NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**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**
Protocol number	A6281313
Protocol version identifier	Amendment 5, 23 October 2015
Date of last version of protocol	4 June 2015
Active substance	H01AC01 Somatropin
Medicinal product	Genotropin®
Product reference	MT-number Genotropin: 16288 (5.0 mg), 10902 (5.3 mg) and 11483 (12.0 mg) Genotropin MiniQuick: 13390 (0.2 mg), 13391 (0.4 mg), 13392 (0.6 mg), 13393 (0.8 mg), 13394 (1.0 mg), 13395 (1.2 mg), 13396 (1.4 mg), 13397 (1.6 mg), 13398 (1.8 mg) and 13399 (2.0 mg).
Procedure number	DK/H/12/1,4,5,13-23/
Author	PPD , PPD , Pfizer Innovations AB, Sweden.

[redacted]

[redacted]

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2. LIST OF ABBREVIATIONS

ABBREVIATIONS AND DEFINITION OF TERMS

AE– Adverse event

BT –Brain Tumor

CM-Concomitant Medications

CO-GHD – Childhood-Onset GH Deficiency

CT- Computed Tomography

eCRFs – electronic Case Report Forms

FBS-Fasting Blood Sugar

GH – Growth Hormone

GHD – GH Deficiency

IEC – Independent Ethics Committee

IGF-I – Insulin-like Growth Factor

IRB – Institutional Review Board

LH – Lymphocytic Hypophysitis

MRI- Magnetic Resonance Imaging

N.A. - Not Applicable

N I – Non Interventional

rhGH – recombinant human GH

SAE – Serious Adverse Event

SAP – Statistical Analysis Plan

SH – Subarachnoid Hemorrhage

SWEGHO – SWEdish Growth Hormone Outcomes

TBI – Traumatic Brain Injury

QoL – Quality of Life

3. RESPONSIBLE PARTIES

3.1. Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD , Dr	PPD , Consultant	PPD PPD	PPD , Sweden
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4. ABSTRACT

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
(Hereafter called the study)

Main author of this protocol is PPD , Pfizer Innovations AB, Sweden.

Rationale and background
KIMS® (Pfizer International Metabolic Database) a non-interventional study sponsored by Pfizer, was run between1994 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 ® 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®, this study 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. The study is planned to be run in Sweden.

Research question and objectives
To assess the long-term treatment outcomes of GH treatment in patients who are prescribed and treated with Genotropin.
Determine the relationships between clinical status, dosage schedule and response to Genotropin treatment.
CCI [redacted]
Compare the outcomes of patients include after 2012 to patients included about 15 years earlier to evaluate possible different outcomes and uses of GH.

Study design
This study is as a prospective national, multi-center, non-interventional 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.

Population
Patients previously followed in KIMS®, new patients fulfilling the inclusion criteria and transition patients with confirmed childhood onset GHD will be asked to participate. All patients should be diagnosed with GHD according to the current medical standards, and treated with Genotropin prescribed in clinical practice. After having given their informed consent, the patient is enrolled in the study. 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 study investigator. Data from patient records, which align with the data to be collected in the database eCRF as specified in this protocol, will be collected and entered into the database. The data will be collected during the patients' routine visits to the clinic.

Data sources
No other data than what is collected during the normal clinical practice are to be entered into the database. Data from local labs and CT/MRI will be collected as available. A password-protected data entry and data management tool, Viedoc ® will be made available to study investigators through the Internet. Data will be manually entered into the database eCRF within Viedoc®. Only information obtained during the course of normal clinical practice is collected.

A study patient code is generated by Viedoc ® for each study patient at the time of their enrollment into the study. Only the treating investigator or an authorized staff member has access to patient identifiable information using the study patient code.

Study size
This is a descriptive study without a pre-specified hypothesis and calculation of sample size is not applicable. Approximately 900 patients are expected to be included.

The study is planned to continue for 5 years.

Data analysis
Study data are analyzed as often as required to address regulatory queries, safety reporting requirements and clinical questions posed by investigators. In addition the study data are analyzed to support study research projects initiated and run by investigators in partnership with Pfizer.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP) for each project which will be dated, filed and maintained by the sponsor.

