



**NON-INTERVENTIONAL STATISTICAL ANALYSIS PLAN  
FOR PRIMARY DATA COLLECTION STUDY**



**Non-Interventional Study Protocol  
A6281313**

**SWEGHO - A PROSPECTIVE NON INTERVENTIONAL STUDY PROTOCOL  
WITH PRIMARY DATA COLLECTION -  
ASSESSMENT OF THE LONG TERM TREATMENT OUTCOMES OF  
GENOTROPIN TREATMENT IN GHD PATIENTS IN SWEDEN  
(A628 somatropin)**

**Statistical Analysis Plan  
(SAP)**

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## 1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable, first version.

## 2 INTRODUCTION

KIMS<sup>®</sup> (Pfizer International Metabolic Database) a non-interventional study sponsored by Pfizer, was run between 1994 and 2012. It evaluated the long-term safety and treatment outcomes of adult patients treated with Genotropin in a real-world clinical setting. As such, KIMS<sup>®</sup> was particularly well-suited to capture information regarding rare adverse events and atypical treatment reactions, on the one hand, and information on treatment outcomes that allowed for cost effective, individualized GH treatment.

Patients are treated with GH over a long time period, usually over several years and for some patients the treatment duration can even be life-long. In order to strengthen the data collected in KIMS<sup>®</sup>, this study-SWEGHO- is designed to further follow up long-term Genotropin therapy treatment outcomes in a real-world clinical setting and to be able to compare patients who started treatment after 2012 with patients who started treatment in 1990-ies.

This Statistical Analysis Plan (SAP) provides detailed methodology for summary and statistical analyses of data of the planned statistical evaluation of Pfizer study “SWEGHO - A PROSPECTIVE NON INTERVENTIONAL STUDY PROTOCOL WITH PRIMARY DATA COLLECTION - ASSESSMENT OF THE LONG TERM TREATMENT OUTCOMES OF GENOTROPIN TREATMENT IN GHD PATIENTS IN SWEDEN (A628 somatropin)”.

This SAP version 1.0 was written with access to only a small sample of patients (without access to the complete study database).

### 2.1 STUDY DESIGN

This study is as a prospective national, multi-center, non-interventional, descriptive study open to adult hypopituitary patients with GHD who are treated with Genotropin as prescribed in clinical practice.

This non-interventional study does not include pre-specified endpoints, but collects information from adult subjects prescribed Genotropin in clinical practice.

### Study population

At the time of the final version 1.0 of the SAP around 340 patienter are included in the study. The study population consists of;

Patients 18 years of age and above who are prescribed Genotropin and who are either;

- a) Newly diagnosed with GHD

- b) Diagnosed with GHD before 2013 and previously treated with Genotropin and followed in KIMS<sup>®</sup>
- c) Transition patients diagnosed with CO-GHD before 2013

More details regarding the including inclusion and exclusion criteria, can be found in the Study Protocol, A6281313 NON-INTERVENTIONAL STUDY PROTOCOL Amendment 5, 23 October 2015 (1).

## 2.2 STUDY OBJECTIVES

The overall purpose of this study is:

- 1) To assess the long term treatment outcomes of GH treatment in patients who are prescribed and treated with Genotropin.

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## 3 ANALYSIS SETS/POPULATIONS

### 3.1 FULL ANALYSIS SET

The full analysis population (FAS) will consist of all correctly enrolled patients who received at least one dose of Genotropin. Erroneously enrolled patients are excluded from FAS since these patients did not meet the inclusion criteria or meet an exclusion criterion (which was discovered after enrollment to the study).

### 3.2 SAFETY ANALYSIS SET

The safety analysis includes all enrolled patients received at least one dose of Genotropin. Erroneously enrolled patients are included in the safety analysis set.

