NON-INTERVENTIONAL STUDY ABSTRACT FOR EXTERNAL DISCLOSURE

Title: KIMS® (Pfizer International Metabolic Database)

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Keywords: Growth hormone deficiency, Genotropin, hypopituitarism.

Rationale and background:

Genotropin® (somatropin) is a recombinant human growth hormone (rhGH) produced through DNA technology. The safety and efficacy profile of growth hormone (GH), and later rhGH, has been demonstrated in clinical trials conducted worldwide. However, because of the limited number and characteristics of subjects enrolled in randomized clinical trials and their relatively short duration of treatment, there has been an increasing interest on the part of physicians to follow GH-treated adult subjects prospectively during and after GH treatment in a real world clinical setting. A clinical practice setting is better for assessing the long-term safety and treatment outcomes of GH therapy and generating information that complements the short-term safety and efficacy data obtained from formal clinical trials.

KIMS (Pfizer International Metabolic Database, previously known as Kabi International Metabolic Survey, Study A6281307 [93-0339]) is a large database of adult hypopituitary subjects with GH deficiency who may or may not be receiving GH replacement therapy. The main purpose of KIMS was to generate information on the safety and treatment outcomes of somatropin therapy as prescribed by physicians in a real world clinical practice setting, to improve understanding of the consequences of GH deficiency (GHD) in adult hypopituitarism, and to contribute to optimization of GH replacement.

Subjects were followed for as long as the KIMS physician found appropriate and as per subject's consent. The subject assignment to a particular therapeutic strategy was not decided in advance by a study protocol but fell within the treating physician's current practice. Due to the non-interventional (NI) nature of the study, no additional diagnostic or monitoring procedures were applied to the subjects and epidemiological methods were used for the analysis of collected data.

Research question and objectives:

The study collected information regarding adult GHD and Genotropin utilization in a real world setting in order to:

- Assess the long-term treatment outcomes and safety in subjects who were prescribed and treated with Genotropin;
- Determine the relationships between clinical status, dosage schedule, history of pretreatment with rhGH, and response to Genotropin treatment;

- Develop the scientific foundation and clinical tools for cost-effective, individualized GH treatment of adult subjects and optimize their management throughout the course of Genotropin treatment;

- Evaluate the impact of GHD on health care costs before and after treatment;

- Contribute to our knowledge of adult GHD, including transition period in childhood-onset growth hormone deficiency and its treatment through the exploratory analysis of collected study data;

- Document clinical practice in management of hypopituitarism over time as well as trends between countries.

Study Design:

KIMS was as an international, multi-center, open-label NI study open to adult and adolescent hypopituitary subjects diagnosed with GHD who either received no GH replacement (reference subjects) or were treated with Genotropin in a real-world clinical practice setting according to the approved indication or as prescribed by physicians in clinical practice. Regular clinical practice could include routine diagnostic procedures (eg, blood samples), interviews, and questionnaires, based on the clinical practice style, standards, and judgment of the KIMS investigator. Subjects were followed by their treating physician throughout the course of Genotropin treatment and after discontinuation for as long as the KIMS investigator considered it appropriate.

KIMS was implemented locally by Pfizer country office personnel or appointed contract research organizations. KIMS was managed by international and national boards, including members elected from participating physicians and Pfizer representatives. Participating countries were responsible for monitoring of study data.

Setting:

Subjects were treated and followed by the KIMS investigator. Data that had been collected during routine examination of subjects included data related to safety, treatment, and research outcome parameters of interest. The data collection period covered before, during and after GH treatment, but because data collection was at the discretion of the individual investigator, the information collected could vary from one investigator to the next. Collected data were subsequently key-coded and analyzed by Pfizer, in collaboration with KIMS investigators, to evaluate safety, treatment and research outcomes of interest.

Subjects and study size, including dropouts:

Subjects included adult and adolescents diagnosed with GHD who consented to participate in the study. Investigators and sites from a total of 31 countries participated and enrolled subjects in this study. Germany and the United Kingdom were the highest recruiters, enrolling 3124 (19.8%) and 3034 (19.2%) subjects, respectively.

A total of 15809 subjects were enrolled, received GH therapy and were included in the analysis. Of these, 3626 (22.9%) subjects were active (subjects with a visit 24 months prior to database closure) and 3003 (19.0%) subjects were non-active (subjects without a visit 24 months prior to database closure) at the time of this report. Of the 15809 subjects, 8574 (54.2%) subjects exited the study and 606 (3.8%) died; a total of 6724 subjects discontinued the study. The most frequent reason for discontinuation was subjects were no longer willing to participate in the study (2270 [14.4%] subjects).