Milestones
Start of data collection is planned to October 2013, end of data collection October 2018. Final study report is planned to October 2019.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	2013 OCT 7	Admin	All sections	From KIMS Xtended to swegho	Change of alias of the study
2	2014 JUNE 30	Admin	11.10	Add safety language regarding reporting time for Overdose, misuse and extravasation	Safety language
3	2015 APRIL 9	Admin	3.1 4.0 9.8 Tabl 1.	Pfizer AB is changed to Pfizer Innovations AB Table 1. Updated definitions of variables	Change of sponsor's name Clarifying variables of data collection
4	2015 June 4	Admin	11	Requirements of Management and reporting of adverse events/adverse reactions regarding: -Reporting period -Causality assessment -Definitions of abnormal lab findings -Definitions of hospitalizations	Safety Language
5	23 OCT 2015	Admin	Editorial changes throughout the protocol		
5			11	Update reporting requirements for Non Serious Adverse Events Update reporting requirements Exposure during pregnancy	Reporting requirements for Non Serious Adverse Events was not correct Update reporting requirements Exposure during pregnancy
5			9.8 Tabl 1.	Clarification of Data Sources	Missing information

6. MILESTONES

Milestone	Planned date
Start of data collection	30 October 2013
End of data collection	30 October 2018
Final study report	30 October 2019

7. RATIONALE AND BACKGROUND

The first suggestions that growth hormone (GH) may play an important role in adults occurred as early as 1962 when Raben reported improved vigor, well-being, and ambition in a 35-year-old hypopituitary patient treated with extracted pituitary GH.1 It was only the introduction of recombinant human GH 2 in the middle of the 1980's, which provided an opportunity for wider and more detailed studies of the effects of GH in adults. It became clear, that GH is not only an essential stimulator of postnatal growth and development but is also primarily a potent anabolic hormone that modulates a large variety of physiological functions e.g., energy balance, lipid and protein metabolism, body composition, body fluid control, bone growth and mineralization, cardiovascular function, and, finally mood, cognition, memory and learning as well as general well-being and quality of life (QoL).3

Given the broad range of GH actions, the widespread diversity in phenotype of patients with GH deficiency (GHD) is not at all surprising; furthermore, depending on the patients' age, different disease presentations should be expected and, indeed, this is the case. In children, the predominant presentation is growth retardation, whilst after completion of linear growth, adverse metabolic changes, increased cardiovascular risk, abnormal body composition, reduced bone mineral density and impaired QoL are the major features. Overall, the adverse effects of GHD in adults lead to an increased cardiovascular risk and have a negative impact on daily life. In adults the disease can persist from childhood – childhood-onset GHD (CO-GHD), or arise in adulthood, adult-onset GHD (AO-GHD). GHD may occur as an isolated hormonal deficit or be part of multiple pituitary hormone deficiency (panhypopituitarism). GHD in adults most frequently results from tumors in the hypothalamic- pituitary region or as a consequence of their treatment e.g., surgery or radiotherapy.3

The safety and efficacy profile of GH and later recombinant human GH (rhGH) including Genotropin® has been demonstrated in clinical trials conducted worldwide. However, because of the limited number and characteristics of patients enrolled in randomized clinical trials and their relatively short duration of treatment in study protocols, there has been an increasing interest on the part of physicians to follow GH-treated adult patients prospectively during GH treatment in a real world clinical setting to better assess the long-term safety and treatment outcomes of GH therapy and generate information that complements the short-term safety and efficacy data obtained from formal clinical trials performed for registrational purpose.

KIMS® (Pfizer International Metabolic Database) a non-interventional study sponsored by Pfizer, was run between1994 and 2012. It evaluated the long-term safety and treatment outcomes of adult patients treated with Genotropin in a real-world clinical setting. A non-interventional study is where the medicinal product(s) is (are) prescribed in the usual manner or in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures, outside the routine clinical practice, shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

Because KIMS® collected information from large patient cohorts followed in daily clinical practice settings and with no restrictions in terms of study duration or included participants, it generated medical information about clinical characteristics and patient management complementary to that generated by randomized clinical trials. As such, KIMS ® 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. Numerous articles based upon data from KIMS have been published in the scientific literature and presented at scientific meetings, see ANNEX 3.