### 3.3 SUBGROUPS

- Adult patient of 18 years of age and above and diagnosed with Childhood onset GHD, labeled Childhood onset GHD (CO-GHD)
- Adult patient of 18 years of age and above, not in the CO-GHD group above and diagnosed with GHD before 2013 and previously treated with Genotropin and followed in KIMS<sup>®</sup>, labeled KIMS GHD (*K-AO-GHD*)
- Adult patient of 18 years of age and above, not in the CO-GHD group above and newly diagnose with GHD, labeled *Naïve-AO-GHD* (N-AO-GHD)

#### 4 ENDPOINTS AND COVARIATES

The patient is treated according to clinical practice. Normal clinical practice may include routine diagnostic procedures such as; blood samples, CTs, MRI and other tests. The decision of what measures to perform is not pre-specified in the protocol but is based on the clinical experience, standards and judgment of the investigator. Data from patient records, which align with the data to be collected in the database eCRF as specified in the study protocol, is collected and entered into the database. The data is collected during the patients' routine visits to the clinic.

Endpoints will be summarized at baseline and at follow up and change from baseline will be derived if appropriate.

Continuous data will be summarized using descriptive statistics where the following parameters will be reported:

- Number of observations (n),
- Mean,
- Quartile 1 (Q1),
- Median,
- Quartile 3 (Q3),
- Standard deviation (SD),
- Range (Min,Max)

Categorical data will be presented as the number and percentage of patients.

In general, all data will be listed. Summary tables will be structured with a column for each of the three subgroups defined in Section 3.3 and a column for the total if other not stated.

The following variables should be captured according to the Study Protocol (if available):

Variable	Role	Data source(s)	
Informed Consent (mandatory)	Before Baseline	Personally signed and dated Informed Consent Document	
<u>BACKGROUND INFORMATION</u> -Age -Gender - Ethnic origin (only CRF) -Age at menarche	Baseline		

-Menopause/Amenorrea -Age at Menopause/Amenorrea -Puberty (Induced, Spontaneous) -Age at end of growth			
<u>MEDICAL HISTORY</u> -Hypertension -Claudication -Coronary Heart Disease -Stroke -Arthrosis -Diabetes -Type I -Type II -Epilepsy -Neoplasm -Other Significant disease -Fractures	Baseline	Patient record and or CRF	
<u>FAMILY HISTORY</u> -Diabetes -Cardiovascular Disease -Hip Fracture -Colon Polyps -Colon Cancer -Neoplasm (other)	Baseline	Patient record and or CRF	
<u>PITUITARY DISEASE</u> -Date of Diagnose -Childhood onset -Brain Tumor -Visual Field deficit -Ophthalmoplegia -Tumor treatment -Tumor Size -Tumor type	Baseline	Patient record and or CRF	
<u>DIAGNOSE OF GHD</u> -Date of Diagnose of GHD -Test method -Date of test	Baseline	Patient record and or CRF	
<u>BASELINE PREVIOUS GH TREATMENT</u> -Treatment start date -Treatment stop date	Baseline	Patient record and or CRF	

<u>EXAMINATION</u> -Weight -Height -BMI -Blood pressure -Heart rate (Supine) -CT/MRI -Waiste, Hip -Body Composition -Additional Hormone Abnormalities	Baseline, Follow up visit	Patient record	
<u>TREATMENT</u> -GH treatment -Concomitant Medication of special interest	Baseline, Follow up visit	Patient record	
<u>LABORATORY</u> -Glucose -HbA1c -IGF-I	Baseline, Follow up visit	Patient record	
ADVERSE EVENT	Follow up visit	Patient record and information obtained from the patient	

#### 4.1 BASELINE AND VISIT WINDOW DEFINITION

Baseline is defined as the baseline visit according to the eCRF.