Variables and data sources:

This NI study did not include pre-specified endpoints, but collected information from adult and adolescent subjects who received either no GH replacement or were treated with Genotropin in a real-world clinical setting to allow for the analysis of the outcomes specified on the following sections:

Safety Outcomes

The safety outcomes included all reported, all causality, and treatment-related serious adverse events (SAEs), treatment-related adverse events (AEs), including neoplasm incidence, heart function, and metabolic parameters like concentration of serum insulin-like growth factor-I (IGF-I), parameters of glucose metabolism, and lipid profile.

This abstract for external disclosure presents summaries of the following, safety endpoints:

- Demographic data;
- AEs;
- SAEs;
- Discontinuation from GH therapy;
- Discontinuations from study;
- Death;
- Serum IGF-I concentration;
- Parameters of glucose and lipid metabolism.

Treatment Outcomes

The treatment outcomes included clinical characteristics including height, weight, waist, and hip circumference, blood pressure, lipid profile, IGF-I, insulin-like growth factor binding protein-3, as well as bone data, body composition data, subject reported outcomes such as Quality of Life-Assessment of Growth Hormone Deficiency in Adults, Psychological General Well-Being, KIMS Patient Life Situation Form, and European Quality of Life-5 Dimensions.

Research Outcomes

The research outcomes included routine diagnostic procedures (eg, blood samples), interviews, and questionnaires collected by investigators based on their specific clinical needs and research interests.

The data collected during treatment and follow-up of study subjects were entered onto Case Report Forms (CRFs). In most cases, the source documents were the hospital or the physician subject charts. In these cases, data collected on the CRFs had to match the data in those charts. The study data analyzed was based on the data reported by the investigators.

Statistical Analyses

Data collected from study subjects were evaluated and analyzed by Pfizer, in collaboration with KIMS investigators, according to the relevant statistical analysis plan, to address research outcomes of interest.

Results:

Demographic Data

Investigators and sites from a total of 31 countries participated in this study. Germany and the United Kingdom were the highest recruiters, enrolling 3124 (19.8%) and 3034 (19.2%) subjects, respectively. There was a similar proportion of male (7990/15809) and female (7813/15809) subjects. For 6 subjects, gender was missing.

The majority of subjects (94.4%) were Caucasian. Overall, the mean age at enrollment was 43.9 years (standard deviation [SD]: 15.33) and median age was 44.8 years (range: 5.6 years-91.2 years).

Regarding prior rhGH treatment status, 9107 (57.6%) subjects had never received rhGH therapy prior to enrollment (true naïve subjects), 2176 (13.8%) subjects were off GH therapy for at least 6 months prior to enrollment (semi-naïve subjects), and 4526 (28.6%) were on rhGH therapy at enrollment (non-naïve subjects).

Summary of Adverse Events:

A total of 8093 (51.2%) subjects were reported to have 27118 AEs during treatment with Genotropin, of which, 4505 (16.6%) AEs were considered treatment-related by the investigator. A total of 3998 (25.3%) subjects were reported to have 7154 SAEs, 1934 (12.2%) subjects were reported to have had an AE that led to discontinuation of study medication, and 869 (5.5%) subjects had a dose reduction due to AEs.

The most frequently reported all causality AEs were arthralgia (730 [4.6%] subjects), headache (572 [3.6%] subjects), influenza (450 [2.8%] subjects), and depression (447 [2.8%] subjects). The most frequently reported treatment-related AEs were arthralgia (407 [2.6%] subjects) and edema peripheral (290 [1.8%] subjects).

Serious Adverse Events:

The most frequently reported SAE was pituitary tumor recurrence (all causality: 320 [2.0%] subjects and treatment-related: 154 [1.0%] subjects).

Discontinuations:

A total of 387 (2.45%) subjects discontinued treatment due to treatment-related SAEs. The most frequently reported treatment-related SAEs which led to treatment discontinuation were pituitary tumor recurrence (59 [0.37%] subjects), craniopharyngioma (18 [0.11%] subjects), and prostate cancer (17 [0.11%] subjects).

Deaths:

The reported incidence of death was highest for 'general disorders and administration site conditions' (148 [26.43%] subjects) and 'neoplasms benign, malignant and unspecified (including cysts and polyps)' (146 [26.07%] subjects).