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, especially for the patients with CO-GHD. Due to the long treatment period it is of great value to continue the assessment further. In order to further strengthen the data previously collected in KIMS®, this study 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. The Swedish KIMS® investigators have in their previous participation in KIMS® showed very high standard of execution and the data excellent quality. Therefore this NIS is particularly well suited to be continued in Sweden. The usefulness of Non-Interventional studies such as KIMS® can be exemplified by the article of Burman[6] et al recently published in JCEM, where two important causes of excess mortality were identified in patients with hypopituitarism. Firstly, a lack of sufficient adrenal response to acute stress and intercurrent illness. Secondly, increased risk of a late appearance of de novo malignant brain tumors in patients who previously received radiotherapy. Both of these findings are important as they reflect preventable events in the management of pituitary disease.

The median follow-up period in KIMS® Sweden was approximately 9 years. One of the goals of this study is to prolong the long-term follow up of Genotropin therapy for patients included in KIMS®. It is anticipated that the study will prolong the median follow-up period with 3-5 years for the Swedish population. Another goal is to identify secular trends in Genotropin treatment regime and characteristics of treatment outcomes over 3 decades of GH replacement in adult patients with GHD. Patients are to be enrolled, treated and followed at the discretion of the investigator (the treating physician), who will collect and enter patient data into electronic case report forms (eCRFs). This non-interventional study does not include a pre-specified hypothesis.

8. RESEARCH QUESTION AND OBJECTIVES

The overall purpose of this study is:

1) To collect long term follow-up information of patients with GHD on Genotropin replacement therapy. The population are patients previously followed in the Swedish KIMS® cohort and adults with CO-GHD treated with growth hormone. The study collects information on long-term treatment outcomes of Genotropin therapy as prescribed in clinical practice.

2) To compare treatment outcome and clinical practice of patients included from 2013 with patients treated from the 1990-ies.

In particular the following questions will be addressed:

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

- Further determine the relationships between clinical status, dosage schedule and response to Genotropin treatment.

- CCI [redacted]

- Compare the outcomes of patients include after 2012 to patients included about 15 years earlier to evaluate possible different outcomes and uses of GH. Reflecting past clinical practice versus clinical practice today.

- Collection of AE according to Pfizer standard.

9. RESEARCH METHODS

9.1. Study design

The study is as a prospective national, multi-center, non-interventional 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 receiving Genotropin treatment in a real world clinic setting.

9.2. Setting

Patients previously followed in KIMS®, new patients fulfilling the inclusion criteria and transition patients with confirmed childhood onset GHD will be asked to participate. All patients should be diagnosed with GHD according to the current medical standards, and treated with Genotropin as prescribed in clinical practice[4, 5].

After having given their informed consent, the patient is enrolled in the study. 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 this protocol, will be collected and entered into the database. The data will be collected during the patients' routine visits to the clinic.

The interval between each the patient's visits, duration of treatment and participation in the study for each individual are at the discretion of the investigator and the patient.

After informed consent has been obtained from the patient, background data are collected and if available in KIMS®, all the data will be transferred automatically into the database. This includes but is not limited to medical history, laboratory, imaging and background data such as Genotropin dosing. Background information, includes: history of birth, family and medical history, pituitary diagnosis, growth, puberty, GH treatment before start in the study (if applicable).

9.3. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Adult patients of 18 years of age and above and fulfilling one of the three alternatives a-c below;

    a) Newly diagnosed with GHD according to the current medical standard.

    b) Diagnosed with GHD before 2013 and previously treated with Genotropin and followed in KIMS®.

    c) Transition patients diagnosed with CO-GHD before 2013.

2. Prescribed Genotropin at the time of inclusion.

3. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

9.4. Exclusion criteria

Patients who participate in any concurrent clinical interventional trial where a non-authorized or authorized study medication is used, during their participation in the study. Concurrent studies which do not include any study interventional items (whether medications or devices) are allowed.

9.5. Study Period

Data are collected from the subject's inclusion of the study until the subject, or investigators decide upon subject's withdrawal from the study ends.

9.6. Baseline Visit

At baseline visit the background information about patient, history of birth, family and medical history, diagnosis, growth, puberty, GH treatment before start in the study (if applicable) and at study start, is collected.

Patients previously followed in KIMS®, appropriate data available in KIMS® will be transferred automatically into the study database and used to contribute to Baseline Visit data.