In order to summarize data by year the following visit window definition will be used for follow-up visits:

1. Each visit will be assigned to a yearly measurement according to the principle Year 1 if visit occurred 1 year from baseline visit  $\pm 6$  months. Year 2 if visit occurred 2 year from baseline visit  $\pm 6$  months, and so on. If a patient has more than one visit in a year (as defined here) principle 2 and 3 below will be applied. Visits occurring between baseline visit and baseline visit + 6 months will not be included in summaries by year.
2. Select the visit that has a IGF-1 value.
3. If more than one visit within a year has an IGF-1 value, select the visit with a IGF-1 value closest to the target date. The target date is defined as follows (using Year 1 as an example); Target date for Year 1 is baseline visit plus exactly 12 months (the date occurring 1 year after baseline visit).

The definition of visit windows will be applied in summary tables. Data from all visits will be reported in listings.

## 4.2 EFFICACY/EFFECTIVENESS ENDPOINT(S)

There is no pre-specified endpoint, but the study collects information from adult subjects prescribed Genotropin in clinical practice.

Each patient will be classified according to his/her IGF-I assessments as follows (in hierarchy);

1. If any of the assessments of IGF-I after Swegho baseline visit, are less than the lower limit of normal (LLN), the patient will be defined as “*IGF-I LLN*”.
2. Else if any of the assessments of IGF-I after Swegho baseline visit, are greater than the upper level of normal (ULN), the patient will be defined as “*IGF-I ULN*”.
3. Else if the patient has no IGF-I reported after Genotropin start, the patient will be defined as “*IGF-I unknown*”.
4. Else the patient will be defined as “*within ref range*”.

Where appropriate, the summaries will be presented by subgroups as defined above.

## 4.3 SAFETY ENDPOINTS

For each patient, the safety event reporting period begins at the time of the patient’s first dose of Genotropin® or the time of the patient’s informed consent if s/he is already exposed to Genotropin®, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

### 4.3.1 Adverse Events

Definitions for the different types of AE including the definition for Serious Adverse Events (SAEs) are given in the study protocol.

The following variables has been collected for each AE and SAE; a diagnosis is preferred as event term rather than only describing symptoms, the date when the AE started and stopped, whether the AE is serious or not, causality assessment, action taken with regard to Genotropin®, AE caused patient to discontinue study and outcome.



All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the available MedDRA Version.

The seriousness criterion will also be listed for SAEs.

#### **4.3.2 Vital signs**

Vital signs include weight, height, bmi, blood pressure (systolic and diastolic), heart rate, body composition, CT/MRI (yes/no) and change in hormonal deficiencies.

#### **4.3.3 Concomitant Medications**

Concomitant medications will be summarized by category, and show number and percentage of patients per concomitant medication category.

### **4.4 OTHER ENDPOINTS/ASSESSMENTS**

Detailed operational definitions for some endpoints/assessments are give below.

Age is defined as age at baseline.

Duration of study will be summarized by subgroup. Duration of study is defined as time from baseline to exit date.

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### **4.5 COVARIATES**

Not applicable, only descriptive summaries are presented.

## **5 HANDLING OF MISSING VALUES**

Patients with missing values of a particular endpoint will not contribute to the analysis.

## **6 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES**

### **6.1 STATISTICAL METHODS**

Data presentations will include tables of descriptive statistics. No statistical analyses using hypothesis testing will be performed or presented.

The presentation of study data will be done after this SAP is finalized and approved and the database has been locked.

This is a non-interventional open study following routine clinical practice without a comparator arm. The findings of the study should therefore be interpreted with caution. One cannot conclude that a treatment with Genotropin is superior to another treatment based on the summaries of this trial.

### **6.2 STATISTICAL ANALYSES**

Not applicable, only descriptive summaries are presented.

## **7 LIST OF TABLES AND TABLE SHELLS**

A list of Tables, Listings and Figures (TLFs) will be presented using TLF mock shells in a separate document (the TLF plan).

## **8 REFERENCES**

1. A6281313 NON-INTERVENTIONAL STUDY PROTOCOL Amendment 5, 23 October 2015.