

# The NordiNet<sup>®</sup> International Outcome Study and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup>: rationale, design, and methodology of two international pharmacoepidemiological registry-based studies monitoring long-term clinical and safety outcomes of growth hormone therapy (Norditropin<sup>®</sup>)

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**Objective:** Randomized controlled trials have shown that growth hormone (GH) therapy has effects on growth, metabolism, and body composition. GH therapy is prescribed for children with growth failure and adults with GH deficiency. Carefully conducted observational study of GH treatment affords the opportunity to assess long-term treatment outcomes and the clinical factors and variables affecting those outcomes, in patients receiving GH therapy in routine clinical practice.

**Design:** The NordiNet<sup>®</sup> International Outcome Study (IOS) and the American Norditropin<sup>®</sup> Studies: Web Enabled Research (ANSWER Program<sup>®</sup>) are two complementary, non-interventional, observational studies that adhere to current guidelines for pharmacoepidemiological data.

**Patients:** The studies include pediatric and adult patients receiving Norditropin<sup>®</sup>, as prescribed by their physicians.

**Measurements:** The studies gather long-term data on the safety and effectiveness of real-life treatment with the recombinant human GH, Norditropin<sup>®</sup>. We describe the origins, aims, objectives, and design methodology of the studies, as well as their governance and validity, strengths, and limitations.

**Conclusion:** The NordiNet<sup>®</sup> IOS and ANSWER Program<sup>®</sup> studies will provide valid insights into the effectiveness and safety of GH treatment across a diverse and large patient population treated in accordance with real-world clinical practice and following the Good Pharmacoepidemiological Practice and STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

**Keywords:** growth hormone replacement therapy, treatment outcome, pharmacoepidemiology, survey

## Introduction

Observational studies are valuable for assessing and charting the real-life management of patients and offer information to complement data from randomized, controlled trials (RCTs).<sup>1,2</sup> RCTs are the recognized principal means of providing high-level evidence on the efficacy and safety of a therapeutic intervention. However, their results may have limited applicability or validity in routine clinical practice, where the patients encountered and the practices adopted in real-world disease management can differ

greatly from those considered and allowed within the protocol of a controlled trial setting<sup>3</sup> (in which, for example, rare and atypical subgroups are excluded). Non-interventional, observational studies can therefore provide synergistic insights into the utilization and the effectiveness of treatments and allow for the evaluation and follow-up of numerous end points and parameters, including those unrelated to a treatment intervention, yet important to disease understanding. They also permit long-term follow-up of large numbers of patients who are prescribed chronic medication according to standard clinical practices. Moreover, for all prescribed therapies, the collection of postmarketing data is critical for the evaluation and characterization of the real-life effect and risk profile of treatments and can help in the detection of rare side effects and treatment interactions.<sup>4</sup> Thus, balanced assessments of therapeutic interventions should draw on a variety of types of research<sup>5</sup> and, within the mix, observational studies can serve a range of purposes – confirming or refuting previous findings, discovering new aspects of disease, and exploring and generating hypotheses for further investigation.<sup>3</sup>

One therapy area in which observational data in particular can provide valuable evidence and insights is the use of growth hormone (GH) to manage a host of conditions associated with GH deficiency (GHD) or in which normal growth is perturbed.<sup>6–9</sup> In this therapy area, there is an established precedent of assessing the response to and safety of long-term treatment with GH and of supporting and complementing the clinical trial evidence base through registry tools.<sup>10</sup>

GH has multiple physiological actions, including the promotion of linear growth in childhood, and is essential for the maintenance of normal body composition throughout life.<sup>6,11,12</sup> GH therapy may be used in childhood, to promote growth in children with GHD and in children with conditions characterized by insufficient growth, and also has a role in the management of adults with GHD. It follows that patients treated with GH, therefore, represent a highly heterogeneous group in terms of age range and clinical characteristics. GH treatment has been used in children for more than 50 years and in adults for over 20 years, and therapy is typically given long term.<sup>11</sup> Many patients receiving GH therapy are enrolled in observational studies that are designed specifically for the brand of GH treatment they are receiving.<sup>10</sup> These databases and observational studies have considerably extended the knowledge of GHD and its treatment, but many issues remain unresolved.

Norditropin<sup>®</sup> (somatropin [rDNA origin] injection) (Novo Nordisk A/S, Bagsværd, Denmark) is a recombinant human GH used as replacement therapy in patients with GHD or

as pharmacological treatment for a number of conditions characterized by insufficient growth.<sup>13–16</sup>

This paper describes two complementary, large-scale, non-interventional, observational studies, the NordiNet<sup>®</sup> International Outcome Study (IOS) (NCT00960128)<sup>17</sup> and the American Norditropin<sup>®</sup> Studies: Web Enabled Research (ANSWER Program<sup>®</sup>) (NCT00615953),<sup>18</sup> that use the same electronic platform (NordiNet<sup>®</sup>/NovoNet<sup>®</sup>) for data management and that have similar aims; namely, to gather long-term data on the effectiveness and safety of Norditropin<sup>®</sup> treatment in the usual clinical setting and to provide insight into the diseases of the specific endocrine patient populations managed with GH therapy. In this paper we present the origins, objectives, methodology, and governance of these studies, followed by a discussion of their validity, strengths, and limitations, and ongoing and future uses for these two specific observational studies.

## Methods

### History

The NordiNet<sup>®</sup> IOS and ANSWER Program<sup>®</sup> are complementary international non-interventional registry studies monitoring the long-term effectiveness and safety of GH replacement therapy, specifically Norditropin<sup>®</sup>, in routine clinical practice. Patients are entered into one or the other study, depending on location of the treating clinic. The NordiNet<sup>®</sup> IOS registry was launched in 2006 and currently aims to recruit to a planned sample size of 17,000 patients over a 10-year period. Prior to 2006, the national German Novo Nordisk non-interventional studies on Norditropin<sup>®</sup>-treated patients, GrowthWin and NordiWin, initiated in 2001 and 2003, respectively, captured data on the long-term safety and efficacy of Norditropin<sup>®</sup> in children and adults. The data from these two studies have been migrated into NordiNet<sup>®</sup> IOS.<sup>19,20</sup> The ANSWER Program<sup>®</sup> is an observational, non-interventional study that was launched in 2002 and includes, in addition, the follow up of some subjects from two 2-year RCTs assessing Norditropin<sup>®</sup> in children with GHD or growth failure. The ANSWER Program<sup>®</sup> plans to recruit approximately 18,000 patients and includes both pediatric and adult patients treated with Norditropin<sup>®</sup>.

### Aims and objectives

The aims and objectives of NordiNet<sup>®</sup> IOS and the ANSWER Program<sup>®</sup> are to assess the clinical outcomes of real-life treatment of pediatric and adult patients with Norditropin<sup>®</sup>, as prescribed by treating physicians according to standard clinical practice. The studies are gathering

long-term data on the effectiveness of treatment and follow short-term and long-term safety in children and adults treated with Norditropin®. They offer insights into the contemporary treatment of specific endocrine patient populations, with respect to demographic, disease, and patient characteristics such as country, age, sex, pubertal status, and diagnoses. The long-term and prospective nature of the studies allows for the analysis of longitudinal data with regard to outcomes and for the possibility of benchmarking and time-trend assessments to evaluate the quality of treatment, adjusted for baseline data.

While the Nordinet® IOS and the ANSWER Program® have separate protocols, these are of similar design, with similar objectives and methods, and both are web-based studies sharing the same electronic platform (Nordinet®/NovoNet®) for data management. This will allow for the combination of data if required, according to specific questions from researchers, authorities, and other pertinent stakeholders.

The overall effectiveness objectives of these studies in children are to investigate the short- and long-term effects of Norditropin® on linear growth and to identify factors that modify linear growth in children treated with Norditropin®. One major goal is to determine the predictive value of baseline parameters such as age, bone age, sex, and diagnostic indication, and of pretreatment peak GH and insulin-like growth factor 1 (IGF-I) levels, on treatment outcomes. The studies are also investigating the effect of treatment in pediatric patients, on body proportion and metabolic parameters.

Both studies have the objective of studying GH-deficient patients in transition, specifically investigating the effects of stopping Norditropin® treatment in pediatric GHD patients who have reached their adult height and the clinical impact of reinitiating treatment on somatic development in these patients.

In adults, the studies are investigating the short- and long-term effects of Norditropin® treatment on body composition and metabolic parameters, and seek to identify factors that modify those parameters.

In both pediatric and adult patients, the safety of Norditropin® is being assessed using physician reports in the databases, of adverse events (AEs), adverse drug reactions (ADRs), medical events of special interest, and pregnancies. If an investigator assesses an AE/ADR as serious (SAE/SADR), he/she is instructed to complete and “sign” an electronic SAE/SADR form, to send the information related to this event to the database within 24 hours. The investigator is further instructed to inform the

local authority about the SAE/SADR, in accordance with country-specific rules.

## Governance of the databases and studies

Data analyses and publication of the combined results from Nordinet® IOS and the ANSWER Program® are governed by an international study committee (ISC). The ISC comprises elected chairpersons drawn from the pediatric and adult clinical endocrinological specialties, each acting as a national clinical representative of a country involved in the IOS and reporting data on at least 100 patients (maximum two representatives per country), and a maximum of five persons from Novo Nordisk. The ISC meets annually, with the power to call additional special meetings and to form working groups. The Nordinet® ISC acts as the custodian of the database and as the ultimate decision-making body concerning the presentation and publication of international data from the studies.

Data access, analyses, and reporting are managed under the guidance of Novo Nordisk, the owners of the data collected. The studies are conducted in accordance with the Declaration of Helsinki; for both studies, patients provide written, informed consent for data collection. All data in Nordinet® IOS and the NovoNet® ANSWER Program® are made anonymous. At the individual center level, approval of the local ethics committee or institutional review board is a prerequisite for enrollment into Nordinet® IOS and the NovoNet® ANSWER Program®, in accordance with country-specific rules.

## Validity of Nordinet® IOS and ANSWER Program® as observational studies

Both Nordinet® IOS and ANSWER Program® are guided by the Good Pharmacoepidemiological Practice guidelines on the design and reporting of observational studies, as defined by the International Society for Pharmacoepidemiology, and the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines.<sup>3,21</sup> Both studies have a written protocol describing the proposed study tasks, milestones and timelines, objectives, and rationale, with full descriptions of the research methods, study conduct, responsibilities of personnel and facilities, resource commitment, communication and archiving plans for data, and the processes for AE reporting.

## Study designs, data sources, and data flow

There are 20 countries participating in the two studies: 19 in Nordinet® IOS (Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Lithuania, The

Netherlands, Norway, Russia, Serbia, Montenegro, Slovenia, Sweden, Switzerland, UK); and the US in the ANSWER Program®.

Those eligible for inclusion in the studies are pediatric and adult patients who are already on Norditropin® treatment or who are starting on Norditropin® treatment. This includes patients in the following pediatric diagnosis groups: children with growth failure or short stature due to GHD (either as an isolated occurrence or as part of multiple pituitary hormone deficiency), small for gestational age (SGA), Turner syndrome, Prader–Willi syndrome, Noonan syndrome (NS), and chronic renal disease; adult patients with GHD; and GHD patients during transition. This latter group includes GHD patients treated with Norditropin® during childhood who achieved adult height and were off treatment for up to a maximum of 2 years before reassessment of GH status and reconfirmation of GHD. In terms of clinical diagnoses, the studies collect data based on investigators' diagnosis and encourage the use of the International Classification of Diseases 10th Revision (ICD-10) criteria as the routine tool for categorization of diagnoses.<sup>22</sup>

The study databases use the same electronic, web-based platform (NordiNet®/NovoNet®) for electronic data capture in the study case report forms (CRFs), which provide automatic data validation at data entry. The data entered into the platforms are specified in the NordiNet®/NovoNet® CRFs, with certain adjustments and/or additions allowed at the investigator's discretion. All the physician investigators are trained in using the web-based application, and the data on the host server are protected by an individual user ID and password. The patient ID remains with a patient even if he or she moves or changes practitioner. This method of assigned patient ID ensures that patients can be followed long term and through transition. The electronic signature enables the investigator to export the data to the central registry database, in accordance with the NordiNet® IOS and ANSWER Program® protocols; the data captured therein constitute the NordiNet® IOS and ANSWER Program® data sets, respectively.

The central registry database is run and supported by Novo Nordisk. All physicians reporting patient data into the database in accordance with agreements specified by Novo Nordisk are considered to be NordiNet® IOS or ANSWER Program® members and investigators.

All patient data reported into the central database are managed by the Clinical Data Management Department, Novo Nordisk Inc (for ANSWER Program®) and the Novo Nordisk Epidemiology Department in Denmark (for NordiNet® IOS). Data managers follow up on data flow and prepare periodic reports to ensure the completeness and correctness of data.

Patient histories and physical examination data are prospectively or retrospectively entered by the participating physician investigators, using the web-based CRFs. The study protocols specify the examination parameters required at baseline and follow-up visits for both pediatric and adult patients (Tables 1 and 2). Physician investigators are encouraged to enter data as soon as possible after clinic visits. At the baseline visit, the following CRF materials are completed: registration form (for enrollment in the ANSWER Program®), diagnosis form, background form, history of examinations/treatments form, baseline form, and menarche form (if appropriate). Once a pediatric GHD patient has reached adult height and GH treatment is discontinued, the patient may continue to be followed up during a transition period for up to 2 years (the patient will be asked to sign a separate transition informed consent for this). If, at that time, reassessment of the patient's GHD diagnostic criteria indicates that the patient satisfies the diagnostic criteria of adult GHD and the patient would like to reinitiate GH treatment, the physician will initiate treatment in the pediatric module but eventually transfer the patient to an adult endocrinologist using the adult module, with all information obtained before reinitiation of GH treatment considered as the baseline information for adult treatment. At follow-up visits, there is a dedicated follow-up form; additional forms are used to collect data on AEs, pregnancy, menarche, consent for off-treatment data collection, diagnosis, change of clinic, and an end-of-registration form (for subjects leaving the registry).

## Study variables

Study data include all relevant demographic and clinical characteristics of the enrolled adult and pediatric patients, the dose of Norditropin® and any dose adjustments made during the course of patient treatment, clinical outcomes, and quality-of-life measurements. The study protocols provide clear guidance concerning the data to be captured (Tables 1 and 2); however, data collection is ultimately conducted in accordance with the routine clinical practice of the center and investigator.

The effectiveness end points assessed in children include the effect of Norditropin® on height gain and body weight, blood biochemistry (including IGF-I, and pituitary and other hormones, as relevant) and bone age. Uniquely, in NordiNet® IOS only, there is an option for automatic assessment of bone age in children, by use of a validated software called BoneXpert® (Visiana, Holte, Denmark).<sup>23</sup>

In adult patients, assessed effectiveness end points include the effect of Norditropin® on body weight and composition,

**Table 1** Pediatric indications: baseline and follow-up visit examination parameters evaluated across the NordiNet<sup>®</sup> IOS and ANSWER<sup>®</sup> Program studies

| Examination parameter <sup>a</sup>  | Baseline visit | Follow-up visits | Follow-up in transition (only GHD) | Last visit |
|---|----------------|------------------|------------------------------------|------------|
| Patient ID  | X              |                  |                                    |            |
| Date of visit   | X              | X                | X                                  | X          |
| <b>Demographic data/background information</b>  |                |                  |                                    |            |
| Date of birth   | X              |                  |                                    |            |
| Sex   | X              |                  |                                    |            |
| Patient consent   | X              |                  |                                    |            |
| Patient consent date  | X              |                  |                                    |            |
| Patient consent for off-treatment data collection, consent date (separate study form) |                |                  | X                                  |            |
| Diagnoses   | X              | (X)              | (X)                                | (X)        |
| Date of diagnoses   | X              | (X)              | (X)                                | (X)        |
| Gestational age   | X              |                  |                                    |            |
| Birth weight  | X              |                  |                                    |            |
| Birth length  | X              |                  |                                    |            |
| Birth head circumference  | X              |                  |                                    |            |
| Pregnancy information (SGA)   | X              |                  |                                    |            |
| Apgar score (SGA)   | X              |                  |                                    |            |
| Mother's measured (or reported) height  | X              |                  |                                    |            |
| Father's measured (or reported) height  | X              |                  |                                    |            |
| Medical history (TS, NS, GHD)   | X              |                  |                                    |            |
| Treatment history (GHD, oncology treatment, radiotherapy, chemotherapy)               | X              |                  |                                    |            |
| Phenotype (TS)  | X              |                  |                                    |            |
| History of examinations   | X              |                  |                                    |            |
| <b>Auxology</b>   |                |                  |                                    |            |
| Height  | X              | X                | X                                  | (X)        |
| Weight  | X              | X                | X                                  | X          |
| Sitting height  | X              | X                |                                    | (X)        |
| Arm span  | X              | X                |                                    | (X)        |
| Hip circumference   | (X)            | (X)              | X                                  | X          |
| Triceps skin fold   | X              | X                | X                                  | X          |
| Upper arm circumference   | X              | X                | X                                  | X          |
| <b>Sexual maturation</b>  |                |                  |                                    |            |
| Breast (Tanner) female  | X              | X                | (X)                                | (X)        |
| Pubic hair (Tanner) (female and male)   | X              | X                | (X)                                | (X)        |
| Genitalia (Tanner) (male)   | X              | X                | (X)                                | (X)        |
| Left testis (male)  | X              | X                | (X)                                | (X)        |
| Right testis (male)   | X              | X                | (X)                                | (X)        |
| Menarche (if occurred)  | X              | X                | (X)                                | (X)        |
| Pregnancy   |                | X                | X                                  | X          |
| <b>Vital signs</b>  |                |                  |                                    |            |
| Pulse   | X              | X                | X                                  | X          |

(Continued)

**Table 1** (Continued)

| Examination parameter <sup>a</sup>   | Baseline visit | Follow-up visits | Follow-up in transition (only GHD) | Last visit |
|--------------------------------------|----------------|------------------|------------------------------------|------------|
| Systolic and diastolic BP            | X              | X                | X                                  | X          |
| Quality of life questionnaire        | X              | X                | X                                  | X          |
| <b>Imaging</b>                       |                |                  |                                    |            |
| Bone age                             | X              | X                |                                    | (X)        |
| Cranial imaging (GHD)                | X              | X                |                                    | (X)        |
| <b>DEXA</b>                          |                |                  |                                    |            |
| <b>BIA</b>                           |                |                  |                                    |            |
| Cardiac ultrasound/imaging (TS, NS)  | X              | X                |                                    | X          |
| Hearing (TS)                         |                |                  |                                    |            |
| <b>GH test (date, type, GH peak)</b> | X              |                  | X                                  |            |
| <b>Biochemistry</b>                  |                |                  |                                    |            |
| IGF-I                                | X              | X                | X                                  | X          |
| IGF-I – SDS                          | X              | X                | X                                  | X          |
| IGFBP-3                              | X              | X                | X                                  | X          |
| HbA <sub>1c</sub>                    | X              | X                | X                                  | X          |
| Thyroid function (TSH, free T4)      | X              | X                | X                                  | X          |
| Fasting blood glucose                | X              | X                | X                                  | X          |
| Fasting insulin                      | X              | X                | X                                  | (X)        |
| LDL                                  | X              | X                | X                                  | X          |
| HDL                                  | X              | X                | X                                  | X          |
| Triglycerides                        | X              | X                | X                                  | X          |
| Total cholesterol                    | X              | X                | X                                  | X          |
| FSH, LH (TS)                         | X              | X                |                                    | X          |
| <b>Additional biochemistry (CRD)</b> |                |                  |                                    |            |
| Hemoglobin                           | X              | X                |                                    | X          |
| Magnesium                            | X              | X                |                                    | X          |
| Potassium                            | X              | X                |                                    | X          |
| Calcium                              | X              | X                |                                    | X          |
| Phosphate                            | X              | X                |                                    | X          |
| Serum albumin                        | X              | X                |                                    | X          |
| Serum creatinine                     | X              | X                |                                    | X          |
| Serum urea                           | X              | X                |                                    | X          |
| Estimated creatinine clearance       | X              | X                |                                    | X          |
| Cystatin C                           | X              | X                |                                    | X          |
| Serum nitrogen                       | X              | X                |                                    | X          |
| Estimated glomerular filtration rate | X              | X                |                                    | X          |
| Alkaline phosphatase (AP)            | X              | X                |                                    | X          |
| Fibroblast growth factor 23          | X              | X                |                                    | X          |
| Ostase (bone-specific AP)            | X              | X                |                                    | X          |
| Serum bicarbonate                    | X              | X                |                                    | X          |
| 25-hydroxy-vitamin D                 | X              | X                |                                    | X          |
| Parathyroid hormone                  | X              | X                |                                    | X          |
| Deoxypyridinoline                    | X              | X                |                                    | X          |
| Protein in urine                     | X              | X                |                                    | X          |
| Creatinine in urine                  | X              | X                |                                    | X          |

(Continued)

**Table 1** (Continued)

| Examination parameter <sup>a</sup>           | Baseline visit | Follow-up visits | Follow-up in transition (only GHD) | Last visit |
|--|----------------|------------------|------------------------------------|------------|
| <b>Dialysis (CRD)</b>                        | X              | X                |                                    | X          |
| <b>GH treatment</b>                          |                |                  |                                    |            |
| Date for start of GH treatment               | X              |                  |                                    |            |
| GH dose                                      | X              | X                | (X)                                | (X)        |
| GH treatment reinitiation                    |                |                  | X                                  |            |
| Number of missed injections since last visit |                | X                | (X)                                | X          |
| Change of GH treatment                       |                | X                | (X)                                | (X)        |
| <b>Concomitant medication</b>                | X              | X                | X                                  | (X)        |
| <b>AEs (details AE study form)</b>           |                | X                | X                                  | X          |
| <b>End of GH treatment</b>                   |                |                  |                                    | (X)        |
| <b>Clinic change</b>                         |                |                  |                                    | X          |
| <b>Date of end of registration in study</b>  |                |                  |                                    | X          |

**Notes:** The ANSWER<sup>®</sup> Program does not include BoneXpert<sup>®</sup> (Visiana, Holte, Denmark) evaluations. <sup>a</sup>The only evaluated parameters are those that are a part of routine practice, in accordance with local requirements. (X) signifies "if relevant."

**Abbreviations:** AE, adverse event; ANSWER, American Norditropin<sup>®</sup> Studies; Web Enabled Research; AP, alkaline phosphatase; BIA, bioelectrical impedance analysis; BP, blood pressure; CRD, chronic renal disease; DEXA, dual-energy X-ray absorptiometry; Free T4, free thyroxin; FSH, follicle stimulating hormone; GH, growth hormone; GHD, growth hormone deficiency; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein-3; IOS, International Outcome Study; LDL, low-density lipoprotein; LH, luteinizing hormone; NS, Noonan syndrome; SDS, standard deviation score; SGA, small for gestational age; TS, Turner syndrome; TSH, thyroid stimulating hormone.

quality of life, blood chemistry (including IGF-I, pituitary hormones and sex hormones routinely, and thyroid and adrenal hormones if necessary).

All data are collected in accordance with routine medical practice and country-specific rules, and the CRFs allow for effectiveness end points to be adapted and edited according to local situations and practices.

## Safety outcomes

The overall safety objectives follow short- and long-term safety in children and adults treated with Norditropin<sup>®</sup>. At every visit, the investigators ascertain the occurrence of AEs and SAEs, regardless of their relation to treatment, medical events of special interest (eg, wrong drug administration), and pregnancies. The investigator reports information related to SAEs and medical events of special interest within 24 hours of obtaining knowledge of the event; pregnancy exposures are reported within 14 calendar days. Nonserious AEs that are not attributed to treatment are not registered.

**Table 2** Adult indications: baseline and follow-up visit examination parameters evaluated across the NordiNet<sup>®</sup> IOS and ANSWER<sup>®</sup> Program studies

| Examination parameter <sup>a</sup>   | Baseline visit | Follow-up visits | Last visit |
|--|----------------|------------------|------------|
| Patient ID   | X              |                  |            |
| Date of visit  | X              | X                | X          |
| Date of birth  | X              |                  |            |
| <b>Demographic data/ background information</b>  |                |                  |            |
| Sex  | X              |                  |            |
| Patient consent  | X              |                  |            |
| Patient consent date   | X              | (X)              | (X)        |
| Diagnoses  | X              | (X)              | (X)        |
| Date of diagnoses  | X              | (X)              | (X)        |
| Medical history (diabetes, tumors, malignant disease, subarachnoid hemorrhage, traumatic brain injury) | X              |                  |            |
| Radiotherapy   | X              |                  |            |
| Chemotherapy   | X              |                  |            |
| Surgery  |                |                  |            |
| <b>Physical examination and vital signs</b>  |                |                  |            |
| Height   | X              |                  |            |
| Weight   | X              | X                | X          |
| Waist circumference  | X              | X                | X          |
| Hip circumference  | X              | X                | X          |
| Upper-arm circumference  | X              | X                | X          |
| Skinfold triceps   | X              | X                | X          |
| Systolic BP  | X              | X                | X          |
| Diastolic BP   | X              | X                | X          |
| Pulse  | X              | X                | X          |
| <b>Smoking</b>   | X              | X                | X          |
| <b>Pituitary imaging</b>   | X              |                  |            |
| <b>DEXA</b>  | X              | X                | X          |
| <b>Bioimpedance</b>  | X              | X                | X          |
| <b>Biochemistry</b>  |                |                  |            |
| GH test (date, type, GH peak)  | X              |                  |            |
| IGF-I  | X              | X                | X          |
| IGF-I – SDS  | X              | X                | X          |
| IGFBP-3  | X              | X                | X          |
| HbA <sub>1c</sub>  | X              | X                | X          |
| Fasting blood glucose  | X              | X                | X          |
| Fasting insulin  | X              | X                | X          |
| Thyroid function (TSH, free T4)  | X              | X                | X          |
| Total cholesterol  | X              | X                | X          |
| HDL  | X              | X                | X          |
| LDL  | X              | X                | X          |
| <b>QoL</b>   | X              | X                | X          |
| <b>GH treatment</b>  | X              | X                |            |
| Date for start of GH treatment   | X              |                  |            |
| GH dose  | X              | X                |            |
| Treatment change   |                | X                | X          |
| <b>Concomitant medication</b>  | X              | X                | X          |
| <b>AE description (details AE study form)</b>  |                | X                | X          |
| Pregnancy  |                | X                | X          |
| <b>Number of missed injections since last visit</b>  |                | X                | X          |
| <b>End of GH treatment</b>   |                |                  | X          |

**Table 2** (Continued)

(Continued)

| Examination parameter <sup>a</sup>   | Baseline visit | Follow-up visits | Last visit |
|--------------------------------------|----------------|------------------|------------|
| Clinic change                        |                |                  | X          |
| Date of end of registration in study |                |                  | X          |

**Notes:** The ANSWER<sup>®</sup> Program does not include BoneXpert<sup>®</sup> (Visiana, Holte, Denmark) evaluations. <sup>a</sup>The only evaluated parameters are those that are a part of routine practice, in accordance with local requirements. (X) signifies "if relevant."

**Abbreviations:** AE, adverse event; ANSWER, American Norditropin<sup>®</sup> Studies; Web Enabled Research; BP, blood pressure; DEXA, dual energy X-ray absorptiometry; GH, growth hormone; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; IGF-I, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; IOS, International Outcome Study; LDL, low-density lipoprotein; SDS, standard deviation score; TSH, thyroid stimulating hormone; QoL, quality of life.

## Data analyses and communication

Statistical analyses of study data will be described per analysis and per publication of the study analyses. Novo Nordisk is committed to communicating, or otherwise making available for public examination, the results of these studies, regardless of the outcomes. Study results, which are reviewed regularly under the governance of the ISC or by investigators and internal study personnel in the ANSWER Program<sup>®</sup>, are presented on a regular basis at major scientific meetings and published in relevant peer-reviewed journals.

## Current data size

As of July 1, 2012, NordiNet<sup>®</sup> IOS had enrolled 11,370 pediatric patients (GHD: 6716; SGA: 2642; Turner syndrome: 999; idiopathic short stature: 99; NS: 104; Prader–Willi syndrome: 85; and other: 567) and 1837 adult patients (GHD: 1528 and other: 309).

As of September 25, 2012, the NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> had enrolled 13,681 pediatric patients (GHD: 7180; SGA: 1024; Turner syndrome: 718; idiopathic short stature: 1452, NS: 184; Prader–Willi syndrome: 120; and other: 2334) and 468 adult patients (GHD: 214 and multiple pituitary hormone deficiency: 254).

## Discussion

The NordiNet<sup>®</sup> IOS and the NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> studies are similarly designed observational studies that capture data, via a web-based platform, describing an international, multicenter cohort of patients receiving Norditropin<sup>®</sup> in routine clinical practice. The primary value of the NordiNet<sup>®</sup> IOS and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> observational studies is to provide real-world data on the clinical effectiveness and safety experience of Norditropin<sup>®</sup> therapy in children, adolescents, and adults, with a special focus on the transition phase. Data from these observational studies will also help to increase understanding of the patient populations

and disease areas under study and provide a valid model for studying treatment effects. The common design allows for the IOS and ANSWER Program<sup>®</sup> data to be pooled, providing a greater number of cases to investigate patient subgroups and infrequent events, and strengthening the statistical power of the data. Specific to the NordiNet<sup>®</sup> IOS study, is the possibility of automatically assessing the bone age in children, and to both studies, the ongoing collection of normative data on body composition and IGF-I, in adults.

These international, prospective studies support research efforts within the field of GH therapy and the design and potential for collation of study data, and stimulate international cooperation among pediatric and adult endocrinologists. As described in this paper, the NordiNet<sup>®</sup> IOS and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> studies are not constrained by the strict and highly specific nature of a trial protocol and, therefore, offer an inclusive picture of the use and effectiveness of Norditropin<sup>®</sup> in clinical practice as well as allowing specific subgroups of patients receiving GH to be followed and assessed. The protocol of the studies attempts to capture numerous end points and informative parameters, including those unrelated to traditional GH treatment end points. The design of the studies and their CRFs allow flexibility not possible within an RCT, permitting investigators to add additional data and to suggest additional parameters and reporting according to their current clinical practices and observations.

The importance of the databases is reflected in the articles that have already published data from NordiNet<sup>®</sup> IOS and the NovoNet ANSWER Program<sup>®</sup>.<sup>24–26</sup> One of these, from the NovoNet ANSWER Program<sup>®</sup>, sought to identify potential predictors of good response to GH, in children with short stature of various etiologies;<sup>24</sup> a second, using data from both studies, focused on comparing 2-year treatment outcomes between patients from different diagnostic subgroups (idiopathic GHD, SGA, idiopathic short stature, or multiple pituitary hormone deficiency),<sup>26</sup> while a third focused exclusively on patients with NS.<sup>25</sup> Other publications have reported on the effects of sex, age, and pubertal status on outcome of GH treatment in children.<sup>27–29</sup>

In addition to offering data on long-term treatment effectiveness and a means to easily discover interactions with other treatments, a unique feature of the NordiNet<sup>®</sup> IOS and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> studies is their intentionally designed capacity to observe and follow pediatric patients during the transition from childhood to adulthood. It is hoped that the studies will provide much needed data on the outcomes of children with GHD, treated with GH in childhood

until adult height is reached, and the effects of treatment discontinuation and of reinitiation in cases of severe GHD that persists into adulthood.

Cost-effectiveness data, increasingly required by prescribers and authorities, can be derived from the databases, which offer current data on GH treatment outcomes across a heterogeneous patient population. These studies also include the assessment of bone age performed by the treating clinician, which may be useful in the routine care of pediatric patients. Collection of data on body composition, using, for example, bioimpedance analysis, and comparison of this data with normative data for adult patients with GHD could also be of great value.

The size of the cohorts studied by NordiNet<sup>®</sup> IOS and the NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> allows the generation of a large collective data set that can be interrogated and analyzed by specific patient subgroups and according to key epidemiological and treatment questions. This means that these studies will offer insights and data on large patient populations (internationally and nationally), while also having the depth and flexibility to allow study of particular subsets of patients within those populations.

There are a number of notable strengths of the NordiNet<sup>®</sup> IOS and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> observational studies. The studies collect retrospective data, yet are prospective in design, aiding prompt recognition of effects and associations, and the patient populations of the studies reflect and provide a means of surveillance of the diverse patient groups given Norditropin<sup>®</sup> in clinical practice, groups which together constitute a large number of patients exposed to Norditropin<sup>®</sup> treatment over a protracted time period. The validity of these studies is enhanced by their strict adherence to contemporary guidelines on the principles and conduct of non-interventional, observational studies, such as those outlined in STROBE and by the Good Pharmacoepidemiological Practice guidelines.<sup>3,21</sup> The software tools used in these studies provide a secure, sophisticated, and reactive database. Independent governance of the studies is assured by an expert and diverse body of counselors, the ISC, which acts as custodian of the data and advises on all aspects of data communication, and on publication of the data, regardless of outcomes, to the medical community.

Potential limitations of the NordiNet<sup>®</sup> IOS and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> studies are those common to any observational registry and include the uncontrolled nature of the study and of data collection, and the potential selection bias due to enrollment of selected clinics. Potential bias can also be caused by the systematic error introduced with use of different

laboratory assays in different clinics. The lack of central laboratory analysis limits the interpretation of relevant blood analyses, especially IGF-I. There is also a risk for information bias due to incomplete reporting, poor quality, or erroneous information recording regarding treatment exposure and treatment outcomes, or due to investigators failing to report confounding factors, misclassifying a diagnosis, or failing to report data accurately. The automated data validation system attempts to mitigate against these aspects of information recording.

The heterogeneous nature of the patient population is both a limitation and strength of the studies. Both studies permit and support local treatment practices; however, centers providing data may have very different access to the use of technologies. Confounders such as these should be included in the analyses and reported accordingly. There is also a continuing need to obtain long-term outcome data on transition patients into adulthood.

In conclusion, the NordiNet<sup>®</sup> IOS and NovoNet<sup>®</sup> ANSWER Program<sup>®</sup> studies will provide valid and important insights into the effectiveness and safety of GH treatment across a diverse and large patient population that is treated in accordance with real-world clinical practice, by following the Good Pharmacoepidemiological Practice guidelines and STROBE guidance on the conduct of observational studies. The studies include an easily performed assessment of bone age and the possibility of calculating cost-effectiveness and will offer unique insights into the management of GHD patients through transition.

## Disclosure

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