The primary and subsequent diagnosis as applicable should be entered according to the KIMS Etiology Classification List (Annex 3).

The correct diagnosis code is one of the most important variables by which the study patients are grouped for statistical analysis.

Depending on the diagnosis background information should be provided as specified below:

- Brain tumour (BT) – collects additional information on treatment of tumour including results of MRI/CT;
- Traumatic Brain Injury (TBI) – collects information on medical history related to TBI;
- Subarachnoid Hemorrhage (SH) – collects information on medical history related to SH;

- Lymphocytic Hypophysitis (LH) – collects information on medical history and diagnosis details.

9.7. Follow-up Visits

At follow-up visit information specified in Table 1 will be collected at each follow up visit and entered manually in eCRFs. In the study this information is gathered on "return visits" eCRFs.

For patients previously followed in KIMS®, data available in KIMS® will be transferred automatically into the study Database after the patients signed informed consent.

Only information from the patients' routine visits will be collected.

9.8. Variables

The variables to be captured are listed in **Table 1**.

Table 1.Variables to be captured (if available).

Variable	Role*	Data source(s)
Informed Consent (mandatory)	Before Baseline	Personally signed and dated Informed Consent Document
BACKGROUND INFORMATION -Age -Gender - Ethnic origin -Age at menarche -Menopause/Amenorre -Age at Menopause/Amenorrea -Puberty (Induced, Spontaneous) -Age at end of growth	Baseline	Patient record and or CRF
MEDICAL HISTORY -Hypertension -Claudication -Coronary Heart Disease -Stroke -Arthrosis -Diabetes -Type I -Type II -Epilepsy -Neoplasm -Other Significant disease -Fractures	Baseline	Patient record and or CRF
FAMILY HISTORY -Diabetes -Cardiovascular Disease	Baseline	Patient record and or CRF

-Hip Fracture -Colon Polyps -Colon Cancer -Neoplasm (other)		
PITUITARY DISEASE -Date of Diagnose -Childhood onset -Brain Tumor -Visual Field deficit -Opthalmoplegia -Tumor treatment -Tumor Size -Tumor type	Baseline	Patient record and or CRF
DIAGNOSE OF GHD -Date of Diagnose of GHD -Test method -Date of test	Baseline	Patient record and or CRF
BASELINE PREVIOUS GH TREATMENT -Treatment start date -Treatment stop date	Baseline	Patient record and or CRF
EXAMINATION -Age -Weight -Height -Blood pressure -CT/MRI -Body Composition -Additional Hormone Abnormalities	Baseline, Follow up visit	Patient record
TREATMENT -GH treatment -Concomitant Medication of special interest	Baseline, Follow up visit	Patient record
LABORATORY -Glucose -HbA1c -IGF-I	Baseline, Follow up visit	Patient record
ADVERSE EVENT	Follow up visit	Patient record and information obtained from the patient

Detailed operational definitions will be included in the Statistical Analysis Plan.

*For patients previously treated in KIMS® historical data will automatically inserted into the Database.

Concomitant Medication of Special Interest:
It is recommended to collect all concomitant medication. The particular attention should be given to the following concomitant medication of special interest:

1. Replacement of other pituitary hormone deficits: sex steroids, glucocorticoids, thyroxine and vasopressin
2. Treatment of prolactin abnormalities
3. Antihypertensive drugs
4. Lipid lowering drugs
5. Anti-diabetic drugs
6. Antidepressant drugs
7. Anti-epileptic drugs

9.9. Data sources

Data collected during the normal clinical practice is to be entered into the study database. Data from local labs and CT/MRI will be collected as available. Data will be manually entered or imported from archived patients records into the study database.
Information collected during the treatment and follow up of study patients is entered into eCRFs contained within Viedoc®, a password protected data entry and data management tool. Viedoc ® will be made available to investigators through the Internet.
Data previously entered for a subject in KIMS® may be made available in the study provided that a new Informed consent, including permission to use KIMS® data, is signed by the subject.

A study patient code is generated by Viedoc ® for each study patient at the time of their enrollment into the study. Only the treating investigator or an authorized staff member has access to patient identifiable information using the study patient code.

Each study investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The eCRFs must be signed by the study investigator or by an authorized staff member to attest that the data contained on the eCRFs are correctly recorded.

9.10. Study size

This is a descriptive study without a pre-specified hypothesis and calculation of sample size is not applicable. Approximately 900 patients are expected to be included.
The study is planned to continue for 5 years and each patient entering the study will be included for the whole time period if not prematurely with-drawn. Hence the total number will be in the range of 900 patients (600 from KIMS® and 250 new adult patients and 50 from the confirmed childhood onset GHD population).

9.11. Data management

As used in this protocol, the term "eCRF" is used to describe an electronic data record. An eCRF should be completed for each included patient. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

eCRFs should be completed as soon as possible during or after the patient's visit. The Investigator must verify that all data entries in the eCRFs are accurate and correct and is required to electronically sign off the clinical data.

All entries, corrections and alterations are to be made by the Investigator or his/her authorized designee. Once clinical data of the eCRF have been submitted to the server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance. The appropriate investigational staff will answer queries generated in the application. This process is audit trailed meaning that the name of investigational staff, time, and date is logged.

Any corrections to entries made in the eCRFs, must be dated, explained (if necessary) and signed. An audit trail of any corrections to original data entry is available in the system.

9.12. Data analysis

Data in this study are analyzed as often as required to address regulatory queries, safety reporting requirements and clinical questions posed by investigators. In addition the study data are analyzed to support research projects initiated and run by investigators in partnership with Pfizer.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP) before any analysis can begin. If analyses are to be performed at several occasions (e.g. interim analyses), the respective SAPs will be dated, filed and maintained by the Sponsor and/or involved investigator(s). Results of these analyses are presented in scientific articles, posters and oral presentations at scientific meetings.

If statistical analyses on data from this study are performed by investigators, independently of Pfizer, the SAP should be approved by Pfizer Medical and a Pfizer statistician. Analysis results are reviewed by Pfizer prior to their presentation and/or publication.

Study data are analyzed as often as required to address regulatory queries, safety reporting requirements and clinical questions posed by investigators. In addition the study data are analyzed to support study research projects initiated and run by investigators in partnership with Pfizer.

In general, data from all patients with correct entered data will be analyzed at regular intervals. Protocol deviations will be listed per patient, describing the nature of the deviation as well as the times and reasons for discontinuation.

9.13. Analysis of safety

Safety outcomes of long-term Genotropin therapy are analyzed to provide information as requested. Frequency and incidence rates of AEs are calculated and compared to data on general populations, when available. Incidence and frequency rates of AEs are also compared between different subgroups in the study.

9.14. Quality control

The study will be monitored according to the monitoring plan.

As used in this protocol, the term case report form (CRF) should be understood to refer to an electronic data record.

A CRF should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry."

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

9.15. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.16. Limitations of the research methods

In order to ensure a comprehensive view of the disease it is important that a majority of the treated patients can be included. Hence both patients with complicated disease as well patients with a less complicated disease should be included. Further is it important to ensure that the data from the different hospitals are qualitatively at a high standard and complete.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

10.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with local legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Requirements

The table below summarizes the requirements for recording safety events on the SWEGHO e-CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the SWEGHO e-CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure.	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the

SWEGHO e-CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

11.2. Reporting period

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; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. 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.
If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Genotropin®, the SAE also must be reported to Pfizer Safety.

11.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to Genotropin® follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Genotropin® caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Genotropin® caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Genotropin® did not cause the event, this should be clearly documented on the SWEGHO e-CRF and the NIS AEM Report Form.

11.4. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings; (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;

- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

11.5. Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with local legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Requirements

The table below summarizes the requirements for recording safety events on the SWEGHO e-CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the SWEGHO e-CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure.	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the

SWEGHO e-CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

11.2. Reporting period

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; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. 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.
If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Genotropin®, the SAE also must be reported to Pfizer Safety.

11.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to Genotropin® follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Genotropin® caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Genotropin® caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Genotropin® did not cause the event, this should be clearly documented on the SWEGHO e-CRF and the NIS AEM Report Form.

11.4. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings; (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;

- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

11.5. Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting

as an adverse event.

11.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" is considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

11.7. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)

- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Genotropin® or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Genotropin® (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to Genotropin® prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source is reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Genotropin®, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Genotropin® in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

  - An identifiable reporter;

  - A suspect product;

  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11.8. Medical device complaint reporting requirements

All complaints about medical devices, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the eCRF. This includes potential near incident or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again, might have led to death or serious deterioration in health.
Pfizer is to be notified of all medical device complaints within 24 hours of awareness of the event by the investigator.

Swedish Procedure for a Medical device complaint that is not associated with an AE:

The following information is needed for filing a claim file:

- An identifiable Pfizer product. If possible, with device number and batch number.
- A description of a fault with the device.
- Complaints sample may need to be requested for examination.

The complaint should be sent to:

E-mail address for device complaints: MC-Sweden.Reklamationer@pfizer.com
Address for sending samples of device: Pfizer AB, Reklamationer, Vetenskapsvägen 12, 191 90 Sollentuna, Sweden
Tel. 08-5505 2000, ask for complaint manager.

11.9. Single reference safety document

The SmPC for Genotropin as registered in Sweden is the reference safety document for this study and should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This NI Study will be registered by Pfizer on www.clincaltrials.gov.

All efforts will be made to ensure that the trial protocol and results arising from the trial are published in an established peer-reviewed journal.

The following types of data output will be available:

1. "Questions to the study database" posed by Investigators and relating to the clinical issues on hypopituitarism and its treatment. The answers to these requests are for the personal use of Investigators in their clinical practice. They must not be publically presented or published.

2. Publications and/ or scientific presentations which communicate the results of data analyses. Publications based on the national data are discussed and endorsed by the advisory board.

Pfizer has no objection to an Investigator publishing his/her part of the study, or to reporting their data after agreement between participating sites. In all cases, communications are compliant with Pfizer publication policies and other Standard Operating Procedures, as required.

Investigators are entitled to propose a research project to be performed on the study data. Such proposals should be endorsed by the Advisory Board in partnership with Pfizer.

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-center study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

12.1. Communication of issues

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of Genotropin, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

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2. Olson KC, Fenno J, Lin N, Harkins RN, Snider C, Kohr WH, Ross MJ, Fodge D, Prender G, Stebbing N. 1981 Purified human growth hormone from E. coli is biologically active. *Nature* 1981 293:408-11.

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4. Ho K.Y. on behalf of the 2007 GH Deficiency Consensus Workshop Participants, Consensus Guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatrics Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia *Eur J Endocrinol* 2007 157 695-700.

5. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M Consensus statement on the management of the GH-treated. *European Journal of Endocrinology* (2005) 152 165–170

6. Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P, Berinder K, Engström BE, Ekman B, Erfurth EM, Svensson J, Wahlberg J, Karlsson FA. Deaths Among Adult Patients with Hypopituitarism: Hypocortisolism During Acute Stress, and De Novo Malignant Brain Tumors Contribute to an Increased Mortality. – a KIMS database analysis. *J Clin Endocrinol Metab* 2013 Mar 1

14. LIST OF TABLES

Table 1.Variables to be captured in SWEGHO.

15. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. KIMS ETIOLOGY CLASSIFICATION LIST

Idiopathic
1.1 Idiopathic GHD

Congenital
Genetic cause of GHD
2.1.1.1 GH-gene-defect (Type 1A dominant or recessive)
2.1.1.2 GH gene-defect (specify)
2.1.1.3 GHRH gene-defect (specify)
2.1.1.9 Other genetic cause of GHD (specify)

Central malformation
2.1.2.1 Septo-optic dysplasia
2.1.2.2 Empty sella syndrome (including pituitary aplasia)
2.1.2.3 Solitary central maxillary incisor syndrome
2.1.2.4 Mid-line palatal cleft
2.1.2.5 Arachnoid cyst
2.1.2.6 Congenital hydrocephalus
2.1.2.9 Other central malformation (specify)

Complex syndrome with congenital GHD
2.1.3.1 Fanconi pancytopenia
2.1.3.2 Rieger syndrome
2.1.3.3 EEC syndrome (Ectrodactyly-Ectodermal Dysplasia-Clefting syndrome)
2.1.3.9 Other complex syndrome with congenital GHD (specify)

Prenatal infection
2.1.4.1 Rubella
2.1.4.9 Other than rubella prenatal infection (specify)

Bio-inactive GH syndrome
2.1.5.1 Kowarski type
2.1.5.9 Other than Kowarski type bio-inactive GH syndrome (specify)

Functional GHD
2.1.6.1 GH-receptor defect (Laron Type)
2.1.6.2 GH-receptor/postreceptor defect (specify)
2.1.6.3 IGF resistance (specify)
2.1.6.9 Other functional GHD (specify)

2.1.9 Congenital unknown

Acquired
Tumors of the pituitary/hypothalamic area

2.2.1.1 Craniopharyngioma
2.2.1.2 Germ cell tumours (specify; dysgerminoma, pinealoma)
2.2.1.3 Hamartoma

Adenoma
2.2.1.4.1 Non-secreting (non-functioning pituitary adenoma - NFPA)
2.2.1.4.2 ACTH (Cushing disease)
2.2.1.4.3 GH (acromegaly)
2.2.1.4.4 Prolactin (prolactinoma)
2.2.1.4.5 Gonadotropin
2.2.1.4.6 TSH
2.2.1.4.7 Co-secreting (specify)
2.2.1.4.9 Other adenoma (specify)
2.2.1.5 Cyst (specify; Rathke's, epidermoid, dermoid)
2.2.1.6 Glioma
2.2.1.7 Meningioma

2.2.1.8 Schwannoma
2.2.1.10 Chordoma
2.2.1.11 Primary pituitary carcinoma
2.2.1.12 Sarcoma
2.2.1.13 Metastatic carcinoma
2.2.1.14 Hematologic metastases
2.2.1.9 Other tumors of pituitary/hypothalamic (specify)

Cranial tumors distant from the pituitary/hypothalamic area

2.2.2.1 Astrocytoma
2.2.2.2 Ependymoma
2.2.2.3 Glioma
2.2.2.4 Medulloblastoma
2.2.2.5 Nasopharyngeal tumour
2.2.2.9 Other cranial tumors distant from the pituitary/hypothalamic area (specify)

Treatment for malignancy outside the cranium

Leukemia
2.2.3.1.1 Lymphatic leukemia
2.2.3.1.2 Myeloid leukemia
2.2.3.1.3 Aplastic leukemia
2.2.3.1.9 Other leukemia (specify)

Lymphoma
2.2.3.2.1 Hodgkin lymphoma
2.2.3.2.2 Non-Hodgkin lymphoma
2.2.3.2.9 Other lymphoma (specify)

Solid tumor
2.2.3.3 Solid tumor (specify)

Other causes of acquired GHD
Head trauma/ injury
2.2.4.1.1 Perinatal head trauma
2.2.4.1.2 Traumatic brain injury
2.2.4.2 CNS infection (specify; meningitis, encephalitis, septic cavernous sinus)
2.2.4.3 Hydrocephalus
2.2.4.4 Granulomatous diseases (specify: sarcoidosis, tuberculosis, syphilis, fungal)
2.2.4.5 Langerhans cell histiocytosis (histiocytosis X, eosinophilic granuloma Hand-Schüller-Christian disease)

Vascular system
2.2.4.6.1 Infarction (apoplexy)
2.2.4.6.2 Postpartum necrosis (Sheehan syndrome)
2.2.4.6.4 Aneurysm
2.2.4.6.5 Sickle cell anemia
2.2.4.6.6 Thalassaemia
2.2.4.6.7 Subarachnoid hemorrhage
2.2.4.6.9 Other vascular (specify)
2.2.4.7 Lymphocytic hypophysitis
2.2.4.8 Hemochromatosis
2.2.4.9 Other (specify)

ANNEX 3. LIST OF PUBLICATIONS BASED ON KIMS DATA

KIMS Reference List - full articles only

Articles (#peer-reviewed)

1998

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1999

2. Ranke M., Dowie J., KIGS and KIMS as Tools for Evidence-Based Medicine Horm Res 1999; 51 (suppl 1): 83-86 *Review*
3. (2)Abs, R et al. GH Replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. Clinical Endocrinology (1999) 50, 703-713. *Original paper*
4. (3)Bengtsson, B-Å et al. The effects of treatment and the individual responsiveness to GH replacement therapy in 665 GH-deficient adults. JCEM 1999;84:3929-35. *Original paper*
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6. (4) Monson J P et al Growth Hormone Deficiency and Replacement in Elderly Hypopituitary Adults. Clinical Endocrinology, 2000; 53:281-9. *Original paper*
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2001

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