# 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 | v2 (current) |
| This version publication date | 18 September 2017 |
| First version publication date | 29 July 2015 |
| Version creation reason | • Correction of full data set<br>Correction of full data set |

## 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<br>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.<br><br>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.<br><br>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 | 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 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.

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