The exit page of the CRF was identified as an additional source for reporting deaths. Forty-six (46) deaths were reported on the exit page of the CRF where causality was not assessed, and therefore, could not be determined. The total number of deaths reported in the study was 606.

There were no clinically relevant changes in vital sign measurements during the study. There were no significant or consistent trends in insulin-like growth factor-I standard deviation score (IGF-I SDS), glucose concentration or lipid metabolism.

Insulin-like Growth Factor-I Standard Deviation Score (IGF-I SDS):

At baseline or start of KIMS, subjects had low serum IGF-I SDS: mean value of -1.3 (SD: 2.20). There was a small numerical increase in IGF-I SDS from Month 6 to Year 18, and mean IGF-I SDS value reached to 0.7 at Year 18.

Glucose Concentration:

Mean fasting blood glucose at baseline was 4.8 mmol/L and random glucose level was 5.7 mmol/L.

Lipid Metabolism (Total Cholesterol, Low Density Cholesterol [LDL], High Density Cholesterol [HDL], and Triglycerides):

The mean total cholesterol was 5.7 mmol/L (SD: 1.27) at baseline and 6.0 mmol/L (SD: 1.20) by Year 18 (last follow-up). The mean LDL was 3.5 mmol/L (SD: 1.10) at baseline and 3.3 mmol/L (SD: 0.67) by Year 18 (last follow-up). The mean HDL was 1.3 mmol/L (SD: 0.41) at baseline and 1.4 mmol/L (SD: 1.07) by Year 18 (last follow-up). The mean triglycerides was 2.1 mmol/L (SD: 1.59) at baseline and 2.7 mmol/L (SD: 1.20) by Year 18 (last follow-up).

Discussion:

KIMS is a large database of adult hypopituitary subjects with GH deficiency who may or may not be receiving GH replacement therapy. The database was first established in 1994 under a survey guideline. It has since evolved to become a NI study sponsored by Pfizer Inc. to evaluate the long-term safety and treatment outcomes of Genotropin therapy in adults as prescribed by physicians in a real world clinical practice setting.

Unlike formal clinical trials in which enrolled subjects are fairly homogenous as a result of specific enrollment criteria, KIMS was open to all subjects with GHD who were either considered for or were being treated with Genotropin and consented to his/her participation in the study. Such broad inclusion criteria together with an open-label study design – both typical for many post-marketing, observational surveillance studies – constitute the major strength of KIMS: long-term follow-up of a large number of subjects. Thus, this study presents data on one of the largest cohorts of adult patients treated with GH for the longest follow-up, and, as such, KIMS is considered to be a substantial contribution to broadening the current knowledge of medical treatment of adult GHD. Over the years, KIMS data have complemented data from clinical trials with Genotropin and have been used to explore specific research questions, to evaluate safety signals, and to respond to numerous regulatory queries regarding the use of Genotropin. The study was terminated on 19 October 2012.

KIMS aims at monitoring the long-term safety and efficacy of Genotropin as prescribed in clinical practice, ie, the treatment regimen, both dosing and schedule are not driven by the study protocol but are at the discretion of each treating physician. Not surprisingly, documentation of everyday clinical practice in an unrestricted manner provides opportunities to better understand treatment outcomes in unselected patient cohorts, monitor the use of drug and various treatment patterns in different countries, as well as more properly assess safety profile as it appears in 'real life' situations.

All data collected for each subject were based on the routine clinical care as received at their clinics, according to individual clinic schedule. Subject data were collected during normal routine examination, ie, no additional diagnostic or monitoring procedures were required, and included subject information available in clinical records. Analysis of data originated from a real world clinical practice setting is challenging and requires precisely defined visit windows for the time-points used in the analysis. Wide definitions of these windows address the issue of data completeness, another limitation of NI studies. As reporting is not driven by a stringent protocol and largely depends on investigators and their engagement, all information available in the database was included in the relevant analyses. Of note, given the nature of the study, and as seen with other NI studies, a potential bias due to underreporting of abnormal findings or AEs cannot be excluded. Despite these limitations, the large number and broad characteristics of patient cohorts, combined with their long-term follow-up, contribute to the value of the data collected in KIMS.

The primary objective of the current analysis was to assess the safety of Genotropin as used in daily clinical practice over a longer period of time. The results of the largest NI study of the safety of Genotropin treatment in adult patients with GHD complement data from clinical trials and confirm the favorable and well-established safety profile of Genotropin therapy,

with no new safety signals or reports of previously unknown adverse drug reactions identified when analyzing the study results.