lipoprotein (a) abnormal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood insulin decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Road traffic accident subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0
Microcytic anaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0
Stomatitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 4 (25.00%) 1	0 / 10 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0	1 / 10 (10.00%) 2
Skin and subcutaneous tissue disorders Alopecia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Acute generalised exanthematous pustulosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Bronchitis			
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	3 / 10 (30.00%)
occurrences (all)	2	1	4
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 4 (50.00%)	2 / 10 (20.00%)
occurrences (all)	4	2	2
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Varicella			

subjects affected / exposed	0 / 8 (0.00%)	2 / 4 (50.00%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Enterocolitis infectious			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Laryngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

The primary and secondary efficacy objectives were not met because of poor subject enrollment and no quality RNA samples obtained to evaluate (RNA degradation in nearly all of the blood samples).
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Notes: