


**OMNITROPE<sup>®</sup>**

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**Long-term safety follow-up after growth hormone treatment (rhGH)  
of short children born Small for Gestational Age (SGA)**

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**International coordinating investigator's protocol approval signature:**

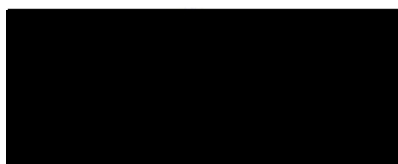
**Omnitrope®**

**EUDRACT number:** 2007-001364-72

**Protocol EP00-402:** Long-term safety follow-up after growth hormone treatment (rhGH) of short children born Small for Gestational Age (SGA)

Protocol version 5.0 (Clean) from 14. July 2014

Prof. Dr. med.   
Coordinating Investigator



July 23, 2014  
Date

## Signature of Principal Investigator

**Omnitrope<sup>®</sup>**

**EUDRACT number:** 2007-001364-72

**Protocol EP00-402:** Long-term safety follow-up after growth hormone treatment (rhGH) of short children born Small for Gestational Age (SGA)

Amended Clinical Study Protocol EP00-402, Version 5.0 from 14. July 2014, Clean and Track Changes to Clinical Study Protocol EP00-402.

I have read the amended protocol version and agree to conduct this trial in accordance with all stipulations of the protocol as amended, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Investigator Signature

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Date

Print name: \_\_\_\_\_

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**Signature page for Sandoz**

**Omnitrope<sup>®</sup>**

**Protocol EP00-402:** Long-term safety follow-up after growth hormone treatment (rhGH) of short children born Small for Gestational Age (SGA)

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## List of abbreviations

AB	Antibody
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case report form
CRO	Contract research organisation
DRL	Drug reference list
EMA	European Medicines Agency
ft4	Free thyroxine
GCP	Good clinical practice
GH	Growth hormone
hGH	Human growth hormone
IEC	Independent ethics committee
IGF-I	Insulin-like growth factor
IGFBP-3	Insulin-like growth factor binding protein 3
IGT	Impaired glucose tolerance
IRB	Institutional review board
ITT	Intention to treat
IUGR	Intrauterine growth retardation
MedDRA	Medical dictionary for regulatory activities
OGTT	Oral glucose tolerance test
PP	Per protocol
RBC	Red blood cell count
rhGH	Recombinant human growth hormone
SAE	Serious adverse event
SAF	Safety population
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
TSH	Thyroid stimulating hormone
WBC	White blood cell count
WHO	World health organisation



## Amendment 4, 14. July 2014

### Rationale for amendment

Patients who have received at least one dose of Omnitrope under the protocol EP00-401 shall be enrolled after the termination of growth hormone treatment in study EP00-402 for an additional 10 year follow up observation.

Amendment 4 is issued to implement changes to the safety data collection and reporting in order to comply with internal safety reporting standards, i.e. to report any serious events irrespective of causality throughout the study. So far, all SAE were collected within the first 30 days after obtained informed consent for EP00-402. After that period, only SAE with suspected causality to study drug administered in EP00-401 study where to be reported.

Therefore, safety reporting is extended by this amendment to reporting of every serious adverse event (SAE), regardless of suspected causality, occurring after the patient has provided informed consent for EP00-402 study and until 30 days after the patient has stopped study participation in EP0-402 study within 24 hours of learning of its occurrence.

At this occasion, the following is changed in addition:

- To ensure consistency between EP00-401 and EP00-402 protocols, wording of inclusion criteria 2 regarding informed consent is changed in order to be identical with respective wording used in protocol EP00-401 study. Wording is updated to specify the case a patient is not able to read *and* write.
- Former protocol amendments 1, 2 and 3 are fully integrated into the protocol
- Protocol is updated regarding publication of study protocol and results, signature of study report and protocol adherence in order to adhere to current standards.
- Minor spelling errors are corrected.

### Study Status

The Study is ongoing.

### Changes to the protocol

The following sections of the protocol were amended:

Integration Amendment 1, 12. March 2012

Integration Amendment 2, 09. May 2012

Integration Amendment 3, 06. June 2013

Integration Amendment 4, 14. July 2014

Protocol synopsis

Section 5.0 "Population"

Section 8.0 "Safety monitoring"

Section 12.0 "Procedures and instructions: Administrative procedures"

The changes of the protocol do not affect the Informed Consent.

Changes to specific sections of the protocol are shown in the track changes version of the protocol ~~using strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board

(IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

## **Amendment 3, 06. June 2013**

### **Rationale for amendment**

This study had been designed in accordance with the post-approval pharmacovigilance plan to extend the safety database of Omnitrope® and to address the EMA's request to investigate the potential of Omnitrope® with regard to the development of diabetes after treatment cessation in short children born SGA. Further, the immunogenicity of Omnitrope® in short children born SGA treated with Omnitrope® under the protocol EP00-401 should be investigated.

Patients fulfilling the diagnosis SGA who have received at least one dose of Omnitrope under the protocol EP00-401 shall be observed after termination of growth hormone treatment in this follow-up study for an additional time period of 10 years.

This amendment aims to document changes regarding requirements for safety monitoring and harmonization of safety related sections in the protocol. In addition, the study synopsis which was created as a separate document earlier was integrated into the protocol.

### **Study Status**

The Study is ongoing.

### **Changes to the protocol**

The following sections of the protocol were amended:

Integration of study synopsis

Section 7.0 "Visit Schedule and assessments"

Section 8.0 "Safety monitoring"

Details of the changes are provided in the protocol amendment document.

The changes of the protocol do affect the Informed Consent.

## Amendment 2, 09. May 2012

### Rationale for amendment

This study had been designed in accordance with the post-approval pharmacovigilance plan to extend the safety database of Omnitrope® and to address the EMA's request to investigate the diabetogenic potential of Omnitrope® during treatment and the development of diabetes after treatment cessation in short children born SGA. Further, the immunogenicity of Omnitrope® in short children born SGA treated with Omnitrope® under the protocol EP00-401 should be investigated.

Patients fulfilling the diagnosis SGA who have received at least one dose of Omnitrope under the protocol EP00-401 shall be observed after termination of growth hormone treatment in this follow-up study for an additional time period of 10 years.

This amendment aims to refrain from further assessment of host cell protein (HCP). The rationale of this change to the protocol is provided in the next section.

### Assessment of host cell protein (HCP)

The EP00-401 and EP00-402 study started after approval of Omnitrope® for marketing authorization. At that time the **assessment of *E.coli* host cell protein (HCP)** antibodies using the anti-HCP antibody western blot was voluntarily included by Sandoz to further monitor the development of anti-HCP antibodies in patients during treatment.

However, the low immunogenicity of Omnitrope (API Kundl) has meanwhile been confirmed in three phase III studies (see "**legend**" below). Therefore Sandoz regards the cessation of the assessment of *E.coli* host cell protein (HCP) antibodies as justified from the time of approval of this amendment.

The analysis of the HCP antibody results (tests performed until this amendment became effective) will be specified in the Statistical Analysis Plan (SAP) provided for each analysis.

### Legend:

The active pharmaceutical ingredient (API) manufacturing process was developed at Sandoz (formerly Biochemie) in Kundl, Austria, in the 1990s using standard *E.coli* technology used also for Genotropin® and most other GH products. Sandoz was familiar with all aspects of this process and kept close control of the impact of any changes on the quality of all intermediates as well as the purified bulk API. At that time for patent reasons, Sandoz had the first batches of API for early clinical trials manufactured at Covance in the US (API Covance) in 1999. This API was used to manufacture finished dosage forms (FDFs) for the first 9 months of the initial Phase III studies in GHD children. Evaluation of the process and the resulting product quality continued in Sandoz's development facilities. In this context, Sandoz performed an assay specifically developed to detect even slightest traces of HCPs in the API preparations. Using this new, more sensitive method, API Covance was found to contain high levels of HCPs. Investigations on the clinical consequences were initiated and it was found that this high level of HCPs was directly correlated to the occurrence of anti-HCP antibodies as well as non-neutralizing anti-rhGH antibodies. Sandoz reacted immediately and introduced two modifications into the API downstream purification process in 2000 leading to a significantly improved HCP clearance without changing any other product characteristics. In-depth physicochemical characterization and comparability exercises demonstrated that API Covance and API Kundl were fully comparable in all quality aspects with the sole exception

of the decreased HCP content. Based on HCP data of API Kundl the limit for *E. coli* host cell proteins was tightened from [REDACTED]. API manufactured at Covance was not used for further development.

Consequently, the FDFs using API Kundl were then introduced into the ongoing Phase III study (after month 9 of overall GH therapy) and immediately thereafter, antibody titers started to drop while all other safety and efficacy parameters remained unchanged. The FDFs using API Kundl were evaluated in two additional clinical phase III studies. In all of these three studies the low immunogenicity of API Kundl has been demonstrated. Finally, efficacy analyses carried out in defined subgroups of the study patients revealed that growth parameters in patients with a positive anti-HCP and anti-rhGH test were not affected and none of the patients showed antibody-related growth attenuation.

In summary, only API manufactured at Sandoz Kundl was used from late clinical development (Phase III) up to process validation and registration.

Commercial manufacturing is controlled using the tight HCP limit of [REDACTED].

### **Study Status**

The Study is ongoing.

### **Changes to the protocol**

The following sections of the protocol were amended:

Section 2.0	“Study purpose”
Section 3.0	“Objectives”
Section 4.0	“Study design”
Section 7.0	“Visit Schedule and assessments”
Section 10.0	“Data analysis”
Section 11.0	“Discussion and rationale for study design features”

Details of the changes are provided in the protocol amendment document.

The changes of the protocol do not affect the Informed Consent.

## **Amendment 1, 12. March 2012**

### **Rationale for amendment**

This study had been designed in accordance with the post-approval pharmacovigilance plan to extend the safety database of Omnitrope® and to address the EMA's request to investigate the diabetogenic potential of Omnitrope® during treatment and the development of diabetes after treatment cessation in short children born SGA. Further, the immunogenicity of Omnitrope® in short children born SGA treated with Omnitrope® under the protocol EP00-401 should be investigated.

Patients fulfilling the diagnosis SGA who have received at least one dose of Omnitrope® under the protocol EP00-401 shall be observed after termination of growth hormone treatment in this follow-up study for an additional time period of 10 years. Due to the duration of the study and length of time between the planned follow-up visits, patients and their parents/guardians will be asked to enroll in a study retention program. This program has been designed to maintain contact with and engage patients and their parents/guardians in order to maximize study compliance. The program will include regular contact, interaction and engagement of patients and parents/guardians during each year of the follow-up until study completion. Additionally the inclusion criteria and the procedure of obtaining written informed consent are described more precisely.

Additionally some minor administrative changes are made.

### **Study Status**

The Study is ongoing.

### **Changes to the protocol**

The following sections of the protocol were amended:

Section 5.0	“Population”
Section 7.0	“Visit Schedule and Assessments”
Section 12.0	“Procedures and instructions: Administrative procedures”
Administrative changes	

Details of the changes are provided in the protocol amendment document.

The changes of the protocol affect the Informed Consent.

## Protocol synopsis

### Title of study:

Long-term safety follow-up after growth hormone treatment (rhGH) of short children born Small for Gestational Age (SGA)

### Study Purpose

Epidemiological evidence suggests that children born SGA may be at an increased risk of insulin resistance and type 2 diabetes in later life. Given that GH therapy has been shown to induce transient resistance to the actions of insulin in children, concerns over the diabetogenic potential of GH therapy in individuals predisposed to metabolic abnormalities, such as children born SGA, have been raised.

This study is performed as part of the Marketing Authorisation Holder's post-marketing pharmacovigilance plan to investigate the long-term safety, in particular the diabetogenic potential and immunogenicity of rhGH therapy in short children born small for gestational age (SGA). The purpose of this study is

- (a) to monitor short children born SGA who participated in study EP00-401 for the development of diabetes for a further 10 years after termination of growth hormone treatment and
- (b) to report the incidence of anti-rhGH antibodies for 6 months after termination of GH treatment.

### Objectives

#### Primary objective(s)

The primary objective of this study is to evaluate the long-term effect of growth hormone treatment on the development of diabetes in short children born SGA for 10 years after the end of treatment.

#### Secondary objectives

The secondary objectives of this study are:

- to report the incidence of anti-rhGH antibodies 6 months after termination of growth hormone treatment.
- to evaluate final height in follow-up period
- to evaluate IGF-1 and IGFBP-3 levels for 10 years after end of growth hormone treatment
- to evaluate incidence and severity of adverse events

### Study design

Long term safety follow-up study of patients that were included in the Phase IV study (EP00-401). Patients will be monitored for safety.

The baseline visit equals the final visit of the study EP00-401. Examinations and laboratory values from the final visit will be transferred to the baseline visit.

### **Safety assessments:**

Carbohydrate metabolism: Fasting plasma glucose and insulin levels will be measured 6 months, 1, 5 and 10 years after the end of treatment. Glycosylated haemoglobin (HbA<sub>1c</sub>) will be measured at 6 months, 1, 5 and 10 years after the end of treatment. An oral glucose tolerance test (OGTT) will be performed 6 months, 1, 5 and 10 years after the end of treatment.

Immunogenicity: Subjects will be screened for anti-rhGH antibodies 6 months after treatment. Only in case of positive antibodies measurements in previous visit follow-up measurements are planned after 1 year, 5 years and 10 years.

Additional safety criteria: Additional criteria for assessing safety will consist of monitoring and recording all adverse events, vital signs and body weight, physical condition, haematology, blood chemistry, thyroid function tests, lipids and urinalysis. Adverse events, body weight and physical condition will be assessed at every study visit. Laboratory tests for safety will be performed, 6 months, 1, 5 and 10 years after the end of treatment.

### **Efficacy assessments:**

The patients' height will be measured at each visit and IGF-1 and IGFBP-3 serum levels will be assessed by a central laboratory 6 months, 1, 5 and 10 years after the end of treatment.

A summary of the study plan is given below.

### **Study Outline**

PHASE	Follow-up				
TIME POINT	0 mo	6 mo	1 yr	5 yrs	10 yrs
VISIT	F0	F1	F2	F3	F4
THERAPY	None				

### **Population**

All patients who participated in the EP00-401 study and received at least one dose of study medication will be asked to enter this safety follow-up period of 10 years. The study will be performed in approximately 40 centres in Europe (incl. one site in [REDACTED] Asia). The treating physicians shall be appropriately qualified and experienced in conducting clinical trials. About 200 subjects are planned to enter the long-term follow-up period. The patients participating in this study are out-patients.

### **Inclusion/exclusion criteria**

The investigator must ensure that all patients who meet the following inclusion and none of the exclusion criteria are offered enrolment in the study. No additional exclusions can be applied by the investigator, in order for the study population to be representative of all eligible patients.



## Inclusion criteria

1. All patients who fulfilled the diagnosis SGA, participated in study EP00-401, and received at least one dose of study medication
2. Written informed consent of patient (for children who can read and write) and parent or legal guardian

## Exclusion criteria

1. Patients unwilling and/or parents/guardians who are not capable of ensuring compliance with the provisions of the study protocol

## Flow Chart Follow up Period

Follow-up Period					
Time Point	baseline = final visit of EP00-401	6 mo ± 4 wks	1 yr ± 4 wks	5 yrs ± 4 wks	10 yrs ± 4 wks Final Visit
Visit	F0 <sup>1</sup>	F1	F2	F3	F4
Written Informed Consent	X				
Physical examination incl. weight (kg), height (cm) and pubertal status (if applicable)		X	X	X	X
Vital signs		X	X	X	X
Haematology		X	X	X	X
Blood chemistry incl. fT4, TSH, HbA1C, fasting plasma glucose and insulin levels		X	X	X	X
Urinalysis		X	X	X	X
Anti-hGH		X	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>
IGF-1, IGFBP-3		X	X	X	X
OGTT		X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Concomitant medication	X <sup>4</sup>	X	X	X	X
Adverse events	X <sup>4</sup>	X	X	X	X

1: equals the final visit of study EP00-401

2: only if positive anti-hGH antibodies in previous visit

3: contraindicated in patients with overt diabetes mellitus

4: documentation of all adverse events / concomitant medications ongoing at the final visit of study EP00-401

## 1.0 Background

This study is performed as part of the Marketing Authorisation Holder's post-marketing pharmacovigilance plan to investigate the long-term safety, in particular the diabetogenic potential and immunogenicity of rhGH therapy in short children born small for gestational age (SGA). Children born SGA who were treated in study EP00-401 with growth hormone due to short stature will be followed up for 10 years after stop of rhGH treatment.

### 1.1. The indication SGA

The most common definition of the term "small for gestational age" (SGA) is a birth weight and/or length of  $\geq 2$  standard deviations (SD) below the mean for the infant's gestational age and sex (based on data derived from a reference population).<sup>1</sup> The standards for neonatal growth were established by Usher and McLean.<sup>2</sup> These decades-old growth curves are based upon measurement of intrauterine growth between 25 and 44 weeks of gestation of white infants born at sea level. Given that the race and ethnicity are known to be important modifiers of foetal growth patterns and that improvements in prenatal care and nutrition as well as the identification of factors that adversely affect the foetus may have resulted in a trend toward larger neonates, efforts should be made to improve the existing reference data.

The term SGA does not refer to foetal growth but to the size of the infant at birth. Intrauterine growth retardation (IUGR), while not a synonym, is commonly used interchangeably with SGA. Technically, IUGR implies a pathophysiological cause for the inhibition of normal growth in utero. Not all SGA infants have suffered from IUGR, while certain infants born after a period of IUGR are not necessarily SGA.

Ultrasound criteria are used as a diagnostic standard in the identification of SGA. Ultrasonic foetal indices such as crown-rump length during the first trimester correlate well with gestational age, but they must be recorded accurately and birth length must subsequently be measured precisely for a correct diagnosis of SGA.<sup>3</sup>

Between 3% and 10% of all live births each year are described as SGA.<sup>4</sup> More than 90% of these children catch up to normal height by 2 to 3 years of age. According to data from the National Centre for Health Statistics (in the US), approximately 91,000 infants were born SGA in 1999 in the United States (the most recent year for which adult birth data are available from the National Centre for Health Statistics).<sup>5</sup> In 2000, 4,058,814 infants were born in the United States according to the data from the National Centre for Health Statistics.<sup>4</sup> Using this figure and defining SGA as the  $\leq 2.3$  percentile, approximately 93,400 SGA infants are born annually in the United States. Extrapolating from that figure, the number of SGA children in the United States between the ages of 2 and 16 years with persistent short stature is estimated to be 146,000.

Catch-up growth of an infant born SGA is defined as accelerated growth that results in the attainment of length and weight within 2 SD of the mean for corresponding sex and age. This surge in growth generally begins immediately after birth, with the largest increases occurring by 6 months of age. SGA babies who fail to display catch-up growth by 2 years of age, are at increased risk of adult short stature.<sup>1,6</sup>

Endocrine and metabolic outcomes may be related to failure to achieve catch-up. While GH levels have a relatively small effect on *in uteri* growth, insulin and insulin-like growth factors (IGFs) are key modifiers of foetal growth and development. Endocrine studies *in uteri* show that growth retarded foetuses have reduced insulin<sup>7</sup> and IGF-I<sup>8</sup> levels and in the neonatal

period, babies born SGA have low IGF-I levels and IGFBP-3 levels despite elevated GH secretion.<sup>9</sup>

Failure of catch-up growth is associated with persistent low IGF-I and IGFBP-3 levels,<sup>10</sup> suggesting ongoing dysfunction of the GH/IGF-I axis. In contrast to their high neonatal GH levels, older SGA children may have reduced GH secretion.

In addition to short stature, SGA infants may be predisposed to a number of developmental problems. Infants born with SGA usually have less body fat than those who are born adequate for gestational age. Serum concentrations of leptin, a protein produced by adipose tissue and involved in the regulation of the appetite and body weight are reduced in short children born SGA, possibly leading to lack of appetite and inadequate consumption of calories.<sup>1,11</sup> SGA can have adverse effects on the health of children during infancy and childhood, including slower physical growth, possibly slower mental development and higher morbidity. Some evidence suggests that SGA may affect brain development, leading to an increased risk of slight yet significant cognitive and neurodevelopmental impairment. For example, one study showed that absence of catch-up growth among male infants who were born SGA was the most important predictor of subnormal performance in standard psychological tests.<sup>12</sup>

SGA children are also more likely to have congenital abnormalities. Severely growth-retarded infants are at markedly increased risk for foetal and neonatal death, hypoglycaemia, hypocalcaemia, polycythaemia.

There is also convincing evidence that SGA is a predisposing factor for the development of hypertension<sup>13</sup>, diabetes<sup>14</sup> and cardiovascular disease<sup>15</sup> in adult life.

### **1.1.1. Type 2 Diabetes and SGA**

Studies in Europe, North America, and the developing world<sup>16,17,18,19,20,21,22</sup> have shown that low birth weight in babies born at term is associated with a higher prevalence of glucose intolerance and type 2 diabetes in adult life. For example, Rich-Edwards and colleagues<sup>22</sup> investigated the relationship between birth weight and type 2 diabetes in more than 69,000 adult women as part of the Nurses Health Study. There was an inverse association between the risk of type 2 diabetes in adulthood and the entire range of birth weight. The trend was strong and statistically significant with adults who weighed < 5 pounds at birth, who had 1.8 times the risk of developing type 2 diabetes compared with their normal birth weight counterparts. Similar results have been found among men and women across a variety of populations.

As with the association between SGA and adult cardiovascular disease, the “foetal origins” hypothesis focuses on the intrauterine environment as the etiologic agent.<sup>23</sup> Alternatively, insulin resistance may be controlled by the same genetic factors that regulate foetal growth.<sup>24,25</sup> Hattersley and colleagues<sup>26</sup> theorize that genetically determined insulin resistance results in impaired insulin-mediated growth in the foetus as well as insulin resistance in adult life. These researchers propose that there is an insulin-resistant genotype that may predispose to low birth weight, insulin resistance, diabetes, and hypertension.

### **1.1.2. Syndrome X and SGA**

Certain chronic and metabolic disorders including hypertension, glucose intolerance, central obesity, and dyslipidaemia tend to cluster in the same individuals, leading to an increased risk of mortality from cardiovascular disease. This syndrome is referred to by several names, including syndrome X, the metabolic syndrome, and insulin resistance syndrome. Several studies have demonstrated an increased prevalence of syndrome X among adults born

SGA.<sup>27,28,29,30,31,32</sup> Moreover, adult overweight and obesity increase the risk of syndrome X, and studies show adults born SGA may have an increased risk of obesity.

Thus, close clinical follow-up of weight, height, and body mass index (BMI) in patients born SGA is particularly important.

Yarbrough and colleagues<sup>32</sup> studied 303 postmenopausal white women aged 50-84 years to examine the relationship between birth weight and the metabolic syndrome. The metabolic syndrome was defined as the grouping of hypertension, dyslipidaemia, and abnormal glucose tolerance in an individual. The metabolic syndrome was present in 7.9% of this study population. Compared with women in the highest birth weight group, those in the lowest birth weight group (mean = 5.51) had a significantly increased prevalence (12.0% vs 4.3%,  $P < 0.05$ ) and 2.41 times the risk (95% CI = 1.06 - 5.51) of developing the metabolic syndrome. In addition, women in the lowest birth weight group who became adults in the highest BMI group had the highest prevalence of the metabolic syndrome (approximately 30%).

Leger and associates<sup>33</sup> conducted a similar study in young adults. The regional cohort comprised 236 subjects born SGA and 281 subjects born adequate for gestational age with a mean age of 20.6 years. After adjusting for sex and BMI, mean plasma glucose concentration 30 minutes after a glucose load was significantly higher in subjects born SGA compared with subjects born adequate for gestational age, as were insulin and pro-insulin concentrations 30 and 120 minutes after a glucose load.

### **1.1.3. Metabolic effects of growth hormone treatment in patients born SGA**

In view of the fact that several studies have found an association between low birth weight and impaired insulin sensitivity, type 2 diabetes, hypertension and cardiovascular disease in later life, and because growth hormone is known to increase fasting and postprandial insulin levels, concern has been expressed regarding the possible detrimental effects of GH therapy in children born SGA.

Sas et al.<sup>34</sup> evaluated the changes in body metabolism, blood pressure and lipid metabolism in 79 GH-treated children therapy (2 dose groups, 1 mg/m<sup>2</sup>/day and 2 mg/m<sup>2</sup>/day). The authors measured skin fold thickness, systemic blood pressure, and blood lipids in the 79 subjects. Compared with normal children, the short children born SGA had significantly lower BMI, higher systolic blood pressure, and normal lipids. During GH treatment, BMI increased significantly over baseline values with no overall changes in body fat percentage compared with age-matched healthy controls. These findings demonstrated that GH therapy decreases adipose tissue mass and increases muscle mass in this group of patients. Both systolic and diastolic blood pressure SDS also decreased significantly ( $P < 0.05$ ) during therapy. After 6 years of therapy, there were no differences in blood pressure measurements between the treatment group and age-matched controls. While pre-treatment mean lipid values were normal, GH treatment was associated with significant changes in the lipid profiles during the first year of therapy; total cholesterol ( $P < 0.001$ ) and LDL cholesterol ( $P < 0.001$ ) decreased significantly and stabilised thereafter.

In the same study,<sup>35, 36</sup> all 79 children underwent standard oral glucose tolerance tests at baseline, after 1 and 6 years of GH treatment and 6 months after discontinuation of GH therapy. Before GH therapy 8% of the children had impaired glucose tolerance (IGT) according to WHO criteria. IGT was found in 4% of children after 6 years of therapy and in 10% of children after stopping GH treatment. GH therapy induced considerably higher fasting and glucose-stimulated insulin levels, indicating insulin resistance. After discontinuation of GH therapy the mean serum glucose levels remained normal and the mean serum insulin

levels decreased significantly, to normal age-matched reference values. HbA<sub>1C</sub> levels were always in the normal range and none of the children developed diabetes mellitus.

## **2.0 Study Purpose**

Epidemiological evidence suggests that children born SGA may be at an increased risk of insulin resistance and type 2 diabetes in later life. Given that GH therapy has been shown to induce transient resistance to the actions of insulin in children, concerns over the diabetogenic potential of GH therapy in individuals predisposed to metabolic abnormalities, such as children born SGA, have been raised.

This study is performed as part of the Marketing Authorisation Holder's post-marketing pharmacovigilance plan to investigate the long-term safety, in particular the diabetogenic potential and immunogenicity of rhGH therapy in short children born small for gestational age (SGA). The purpose of this study is

- (a) to monitor short children born SGA who participated in study EP00-401 for the development of diabetes for a further 10 years after termination of growth hormone treatment and
- (b) to report the incidence of anti-rhGH antibodies (ABs) for 6 months after termination of GH treatment.

## **3.0 Objectives**

### **3.1. Primary objective(s)**

The primary objective of this study is to evaluate the long-term effect of growth hormone treatment on the development of diabetes in short children born SGA for 10 years after the end of treatment.

### **3.2. Secondary objectives**

The secondary objectives of this study are:

- to report the incidence of anti-rhGH antibodies (ABs) 6 months after termination of growth hormone treatment.
- to evaluate final height in follow-up period
- to evaluate IGF-I and IGFBP-3 levels for 10 years after end of growth hormone treatment
- to evaluate incidence and severity of adverse events

## **4.0 Study design**

Follow-up, observational study of patients that were included in the Phase IV study (EP00-401). Patients will be monitored for safety.

The baseline visit equals the final visit of the study EP00-401. Examinations and laboratory values from the final visit will be transferred to the baseline visit.

### Safety assessments:

Carbohydrate metabolism: Fasting plasma glucose and insulin levels will be measured 6 months, 1, 5 and 10 years after the end of treatment. Glycosylated haemoglobin (HbA<sub>1c</sub>) will be measured at 6 months, 1, 5 and 10 years after the end of treatment. An oral glucose tolerance test (OGTT) will be performed 6 months, 1, 5 and 10 years after the end of treatment.

Immunogenicity: Subjects will be screened for anti-rhGH antibodies (ABs) 6 months after treatment. Only in case of positive antibodies measurements in previous visit follow-up measurements are planned after 1 year, 5 years and 10 years.

Additional safety criteria: Additional criteria for assessing safety will consist of monitoring and recording all adverse events, vital signs and body weight, physical condition, haematology, blood chemistry, thyroid function tests, lipids and urinalysis. Adverse events, body weight and physical condition will be assessed at every study visit. Laboratory tests for safety will be performed, 6 months, 1, 5 and 10 years after the end of treatment.

### Efficacy assessments:

The patients' height will be measured at each visit and IGF-I and IGFBP-3 serum levels will be assessed by a central laboratory 6 months, 1, 5 and 10 years after the end of treatment.

A summary of the study plan is given below.

### Study Outline

PHASE	Follow-up				
TIME POINT	0 mo	6 mo	1 yr	5 yrs	10 yrs
VISIT	F0	F1	F2	F3	F4
THERAPY	None				

Interim analyses are planned at the following time points:

- 2022 with data of patients who completed 1 year of follow-up
- 2026 with data of patients who completed 5 years of follow-up
- 2031 with data of patients who completed 10 years of follow-up

## 5.0 Population

All patients who participated in the EP00-401 study and received at least one dose of study medication will be asked to enter this observational period of 10 years. The study will be performed in approximately 40 centres in Europe (incl. one site in [REDACTED] Asia). The treating physicians shall be appropriately qualified and experienced in conducting clinical trials. About 200 subjects are planned to enter the long-term follow-up period. The patients participating in this study are out-patients.

## **5.1. Inclusion/exclusion criteria**

The investigator must ensure that all patients who meet the following inclusion and none of the exclusion criteria are offered enrolment in the study. No additional exclusions can be applied by the investigator, in order for the study population to be representative of all eligible patients.

### **5.1.1. Inclusion criteria**

1. All patients who fulfilled the diagnosis SGA, participated in study EP00-401, and received at least one dose of study medication
2. Written informed consent of patient (for children who can read and write) and parent or legal guardian

### **5.1.2. Exclusion criteria**

1. Patients unwilling and/or parents/guardians who are not capable of ensuring compliance with the provisions of the study protocol

## **6.0 Treatment**

### **6.1. Investigational drug**

Not applicable. This is an observational follow-up study without intake of any investigational drug.

#### **6.1.1. Concomitant treatment**

All kind of medications, except investigational medicinal products, are allowed. Administration of all drugs must be reported in the appropriate section of the Case Report Forms (CRFs), along with dose information, dates of administration and reason for use.

Any diagnostic, therapeutic or surgical procedure should be recorded, including the date, indication, descriptions of the procedure and clinical findings.

#### **6.1.2. Study discontinuation**

Study must be discontinued if the investigator concludes that continuation would result in significant safety risk for that patient.

Patients who discontinue study before completing the study should not be considered withdrawn from the study, and should be scheduled for a visit as soon as possible, at which time all of the assessments for the final visit will be performed. A Study Discontinuation form should be completed, giving the date and reason for stopping the study. At a minimum, all patients who discontinue, including those who refuse to return for a final visit, will be contacted for safety evaluations during the following 30 days.

### **6.1.3. Premature patient withdrawal**

Patients *may* voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients should also be withdrawn at any time if the investigator concludes that it would be in the patient's best interest. Patients *must* be withdrawn from the study if any of the following occur:

- Withdrawal of informed consent

Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety. Patients may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow-up for any reason. For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient:

- at least one telephone call and
- at least one registered letter.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for the patient's premature withdrawal from the study and record this information on the CRF.

## **7.0 Visit Schedule and assessments**

The flowchart lists all assessments and indicates with an "X" the visits during which they are performed. Patients should be seen for all visits at the designated time-point or as close to it as possible. A time window for the visits of up to +/- four weeks will be allowed.

All data obtained from the assessments listed in the flowchart and described in detail in the subsections below must be supported in the patient's source documentation.

The study visit schedule consists of 5 visits within 10 years. The study plan timetable (see flow chart) indicates the number and timing of the planned visits. During these visits, the mentioned safety parameters will be assessed. It is important to maintain the visit schedule as accurately as possible. If any individual visit date does not conform to the planned schedule, the subsequent visit should be realigned to maintain the schedule relative to the start of the follow-up period. As part of the retention program, patients and/or parents/guardians as appropriate will receive reminders about attending their study visits to help maximize study compliance.

The clinical and laboratory investigational plan per visit is summarized in the flow-chart.

### **7.1. Procedures by visits**

#### **7.1.1. Baseline visit (F0)**

This visit equals the final visit of EP00-401. Examinations and laboratory values from the final visit will be transferred to the baseline visit

- Written informed consent will be obtained



- Concomitant medication recording
- Adverse Events recording including all events from study EP00-401 which are ongoing at the time of start of the follow-up phase

### **7.1.2. 6 months visit (F1)**

This visit has to be performed 6 months after termination of growth hormone treatment. The following investigations and assessments will be performed during clinical examination:

- Physical examination including height, body weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Blood sampling for laboratory testing: Haematology and clinical chemistry including thyroid function, fasting plasma glucose, fasting plasma insulin and HbA<sub>1C</sub>
- Urinalysis
- IGF-I and IGFBP-3 determination
- Blood sampling for anti-hGH antibodies
- OGTT
- Concomitant medication recording
- Adverse Events recording

### **7.1.3. 1 year visit (F2), 5 year visit (F3), 10 year visit (F4, final visit)**

The following investigations and assessments will be performed during clinical examination:

- Physical examination including height, body weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Blood sampling for laboratory testing: Haematology and clinical chemistry including thyroid function, fasting plasma glucose, fasting plasma insulin and HbA<sub>1C</sub>
- Urinalysis
- IGF-I and IGFBP-3 determination
- Only if positive antibodies in previous visit: Blood sampling for anti-hGH antibodies
- OGTT
- Concomitant medication recording
- Adverse Events recording

## **7.2. Patient compliance**

Patient compliance will be assessed corresponding to visit schedule.

## **7.3. Safety**

### **7.3.1. Methods and timing for assessing, recording and analysis of parameters**

At each visit, which should take place preferably in the morning, patient's height and weight will be assessed and noted. If applicable, pubertal status should be assessed by the investigator and expressed in stages as described by Tanner and Whitehouse<sup>37</sup>.

Patients will also undergo a general physical examination and will also be questioned about and examined for any adverse events

### 7.3.2. Weight measurements

Weight will be measured according to the usual clinical practice.

### 7.3.3. Carbohydrate metabolism:

Fasting plasma glucose and insulin levels will be measured 6 months, 1, 5 and 10 years after the end of treatment. In case of elevated fasting blood glucose ( $\geq 100$  mg/dl or  $\geq 5.6$  mmol/l) a second sample for fasting blood glucose will be measured within 2 weeks.

After an overnight fast, venous blood samples will be taken to assay fasting glucose and insulin levels. Insulin resistance will be estimated using both the homeostasis model assessment (HOMA)<sup>38</sup> and quantitative insulin sensitivity check index (QUICKI).<sup>39 40</sup>

$$\text{HOMA} = \frac{\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mg/dl)}}{405 *}$$

\*use constant 22.5 instead of 405 if glucose concentration is reported in mmol/L

$$\text{QUICKI} = \frac{1}{\log \text{fasting insulin } (\mu\text{U/ml}) + \log \text{fasting glucose (mg/dl)}}$$

Glycosylated haemoglobin (HbA<sub>1c</sub>) will be measured at 6 months, 1, 5 and 10 years after the end of treatment.

An oral glucose tolerance test (OGTT) will be performed at 6 months, 1, 5 and 10 years after the end of treatment.

The OGTT is a provocation test to examine the efficiency of the body to metabolise glucose. The OGTT provides information on latent diabetes states. The OGTT will be carried out according to WHO criteria (2002). After 3 days of an unrestricted, carbohydrate-rich diet, and after overnight fasting, 75 grams of glucose (for children: 1.75 grams of glucose per kg body weight (up to a maximum of 75 g) will be administered orally after being dissolved in 250-300 ml of water. Blood samples will be taken 10 minutes before, and 120 minutes after the glucose load. Diabetes mellitus is defined by  $\geq 200$  mg/dl or  $\geq 11.1$  mmol/L blood glucose after 120 minutes.

OGTT is contraindicated in patients with overt diabetes mellitus.

### 7.3.4. Immunogenicity

Subjects will be screened for anti-rhGH antibodies (ABs) at baseline and visit F1. Only in the case of development of anti-rhGH antibodies (ABs) in the previous visit follow-up measurements will be made 1, 5 and 10 years after the end of treatment.

### **7.3.5. Physical examination**

At each scheduled visit (at baseline, 6 months, 1, 5 and 10 years after treatment), a thorough physical examination including of the following will be made: head (external), eyes, ears, nose and throat, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system and, where appropriate, others. Additionally if applicable, pre-pubertal or pubertal status will be documented by physical examination.

### **7.3.6. Vital signs**

Vital signs (blood pressure and pulse rate) will be recorded at each visit in a standardised manner, i.e., after the patient has rested for five minutes in the sitting position.

### **7.3.7. Laboratory evaluations**

#### **7.3.7.1. Local Laboratories**

Local laboratories will be responsible for performing haematology including complete blood count (automated 5-part differential recommended) and platelet counts, biochemistry, thyroid function and urinalysis. All supernatants of these samples are destroyed after analysis.

The following laboratory safety tests will be performed 6 months, 1, 5 and 10 years after termination of treatment, unless more frequent assessment is clinically indicated.

Haematology: Haemoglobin, haematocrit, white blood cell count (total and differential) (WBC), red blood cell count (RBC), platelet count, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), HbA<sub>1C</sub>, erythrocyte sedimentation rate (ESR).

Biochemistry: Creatinine, urea, aspartate aminotransferase (SGOT/AST), alanine aminotransferase (SGPT/ALT), gamma-glutamyltransferase (gamma-GT), alkaline phosphatase, total bilirubin, albumin, total protein, HDL, LDL, sodium, potassium, chloride, glucose\*, insulin\*, uric acid, total cholesterol\*, triglycerides\*, calcium, phosphorus.

Thyroid function: Free thyroxine (fT4) and thyroid stimulating hormone (TSH).

Urinalysis: pH, glucose, ketones, bilirubin, protein..

\*fasting serum levels; fasting is defined as no caloric intake for at least 8h

#### **7.3.7.2. Central Laboratory**

Central laboratory will process samples for antibody analysis, IGF-I and IGFBP-3. Instructions on preparation and shipment of samples will be provided in the corresponding Manual. Serum samples have to be stored deep frozen between -20°C and -70°C for central determination of IGF-I, IGFBP-3 and anti-hGH antibodies. For central laboratory details please refer to Investigator File. All supernatants of samples will be destroyed after analysis with exemption of samples for antibody analyses which will be stored by the sponsor according Good Laboratory Practice (GLP) Guidelines in order to potentially re-analyze anti-hGH antibodies at a later stage, if needed.

## **7.4. Efficacy**

### **7.4.1. Height measurements**

Height will be measured according to the usual clinical practice

### **7.4.2. IGF-I and IGFBP-3 serum levels**

IGF-I and IGFBP-3 serum levels will be assessed 6 months, 1, 5 and 10 years after the end of treatment.

## **7.5. Tolerability/acceptability**

Not applicable

## **7.6. Resource utilization**

Not applicable

## **8.0 Safety monitoring**

### **8.1. Adverse events**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Despite the above definition any appearance or worsening of any undesirable sign, symptom, or medical condition observed after start of the study and associated with study conduct (e.g. blood sample drawing) must also be recorded on the Adverse Event page of the patient's CRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade
  - Mild: No effect on normal daily activities/ awareness of symptoms but easily tolerated
  - Moderate: Effect on normal daily activities
  - Severe: Inability to perform daily activities
2. its relationship to the study drug(s) (suspected/not suspected)
  - Not suspected: The temporal relationship of the clinical event to trial drug administration makes a causal relationship unlikely, or other drugs, therapeutic

interventions or underlying conditions provide a sufficient explanation for the observed event.

- Suspected: The temporal relationship of the clinical event to trial drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

3. its duration (start and end dates or if continuing at final exam)

4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); concomitant medication given; non-drug therapy given, patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

## **8.2. Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent for EP00-402 study and until 30 days after the patient has stopped study participation in EP00-402 study, must be reported to the sponsor within 24 hours of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug given in the EP00-401 study, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor. The telephone and fax number of the contact persons, specific to the site, are listed in the investigator folder provided to each site.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Summary of Product Characteristics (SmPC) or Package Insert (new occurrence) and is thought to be related to the study drug taken in the EP00-401 study, the sponsor may urgently require further information from the investigator for Health Authority reporting. The sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **8.3. Pregnancies**

To ensure patient safety, each pregnancy in a patient who received study drug in EP00-401 study must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of any pregnancy outcome to the sponsor study drug taken in EP00-401 study. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

### **8.4. Data Monitoring Board**

Not applicable

## **9.0 Data review and database management**

### **9.1. Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sandoz representative or designee will review the protocol and CRFs with the investigators and their staff. During the study, the monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice as well as the progress of enrollment. Key trial personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data. The investigator must also keep a copy of the signed informed consent form.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Sandoz monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables.

Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

### **9.2. Data collection**

Designated investigator staff must enter the information required by the protocol onto the Sandoz CRFs that are printed on 2-part, non-carbon-required paper. Study monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The original CRFs are forwarded to the CRO by monitors or by the investigational site, the copy is being retained at the investigational site. Once the CRFs are received by the CRO, their receipt is recorded, the original copy is scanned and forwarded to the responsible data management staff for processing. After scanning the original copy is placed in Central Files.

## **10.0 Data analysis**

The analyses will be described in more detail in Statistical Analysis Plans which will be written for each of the interim analyses as well as for the final analysis.

### **10.1. Population for analysis**

The safety population (SAF) will comprise all subjects who enter the observational period. The SAF population will be the basis for all safety analyses. Efficacy analyses will additionally be carried out for the ITT and PP populations as defined for the final analysis of study EP00-401.

## **10.2. Patient demographics/other baseline characteristics**

Descriptive statistics will be used to describe background and demographic variables such as age, weight, and height, and frequency tables will be used to describe the gender and race of the patients.

## **10.3. Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

### **10.3.1. Study drug administration:**

The extent of exposure in the EP00-401 study will be analyzed using descriptive statistics. Tables showing descriptive statistics for the total dose per kg body weight will be presented.

### **10.3.2. Concomitant medication:**

Concomitant medication will be coded according to WHO-DRL and the medications will be tabulated by ATC term.

## **10.4. Analysis of safety endpoints**

### **10.4.1. Carbohydrate metabolism:**

Fasting plasma glucose and insulin levels will be measured at baseline, 6 months, 1, 5 and 10 years after the end of treatment. For each of these visits descriptive statistics will be calculated and presented together with the absolute and relative changes as compared to baseline.



Insulin resistance will be estimated using both the homeostasis model assessment (HOMA)<sup>38</sup> and quantitative insulin sensitivity check index (QUICKI).<sup>39</sup> The effect of Omnitrope<sup>®</sup> treatment on HOMA and QUICKI scores, calculated subsequent for each plasma glucose and insulin measurement, will be evaluated at each visit using descriptive statistics for the observed values along with the changes from baseline.

Glycosylated haemoglobin (HbA<sub>1C</sub>) will be measured at baseline, 6 months, 1, 5 and 10 years after the end of treatment. The effect of treatment on the HbA<sub>1C</sub> levels will also be displayed using descriptive statistics.

An oral glucose tolerance test (OGTT) will be performed at baseline, 6 months, 1, 5 and 10 years after the end of treatment.

### **Immunogenicity**

Subjects will be screened for anti-rhGH antibodies (ABs) at baseline and 6 months after the end of treatment. For each time point the number and percentage of patients with anti-rhGH antibodies (ABs) will be tabulated.

Antibody-induced lack or loss of efficacy will be examined by comparing height outcome data between antibody-positive and antibody-negative subjects.

#### **10.4.2. Safety lab:**

Haematology and blood chemistry results will be displayed by visit using descriptive statistics and/ or frequency tables depending on the type of variable (continuous or discrete). Shift tables for the number and percentage of clinically significant results will also be provided.

#### **10.4.3. (Serious) Adverse events:**

Adverse events will be coded using MedDRA (Version to be determined depending on the time of the analysis). The number and percentage of patients having at least one (serious) adverse event will be tabulated separately for the treatment and for the follow-up period. The (serious) adverse events will be displayed by system organ class and preferred term and the relationship to the study drug and the intensities will be shown in corresponding frequency tables.

#### **10.4.4. Vital signs / weight:**

The development of the vital signs (blood pressure, pulse) as well as weight and BMI will be analyzed using descriptive statistics for each visit.

### **10.5. Analysis of efficacy endpoints**

#### **10.5.1. Pharmacodynamic endpoints:**

These are IGF-I and IGFBP-3 serum levels, which will be assessed at baseline, 6 months, 1, 5 and 10 years after the end of treatment.

The effect of treatment on serum IGF-I and IGFBP-3 levels will be evaluated using descriptive statistics for the observed values at each visit together with the absolute and relative changes as compared to baseline.

#### **10.5.2. Height measurements:**

The patients' height will be tabulated for each visit using descriptive statistics.

## **10.6. Interim analysis**

Interim analyses are planned at the following time points:

- 2022 with data of patients who completed 1 year of follow-up
- 2026 with data of patients who completed 5 years of follow-up
- 2031 with data of patients who completed 10 years of follow-up

## **10.7. Sample size calculation**

All patients who participated in the EP00-401 study and received at least one dose of study medication are intended to enter the observational period.

## **10.8. Power for analysis of critical secondary variables**

Not applicable

# **11.0 Discussion and rationale for study design features**

This study has been designed in accordance with the post-approval pharmacovigilance plan to extend the safety database of Omnitrope® and to address the EMEA's request:

- to investigate the diabetogenic potential of growth hormone in short children born SGA, and
- to further investigate the immunogenicity of growth hormone in short children born SGA.

More specifically, the primary objective of this study is:

- to monitor the development of diabetes during a long-term follow-up period (10 years) after treatment cessation.

The secondary objectives of this study are:

- to monitor the development of anti-hGH for 6 months after treatment cessation,
- to evaluate the safety (incidence and occurrence of adverse events) for 10 years after treatment cessation

To address concerns regarding the risk of developing diabetes mellitus in GH-treated children born SGA, specific parameters such as fasting plasma glucose and insulin levels will be measured for a number of years after the end of treatment.

Subjects will be monitored for safety throughout the observational period.

# **12.0 Procedures and instructions: Administrative procedures**

## **12.1. Changes to the protocol**

Any change or addition to this protocol requires a written protocol amendment that must be approved by Sandoz and the international Coordinating Investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC and the regulatory authority, where applicable, must be given to the study monitor.

## **12.2. Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol violations. Under no circumstances should the investigator contact the sponsor or its agents, if any, monitoring the trial to request approval of a protocol violation, as no authorized violations are permitted. If the investigator feels a protocol violations would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol violations will be recorded and reported in the CSR.

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

## **12.3. Publication of study protocol and results**

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as [clinicaltrials.gov](http://clinicaltrials.gov). In addition, upon study completion and finalization of the CSR the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **12.4. Signatory investigator for study report**

ICH E3 guidelines recommend, and EMEA Directive 2001/83/EC requires that a CSR which forms part of a marketing authorization application is signed by a Coordinating Investigator. The Coordinating Investigator will have the responsibility to review the study results and CSR, and to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study.

## **12.5. Ethics and Good Clinical Practice**

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki, Directive 2001/20/EC, EU Clinical trials Directive, Directive 2005/28/EC, EU GCP Directive 91/507/EEC and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

### **12.5.1. Institutional Review Board/Independent Ethics Committee**

Before implementing this study, the protocol, the curriculum vitae of the investigators, the proposed informed consent form and other information to subjects, will be submitted to a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) according to national law. The study will only be performed at a study site if a full approval of the protocol has been obtained by the IRB/IEC.

### **12.5.2. Informed consent**

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. To cover adolescence of the patients with adequate patient information/ informed consent documents, three different types of documents, one for children between 4 and 6 years of age, one for children between 6 and 12 years of age, and one for children above 12 years of age should be used for this follow-up study. At all events, written informed consent has to be obtained from the patients' parents or legal guardian. Additionally, children who can read and write should also sign the informed consent document corresponding to their relevant age group.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval.

### **12.5.3. Declaration of Helsinki**

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki which can be accessed via the website of the World Medical Association at <http://www.wma.net/e/policy/b3.htm>.

[The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004]

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