Official Title: Long-term Phase IV Multicentre Study on the Safety and Efficacy of Omnitrope® (rhGH) in Short Children Born Small for Gestational Age (SGA)

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SANDOZ A Novartis Division

Omnitrope®

Study protocol EP00-401

Long-term phase IV multicentre study on the safety and efficacy of Omnitrope® (rhGH) in short children born Small for Gestational Age (SGA)

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List of abbreviations

AB	Antibody
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ANC	Absolute neutrophil count
BMI	Body Mass Index
BW	Body weight
CA	Calendar Age
CBC	complete blood count
CRF	Case report form
CRO	Contract research organization
EMEA	European Agency for the Evaluation of Medicinal Products
fT4	Free thyroxine
GCP	Good clinical practice
GH	Growth hormone
HDL	High-density lipoproteins
hGH	Human growth hormone
HIV	Human immunodeficiency virus
HSDS	Height standard deviation score
HV	Height velocity
HVSDS	Height velocity standard deviation score
IEC	Independent ethics committee
IGFBP-3	Insulin-like growth factor binding protein 3
IGF-I	Insulin-like growth factor
IGT	Impaired glucose tolerance
IRB	Institutional review board
IUGR	Intrauterine growth retardation
LDL	Low-density lipoproteins
LHRH	Luteinising hormone-releasing-hormone
OGTT	Oral glucose tolerance test
RBC	Red blood cell count
rhGH	Recombinant human growth hormone
SAE	Serious adverse event
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
SGOT	Serum-Glutamat-Oxalacetat-Transaminase
SGPT	Serum-Glutamat-Pyruvat-Transaminase
SmPC	Summary of medicinal Product Characteristics
SOP	Standard operating procedure
TSH	Thyroid stimulating hormone
WBC	White blood cell count
WHO	World Health Organization

[redacted]

Amendment 5

Amendment rationale

Patients treated with rhGH in study EP00-401 were allowed to enter the post-treatment observation EP00-402 to monitor the occurrence of type 2 diabetes mellitus over a 10-years' time span after treatment completion. According to the termination in 2018 of the complementary EP00-402 study: "A phase IV multicenter, long-term safety follow-up planned for 10 years after stopping growth hormone treatment in patients who have completed study EP00-401", references to patients' enrolment into the terminated EP00-402 study were removed from the EP00-401 protocol by this amendment.

This protocol amendment provides also further clarification of the lost to follow up definition. This clarification is implemented to limit protocol deviations resulting from prolonged interruption(s) of Omnitrop dosing and to facilitate compliance to visit schedule.

Study status

A total of 278 patients had been enrolled in the study. The last subject was enrolled on 29-Apr-2010. As of 31-Dec-2019, 32 patients, hereof 7 female patients, are still on Omnitrope therapy and will continue treatment until they reach their final height. So far, no case of pregnancy has been reported in the study. One hundred twenty seven female patients have already completed the study. Clinical Study Report with the final results for the long-term observation study EP00-402 was submitted to EMA on the 18-April-2019.

Changes to the protocol will allow to limit protocol deviations due to prolonged interruptions of Omnitrop treatment.

Changes to the protocol

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.

List of changes made in this amendment are:

Section Protocol synopsis

- Reference to inclusion into EP00-402 study removed

Section 2 Study Purpose

- Reference to inclusion into EP00-402 study removed

Section 6.5.9 Study drug discontinuation Reference to inclusion into EP00-402 study removed

Section 6.5.10 Premature withdrawal Reference to inclusion into EP00-402 study removed

- Definition of lost to follow up clarified

Section 11 Discussion and rationale for study design features

- Reference to inclusion into EP00-402 study removed

The changes described in this amended protocol are considered non-substantial.

[redacted]

This amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committees (IECs) and Health Authorities (HA) for approval or notification as required according to local regulations.

The changes herein do not affect the Informed Consent Form.

[redacted]

Protocol synopsis

Title of study:

Long-term phase IV multicentre study on the safety and efficacy of Omnitrope® (rhGH) in short children born Small for Gestational Age (SGA)

Study Purpose:

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). In addition, within a supplemental follow-up study (Protocol number EP00-402) Sandoz was documenting the long-term safety during a follow-up period of 10 years after stopping growth hormone treatment and till closure of the study.

Objectives:

The primary objective of this study is to evaluate the long-term effect of growth hormone treatment on the development of diabetes during the treatment period in short children born SGA. The secondary objectives of this study are:

- to report the incidence of anti-rhGH antibodies (ABs) during treatment
- to evaluate the efficacy (with respect to changes in height parameters) of Omnitrope® treatment in short children born SGA
- to evaluate IGF-I and IGFBP-3 levels during treatment
- to evaluate incidence and severity of adverse events

Inclusion/Exclusion criteria

Inclusion criteria:

1. Pre-pubertal (Tanner stage I) children born SGA
   Boys: ≥ 4 years of age (bilateral testicular volume <4 ml) (Marshall 1979)
   Girls: ≥ 4 years of age (bilateral Tanner breast stage 1) (Marshall 1969)
2. Growth disturbance defined as current height SDS < -2.5 (and parental adjusted SDS < -1) for chronological age and sex according to country specific references. If country specific references are not available, pre-defined published references will be used.
3. Birth weight and/or length below -2 SD for gestational age (according to country specific references). For the evaluation of gestational age, the date of the last menstrual period or ultrasonographic data obtained during the pregnancy should be used**.** If country specific references are not available, pre-defined procedures / published references will be used.
4. Height records between 18 months and 6 months prior to the start of GH treatment must be available
5. Calculated height velocity SDS < 0 during the last year according to Prader (1989).
6. Written informed consent of patient (for children who can read and write) and parent or legal guardian

Exclusion criteria:

1. Onset of puberty
2. Closed epiphyses
3. Diabetes mellitus type I or type II
4. Fasting blood glucose ≥ 100 mg/dl or ≥ 5.6 mmol/l measured in venous blood sample
5. Abnormal findings in OGTT defined by ≥ 140 mg/dl or ≥ 7.8 mmol/l after 120 minutes
6. Known IGF-I level above +2SD for sex and age

[redacted]

7. Acute critical illness e.g. suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure
8. Known to be hepatitis B or hepatitis C positive or HIV-positive, known to have advanced diseases such as AIDS or tuberculosis
9. Any other disease, genetic disorder or malformation or treatment known to be associated with growth retardation, e.g. Turner or Noonan syndrome, Laron syndrome, Russell-Silver syndrome, Prader-Willi syndrome, skeletal dysplasias, chronic renal failure, cystic fibrosis, heart and liver diseases, malabsorption (coeliac disease), malnutrition, patients receiving radiation therapy of head or spinal cord
10. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
11. Known or suspected hypersensitivity to rhGH or any of the excipients (e.g. benzyl alcohol)
12. Previous treatment with any hGH preparation
13. Oral, inhalative or parenteral treatment with glucosteroids, except for physiological replacement, or hypothyroidism which has been left untreated, or was inadequately treated, or treated for less than 3 months
14. Treatment with LHRH / gonadotropin releasing hormone (GnRH) analoga (e.g. triptorelin)
15. Treatment with antidiabetic medication (e.g. metformin, insulin)
16. Drug abuse, substance abuse, or alcohol abuse
17. Known to be immunocompromised
18. Intake of growth promoting medication, e.g. anabolic steroids
19. Use of other investigational drugs within 30 days of enrolment
20. Patients unwilling and/or parents/guardians who are not capable of ensuring compliance with the provisions of the study protocol

Investigational therapy:

Omnitrope® (rhGH) supplied as **Omnitrope® 5 mg/ 1.5 ml and 10mg / 1.5 ml solution for injection**. These formulations will be referred to as Omnitrope® throughout this document.

A dose of 0.035 mg/kg body weight (BW) per day will be administered by daily subcutaneous injection in the evening. Dose adjustments will be allowed during therapy consistent with label recommendations.

Study design:

Phase IV, prospective, open label, non-comparative, multicentre trial. Omnitrope® treatment will continue until final height is reached. Treatment should be discontinued after the first year of treatment if the height velocity SDS is below +1. Treatment should be discontinued if height velocity is below 2 cm/year [redacted]

Measurements of carbohydrate metabolism (in terms of fasting plasma glucose, insulin and HbA_{1c} levels) will be performed throughout treatment. Anti-rhGH antibodies (ABs) will be measured during Omnitrope® treatment. Patients will be monitored for safety and efficacy throughout treatment.

Efficacy assessments:

Height, standardised height (HSDS), height velocity (HV) and standardised HV (HVSDS) will be assessed at baseline, every 3 months during the first two years of GH treatment and semi-annually thereafter until final height is reached (end of treatment).

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IGF-I and IGFBP-3 serum levels will be assessed by a central laboratory at baseline, at 3, 6, 9 and 12 months, then biannually during treatment, and at the end of treatment.

Safety assessments:

Carbohydrate metabolism: Fasting plasma glucose and insulin levels will be measured at baseline, at 6 and 12 months, then annually during GH treatment, and at the end of treatment. Glycosylated haemoglobin (HbA_{1C}) will be measured at baseline, at 6 and 12 months, then annually during GH treatment and at the end of treatment. An oral glucose tolerance test (OGTT) will be performed at baseline, at 6 and 12 months and then annually during GH treatment, and at the end of treatment.

Immunogenicity: Subjects will be screened for anti-rhGH antibodies (ABs) at baseline, at 3, 6, 9, 12, 18 and 24 months, then annually during GH treatment and the end of treatment. Antibody-induced lack or loss of efficacy will be examined by comparing height outcome data between antibody-positive and antibody-negative subjects.

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. Fundoscopy will be performed if intracranial hypertension is suspected (severe or recurrent headache, visual problems, nausea and/or vomiting). Adverse events, body weight and physical condition will be assessed at every study visit during Omnitrope® treatment. Laboratory tests for safety will be performed at baseline, at 6 and 12 months, then annually thereafter for the remainder of GH treatment, unless more frequent assessment is clinically indicated.

[redacted]

Flow Chart Treatment Period

		Treatment Period													
TIME POINT	Screening	Start	3 mo ± 3wks	6 mo ± 3wks	9 mo ± 3wks	12 mo ± 3wks	15 mo ± 3wks	18 mo ± 3wks	21 mo ± 3wks	24 mo ± 3wks	30 mo ± 3wks	36 mo ± 3wks	42 mo, 54 mo etc… ± 3wks	48 mo, 60 mo, etc… ± 3wks	End ± 3wks
VISIT	00	01	02	03	04	05	06	07	08	09	10	11	12, 14 etc… annual visits	13, 15 etc… annual visits	Final visit
Written Informed consent	X														
Demographic data	X														
Medical History	X														
SGA Diagnosis	X														
Physical examination, weight (kg) and height (cm), pubertal status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology		X		X		X				X		X		X	X
Blood chemistry incl. fT4, TSH, $HbA_{1C,}$ fasting plasma glucose and insulin levels		X		X		X				X		X		X	X
Urinalysis		X		X		X				X		X		X	X
Pregnancy test				X[1]		X[1]				X[1]		X[1]		X[1]	X[1]
Anti-hGH AB		X	X	X	X	X		X		X		X		X	X
IGF-I, IGFBP-3		X	X	X	X	X		X		X	X	X	X	X	X
OGTT		X		X		X				X		X		X	X

[redacted]

[redacted]

		Treatment Period													
TIME POINT	Screening	Start	3 mo ± 3wks	6 mo ± 3wks	9 mo ± 3wks	12 mo ± 3wks	15 mo ± 3wks	18 mo ± 3wks	21 mo ± 3wks	24 mo ± 3wks	30 mo ± 3wks	36 mo ± 3wks	42 mo, 54 mo etc… ± 3wks	48 mo, 60 mo, etc… ± 3wks	End ± 3wks
VISIT	00	01	02	03	04	05	06	07	08	09	10	11	12, 14 etc… annual visits	13, 15 etc… annual visits	Final visit
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundoscopy		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Drug dispensing and recording		X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug return (accountability) and recording			X	X	X	X	X	X	X	X	X	X	X	X	X

1: urine pregnancy test only in female patients after onset of menarche

[redacted]

3: Fundoscopy will be performed only if intracranial hypertension is suspected

[redacted]

1 Background

1.1 Investigational product

The active substance of Omnitrope® is somatropin, a growth hormone produced by a genetically modified strain of *Escherichia coli.* Omnitrope® is a biological medicinal product authorized in the EU. Omnitrope® , 1.3 mg/ml and 5 mg/ml, powder and solvent for solution for injection, Omnitrope® 5 mg/ 1.5 ml solution for injection and Omnitrope® 10mg/ 1.5 ml solution for injection, obtained marketing authorization in the following indications:

Children

- Growth disturbance due to insufficient secretion of growth hormone (GH) and growth disturbance associated with Turner syndrome and chronic renal insufficiency.
- Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS <0 during the last year) by 4 years of age or later.
- Prader-Willi syndrome (PWS) for improvement of growth and body composition. The diagnosis PWS should be confirmed by appropriate genetic testing.

Adults

- Replacement therapy in adults with pronounced growth hormone deficiency.

Detailed conditions for the use of Omnitrope® are described in the Summary of Product Characteristics (SmPC).

1.2 The indication SGA

The most common definition of the term "small for gestational age" (SGA) is a birth weight and/or length of ≥ 2 standard deviations (SD) below the mean for the infant's gestational age and sex (based on data derived from a reference population) (Lee et al 2003). The standards for neonatal growth were established by Usher and McLean (Usher and McLean 1969). 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.

Impaired foetal growth may be due to placental, foetal and maternal causes. Placental factors include any mismatch between placental perfusion and foetal oxygenation. Placental

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insufficiency, placental abruption, infarction, and vascular abnormalities are the most common contributors to foetal growth impairment.

15% - 20% of SGA cases may be a result of foetal factors, including genetic and chromosomal abnormalities, congenital malformations, innate metabolic problems, infections, and multiple gestations (Lin and Santolaya-Forgtas 1998). Maternal factors include medical conditions (such as hypertension, diabetes mellitus, systemic lupus erythematosus, renal disorders, collagen vascular diseases, infections), demographic factors (age, height, weight, maternal and paternal ethic origin, parity), nutritional status, cigarette smoking, illicit drug use, alcohol abuse, and the use of certain therapeutic drugs (Lee et al 2001).

Ultrasound criteria are used as a diagnostic standard in the identification of SGA. Ultrasonographic 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 (Degani 2001).

Between 3% and 10% of all live births each year are described as SGA (Rosenfeld and Cariati 2002). 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 (Ventura et al 1999)). In 2000, 4,058,814 infants were born in the United States according to the data from the National Centre for Health Statistics (Rosenfeld and Cariati 2002). Using this figure and defining SGA as the ≤ 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 (Albertsson-Wikland and Karlberg 1997).

Endocrine and metabolic outcomes may be related to failure to achieve catch-up. While GH levels have a relatively small effect on *in utero* growth, insulin and insulin-like growth factors (IGFs) are key modifiers of foetal growth and development. Endocrine studies *in utero* show that growth retarded foetuses have reduced insulin (Economides et al 1989) and IGF-I (Lassarre et al 1991) levels and in the neonatal period, babies born SGA have low IGF-I levels and IGFBP-3 levels despite elevated GH secretion (Cance-Rouzaud et al 1998). Failure of catch-up growth is associated with persistent low IGF-I and IGFBP-3 levels (Boguszewski et al 1997), 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

[redacted]

(Boguszewski et al 2000). 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 (Lundgren 2001).

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, polycythemia.

There is also convincing evidence that SGA is a predisposing factor for the development of hypertension (Barker et al 1990), diabetes (Hales et al 1991) and cardiovascular disease (Barker et al 1993) in adult life.

1.2.1 Type 2 Diabetes and SGA

Studies in Europe, North America, and the developing world (Reynolds and Phillips 1998, Phillips 1996, Boyko 2000, Curhan et al 1996, Lithell et al 1996, McCance et al 1994, Rich-Edwards et al 1999) 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 (Rich-Edwards et al 1999) 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. Alternatively, insulin resistance may be controlled by the same genetic factors that regulate foetal growth (Stern et al 2000, Rich-Edwards et al 1997). Hattersley and colleagues (Hattersley and Tooke 1999) 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.

1.2.2 Syndrome X and SGA

Certain chronic and metabolic disorders including hypertension, glucose intolerance, central obesity, and dyslipidemia 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 (Valdez et al 1994, Li et al 2001, Ong and Dunger 2002, Yarbrough et al 1998). Moreover, adult overweight and obesity increase the risk of syndrome X, and studies show adults born

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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 (Yarbrough et al 1998) 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, dyslipidemia, 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 (Leger et al 1997) 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.

1.2.3 Growth Hormone therapy in SGA patients

Growth Hormone (GH) therapy is indicated for children who were born SGA and have persistent short stature (below - 2 SD); are at least 2 years of age; and are growing at an average or subnormal rate of age, provided that other causes for short stature such as growth inhibiting medication, chronic disease, endocrine disorders, emotional deprivation or syndromes (except Silver Russell syndrome) have been ruled out (Lee et al 2001).

The aims for GH therapy in children born SGA who fail to catch up are to:

- Increase height during childhood,
- Sustain the height gain in adolescence, and
- Normalise final adult height.

Results of several trials indicate that high-dose GH therapy accelerates short-term height velocity in short children born SGA.

In the first studies examining the effects of GH therapy in children with insufficient catch-up growth, GH was given with low frequency or in substitution doses. Since the growth responses were inconsistent, researchers began to evaluate high-dose GH schedules.

