Clinical trial results:
An Open Study of the Safety and Efficacy of Saizen®, (Recombinant Human Growth Hormone, r-hGH), in Children Born With Serious Intra-uterine Growth Retardation (IUGR) Treated to Final Height

Summary

EudraCT number	2015-001708-69
Trial protocol	Outside EU/EEA
Global end of trial date	17 February 2010

Results information

Result version number	v2 (current)
This version publication date	04 June 2016
First version publication date	05 August 2015
Version creation reason	• Correction of full data set Correction of full data set

Trial information

Trial identification

Sponsor protocol code	20184

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01400698
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	17 February 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to follow children born with serious IUGR, and treated with 1.4 International units per kilogram per week(IU/kg/week)[0.47 milligram per kilogram per week (mg/kg/week)] of Saizen according to various therapeutic schedules, until they reach final height while assessing both efficacy and safety (studies A, B and C).

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 the Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 1998
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: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	51
Adolescents (12-17 years)	40
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who completed 3 or 2 years treatment and at least 1 year post treatment observation in Sponsor Studies GF 4001 (Safety and Efficacy of Saizen in the Treatment of Young Children Born with Severe IUGR or GF 6283 (Effect of Intermittent versus Continuous Saizen Therapy in Young Children Born with Severe IUGR), respectively were enrolled.

Pre-assignment

Screening details:

Overall, 91 subjects who had participated in and successfully completed either study 4001 or 6283 were enrolled in study 20184.

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® Continuous (A1)

Arm description:

Subjects with bone age less than or equal to (<=) 12 years for girls or 14 years for boys and height <=-2 standard deviation (SD) received continuous treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc) until they reached final height for a maximum duration of 10.6 years.

Arm type	Experimental
Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	r-hGH, Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Continuous treatment with recombinant human Growth Hormone (r-hGH) 0.067 mg/kg/day sc.

Arm title	Saizen® Intermittent (A2)

Arm description:

Subjects with bone age <=12 years for girls or 14 years for boys and height <=-2 SD received intermittent treatment with r-hGH 0.067 mg/kg/day sc until they reached final height for a maximum duration of 10.6 years. Intermittent treatment was given on an individual basis depending on the height achieved during the study.

Arm type	Experimental
Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	r-hGH, Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Intermittent treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc).

Arm title	Observed, Not Randomized (B0)

Arm description:

Subjects with bone age <=12 years for girls or 14 years for boys and height greater than (>) -2 SD were observed until first signs of puberty but not randomized.

Arm type	Observation only

No investigational medicinal product assigned in this arm

Arm title	Observed Then Randomized to Saizen® (B1)

Arm description:

Subjects with bone age <=12 years for girls or 14 years for boys and height >-2 SD were observed until first signs of puberty and if remained at a height >-2 SD, were randomized to receive continuous treatment with r-hGH 0.067 mg/kg/day sc until they reached final height for a maximum duration of 10.6 years. Subjects whose height fell to <=-2 SD before the first sign of puberty, were randomized to either Saizen® Continuous (A1) or Saizen® Intermittent (A2) treatment group.

Arm type	Experimental
Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	r-hGH, Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Continuous treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc).

Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	r-hGH, Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Intermittent treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc).

Arm title	Observed Then Randomized to Observation (B2)

Arm description:

Subjects with bone age <=12 years for girls or 14 years for boys and height >-2 SD were observed until first signs of puberty and if remained at a height >-2 SD, were randomized to observation group with no treatment until they reached final height for a maximum duration of 10.6 years. Subjects whose height fell to <=-2 SD before the first sign of puberty, were randomized to either Saizen® Continuous (A1) or Saizen® Intermittent (A2) treatment group.

Arm type	Experimental
Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	r-hGH, Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Continuous treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc).

Investigational medicinal product name	Saizen
Investigational medicinal product code	
Other name	r-hGH, Somatropin
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Intermittent treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc).

Arm title	Observation (C)

Arm description:

Subjects with bone age >12 years for girls or 14 years for boys or refused to be treated in any of the above groups were followed without treatment until they reached final height for a maximum duration of 10.6 years.

Arm type	Observation only
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Saizen® Continuous (A1)	Saizen® Intermittent (A2)	Observed, Not Randomized (B0)
Started	23	23	2
Completed	8	12	0
Not completed	15	11	2
Consent withdrawn by subject	8	2	-
Protocol violation	-	1	-
Adverse event	1	-	-
Non-compliance	-	1	-
Unspecified	4	2	-
Lost to follow-up	2	5	2

Number of subjects in period 1	Observed Then Randomized to Saizen® (B1)	Observed Then Randomized to Observation (B2)	Observation (C)
Started	14	14	15
Completed	6	7	9
Not completed	8	7	6
Consent withdrawn by subject	4	1	3
Protocol violation	-	1	-
Adverse event	-	-	-
Non-compliance	1	-	-
Unspecified	2	1	-
Lost to follow-up	1	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	91	91	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 10.3 ± 3	 -	
Gender categorical Units: Subjects			
Female	41	41	
Male	50	50	
Original Study Units: Subjects			
GF4001	52	52	
GF6283	39	39	
Race/Ethnicity, Customized Units: Subjects			
Asian	2	2	
Black	1	1	
White	88	88	
Birth Height Units: Centimeters (cm) arithmetic mean standard deviation	 42.8 ± 3.7	 -	
Birth Weight Units: gram(s) arithmetic mean standard deviation	 2085.3 ± 551.8	 -	
Length of Gestation Units: Weeks arithmetic mean standard deviation	 37.9 ± 2.6	 -	

End points

End points reporting groups

Reporting group title	Saizen® Continuous (A1)
Reporting group description:	
Subjects with bone age less than or equal to (<=) 12 years for girls or 14 years for boys and height <=-2 standard deviation (SD) received continuous treatment with recombinant human Growth Hormone (r-hGH) 0.067 milligram/kilogram/day (mg/kg/day) subcutaneously (sc) until they reached final height for a maximum duration of 10.6 years.	
Reporting group title	Saizen® Intermittent (A2)
Reporting group description:	
Subjects with bone age <=12 years for girls or 14 years for boys and height <=-2 SD received intermittent treatment with r-hGH 0.067 mg/kg/day sc until they reached final height for a maximum duration of 10.6 years. Intermittent treatment was given on an individual basis depending on the height achieved during the study.	
Reporting group title	Observed, Not Randomized (B0)
Reporting group description:	
Subjects with bone age <=12 years for girls or 14 years for boys and height greater than (>) -2 SD were observed until first signs of puberty but not randomized.	
Reporting group title	Observed Then Randomized to Saizen® (B1)
Reporting group description:	
Subjects with bone age <=12 years for girls or 14 years for boys and height >-2 SD were observed until first signs of puberty and if remained at a height >-2 SD, were randomized to receive continuous treatment with r-hGH 0.067 mg/kg/day sc until they reached final height for a maximum duration of 10.6 years. Subjects whose height fell to <=-2 SD before the first sign of puberty, were randomized to either Saizen® Continuous (A1) or Saizen® Intermittent (A2) treatment group.	
Reporting group title	Observed Then Randomized to Observation (B2)
Reporting group description:	
Subjects with bone age <=12 years for girls or 14 years for boys and height >-2 SD were observed until first signs of puberty and if remained at a height >-2 SD, were randomized to observation group with no treatment until they reached final height for a maximum duration of 10.6 years. Subjects whose height fell to <=-2 SD before the first sign of puberty, were randomized to either Saizen® Continuous (A1) or Saizen® Intermittent (A2) treatment group.	
Reporting group title	Observation (C)
Reporting group description:	
Subjects with bone age >12 years for girls or 14 years for boys or refused to be treated in any of the above groups were followed without treatment until they reached final height for a maximum duration of 10.6 years.	
Subject analysis set title	Non-Final Height: Not Treated
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all subjects who did not achieve the final height during the study period and did not receive r-hGH 0.067 mg/kg/day sc either continuously or intermittently.	
Subject analysis set title	Non-Final Height: Treated
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all subjects who did not achieve the final height during the study period and received r-hGH 0.067 mg/kg/day sc either continuously or intermittently.	
Subject analysis set title	Final Height: Not Treated
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all subjects who achieved the final height during the study period and did not receive r-hGH 0.067 mg/kg/day sc either continuously or intermittently.	
Subject analysis set title	Final Height: Treated
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes all subjects who achieved the final height during the study period and received r-hGH 0.067 mg/kg/day sc either continuously or intermittently.

Primary: Final height

End point title	Final height[1]

End point description:

Final height was defined as the height reached 1 year after height velocity (HV) was less than 2 centimeter/year (cm/year). Height velocity was the change in height since the previous year's measurement. Height was measured with a wall-mounted stadiometer (or in supine position if the subject's age was less than 3 years) and the measurement was repeated thrice by the same observer. The mean of the values obtained in the repeated measurements was taken for the analysis. This endpoint was assessed in Intention-to-treat (ITT) population included all subjects enrolled in this study. Safety population was identical in this study.

End point type	Primary

End point timeframe:

One year after final height was attained up to 10.6 years

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 statistics was planned for this endpoint.

End point values	Non-Final Height: Not Treated	Non-Final Height: Treated	Final Height: Not Treated	Final Height: Treated
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	13	22	46
Units: cm				
arithmetic mean (standard deviation)	145.9 (± 16.08)	150.06 (± 12.89)	153.27 (± 8.71)	155.59 (± 8.38)

Statistical analyses

No statistical analyses for this end point

Primary: Height standard deviation score (HSDS)

End point title	Height standard deviation score (HSDS)[2]

End point description:

HSDS was calculated as height minus reference mean height divided by SD of the reference mean height, both given by the reference growth table (Sempe) for the corresponding chronological age at the height measurement. Greater HSDS indicate greater height. (Sempe M et al., 1979). This endpoint was assessed in ITT population.

End point type	Primary

End point timeframe:

One year after final height was attained up to 10.6 years

Notes:

[2] - 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 statistics was planned for this endpoint.

End point values	Non-Final Height: Not Treated	Non-Final Height: Treated	Final Height: Not Treated	Final Height: Treated
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	13	22	46
Units: standard deviation score				
arithmetic mean (standard deviation)	-1.45 (± 0.76)	-1.9 (± 1.73)	-2.33 (± 1.01)	-1.99 (± 0.88)

Statistical analyses

No statistical analyses for this end point

Secondary: Parental Adjusted Height Standard Deviation Score (PAHSDS)

End point title	Parental Adjusted Height Standard Deviation Score (PAHSDS)

End point description:

PAHSDS is the distance between the subject's current and target heights, expressed in units of SD of the height distribution of the reference population. Target height is a measure of the height which the subject could hypothetically reach based only on his parents' heights. Target height standard deviation score (THSDS) was calculated as target height minus mean adult height of the reference population divided by SD of the mean adult height of the reference population. This endpoint was assessed in ITT population.

End point type	Secondary

End point timeframe:

One year after final height was attained up to 10.6 years

End point values	Non-Final Height: Not Treated	Non-Final Height: Treated	Final Height: Not Treated	Final Height: Treated
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	13	22	46
Units: Standard deviation score				
arithmetic mean (standard deviation)	-0.82 (± 0.59)	-1.52 (± 1.92)	-1.64 (± 1.61)	-1.24 (± 1.39)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Duration of treatment

End point title	Duration of treatment

End point description:

ITT population included all subjects enrolled in this study. Safety population was identical in this study. Here, 'N' (number of subjects analyzed) signifies those subjects who were treated and hence, were evaluated for this measure.

End point type	Post-hoc

End point timeframe:

Up to 10.6 years

End point values	Non-Final Height: Treated	Final Height: Treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	46		
Units: Years				
arithmetic mean (standard deviation)	4.09 (± 2.92)	4.51 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Duration of participation in the study

End point title	Duration of participation in the study

End point description:

ITT population included all subjects enrolled in this study. Safety population was identical in this study. Here, 'N' (number of subjects analyzed) signifies those subjects who were evaluated for this measure.

End point type	Post-hoc

End point timeframe:

Up to 10.6 years

End point values	Non-Final Height: Not Treated	Non-Final Height: Treated	Final Height: Not Treated	Final Height: Treated
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	13	22	46
Units: Years				
arithmetic mean (standard deviation)	2.08 (± 2.27)	5.29 (± 2.89)	4.1 (± 2.87)	7.02 (± 2.06)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 30 after end of study

Adverse event reporting additional description:

An adverse event (AE) was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Treated

Reporting group description:

Included all subjects who received r-hGH 0.067 mg/kg/day sc either continuously or intermittently.

Reporting group title	Not Treated

Reporting group description:

Included all subjects who did not receive r-hGH 0.067 mg/kg/day sc either continuously or intermittently

Serious adverse events	Treated	Not Treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 59 (22.03%)	1 / 32 (3.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital jaw malformation			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hereditary haemorrhagic telangiectasia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Ear tube removal			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillectomy			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Keratoconus			
subjects affected / exposed	0 / 59 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia, obstructive			

subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Epiphysiolysis			
subjects affected / exposed	4 / 59 (6.78%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee deformity			
subjects affected / exposed	2 / 59 (3.39%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb asymmetry			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 59 (1.69%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treated	Not Treated	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 59 (88.14%)	16 / 32 (50.00%)	
Nervous system disorders			
Headache			

subjects affected / exposed	10 / 59 (16.95%)	1 / 32 (3.13%)	
occurrences (all)	14	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 59 (10.17%)	1 / 32 (3.13%)	
occurrences (all)	7	2	
Eczema			
subjects affected / exposed	4 / 59 (6.78%)	1 / 32 (3.13%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 59 (11.86%)	0 / 32 (0.00%)	
occurrences (all)	8	0	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	9 / 59 (15.25%)	5 / 32 (15.63%)	
occurrences (all)	14	6	
Bronchitis			
subjects affected / exposed	8 / 59 (13.56%)	3 / 32 (9.38%)	
occurrences (all)	11	6	
Gastroenteritis			
subjects affected / exposed	7 / 59 (11.86%)	3 / 32 (9.38%)	
occurrences (all)	8	3	
Nasopharyngitis			
subjects affected / exposed	6 / 59 (10.17%)	0 / 32 (0.00%)	
occurrences (all)	11	0	
Influenza			
subjects affected / exposed	6 / 59 (10.17%)	0 / 32 (0.00%)	
occurrences (all)	8	0	
Ear infection			
subjects affected / exposed	4 / 59 (6.78%)	2 / 32 (6.25%)	
occurrences (all)	4	3	
Rhinitis			
subjects affected / exposed	4 / 59 (6.78%)	1 / 32 (3.13%)	
occurrences (all)	4	1	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/16772718

http://www.ncbi.nlm.nih.gov/pubmed/9641731