Clinical trial results:
First Year Growth Response Associated Genetic Markers Validation Phase IV Open-label Study in Growth Hormone Deficient and Turner Syndrome Pre-pubertal Children: the PREDICT Pharmacogenetics Validation Study

Summary

EudraCT number	2011-000460-10
Trial protocol	GB ES CZ IT
Global end of trial date	03 October 2012

Results information

Result version number	v1
This version publication date	13 June 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	200104-010 (PREDICT)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01419249
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, 49 6151725200, service@merckgroup.com
Scientific contact	Communication Center, 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	03 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2012
Global end of trial reached?	Yes
Global end of trial date	03 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm that at least one of the genetic markers associated to the amplitude of first year growth response to recombinant human growth hormone (r-hGH) treatment identified in PREDICT Long-Term Follow-Up (LTFU) Study (28614) is replicated in an independent population of this study of prepubertal children with either idiopathic growth hormone deficiency (IGHD) or Turner Syndrome (TS).

Protection of trial subjects:

Patient 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	22 September 2011
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	Spain: 48
Country: Number of subjects enrolled	United Kingdom: 43
Country: Number of subjects enrolled	Czech Republic: 108
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Germany: 88
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	Argentina: 59
Worldwide total number of subjects	461
EEA total number of subjects	369

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)	231
Adolescents (12-17 years)	204
Adults (18-64 years)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject in: 22 Sep 2011
Last subject in: 03 Oct 2012

Pre-assignment

Screening details:

A total of 461 subjects were screened and gave signed informed consent to participate in the study. However, 458 subjects were enrolled in the study as for 3 subjects information concerning diagnosis was missing.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Idiopathic Growth Hormone Deficiency (IGHD) Cohort

Arm description:

Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Arm type	Experimental
Investigational medicinal product name	r-hGH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with pre-established diagnosis of IGHD and TS who were treated with r-hGH therapy for 1 year, were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Arm title	Turner Syndrome (TS) Cohort

Arm description:

Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Arm type	Experimental
Investigational medicinal product name	r-hGH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with pre-established diagnosis of IGHD and TS who were treated with r-hGH therapy for 1 year, were observed in this retrospective cohort study wherein blood sampling will performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Number of subjects in period 1[1]	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort
Started	318	140
Completed	318	140

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 461 subjects were screened and gave signed informed consent to participate in the study. However, only 458 subjects were enrolled in the study as for 3 subjects diagnosis information was missing.

Baseline characteristics

Reporting groups	
Reporting group title	Idiopathic Growth Hormone Deficiency (IGHD) Cohort
Reporting group description:	
Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.	
Reporting group title	Turner Syndrome (TS) Cohort
Reporting group description:	
Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.	

Reporting group values	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort	Total
Number of subjects	318	140	458
Age categorical Units: Subjects			
Age continuous			
out of 458 subjects, age data is presented only for 425 subjects which were included in Full Analysis Set (FAS) population. FAS population included all the participants who had provided informed consent and had non-missing height at start (defined as within one month prior to treatment start date) and at 1 year (+/- 120 days) of r-hGH treatment and had pharmacogenomics data available.			
Units: years			
arithmetic mean	11.9	12.04	
standard deviation	± 4.47	± 4.57	-
Gender categorical			
out of 458 subjects, gender data is presented only for 425 subjects which were included in Full Analysis Set (FAS) population. FAS population included all the participants who had provided informed consent and had non-missing height at start (defined as within one month prior to treatment start date) and at 1 year (+/- 120 days) of r-hGH treatment and had pharmacogenomics data available.			
Units: Subjects			
Female	85	132	217
Male	208	0	208
Other (Unknown)	25	8	33

End points

End points reporting groups

Reporting group title	Idiopathic Growth Hormone Deficiency (IGHD) Cohort

Reporting group description:

Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Reporting group title	Turner Syndrome (TS) Cohort

Reporting group description:

Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Primary: Change From Baseline in Height at Year 1 (cm)

End point title	Change From Baseline in Height at Year 1 (cm)[1]

End point description:

Change from baseline in height at year 1 was one of the growth parameter to assess the first year growth response to r-hGH treatment.This OM was anlayzed in FAS population which included all the participants who had provided informed consent and had non-missing height at start (defined as within one month prior to treatment start date) and at 1 year (+/- 120 days) of r-hGH treatment and had pharmacogenomics data available.

End point type	Primary

End point timeframe:

Baseline and Year 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: No genetic markers were identified as associated with the growth response endpoints by the
bioinformatics analysis. Therefore, no sensitivity analysis was performed and no predictive models were to be developed. Only descriptive analysis was performed.

End point values	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	132		
Units: Centimeter				
arithmetic mean (standard deviation)				
Baseline	103.6 (± 18.1)	103.5 (± 16.3)		
Change at Year 1	9.8 (± 2.7)	8.6 (± 2)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Standard Deviation Score (SDS) at Year 1

End point title	Change From Baseline in Height Standard Deviation Score (SDS) at Year 1[2]

End point description:

Height SDS was calculated as height minus reference mean height divided by standard deviation of the reference population. Height SDS reflects the height relative to a reference population of the same age and gender. Change from baseline in height SDS at Year 1 was one of the growth parameter to assess the first year growth response to r-hGH treatment. This OM was anlayzed in FAS population which included all the participants who had provided informed consent and had non-missing height at start (defined as within one month prior to treatment start date) and at 1 year (+/- 120 days) of r-hGH treatment and had pharmacogenomics data available.