De Zegher et al (2002) evaluated the effects of daily high-dose GH therapy over 2 years in 50 short, prepubertal, non-GH-deficient children born SGA in an open-label, controlled, multicentre trial. Catch-up growth was observed in none of the untreated and in all of the treated children. Both treatment groups experienced significantly greater height velocity ($P < 0.001$), height velocity SDS ($P < 0.001$), and height gain SDS ($P < 0.001$) compared with the control group. There were, however, no significant differences between the two GH doses. Height velocity was greater in the first year of treatment compared with the second. The mean gain in height for the treatment groups was 2.3 SDS. GH-induced catch-up growth was

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associated with an acceleration of bone maturation. There were associated elevations in serum concentrations of insulin, IGF-I and IGFBP-3.

In a follow-up study, De Zegher et al (1999) reported on the further prepubertal growth of the children treated in the previous study after withdrawal of the high-dose GH treatment. Of the 38 treated children, none developed precocious puberty and 22 remained prepubertal. Height increased by an average of 2.5 SD over the 2-year treatment period and decreased by 0.4 SD during the first and 0.3 SD in the second year after GH withdrawal. No further GH treatment was given to those children (n=13) whose mean adjusted height stabilised at an SDS of around -1.0 after completion of the first treatment phase. When stature was very short at the completion of the first phase (mean adjusted height = -3.3 SD score; n=9), a second course of GH treatment of 0.2 IU/kg/day was initiated either 2 years (n=5) or 3 years (n=4) after initial GH withdrawal.

This second treatment phase was associated with further growth and also resulted in a mean adjusted height of -1.0 SD score.

De Zegher et al (2000) also reported the data of four randomized, multicentre studies examining the effects of continuous and discontinuous GH therapy in a total of 49 untreated and 139 treated children born SGA. At the start of the study, the average age of the children was 5.2 years. Two studies examined the effects of continuous GH treatment at a dose of 0.033 or 0.067 mg/kg/day over a 6-year period. The other 2 studies examined the impact of discontinuous GH treatment at a range of 0.033-0.10 mg/kg/day. In the discontinuous regimen, the initial treatment period of 2 to 3 years was followed by a withdrawal phase of 1 to 2 years and then either none, one, or more additional treatment phases at the same dose. Continuous GH treatment for 6 years was associated with mean increases in height of 2.0 SD for the low-dose and 2.7 SD for the high-dose regimens. Discontinuous GH treatment, with an average dose of 0.032 mg/kg/day over the course of 6 years, resulted in a mean height increase of 1.6 SD. Patients in the untreated group, on the other hand, increased their height by a mean of only 0.2 SD. Bone maturation progressed similarly in all treatment groups. The average GH doses over the 6 year period, parental-adjusted height SD scores, and age at start of treatment were the prime predictors of the growth response.

Sas et al (1999) began a randomized, double-blind, dose-response, multicentre trial on the long-term effects of continuous GH therapy (five years) in 79 prepubertal children with short stature born SGA. Twenty-two patients with GH deficiency were included in the study and there was no untreated control group. Patients were randomized to receive 3 IU/m^2 body surface per day or 6 IU/m^2 body surface per day. Five of the 79 children dropped out of the study for such reasons as poor compliance, concomitant treatment, and possible GH insensitivity. Their data were not included in the analysis. After 5 years of treatment, the mean height SD for chronological age was increased significantly over baseline ($P < 0.001$). In addition, almost every subject had reached a height within the normal range after the treatment period. Except for the children who remained prepubertal over the course of the 5 years, there was no significant growth difference in response to the 2 doses. GH treatment was associated with an acceleration of bone maturation, increase in bone age, and increase in predicted adult height regardless of the GH dose.

On the basis of efficacy data but taking into account the concerns of long-term safety, the Committee for Proprietary Medicinal Products (CPMP) of EMEA recommended that the

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treatment with GH of the children with growth disturbance (current height SDS <-2.5 and parental adjusted height SDS <-1) born SGA, who failed to show catch-up growth by 4 years of age or later, should be initiated at a dose of 0.035 mg/kg/day and continued until final height is reached (CPMP/3477/03).

1.2.4 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 (2000) evaluated the changes in body metabolism, blood pressure and lipid metabolism in 79 GH-treated children (2 dose groups, 1 mg/m^2/day and 2 mg/m^2/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 (Hokkon-Koelega et al 2004, Sas et al 2001), 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_{1C} levels were always in the normal range and none of the children developed diabetes mellitus.

2 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. However in most recent investigations which followed-

up SGA patients after treatment completion no increased risk of insulin resistance or type 2 diabetes could be observed in the long-term perspective (van der Steen et al 2017, Poidvin et al 2017, Poidvin et al 2017).

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). Within an additional study EP00-402, Sandoz was documenting the long-term safety during a follow-up period of 10 years after stopping growth hormone treatment till study closure.

The purpose of this study is

(a) to monitor short children born SGA for the development of diabetes during Omnitrope® treatment and

(b) to report the incidence of anti-rhGH antibodies (ABs) during treatment GH treatment.

3 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 during treatment.

3.2 Secondary objectives

The secondary objectives of this study are:

- to report the incidence of anti-rhGH antibodies (ABs) during Omnitrope® treatment
- to evaluate the efficacy (with respect to changes in height parameters) of Omnitrope® treatment in short children born SGA
- to evaluate IGF-I and IGFBP-3 levels during treatment
- to evaluate incidence and severity of adverse events

4 Study design

This study is designed as a phase IV, prospective, open label, non-comparative, multicentre trial. Safety and efficacy will be assessed periodically during treatment.

Treatment should be discontinued after the first year of treatment if the height velocity SDS is below +1. Treatment will continue until final height (height velocity < 2 cm/year, [redacted] is reached but will be discontinued earlier if medically indicated or if there is inadequate response to treatment.

A summary of the study plan is given below.

[redacted]

Table 4-1 Study Outline

PHASE	Treatment						
TIME POINT	Start	3 mo	6 mo	9 mo	12 mo	Study visits until final height	End
VISIT	01	02	03	04	05	06, 07, 08, 09, etc.	End of treatment
THERAPY	0.035 mg/kg BW/day						

5 Population

The study population will consist of a representative group of children of both sexes, aged ≥ 4, with short stature born small for gestational age (SGA).

SGA is defined as per the label indication authorised by the EMEA:

"Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS < 0 during the last year) by 4 years of age or later."

Standardized and controlled Enrolment Authorization:

To assist Investigators to avoid errors in the local calculation of the auxological parameters by applying different ways of calculation and to ensure that only patients in strict adherence to the SGA definition in the study protocol are enrolled, a standardized and controlled procedure for patient enrolment authorization ("Enrolment Authorization Fax") was implemented after the first 60 patients were enrolled in the study (by November 2008).

For the patients enrolled before implementation of the "Enrolment Authorization Fax" a standardized approach for the recalculation of growth indication for inclusion according to inclusion criteria 2, 3 and 5 was implemented in March 2009.

Historical data will be used to screen the subjects for eligibility, i.e. records of birth length and weight, as well as height and weight measurements taken 1 year (between 18 months and 6 months) before the start of GH treatment for calculation of HVSDS. For the evaluation of gestational age, the date of the last menstrual period will be used, however, if this is not known, ultrasonographic data obtained during the pregnancy may be used.

The study will be performed in approximately 40 centres in Europe. The treating physicians shall be appropriately qualified and experienced in the diagnosis and management of SGA. The patients will be treated as out-patients.

[redacted] Subjects dropping out before completing 1 year of treatment will be replaced.

[redacted]

[redacted]

[redacted]

Patients who have started their treatment with Omnitrope® 5 mg/ml powder and solvent for injection will continue with Omnitrope® **5** mg/**1.5** ml solution for injection from Visit 5 on (i.e. after 12 months of treatment with Omnitrope® 5 mg/ml powder and solvent for injection). Depending on the weight and corresponding injection volume patients may also switch to Omnitrope® 10 mg/ 1.5 ml solution for injection.

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. Pre-pubertal (Tanner stage I) children born SGA
   Boys: ≥ 4 years of age (bilateral testicular volume < 4 ml)
   Girls: ≥ 4 years of age (bilateral Tanner breast stage 1)
2. Growth disturbance defined as current height SDS < -2.5 (and parental adjusted SDS < -1) for chronological age and sex according to country specific references. If country specific references are not available, pre-defined published references will be used.
3. Birth weight and/or length below -2 SD for gestational age (according to country specific references). For the evaluation of gestational age, the date of the last menstrual period or ultrasonographic data obtained during the pregnancy should be used**.** If country specific references are not available, pre-defined procedures / published references will be used.
4. Height records between 18 months and 6 months prior to the start of GH treatment must be available
5. Calculated height velocity SDS < 0 during the last year according to Prader (1989).
6. Written informed consent of patient (for children who can read and write) and parent or legal guardian

5.1.2 Exclusion criteria

1. Onset of puberty
2. Closed epiphyses
3. Diabetes type I or type II
4. Fasting blood glucose ≥ 100 mg/dl or ≥ 5.6 mmol/l measured in venous blood sample
5. Abnormal findings in OGTT defined by ≥ 140 mg/dl or ≥ 7.8 mmol/l after 120 minutes
6. Known IGF-I level above +2SD for sex and age
7. Acute critical illness e.g. suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure.
8. Known to be hepatitis B or hepatitis C positive or HIV-positive, known to have advanced diseases such as AIDS or tuberculosis

[redacted]

9. Any other disease, genetic disorder or malformation or treatment known to be associated with growth retardation, e.g. Turner or Noonan syndrome, Laron syndrome, Russell-Silver syndrome, Prader-Willi syndrome, skeletal dysplasias, chronic renal failure, cystic fibrosis, heart and liver diseases, malabsorption (coeliac disease), malnutrition, patients receiving radiation therapy of head or spinal cord
10. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
11. Known or suspected hypersensitivity to hGH or any of the excipients (benzyl alcohol)
12. Previous treatment with any hGH preparation
13. Oral, inhalative or parenteral treatment with glucosteroids, except for physiological replacement, or hypothyroidism which has been left untreated, or was inadequately treated, or treated for less than 3 months
14. Treatment with LHRH / gonadotropin releasing hormone (GnRH) analoga (e.g. triptorelin)
15. Treatment with antidiabetic medication (e.g. metformin, insulin)
16. Drug, substance, or alcohol abuse
17. Known to be immunocompromised
18. Intake of growth promoting medication, e.g. anabolic steroids
19. Use of other investigational drugs within 30 days of enrolment
20. Patients unwilling and/or parents/guardians who are not capable of ensuring compliance with the provisions of the study protocol

6 Treatment

6.1 Investigational drug

6.1.1 Omnitrope® 5 mg/ml powder and solvent for solution for injection

Omnitrope® 5 mg/ml is supplied with 1 vial containing somatropin as a powder and a cartridge containing diluent (bacteriostatic water for injection containing 1.5% benzyl alcohol as preservative). Omnitrope® is to be stored refrigerated at 2ºC to 8ºC and protected from light. Freezing must be avoided.

After reconstitution by means of a specifically designed reconstitution set ("Transfer Set") provided by Sandoz, one cartridge contains 5.0 mg (15 IU) somatropin per ml.

The reconstituted Omnitrope® solution for injection can be stored up to 21 days at 2ºC to 8ºC in the refrigerator. The cartridges are designed to be used in a pen injection device, the Omnitrope® Pen, which will be provided by Sandoz.

Parents and patients, if appropriate, will be sufficiently trained on the use of the Transfer set and the dose and injection technique by means of the Omnitrope® Pen.

[redacted]

6.1.2 Omnitrope® 5 mg/ 1.5 ml and Omnitrope® 10 mg/ 1.5 ml solution for injection

Omnitrope® 5 mg/ 1.5 ml (injection containing 0.9 % benzyl alcohol as preservative) **and Omnitrope® 10mg/ 1.5 ml** are supplied in cartridges containing solution for injection. Omnitrope® is to be stored refrigerated at 2ºC to 8ºC and protected from light. Freezing must be avoided.

The cartridges are designed to be used in a pen injection device, the Omnitrope® Pen will be provided by Sandoz. After opening and first injection the cartridge should remain in the pen and has can be stored up to 28 days at 2ºC to 8ºC in the refrigerator.

Parents and patients, if appropriate, will be sufficiently trained on the dose and injection technique by means of the Omnitrope® Pen.

6.2 Treatment groups

There will only be one treatment group.

6.3 Treatment assignment

This study is not randomized.

Each patient is uniquely identified in the study by a combination of his/her centre number and patient number. The centre number is assigned by Sandoz to the investigative site. Upon signing the informed consent form, the first patient is assigned patient number 001 per site, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 002, the third patient is assigned patient number 003). Once assigned to a patient, a patient number will not be reused. If the patient fails to start treatment for any reason, the reason for not being started on treatment will be entered on the Screening Log, and the Demography CRF should also be completed.

Only this unique identifier number will be used to identify the enrolled patients.

6.4 Treatment blinding

Treatment during this study is open-label.

6.5 Treating the patient

6.5.1 Dose

A daily dose of 0.035 mg/kg per day will be administered by subcutaneous injection in the evening. A table is provided in the appendix for calculation of the individual dose according to the individual body weight.

6.5.2 Study drug administration

Each study site will be supplied, by Sandoz, with study drug in country specific packaging identifying the medication as study drug. Investigator staff will identify the study drug for dispensing to the patient using the centre and patient code number. Prior to dispensing study

[redacted]

drug to the patient, investigator staff shall transfer the tear-off label with the serial number of the vials to the respective CRF page.

A daily dose of 0.035 mg/kg per day will be administered by subcutaneous injection in the evening. The injection site should be varied to prevent lipoatrophy.

The investigator should instruct the patient to administer the study drug exactly as prescribed (promote compliance). All doses dispensed to the patient and all dose changes during the study must be recorded on the Dose Administration Record CRF.

For handling of study medication please refer to section 6.1.

6.5.3 Treatment duration

Omnitrope® treatment will continue until final height is reached. Treatment should be discontinued after the first year of treatment if the height velocity SDS is below +1 (see also 6.5.9 Study drug discontinuation). [redacted]

A standardized controlled procedure for the calculation of the treatment response ("Treatment Response Control Fax") was implemented.

6.5.4 Permitted study drug dose adjustments

Dose adjustments will be allowed during therapy consistent with label recommendations to take individual responsiveness into consideration. This dose may be adjusted at subsequent study visits; investigators are requested to adapt the dose at every study visit according to the changing body weight after initiation of therapy.

For patients who are unable to tolerate the protocol-specified dose scheme, dose adjustments and interruptions up to 3 weeks are permitted in order to keep the patient on study drug. This may for instance be required if transient labelled side effects occur. Please also refer to section 6.5.10.

All changes must be recorded on the Dose Administration Record CRF.

6.5.4.1 Dose reduction

If IGF-I exceeds +2SD compared to references for age and pubertal status, the IGF-I/IGFBP-3 ratio will be determined. If IGF-I/IGFBP-3 ratio also exceeds +2SD, a dose reduction is recommended. The extent of the dose reduction will be at the discretion of the investigator.

6.5.5 Dose increase

An increase of recommended dose of 0.035 mg/kg per day is not allowed, especially if based on concomitant treatment e.g. treatment with LHRH/GnRH analoga. In case an increase of the dose is required for obtaining increased growth velocity, the patient has to discontinue the study.

6.5.6 Rescue medication

Not applicable

[redacted]

6.5.7 Prohibited medication

Treatment with antidiabetic medication (e.g metformin, insulin) is not allowed during the study. If treatment with antidiabetics becomes necessary, the patient has to discontinue the study.

6.5.8 Concomitant treatment

Other medication which is considered necessary for the patient's welfare may be given at the discretion of the investigator. Administration of all such 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.

6.5.9 Study drug discontinuation

Treatment can be terminated at any time, at the discretion of the investigator or the Sponsor, or at the patient's request, in the event of an AE or due to treatment failure.

Study drug treatment has to be discontinued in the following cases during treatment period:

- Occurrence of overt diabetes mellitus; defined as fasting blood glucose $\geq$126 mg/dl or $\geq$ 7.0 mmol/l and abnormal findings in OGTT defined by $\geq$ 200 mg/dl or $\geq$ 11.1 mmol/l after 120 minutes. For further instruction see appendix
- Requirement of an increase of the recommended dose to obtain increased growth velocity
- Renal transplantation
- Diagnosis of benign intracranial hypertension
- Malignancy
- Pregnancy
- Withdrawal of informed consent
- Treatment failure

Treatment failure is defined as: Inadequate response to treatment, e.g. height velocity standard deviation score (HVSDS) below +1 in the first year.

Furthermore a standardized controlled procedure for the calculation of the treatment response (via "Treatment Response Control Fax") was implemented (see also 6.5.3 treatment duration) to ensure a unified flawless computation and to authorize treatment continuation, if applicable (managed by Data Management at Metronomia). In case the Investigator does not agree with the assessment by Data Management, Sandoz is informed and initiates the re-assessment of the treatment response data via an independent specialist reader.

Patients who are withdrawn from the study before completing at least one year of treatment with Omnitrope® will be replaced.

Study drug must be discontinued if the investigator concludes that continuation would result in significant safety risk for that patient and in the event of pregnancy.

[redacted]

Patients who discontinue study drug before completing the study should not be considered withdrawn from the study and should be scheduled for a final visit as soon as possible, at which time all of the assessments for the final visit will be performed.

A Study Drug Discontinuation form should be completed, giving the date and reason for stopping the study drug. All patients who discontinue study drug, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 4 weeks following the last dose of the study drug.

Patients who discontinued this study for any reason will not be able to re-enter the study.

6.5.10 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.

A patient is considered to be lost to follow up in case patient status is unclear because they fail to appear for study visit within visit window without stating an intention to withdraw and the patient does not react to at least three attempts of the investigator to schedule the visit within visit window (the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.)

A patient who does not attend the visit during visit window is considered as lost to follow up, unless

- (s)he experiences medical condition, which prevents her/him from appearing to the visit within visit window and
- patient notifies the investigator about this condition during visit window or earlier and
- before or during visit window sponsor grants upfront written approval for the visit outside of visit window.

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. For lost to follow up patients the termination fax specifying the reason of withdrawal should be provided to DM within 4 weeks of calculated visit date.

6.5.11 Emergency unblinding of treatment assignments

Not applicable.

[redacted]

6.6 Contraception measures

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become menarchal during the study.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.

Urine pregnancy tests will be performed for all females of child-bearing potential according to the schedule in the Flow Chart. Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant must be discontinued from study drug.

All female patients of child-bearing potential, defined as all women physiologically capable of becoming pregnant must use effective methods of contraception during dosing of study treatment. Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization. For female subjects participating in the study, the vasectomized male partner must be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception it is recommended that the female patients of childbearing potential is exerting abstinence for a period of 3 months until safe onset of action of the oral contraception.

[redacted]

7 Visit Schedule and assessments

The Flow Chart (synopsis) lists 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 +/- three weeks will be allowed.

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

The study visit schedule consists of screening period for up to 8 weeks prior to the initiation of therapy followed by an open treatment period until final height is reached. The study plan timetable (please refer to the Flow Chart Treatment Period) indicates the number and timing of the planned visits. During these visits, the mentioned efficacy and safety parameters will be assessed. It is important to maintain the visit schedule during the treatment period 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 treatment period.

The clinical and laboratory investigational plan per visit is summarized in the Flow Chart Treatment Period.

7.1 Procedures by visits

7.1.1 Screening Period (Visit 00)

At the screening visit (to be performed within 8 weeks prior to visit 1), all data to confirm the diagnosis SGA will be collected in addition to demographic and baseline data to determine the patient's eligibility for study participation.

- Demographics (date of birth, sex, ethnic origin)
- Medical and surgical history
- Prenatal history
  - Placental dysfunction (eclampsia, infarcts), genetic causes
  - Maternal disease
  - Gestational age
  - Birth history
    - Vaginal/caesarean, Apgar-score, blood pH, body weight, body length, neonatal complications (need for glucose, respiratory support)
  - Infant growth data
    - Retrospective weight, length, feeding mode
  - Pre-treatment growth data
    - Height measurement between 18 months and 6 months prior to the start of Omnitrope® treatment to enable calculation of pre-treatment height velocity
    - Current standing height
  - Physical examination, puberty stage and vital signs

[redacted]

- Body mass index
- Parental height and weight
- Growth hormone secretion
  - Collection of historical data with regard to growth hormone secretion
- Written informed consent will be obtained before any measurements are made.
- Recording of patient's and parents' data in the respective CRF
- Patients history and details of concomitant medications
- Recording of historical X-ray radiograph of the patient's left hand and wrist

7.1.2 Start of Treatment (Visit 01)

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 and fasting plasma insulin
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- OGTT
- Urinary analysis (dip stick)
- [redacted]
- Concomitant medication recording
- Adverse Events recording
- Drug dispensing and recording

At this visit, patients/parents will be carefully instructed by the investigator/clinical staff on the use of the pen injector, the pen needle, and the appropriate injection technique including cleaning of the injection site and discharging of the used needle. The first injection of Omnitrope® will be administered. Patients will receive a three months supply of study drug packed in a cool box and will be instructed to place the study medication in the refrigerator at home as soon as possible. The dispensed study drug will also be recorded in the Drug Accountability Form.

7.1.3 3-Month Treatment Visit (Visit 02)

At visit 02, the following investigations will be performed:

- Physical examination including height, weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed

[redacted]

- Drug dispensing, drug accountability and recording

7.1.4 6-Month Treatment Visit (Visit 03)

At visit 03, the following investigations will be performed:

- Physical examination including height, 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 and fasting plasma insulin
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- OGTT
- Urinary analysis (dip stick)
- Pregnancy test (only in female patients after onset of menarche)
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.5 9-Month Treatment Visit (Visit 04)

At visit 04, the following investigations will be performed:

- Physical examination including height, weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.6 12-Month Treatment Visit (Visit 05)

At visit 05, the following investigations will be performed:

- Physical examination including height, 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 and fasting plasma insulin
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- OGTT
- Urinary analysis (dip stick)
- Pregnancy test (only in female patients after onset of menarche)

[redacted]

- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.7 15-Month Treatment Visit (Visit 06)

At visit 06, the following investigations will be performed:

- Physical examination including height, weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.8 18-Month Treatment Visit (Visit 07)

At visit 07, the following investigations will be performed:

- Physical examination including height, weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.9 21-Month Treatment Visit (Visit 08)

At visit 08, the following investigations will be performed:

- Physical examination including height, weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

[redacted]

7.1.10 24-Month Treatment Visit (Visit 09) and subsequent visits performed annually (Visit 11, Visit 13 etc)

The following investigations will be performed:

- Physical examination including height, 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 and fasting plasma insulin
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- OGTT
- Urinary analysis (dip stick)
- Pregnancy test (only in female patients after onset of menarche)
- [redacted]
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.11 30-Month Treatment Visit (Visit 10) and subsequent visits performed annually (Visit 12, Visit 14 etc)

The following investigations will be performed:

- Physical examination including height, weight and pubertal status
- Vital signs (blood pressure and heart rate)
- Blood sampling for IGF-I and IGFBP-3 determination
- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug dispensing, drug accountability and recording

7.1.12 Final Visit of treatment period

At final visit of treatment period, the following investigations will be performed:

- Physical examination including height, 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 and fasting plasma insulin
- Blood sampling for anti-hGH antibodies, IGF-I and IGFBP-3 determination
- OGTT
- Urinary analysis (dip stick)
- Pregnancy test (only in female patients after onset of menarche)

[redacted]

[redacted]

- Concomitant medication recording
- Adverse Events recording
- Fundoscopy, if needed
- Drug accountability and recording

7.2 Treatment exposure and compliance

Patient compliance will be assessed by the collection of used, partly used and unused vials as well as cartridges at each visit. The number of returned vials and the quantity of unused treatment remaining in the vials will provide information on treatment compliance, which will be recorded in the source document at each visit. Patients must comply with the dose schedule. The daily dose should be maintained in the range between 80% and 120% of the recommended daily dose of 0.035 mg/kg BW depending on the patient's responsiveness.

7.3 Efficacy

7.3.1 Methods and timing for assessing, recording and analysis of efficacy parameters

At each visit, which should take place preferably in the morning, patient's height and weight will be assessed and noted.

7.3.2 Anthropometric Measurements

Height measurements will be performed using a wall-mounted stadiometer. Whenever possible, a patient will be measured at each visit at a similar daytime by the same trained person to minimise observer bias. The technique as described by Tanner et al (1966) should be used.

7.3.3 Presentation and Calculation of Auxological Data

Height velocity (HV) will be calculated in cm/year as the difference between two height measurements divided by the time interval in days between these two measurements multiplied by 365.25.

Height and height velocity will not only be expressed in cm and cm/year, respectively, but also in Standard Deviation Scores (SDS), the relative deviation from the mean value of normally growing children of same sex and chronological age or bone age. The SDS values for height and HV will be calculated according to the following formula SDS= (X1-X2)/SD, where X1 means the measured value, X2 the mean value for the relevant chronological age (or bone age, where appropriate), and SD stands for the standard deviation for the mean of relevant age. For the calculation of HVSDS, the mean between the CA at the two height measurements should be considered as the relevant CA.

Since the formula for the calculation of SDS is not common practice in all countries (especially for the calculation of height SDS) the inclusion of a patient is evaluated according

[redacted]

to national common practice. The following formula is widely used and allowed for inclusion instead of the formula used for the statistical analysis of the study cited above:

$$SDS = \frac{measuredvalue - median}{0.5 * (\text{median} - \text{3rd percentile})}$$

All standardized controlled procedures and methods applied for the calculation of auxological data (with reference to Inclusion Criteria No. 2, 3 and 5) to ensure a common basis and comparability of data derived from the different countries will be filed in the Trial Master File and described in the Clinical Study Report.

7.3.4 Weight measurements

Weight will be measured according to the usual clinical practice.

[redacted]

7.4 Safety

7.4.1 Carbohydrate metabolism

Fasting plasma glucose and insulin levels will be measured at baseline, at 6 and 12 months, then annually during GH treatment, and at the end of treatment.

After an overnight fast, venous blood samples will be taken to assess fasting glucose and insulin levels. Insulin resistance will be estimated using both the homeostasis model assessment (HOMA) (Matthews et al 1985) and quantitative insulin sensitivity check index (QUICKI) (Katz et al 2000, WHO 2002).

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

*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_{1C}) will be measured at baseline, at 6 and 12 months and then annually during GH treatment, and at the end of treatment.

[redacted]

An oral glucose tolerance test (OGTT) will be performed at baseline, at 6 and 12 months and then annually during GH treatment, and at 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, 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.

7.4.2 Immunogenicity

Subjects will be screened for anti-rhGH antibodies (ABs) at baseline, at 3, 6, 9, 12, 18 and 24 months, then annually during GH treatment and at the end of treatment. Antibody-induced lack or loss of efficacy will be examined by comparing height outcome data between antibody-positive and antibody-negative subjects.

7.4.3 Fundoscopy

Fundoscopy will be performed only if intracranial hypertension is suspected (severe or recurrent headache, visual problems, nausea and/or vomiting).

7.4.4 Physical examination

Patients will undergo a general physical examination and will also be questioned about and examined for any local or systemic adverse events. At each scheduled visit during 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. Prepubertal or pubertal status should be assessed by the investigator and expressed in stages as described by Tanner and Whitehouse (1976).

7.4.5 Vital signs

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

7.4.6 Laboratory evaluations

7.4.6.1 Local Laboratories

Local laboratories will be responsible for performing blood serum and urine determinations; clinical chemistry and complete blood count (CBC) (automated 5-part differential recommended), absolute neutrophil count (ANC) and platelet counts.

All supernatants of samples are destroyed after analysis.

The following laboratory safety tests will be performed at baseline, at 6 and 12 months and annually thereafter for the remainder of GH treatment, and at the end of treatment, unless more frequent assessment is clinically indicated.

[redacted]

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), HbA1C, 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. Pregnancy test only in girls after onset of menarche.

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

7.4.6.2 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 stored deep frozen at –70°C for central determination of IGF-I, IGFBP-3 and anti-hGH antibodies. For central laboratory details please refer to lab manual.

7.4.6.2.1 Anti-hGH antibodies

Anti-hGH antibodies serum levels will be assessed at baseline, at 3, 6, 9, 12, 18 and 24 months, then annually during treatment, and at the end of treatment.

Samples will be stored by the sponsor according currently applicable guidelines in order to potentially re-analyze anti-hGH antibodies at a later stage, if needed.

7.4.6.2.2 IGF-I and IGFBP-3 serum levels

IGF-I and IGFBP-3 serum levels will be assessed at baseline, at 3, 6, 9 and 12 months, then every 6 months during treatment, and at the end of treatment. All supernatants of samples are destroyed after analysis.

7.4.7 Adverse events

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign, including abnormal laboratory findings, symptom or disease) in a subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a investigational medicinal product.

[redacted]

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be identified when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- the investigator considers them to be clinically relevant,
- they require therapy.

Clinically relevant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, relevant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease.

Adverse events must be recorded on the adverse events CRF with the following information within 10 days of learning of its occurrence (if the event is serious (refer to Section 7.4.8) it must be recorded in the CRF within 24 hours of learning of its occurrence):

- the severity grade (indicating most severe grade during the course of the adverse event)
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- 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.
  - If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is as follows:
    - the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration
    - both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
- its duration (start and end dates) or ‘ongoing’ at the 30 day safety follow-up /end of study visit
- whether it constitutes a serious adverse event (SAE) (see Section 7.4.8 for the definition of SAE)

[redacted]

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1

- action taken: All adverse events must be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given, subject hospitalized/subject's hospitalization prolonged.
- Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is identified, it must be followed until its resolution or until it is judged to be permanent, and assessment must 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.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the subject informed consent form and must be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding report. New information might require an update to the informed consent form and has then to be discussed with the subject.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to the sponsor.

7.4.8 Serious adverse events

A SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- 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 (specify what this includes)
  - 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 subject's general condition

[redacted]

- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Death without known medical event must always be reported as SAE.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Medical and scientific judgment must be exercised in deciding whether other situations should be considered serious AEs, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is also considered a serious adverse event.

7.5 Tolerability/acceptability

Not applicable

7.6 Resource utilization

Not applicable

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure subject safety, the investigator has to report every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until 30 days after following the last administration of study treatment must be reported to the sponsor (or designated CRO) within 24 hours of learning of its occurrence using the SAE reporting form, and recorded in the CRF.

Any SAEs experienced after this 30 day period should only be reported to the sponsor (or designated CRO) if the investigator suspects a causal relationship to the study drug.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. Likewise, queries issued by the sponsor regarding the SAE must be responded to within 24 hours.

An SAE that is considered completely unrelated to a previously reported one must be reported separately as a new event.

[redacted]

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form within 24 hours to the sponsor. The contact details for SAE reporting 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 at the study site.

Follow-up information must be provided using a new SAE Report Form stating that this is a follow-up to the previously reported SAE. The follow-up information must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, the sponsor may urgently require further information from the investigator for Health Authority reporting. The sponsor may need 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

8.2 Reporting procedures for technical complaints

Any technical complaint about the study drug needs to be reported to the sponsor within 24 hours of identification of the defect (for details refer to the study drug handling manual). Technical complaints are complaints about an optical, organoleptic, qualitative, quantitative, mechanical or functional defect of a pharmaceutical product or medical device. This may include:

- Any fault of quality and/or effectiveness e.g. particles
- Any fault of the containers and outer packages e.g. surface imperfection, container leakage, broken syringe/plunger, missing contents, device malfunction
- Any fault of the labeling e.g. missing or illegible label
- Any falsification of the medicinal product or device e.g. suspected product mix-up, or tampering.

For reporting of adverse events caused by the defect (if applicable) refer to Section 7.4.7.

8.3 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

[redacted]

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors, misuse or abuse will be collected and reported in the CRF AE page irrespective of it being associated with an AE/SAE.

8.4 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Sandoz within 24 hours of learning of its occurrence. The pregnancy must 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 must be recorded on a Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up must be recorded on the same form and must include an assessment of the possible relationship to the Sandoz study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Data Monitoring Board

Not Applicable

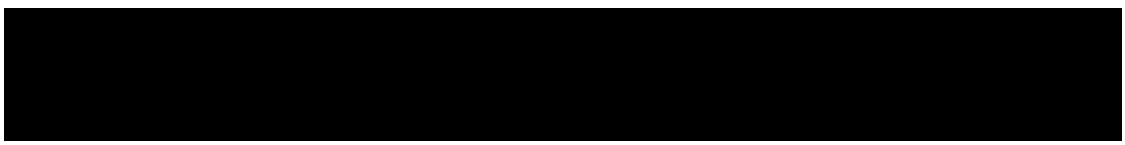
9 Data review and database management

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, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted according to specifications. 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. 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.

9.3 Medical Monitoring

Medical Monitoring is the summary of all Medical Review activities performed throughout the entire conduct of the study on different levels by different parties. This is to ensure patients' safety and welfare and consistency of data. Medical Review is performed by CRAs during the Monitoring Visit (PRA), at Data Management/Data Validation (Metronomia), and at the sponsor (Study and Program Management at Sandoz). All tasks comprised to warrant a common understanding of duties and schedules of the respective parties in charge have been laid down in writing and filed in the Trial Master File.

10 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 Analysis sets

10.1.1 Safety analysis set

The safety analysis set (SAF) will comprise all subjects who receive at least one dose of study medication and had at least one post-baseline safety assessment.

10.1.2 Full analysis set

The full analysis set (FAS) will follow the intent-to-treat-principle and therefore consists of all patients who received at least one dose of study medication.

The assignment of the patients to the respective analysis set will be done prior to each interim and to the final analysis during a specific data review meeting.

[redacted]

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.

Relevant medical history and current medical conditions, previous medication, results of laboratory screens, drug tests, and any other relevant information will be listed and summarized using descriptive statistics or frequency tables depending on the type of variable (continuous or discrete).

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

10.3.1 Study drug administration

The extent of exposure will be analyzed using descriptive statistics. Tables showing descriptive statistics for the dose per kg body weight will be presented by visit to assess the appropriateness of the applied doses.

10.3.2 Concomitant medication

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

10.3.3 Treatment compliance

The percentage of medication used compared to the amount prescribed will be analyzed for each visit and the frequency of non-compliant patients (daily dose range <80% or >120%) will be tabulated.

10.4 Analysis of safety endpoints

10.4.1 Carbohydrate metabolism

Fasting plasma glucose and insulin levels will be measured at baseline, at 6 and 12 months, then annually during GH treatment, and at 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) (Matthews et al 1985) and quantitative insulin sensitivity check index (QUICKI) (Katz et al 2000, WHO 2002). The effect of Omnitrope® treatment on HOMA and QUICKI scores, calculated subsequent to 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_{1C}) will be measured at baseline, at 6 and 12 months and then annually during GH treatment, and at the end of treatment. The effect of treatment on the HbA_{1C} levels will also be displayed using descriptive statistics.

[redacted]

An oral glucose tolerance test (OGTT) will be performed at baseline, at 6 and 12 months and then annually during GH treatment, and at the end of treatment.

10.4.2 Immunogenicity

Subjects will be screened for anti-rhGH antibodies (ABs) at baseline, at 3, 6, 9, 12, 18 and 24 months, then annually during treatment, and at 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.

10.4.3 Safety lab / urine analysis

Haematology, blood chemistry and urine analysis 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.

10.4.4 (Serious) Adverse Events / Incidents

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. The (serious) adverse events will be displayed by system organ class and preferred term and the relationship to the study drug, intensities and outcome will be shown in corresponding frequency tables.

Since incidents are qualified as clinical SAEs they are handled in the same way as all other clinical SAEs. A near incident is handled as a clinical SAE in case of seriousness, otherwise as an adverse event.

10.4.5 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.

10.4.6 Physical examination

Shift tables for normal / abnormal findings will be presented by body system for each visit versus baseline.

10.5 Analysis of efficacy endpoints

10.5.1 Auxological endpoints

These are height, height SDS, height velocity and height velocity SDS. These parameters will be monitored at baseline, at every 3 months during GH treatment and at the end of treatment. The effectiveness of treatment in inducing growth will be determined by descriptive statistics of the height at each scheduled visit including a comparison to the height at baseline. Similar analyses will be conducted for the height SDS.

[redacted]

The effectiveness of treatment in accelerating linear growth rate will be determined by analyzing the annual height velocity in cm/year (the difference between two height measurements divided by the time interval between these two measurements multiplied by 365.25) at each scheduled visit and by comparing it to the height velocity determined at baseline using historical data. Similar analyses will be conducted for the height velocity SDS.

Treatment will be considered to be ineffective (leading to drug discontinuation) if HVSDS remains below +1 in the first year of treatment.

10.5.2 Pharmacodynamic endpoints

These are IGF-I and IGFBP-3 serum levels, which will be assessed at baseline, at 3, 6, 9 and 12 months, then bi-annually during treatment, and at 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.

[redacted]

10.6 Interim analysis

Interim analyses are planned at the following time points:

- Q4/2011 with data of patients who completed 1 year of treatment
- Q4/2012 with data of patients who completed 2 years of treatment
- Q4/2020 with data of patients who finished treatment

Additional *ad-hoc* interim analyses will be performed in case needed for interactions with health authorities.

10.7 Sample size calculation

There was no formal sample size calculation for this study which is intended to exploratorily investigate the long-term effect of the treatment with respect to the development of diabetes. No such incidences are currently available to allow for a rigorous sample size estimation. Results obtained in this study will be compared to data published in the literature.

200 subjects were agreed upon during the discussion with the EMEA. Taking into account a drop-out rate of 20%, 240 patients will be included in the study. Subjects dropping out before completing 1 year of treatment will be replaced.

10.8 Power for analysis of critical secondary variables

Not applicable

[redacted]

10.9 Subgroup analyses

Since the study population will consist of subjects treated with Omnitrope® 5 mg/ml powder for the first twelve months and with Omnitrope® 5 mg/1.5 ml solution for injection thereafter as well as of subjects treated continuously with Omnitrope® 5 mg/1.5 ml solution for injection, a corresponding subgroup analysis will be performed. The main focus of such subgroup analysis will be on the comparison of the safety profiles during the first twelve months of treatment as well as on the effects on the growth related parameters for the first twelve months of treatment and also for the whole treatment period.

Further subgroup analysis will be done for an overweight population with **international cut-off points for BMI for overweight by sex and age as defined by the percentile that passes through BMI of 25 at age 18.**

All comparisons will be performed descriptively using adequate frequency tables and descriptive statistics. Details of the analyses will be laid down in the statistical analysis plans for the respective (interim) analyses.

11 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 Omnitrope® in short children born SGA, and
- to further investigate the immunogenicity of Omnitrope® in short children born SGA.

More specifically, the primary objective of this study is:

- to monitor the development of diabetes during Omnitrope® treatment.

The secondary objectives of this study are:

- to monitor the development of anti-hGH antibodies during Omnitrope® treatment,
- to evaluate the safety (incidence and occurrence of adverse events) of Omnitrope® treatment in short children born SGA, and
- to evaluate the efficacy (with respect to changes in height parameters, serum IGF-I and IGFBP-3 levels) of Omnitrope® treatment in short children born SGA.

All included subjects will receive Omnitrope® 0.035 mg/kg/day as per recommended dose for short stature secondary to SGA. Dose adjustments will be allowed during therapy consistent with label recommendations. Omnitrope® treatment will continue until final height is reached but will be discontinued earlier if there is inadequate response to treatment (e.g., height velocity standard deviation score (HVSDS) remains below +1 in the first year).

To address concerns regarding the risk of developing diabetes mellitus in GH-treated short children born SGA, specific parameters such as fasting plasma glucose and insulin levels will be measured at pre-defined time points throughout treatment with Omnitrope®.

Subjects will be monitored for safety throughout treatment. Height, height SDS, HV and HVSDS will be determined until final height is reached.

[redacted]

12 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, the Coordinating Investigator as well as the Principal Investigator(s) 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 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, The Rules Governing Medicinal Products in the European Community.

Directive 2001/20/EC, EU Clinical Trials Directive

Directive 2005/28/EC, EU GCP Directive

91/507/EEC, The Rules Governing Medicinal Products in the European Community

MEDDEV 2.12-1 rev 5, Guidelines on a Medical Devices Vigilance System

US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki 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.

12.2.1 Institutional Review Board/ Independent Ethics Committee

Before implementing this study, the protocol, the investigator brochure, 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.

12.2.2 Informed consent

The investigator must explain to each patient (and/ 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

[redacted]

time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

To cover adolescence of the patients with adequate patient information documents, three patient information documents, one for children between 4 and 6 years of age, one for children between 7 and 12 years of age, and one for children ≥ 13 years of age are used within this clinical trial. Children who can read and write should sign the informed consent on the basis of the patient information document according to their relevant age group. At all events written informed consent has to be obtained from the patients' parents or legal guardian.

These informed consent(s) should be given by means of a standard written statement, written in non-technical language. The subject/parents or legal guardian 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 and ~~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.

Female patients of child bearing potential must be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they must discontinue the study.

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.

12.2.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki.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.

13 References

Albertsson-Wikland K and Karlberg J (1997). Postnatal growth of children born small for gestational age. Acta Paediatr Suppl; 423:193-5

Barker DJ et al (1990). Fetal and placental size and risk of hypertension in adult life. BMJ; 301:259-62

Barker DJ et al (1993). Fetal nutrition and cardiovascular disease in adult life. Lancet; 341:938-41

Boguszewski M et al (1997). Hormonal status of short children born small for gestational age. Acta Paediatr Suppl; 423:189-92

[redacted]

Boguszewski MC et al (2000). Serum leptin in short children born small for gestational age: dose-dependent effect of growth hormone treatment. Horm Res, 54:120-25

Boyko EJ (2000). Proportion of type 2 diabetes cases resulting from impaired fetal growth. Diabetes Care; 23:1260-64

Cance-Rouzaud A et al (1998). Growth hormone, insulin-like growth factor-I and insulin-like growth factor binding protein-3 are regulated differently in small-for-gestationa-age and appropriate-for-gestational-age neonates. Biol Neonate; 73:347-55

Cole TJ et al (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ; 320:1240-43

Curhan GC et al (1996). Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. Circulation; 94: 3246-50

De Zegher et al (2002). High-dose growth hormone (GH) treatment in non-GH-deficient children born small for gestational age induces growth responses related to pretreatment GH secretion and associated with a reversible decrease in insulin sensitivity.
J Clin Endocrinol Metab; 87:148-51

De Zegher F et al (1999). Early, discontinuous, high dose growth hormone treatment to normalize height and weight of short children born small for gestational age: results over 6 years. J Clin Endocrinol Metab; 84:1558-61

De Zegher F et al (2000). Growth hormone treatment of short children born small for gestational age: growth responses with continuous and discontinuous regimens over 6 years. J Clin Endocrinol Metab; 85:2816-21

Degani S (2001). Fetal biometry: clinical, pathological, and technical considerations. Obstet Gynecol Surv; 56:159-67

Economides DL et al (1989). Plasma insulin in appropriate- and small-for-gestational-age fetuses. Am J Obstet Gynecol; 160:1091-4

Greulich WW, Pyle SI (1959). Radiographic atlas of skeletal development of hand and wrist. 2nd Edition; Stanford University Press, California, USA

Hales CN et al (1991). Fetal and infant growth and impaired glucose tolerance at age 64. BMJ; 303:1019-1022

Hattersley AT and Tooke JE (1999). The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. Lancet; 353:1789-92

Hokken-Koelega ACS et al (2004). Small for Gestational Age (SGA): Endocrine and metabolic consequences and effects of growth hormone treatment. J Ped Endocrinol Metab; 17 (Suppl 3):463-9

Katz A et al (2000). Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrin Metab; 85: 2402-10

[redacted]

Lassarre C et al (1991). Serum insulin-like growth factors and insulin-like growth factor binding proteins in the human fetus. Relationships with growth in normal subjects and in subjects with intrauterine growth retardation. Pediatr Res; 29:219-25

Lee PA et al (2001). International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age. Pediatrics; 111:1253-61

Leger J et al (1997). Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study. BMJ; 315:341-347

Li C et al (2001). Effects of low birth weight on insulin resistance syndrome in caucasian and African-American children. Diabetes Care; 24:2035-42

Lin CC and Santolaya-Forgtas J (1998). Current concepts of fetal growth restriction: part I. Causes, classification, and pathophysiology. Obstet Gynecol; 92:1044-55

Lithell HO et al (1996). Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. BMJ; 312:406-10

Lundgren EM et al (2001). Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. Pediatr Res; 50:91-6

Marshall WA, Tanner JM (1969). Variations in Pattern of Pubertal Changes in girls. Arch Dis Childh; 44:291-303

Marshall WA, Tanner JM (1970). Variations in Pattern of Pubertal Changes in boys. Arch Dis Childh; 45:13-23

Matthews DR et al (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man.
Diabetologia; 28:412-9

McCance et al (1994). Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? BMJ; 308:942-5

Ong KK and Dunger DB (2002). Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults.
Best Pract Res Clin Endocrinol Metab; 16:191-207

Phillips DI. Insulin resistance as a programmed response to fetal undernutrition.
Diabetologia 1996; 39:1119-22

Poidvin et al (2017) Risk of Diabetes Treated in Early Adulthood After Growth Hormone Treatment of Short Stature in Childhood J Clin Endocrinol Metab, 102(4):1291–8

Prader A, Largo RH, Molinari L, Issler C (1989). Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development.
Helv Paediatr Acta Suppl; 52:1-125

Reynolds RM and Phillips DI (1998). Long-term consequences of intrauterine growth retardation. Horm Res; 49 (Suppl 2):28-31

[redacted]

Rich-Edwards JW et al (1997). Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ; 315:396-400.

Rich-Edwards JW et al (1999). Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med; 130:278-84

Rosenfeld R and Cariati S (2002). The role of growth hormone therapy in short children born small for gestational age. Medscape CME

Sas T et al (1999). Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind dose-response trial. J Clin Endocrinol Metab; 84:3064-70

Sas T et al (2000). Body composition, blood pressure, and lipid metabolism before and during long-term growth hormone (GH) treatment in children with short stature born small for gestational age either with or without GH deficiency. J Clin Endocrinol Metab; 85:3786-92

Sas T et al (2001). Carbohydrate metabolism during long-term growth hormone treatment in children with short stature born for small for gestational age. Clin Endocrin; 54:243-51

Stern MP et al (2000). Birth weight and the metabolic syndrome: thrifty phenotype or thrifty genotype? Diabetes Metab Res Re; 16:88-93

Tanner JM, Whitehouse RH (1976). Clinical longitudinal standards for height, height velocity, and weight velocity and the stages of puberty. Arch Dis Child; 51:170-9

Tanner JM, Whitehouse RH, Takaishi M (1966). Standards from birth to maturity for height, weight, height velocity, and weight velocity for British children, 1965, Part I Arch Dis Child; 41:454-71

Usher R and McLean F (1969). Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr; 74:901-10

Valdez R et al (1994). Birthweight and adult health outcomes in a biethnic population in the USA. Diabetologia; 37:624-31

Van der Steen et al. (2017). Metabolic health of young adults who were born small for gestational age and treated with growth hormone, after cessation of growth hormone treatment: a 5-year longitudinal study. Lancet Diabetes Endocrinol; 5(2):106-16

Ventura SJ et al (2001). Births: final data for 1999. Natl Vital Stat Rep; 49:1-100

WHO 2002: Laboratory Diagnosis and Monitoring of diabetes mellitus

Yarbrough DE et al (1998). Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women: the Rancho Bernardo Study. Diabetes Care; 21:1652-8

[redacted]

Appendices

Tanner Breast Stages

Stage 1	Pre-adolescent; elevation of papilla only.
Stage 2	Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.
Stage 3	Further enlargement of breast and areola, with no separation of their contours.
Stage 4	Projection of areola and papilla to form a secondary mound above the level of the breast.
Stage 5	Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

Source: Marshall WA, Tanner JM: Variations in Pattern of Pubertal Changes in girls.
Arch Dis Childh 1969; 44: 291-303

Handling of elevated blood glucose levels and OGTT

Fasting blood glucose levels	OGTT	Patient outcome
impaired	impaired	Ongoing
overt	impaired	Ongoing
overt	overt	Discontinuation

As the OGTT is more sensitive than fasting blood glucose assessment, the final decision with regards to discontinuation will be eventually based on the result of the OGTT.

In case of the unlikely situation that fasting blood glucose levels = normal/impaired and OGTT=overt, patient outcome = discontinuation.

Overt levels are defined as:

- Fasting blood glucose $\geq$126 mg/dl or $\geq$ 7.0 mmol/l
- OGTT $\geq$ 200 mg/dl or $\geq$ 11.1 mmol/l after 120 minutes

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Recommended Dosage of Omnitrope®

5 mg / 1.5 ml cartridge				10 mg / 1.5 ml cartridge	
Weight in kg	Dose dialed in mg	Weight in kg	Dose dialed in mg	Weight in kg	Dose dialed in mg
5.0 – 6.4	0.20	45.0 – 46.4	1.60	5.0 - 7.8	0.2
6.5 – 7.8	0.25	46.5 – 47.8	1.65	7.9 – 10.7	0.3
7.9 – 9.2	0.30	47.9 – 49.2	1.70	10.8 – 13.5	0.4
9.3 – 10.7	0.35	49.3 – 50.7	1.75	13.6 – 16.4	0.5
10.8 – 12.1	0.40	50.8 – 52.1	1.80	16.5 – 19.2	0.6
12.2 – 13.5	0.45	52.2 – 53.5	1.85	19.3 – 22.1	0.7
13.6 – 14.9	0.50	53.6 – 54.9	1.90	22.2 – 24.9	0.8
15.0 – 16.4	0.55	55.0 – 56.4	1.95	25.0 – 27.8	0.9
16.5 – 17.8	0.60	56.5 – 57.8	2.00	27.9 – 30.7	1.0
17.9 – 19.2	0.65	57.9 – 59.2	2.05	30.8 – 33.5	1.1
19.3 – 20.7	0.70	59.3 – 60.7	2.10	33.6 – 36.4	1.2
20.8 – 22.1	0.75	60.8 – 62.1	2.15	36.5 – 39.2	1.3
22.2 – 23.5	0.80	62.2 – 63.5	2.20	39.3 – 42.1	1.4
23.6 – 24.9	0.85	63.6 – 64.9	2.25	42.2 – 44.9	1.5
25.0 – 26.4	0.90	65.0 – 66.4	2.30	45.0 – 47.8	1.6
26.5 – 27.8	0.95	66.5 – 67.8	2.35	47.9 – 50.7	1.7
27.9 – 29.2	1.00	67.9 – 69.3	2.40	50.8 – 53.5	1.8
29.3 – 30.7	1.05	69.4 – 70.7	2.45	53.6 – 56.4	1.9
30.8 – 32.1	1.10	70.8 – 72.1	2.50	56.5 – 59.2	2.0
32.2 – 33.5	1.15	72.2 – 73.5	2.55	59.3 - 62.1	2.1
33.6 – 34.9	1.20	73.6 – 75.0	2.60	62.2 – 64.9	2.2
35.0 – 36.4	1.25	75.1 – 76.4	2.65	65.0 – 67.8	2.3
36.5 – 37.8	1.30	76.5 – 77.8	2.70	67.9 – 70.7	2.4
37.9 – 39.2	1.35	77.9 – 79.3	2.75	70.8 – 73.5	2.5
39.3 – 40.7	1.40	79.4 – 80.7	2.80	73.6 – 76.4	2.6
40.8 – 42.1	1.45	80.8 – 82.1	2.85	76.5 – 79.3	2.7
42.2 – 43.5	1.50	82.2 – 83.5	2.90	79.4 – 82.1	2.8
43.6 – 44.9	1.55	83.6 – 85.0	2.95	82.2 – 85.0	2.9

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