End point type	Primary

End point timeframe:

Baseline and Year 1

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: No genetic markers were identified as associated with the growth response endpoints by the bioinformatics analysis. Therefore, no sensitivity analysis was performed and no predictive models were to be developed. Only descriptive analysis was performed.

End point values	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	132		
Units: standard deviation score				
arithmetic mean (standard deviation)				
Baseline	-2.6 (± 1.06)	-2.17 (± 1.03)		
Change at Year 1	0.98 (± 0.67)	0.71 (± 0.48)		

Statistical analyses

No statistical analyses for this end point

Primary: Height Velocity Standard Deviation Score (SDS) at Year 1

End point title	Height Velocity Standard Deviation Score (SDS) at Year 1[3]

End point description:

Height velocity SDS was calculated as height velocity minus reference mean height velocity divided by standard deviation of the reference population. Height velocity SDS reflects the height velocity relative to a reference population of the same age and gender. Height velocity SDS at Year 1 was one of the growth parameter to assess the first year growth response to r-hGH treatment. This OM was anlayzed in FAS population which included all the participants who had provided informed consent and had non-missing height at start (defined as within one month prior to treatment start date) and at 1 year (+/- 120 days) of r-hGH treatment and had pharmacogenomics data available.

End point type	Primary

End point timeframe:

1 Year

Notes:

[3] - 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: No genetic markers were identified as associated with the growth response endpoints by the bioinformatics analysis. Therefore, no sensitivity analysis was performed and no predictive models were to be developed. Only descriptive analysis was performed.

End point values	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	132		
Units: Standard deviation score				
arithmetic mean (standard deviation)				
Year 1	4.18 (± 2.9)	2.59 (± 1.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the Contribution of Validated Genetic Markers to the Amplitude of First Year Growth Response to r-hGH Therapy in IGHD Children Using Growth Hormone Deficiency Kabi-Pharmacia International Growth Study (GHD KIGS) Predictive Model

End point title	Evaluation of the Contribution of Validated Genetic Markers to the Amplitude of First Year Growth Response to r-hGH Therapy in IGHD Children Using Growth Hormone Deficiency Kabi-Pharmacia International Growth Study (GHD KIGS) Predictive Model

End point description:

GHD KIGS predictive model includes various clinical, auxological and biological markers which are as follows: maximum growth hormone (GH) response to provocation test; age at onset of therapy; birth weight SDS; average GH dose received during the first year of r-hGH therapy; height SDS at start of therapy; the difference between the pre-treatment height SDS of the subject and the mid parental height SDS; and weight SDS at start of therapy.

End point type	Secondary

End point timeframe:

Year 1

End point values	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Participants				
Year 1				

Notes:

[4] - No genetic markers were identified therefore, the data for this outcome measure was not analysed

[5] - No genetic markers were identified therefore, the data for this outcome measure was not analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the Contribution of Validated Genetic Markers to the

Amplitude of First Year Growth Response to r-hGH Therapy in TS Girls Using Turner Syndrome Kabi-Pharmacia International Growth Study (TS KIGS) Predictive Model

End point title	Evaluation of the Contribution of Validated Genetic Markers to the Amplitude of First Year Growth Response to r-hGH Therapy in TS Girls Using Turner Syndrome Kabi-Pharmacia International Growth Study (TS KIGS) Predictive Model

End point description:

TS KIGS predictive model includes various clinical, auxological and biological markers which are as follows: maximum GH response to provocation test; age at onset of therapy; birth weight SDS; average GH dose received during the first year of r-hGH therapy; height SDS at start of therapy; the difference between the pre-treatment height SDS of the subject and the mid parental height SDS; and weight SDS at start of therapy.

End point type	Secondary

End point timeframe:

Year 1

End point values	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Participants				
Year 1				

Notes:

[6] - No genetic markers were identified therefore, the data for this outcome measure was not analysed

[7] - No genetic markers were identified therefore, the data for this outcome measure was not analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 1 year

Adverse event reporting additional description:

As it is a retrospective study, only serious adverse events which were considered by the investigator to be at least possibly related to the conduct of the trial were collected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Idiopathic Growth Hormone Deficiency (IGHD) Cohort

Reporting group description:

Participants with pre-established diagnosis of IGHD who were treated with recombinant human growth hormone (r-hGH) therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Reporting group title	Turner Syndrome (TS) Cohort

Reporting group description:

Participants with pre-established diagnosis of TS who were treated with r-hGH therapy for at least 1 year were observed in this retrospective cohort study wherein blood sampling was performed for genotyping of the various genetic markers along with collection of retrospective data relative to the r-hGH treatment.

Serious adverse events	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 293 (0.00%)	0 / 132 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Idiopathic Growth Hormone Deficiency (IGHD) Cohort	Turner Syndrome (TS) Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 293 (0.00%)	0 / 132 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As it is a retrospective study, only serious adverse events which were considered by the

investigator to be at least possibly related to the conduct of the trial were collected.

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.

No genetic markers were identified, therefore data for the secondary outcome measures was not analyzed.

Notes: