Non-Interventional Study Protocol

Study Protocol Number	EMR 200098_008
Title	Prospective and retrospective, single-cohort, multicentre observational long-term study in short children born small for gestational age (SGA) after treatment with Saizen® or with other recombinant human growth hormone (r-hGH) products
Short Title	SAizen® Long Term Observational study (SALTO)
Phase	IV
EudraCT Number	Not applicable
EU PAS Number	EUPAS16520
Coordinating Investigator	PPD PPD Tel: PPD Fax: PPD
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany *Medical Responsible:* PPD PPD EMD Serono, Inc 45A Middlesex Turnpike Billerica, MA 01821, USA Tel : PPD Mobile : PPD email :PPD

Clinical Research Scientist:
PPD , PhD
PPD
EMD Serono, Inc
One Technology Place
Rockland, MA 02370, USA
Mobile : PPD
email:PPD

Sponsor's Legal Representative (EU)	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Study Protocol Version	Final; Version 5.0; 23 April 2018 (for Protocol Amendment No. 5)

– Confidential –

Signature Page

Protocol Lead responsible for designing the study: PPD

I approve the design of the study.

PPD

Signature

PPD

Date of Signature

PPD

EMD Serono, Inc.
45A Middlesex Turnpike
Billerica, MA 01821, USA
Tel : PPD
Mobile : PPD
Email: PPD

Qualified Person for Pharmacovigilance: PPD

I approve the pharmacovigilance of the study.

Signature

Date of Signature

PPD

Merck KGaA, Frankfurter Strasse 250,
Postcode: F133, 64293 Darmstadt, Germany
Phone: PPD

Signature Page

Protocol Lead responsible for designing the study: PPD

I approve the design of the study.

Signature *Date of Signature*

PPD

PPD

EMD Serono, Inc.
45A Middlesex Turnpike
Billerica, MA 01821, USA
Tel : PPD
Mobile : PPD
Email: PPD

Qualified Person for Pharmacovigilance: PPD

I approve the pharmacovigilance of the study.

PPD PPD

Signature *Date of Signature*

PPD

Merck KGaA, Frankfurter Strasse 250,
Postcode: F133, 64293 Darmstadt, Germany
Phone: PPD

Coordinating Investigator PPD

I agree to conduct the study in accordance with this Protocol and in compliance with all applicable regulatory requirements.

PPD

Signature

PPD

Date of Signature

PPD MD

PPD

Telephone number: PPD

Fax number: PPD

Email: PPD

Further Sponsor Responsible Persons

PPD
PPD

EMD Serono, Inc
One Technology Place
Rockland, MA 02370, USA
Mobile: PPD

PPD
PPD

EMD Serono, Inc
One Technology Place
Rockland, MA 02370, USA
Mobile: PPD

PPD
PPD

EMD Serono, Inc.
45A Middlesex Turnpike,
Billerica, MA 01821, USA
Phone: PPD

PPD
PPD

Merck KGaA, Frankfurter Strasse 250,
Postcode: F133/3.OG, 411, 64293 Darmstadt, Germany
Phone: PPD
Fax: PPD

Principal Investigator Signature

Study Title	Prospective and retrospective, single-cohort, multicentre observational long-term study in short children born small for gestational age (SGA) after treatment with Saizen® or with other recombinant human growth hormone (r-hGH) products
EudraCT Number	Not applicable
Protocol Version/Date	Version 5.0, dated 23 April 2018
Centre Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this site and affirm that:

- I understand and will conduct the study according to the protocol, any approved protocol amendments and all applicable Regulatory Authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

Signature	*Date of Signature*

Name, academic qualification

Position (job title)

Address of Institution

Telephone number

Fax number

Email address

Table of Contents

List of Abbreviations

AE	Adverse Event
BMI	Body mass index
BP	Blood pressure
CICF	Contact Information Consent Form
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EC	Ethics Committee
eCRF	Electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
FPI	First Patient In
GH	Growth hormone
GP	General Practitioner
HV SDS	Height velocity standard deviation score
IGF-1	Insulin-like growth factor-1
LPI	Last Patient In
LPO	Last Patient Out
NCR Paper	Non carbon copy paper
OGTT	Oral glucose tolerance test
PAC	Post-approval commitment
PMC	Patient Management Centre
PP	Per Protocol
r-hGH	Recombinant human growth hormone
SAE	Serious Adverse Event
SALTO	SAizen® Long Term Observational study
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal

List of Figures

List of Tables

1 Synopsis

Study title	Prospective and retrospective, single-cohort, multicentre observational long-term study in short children born small for gestational age (SGA) after treatment with Saizen® or with other recombinant human growth hormone (r-hGH) products
Short Title	SAizen® Long Term Observational study (SALTO)
Study number	EMR 200098_008
EudraCT number	Not applicable
EU PAS number	EUPAS16520
Sponsor	Merck KGaA, Darmstadt, Germany
Phase	Phase IV
Study under IND	☐ yes ☒ no
FDA "covered study"	☐ yes ☒ no
Study center(s)/country(ies)	Approximately 40 to 60 centres globally
Planned study period (first enrolment-last subject out)	First subject enrolled after cessation of Saizen® treatment in 2011; expected last subject in by 2020 and last subject out by 2030.
Study objectives	**Primary objective of the study:** • To assess the long-term safety of Saizen® or other r-hGH treatment for 10 years after cessation of treatment, in terms of occurrence of type 2 diabetes mellitus and malignancies, in a minimum of 200 subjects born SGA who received Saizen® or other r-hGH products for the treatment of short stature **Secondary objectives of the study:** • To assess occurrence of metabolic syndrome • To assess glucose metabolism parameters • To characterize the observed malignancies • To correlate the occurrence of metabolic syndrome and/or glucose metabolism disorders or malignancy to familial inheritance • To correlate the occurrence of metabolic syndrome and glucose metabolism disorders or malignancy to subject characteristics and medical history.

Study design and plan	Prospective and retrospective, single-cohort, multicentre, multinational observational long-term follow-up study in subjects born SGA who received Saizen® or other r-hGH products for the treatment of short stature. The study will comprise a 10-year safety follow-up period after cessation of r-hGH treatment in short children born SGA who had received Saizen® or other r-hGH products in the frame of a sponsored clinical study or in the post-marketing setting. The subjects may be enrolled up to 5 years after treatment cessation.
Planned number of subjects	We aim to enrol approximately 300 subjects in the study in order to have a target of 200 subjects completing the study
Schedule of visits and assessments	Following cessation of r-hGH therapy, subjects will be enrolled in the study after signing an informed consent form. No specific medical visits are scheduled for study subjects because of the observational nature of the study. Only data available as per the subject's routine medical care will be collected. During the course of the study, subjects are not required to visit the study Investigator. Subjects may go to their general practitioner (GP) or other treating physician for their routine medical visits. Therefore, the medical data of interest (when/if available) will be collected by the investigator from the patient's treating physician/GP. In addition, the investigator will contact the subjects 5 and 10 years after discontinuation of r-hGH therapy in order to obtain information on any change in medical condition. The clinical research organization's (CRO) dedicated patient management centre (PMC) will contact the subject at least once a year to update and confirm subjects' and treating physicians' contact information, and to identify any change in health status/medical history.
Diagnosis and main inclusion and exclusion criteria	**Inclusion criteria** Eligible subjects (are): • Male and female subjects who were born SGA • Have received r-hGH therapy for the treatment of short stature due to SGA • Have permanently discontinued r-hGH treatment within 5 years prior to study enrolment • Parents or guardians and/or subjects have given written informed consent.

	Exclusion criteria • Patients unwilling and/or parents/guardians who are not capable of ensuring compliance with the study protocol. • Patients enrolled in an interventional trial • Patients enrolled in an observational trial of a similar nature to the SALTO study, where the protocol includes reporting of incidence of type 2 diabetes mellitus and/or malignancies after cessation of r-hGH therapy.
Investigational Medicinal Product (s): dose/mode of administration/dosing schedule	Not Applicable (observational study).
Reference therapy(ies): dose/mode of administration/ dosing schedule	None (post-treatment observational study).
Planned treatment duration per subject	None (post-treatment observational study).
Primary endpoint(s)	• Incidence of type 2 diabetes mellitus • Incidence of any malignancy
Secondary endpoint(s)	• Incidence of metabolic syndrome and changes in glucose metabolism parameters (glycaemia parameters – fasting plasma glucose and postprandial glucose, fasting plasma insulin levels, HbA1c, 2-hour oral glucose tolerance test (OGTT) results, blood pressure, lipid parameters). • Parameters related to malignancies (typology, size and location as applicable, grading, severity, treatment, outcome) • Correlation of type 2 diabetes mellitus and/or malignancy will be established against blood pressure, body mass index, lipid parameters, medical history and familial inheritance
Statistical methods (includes sample size calculation)	It has been agreed with the Health Authorities to organize an observational study to follow-up 200 short children born SGA for 10 years after cessation of treatment with Saizen® or other r-hGH products. In order to compensate for an estimated 35% loss to follow-up, we will recruit 150% of the requested target number of 200 subjects. Hence, a sample size of approximately 300 subjects is targeted for study enrolment.

	Numbers and proportions of subjects having the events (type 2 diabetes mellitus and any malignancy), will be computed, as will the incidence rate per subject-years of follow-up during the 10-year follow-up. Analysis of correlations of the primary endpoints with subject characteristics (e.g., age, blood pressure, Body Mass Index [BMI], family history) and possible confounding factors of the diseases (e.g., concomitant treatment, environmental factors) will be conducted. Exploratory analysis will be performed for each brand of r-hGH product if permitted by sample size per brand.

2 Sponsor, Investigators and Study Administrative Structure

The Sponsor of this study is Merck KGaA, Darmstadt, Germany.

The Coordinating Investigator of this study is PPD

Data collection, management and analysis will be performed by the Contract Research Organisation (CRO) PPD, on behalf of the study Sponsor. The CRO will have a dedicated patient management centre (PMC) to directly contact subjects either by email, letter or phone.

PPD will be responsible for the clinical trial documents to be submitted to regulatory authorities, the conduct of the clinical trial, data management, statistical analysis, as well as clinical trial and safety reporting. Further details will be provided in a separate document and updated as necessary. Clinical quality assurance will be performed under the responsibility of the Development Quality Assurance department at Merck KGaA Darmstadt, Germany.

Investigators (i.e., paediatricians and/or endocrinologists) of this study are the ones who treat short children born SGA with Saizen® or other r-hGH products at their clinics and will be responsible for screening and enrolling eligible subjects in this study (see section 9.1).

Subjects who will be enrolled in the study are those who have permanently terminated/discontinued r-hGH therapy for the treatment of growth disturbance in short children born SGA, and who might have been enrolled in previous sponsored clinical studies in the SGA indication or may come from a post-marketing setting. During the course of the study, subjects are not required to visit the study Investigator. Therefore, to ensure adequate collection of the post-treatment data, Investigators will obtain medical information through the subject's treating physician/GP.

3 Background Information

Treatment with Saizen® for short children born small for gestational age (SGA) was approved in Europe in 2005. During the approval process, the company was requested by the Health Authorities to conduct a study in about 200 subjects born SGA after the cessation of their treatment with Saizen® and to focus on the risk of developing type 2 diabetes mellitus and malignancies. Therefore, the company has agreed with the Italian Health Authorities (Italy being the Reference Member State of the registration procedure of Saizen® in Europe) to fulfil this request as a Post-Approval Commitment.

Saizen®, recombinant human growth hormone (r-hGH), was initially registered in 1988 for the long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH). The following indications have been registered as further steps: Growth failure in girls due to gonadal dysgenesis (Turner Syndrome), Growth failure in pre-pubertal children due to chronic renal failure and GH deficiency in adults. These indications were extended in April 2005 to the treatment of short children born SGA without signs of catch-up growth (3).

The diagnosis of SGA is based on anthropometric parameters at birth and thus requires: 1) accurate knowledge of the gestational age, 2) accurate measurements of weight, length, and head circumference at birth and 3) a cut-off against reference data from the relevant population (< -2 standard deviation score [SDS] from the mean of weight and/or length). Babies born SGA represent a significant proportion of subjects with short stature as adults (4). Approximately 10% of children born SGA fail to catch up with regard to growth during childhood and remain short, with a height below -2SDS (5).

It has been hypothesized that the persistence of short stature in SGA subjects may be the manifestation of a GH or an IGF-1 resistance. In point of fact, the majority of SGA subjects have normal values of GH secretion and only some show evidence of GH deficiency. More inclusive of SGA subjects at large, serum levels of IGF-1 and to some extent IGF-BP3 are found to be significantly decreased (< -1 SD from mean levels) but with a wide range of levels indicating possible heterogeneity in the mechanism of growth failure from insufficient IGF-1 to IGF-1 insensitivity (4). This is the basis of the Barker hypothesis, which suggests that an *in utero* imprinting occurs leading to resistance to multiple hormones; thus, even if SGA growth failures are due to causes other than GH deficiency, these children can be considered as having manifestations of a GH and/or IGF-1 resistance status (6).

The use of GH in SGA has been explored for nearly 40 years. Early intervention with GH for those with severe growth retardation is warranted. In current practice, SGA children over the age of 4 years can be considered for GH treatment when their current height is < -2.5 SDS and when they have failed to show catch-up growth (HV SDS < 0 during the last year) (7),(8). Average height gains after 3 years of GH treatment range from 1.2 to 2.0 SD for doses of 35 to 70 µg/kg/d (4). The recommended daily dose according to product labelling is 0.035 mg/kg body weight (or 1 mg/m^2 per day, equal to 0.1 IU/kg/day or 3 IU/m^2/day) every day, by subcutaneous administration.

Further effects of long-term GH treatment include beneficial effects on body composition, carbohydrate metabolism, blood pressure and lipids in short children born SGA (9). A consistent positive dose-effect relationship on catch-up growth has also been demonstrated with Saizen® (10).

Children born SGA can show some degree of insulin resistance (4). GH treatment has been acknowledged to induce insulin resistance (11) and it was thus recommended that the treatment of children with recombinant GH should be submitted to long-term follow-up. Large international databases have been designed to have some degree of extended monitoring (12). Within the context of the approval of Saizen® in short children born SGA, the long-term follow-up study will focus on:

1. **Type 2 diabetes mellitus and metabolic syndrome risk**: low birth weight might increase risk of type 2 diabetes and metabolic syndrome in adulthood (5). GH has been associated with increased insulin levels and insulin resistance (13), (14). It is currently unknown whether GH therapy for SGA is associated with benefits or amplification of metabolic consequences in adulthood (4). Therefore, long-term follow-up is recommended (4). A recent study in a small population shows that at 6.5 years after discontinuation of GH treatment, risk factors for type 2 diabetes and metabolic syndrome were comparable in treated and untreated young SGA adults, with increased fasting glucose and higher fasting insulin levels during treatment recovering after discontinuation (5),(19).

2. **Malignancy risk**: low birth weight has not been shown to be associated with increased risk of cancer in general, with the possible exceptions of testicular and renal cancer (4). A number of studies were retrieved in the published literature discussing the occurrence and/or recurrence of cancer or neoplasm during GH therapy. In one medium-sized and two large studies, GH therapy was not associated with an increase in the incidence of a first cancer compared to the general population.

   However, GH treatment during childhood of survivors of cancer treatment has also been shown to increase slightly the relative risk of a second neoplasm (15), (16). Growth hormone therapy studied in two populations of cancer survivors, one with a control group, found an elevated risk of developing a secondary solid tumour in childhood cancer survivors treated with GH compared with non-treated survivors for one and a statistically significant raised frequency of colon cancer mortality after pituitary-derived GH treatment in another.

   This observation is however disputed, given that other surveillance studies revealed no increase in observed cancer risk (17). The above results are based on a very small number of cases and may therefore require cautious interpretation.

   There have been rare reports of brain tumours (de novo/recurrence) or leukaemia and extra-cranial solid tumour in subjects treated with Saizen® in the post-marketing surveillance period. From the currently available data, there is no evidence suggesting that Saizen® may increase the risk of cancers in treated subjects. It must also be noted that with an overall increase in subject-years of exposure, adverse events (AEs) which are related to commonly experienced medical conditions (as seen in the general population) tend to also be reported in the population treated with GH. However, no increase of reporting rates concerning neoplasms, both de novo and recurrence, was identified cumulatively since first marketing authorization of Saizen®.

4 Study Objectives

Primary objective of the study:

- To assess the long-term safety of Saizen® or other r-hGH treatment for 10 years after cessation of treatment, in terms of occurrence of type 2 diabetes mellitus and malignancies, in a minimum of 200 subjects born SGA who received Saizen® or other r-hGH products for the treatment of short stature

Secondary objectives of the study:

- To assess occurrence of metabolic syndrome
- To assess glucose metabolism parameters
- To characterize the observed malignancies
- To correlate the occurrence of metabolic syndrome and/or glucose metabolism disorders or malignancy to familial inheritance
- To correlate the occurrence of metabolic syndrome and glucose metabolism disorders or malignancy to subject characteristics and medical history.

5 Investigational Plan

5.1 Overall Study Design and Plan

This study is a prospective and retrospective, single-cohort, multicentre, observational long-term post-approval commitment study in subjects born SGA, with no specific age restrictions, who received Saizen® or other r-hGH products for the treatment of short stature. It is a multinational study that will be performed at up to approximately 40 to 60 sites globally. The study will consist of a 10-year post-treatment safety assessment in subjects who were previously treated with r-hGH and who completed or permanently discontinued r-hGH therapy. Eligible subjects may have been enrolled in sponsored clinical studies or may have received r-hGH products in a post-marketing setting. Subjects may be enrolled at any time from the day after their last r-hGH dose up until 5 years after treatment cessation. The maximum duration of follow-up will be 10 years after treatment cessation. All subjects must have received r-hGH products for the treatment of short stature due to SGA as approved per country product label. There is no control group.

The overall objective is to collect safety data with a primary focus on type 2 diabetes mellitus and malignancies during the 10-year follow-up period after termination of r-hGH treatment in the SGA subjects (see section 4).

The aim is to have a final study population of 200 subjects after 10 years of follow-up for analysis. Approximately 300 subjects will be enrolled at study initiation in order to compensate for anticipated loss to follow-up (see section 8.1).

All subjects must sign the Informed Consent Form (ICF) to be enrolled in the study. Subjects may sign the ICF on the day after r-hGH treatment discontinuation (see section 9.2) and up to 5 years after treatment cessation. Prior to enrolment into the study, subjects who are currently being treated with an r-hGH product may be asked to optionally sign a Contact Information Consent Form (CICF) in order to allow the CRO's PMC to contact the subjects and track subject contact information only (see section 9.2).

Because SALTO is a post-treatment observational study, no scheduled study-specific visits, assessments or interventions are scheduled during the study (see section 7.1).

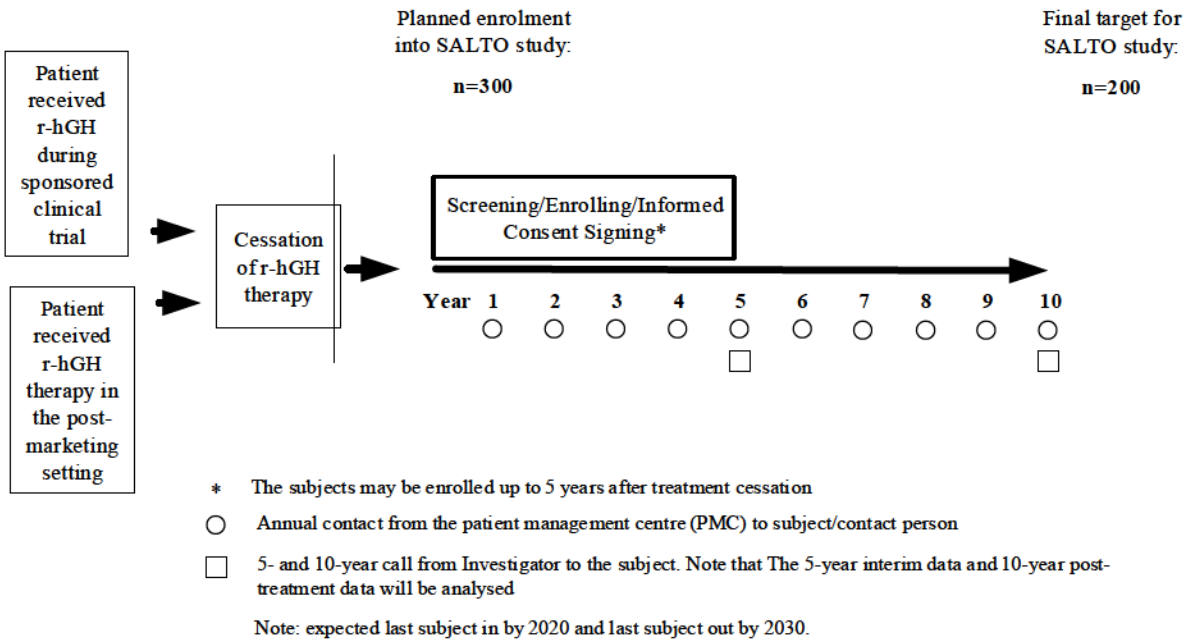
However, clinical data will be collected by the Investigator on an ongoing basis and when available during the course of this study through the subject's treating physician/GP or when provided directly by the subject/person of contact (see sections 7.1; 9.1; 9.2; 10.1). Additionally, the investigator will contact the subjects at roughly 5 and 10 years after discontinuation of r-hGH treatment in order to obtain any additional available relevant medical information (see section 7.1).

In order to minimize the subject loss during the 10 years of the follow-up study, the CRO's dedicated PMC will contact the subjects once a year to update/confirm subjects' and treating physicians' contact information in order to send them the "Yearly Subject and Investigator SALTO kits", and to identify any change in health status/medical history. If any relevant change is identified by the PMC, the PMC will notify the investigator, who will gather the relevant information from the treating physician/GP (see section 7.1).

The 5-year interim data and 10-year post-treatment data will be analysed (see section 8.6). If possible, correlation of type 2 diabetes mellitus and/or malignancy will be assessed against blood pressure, body mass index, lipid parameters, medical history and familial inheritance studies (see section 8.5).

Thus, it is anticipated that most subjects will participate in the present study between 2020 and 2030 (see Figure 1). First patient in in 2011, last patient in by 2020, and last patient out by end of 2030.

Figure 1 Study Design



5.2 Discussion of Study Design

The principal clinical concerns relating to treatment of children born SGA who are treated with GH are the potential for development of metabolic abnormalities associated with insulin resistance (metabolic syndrome or type 2 diabetes mellitus) and the potential for the development of malignancy, as described above. These potential concerns are reflected in the choice of primary and secondary endpoints.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Study Population

The subject population for this study will be any subject born SGA that was treated with Saizen® or other r-hGH products for short stature, and who has permanently ended r-hGH treatment within 5 years prior to enrolment in this study.

5.3.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

Eligible subjects (are):

- Male and female subjects who were born SGA
- Have received r-hGH therapy for the treatment of short stature due to SGA
- Have permanently discontinued r-hGH treatment within 5 years prior to study enrolment
- Parents or guardians and/or subjects have given written informed consent.

5.3.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfil any of the following exclusion criteria:

- Patients unwilling and/or parents/guardians who are not capable of ensuring compliance with the study protocol.
- Patients enrolled in an interventional trial
- Patients enrolled in an observational trial of a similar nature to the SALTO study, where the protocol includes reporting of incidence of type 2 diabetes mellitus and/or malignancies after cessation of r-hGH therapy

5.3.3 Criteria for Randomization or Initiation of Treatment with the Investigational Medicinal Product

Not applicable – this is a post-treatment observational study.

5.3.4 Criteria for Subject Withdrawal

5.3.4.1 Withdrawal from the Study

Subjects will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and they are not obliged to state their reasons.

Withdrawal will be mandatory if the subject is reported to have started an r-hGH therapy during the course of the study.

Subjects who have withdrawn will not be replaced, and the reason for withdrawal will be collected.

5.3.4.2 Withdrawal from the Investigational Medicinal Product

Not applicable – post-treatment observational study.

5.3.5 Premature Discontinuation of the Study

The whole study may be terminated or suspended upon request of Competent Authorities.

5.3.6 Definition of End of Study

The study will end once the last enrolled subject has completed the study (i.e., early termination or 10 years of follow-up after cessation of treatment).

5.3.7 Medical Care of Subjects after End of Study

The study is a post-treatment observational study. The participation of the subject in the study will not have any impact on their routine medical care. Consequently, the end of the study will also have no impact on their medical care.

6 Investigational Medicinal Product(s) and Other Drugs Used in the Study

Not applicable – post-treatment observational study.

6.1 Description of Investigational Product(s)

Not applicable - No investigational medicinal product will be administered during this study, which is a post-treatment follow-up of subjects previously treated with Saizen® or other r-hGH products. The dose and mode of administration of previous r-hGH treatments are those established by the approved prescribing information for each product.

6.2 Dosage and Administration

Not applicable – post-treatment observational study.

6.3 Assignment to Treatment Groups

Not applicable – post-treatment observational study.

6.4 Other Drugs to be used in the Study

Not applicable – post-treatment observational study.

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines

All therapies and medications are allowed during the study, except treatment with r-hGH.

6.5.2 Non-permitted Medicines

No therapies or medications are prohibited during the study, except treatment with r-hGH.

6.5.3 Other Study Considerations

None.

6.5.4 Special Precautions

None.

6.6 Packaging and Labelling

Not applicable - post-treatment observational study.

6.7 Preparation, Handling and Storage

Not applicable - post-treatment observational study.

6.8 Investigational Medicinal Product Accountability

Not applicable - post-treatment observational study.

6.9 Assessment of Investigational Medicinal Product Compliance

Not applicable - post-treatment observational study.

6.10 Method of Blinding

Not applicable - post-treatment observational study.

6.11 Emergency Unblinding

Not applicable - post-treatment observational study.

6.12 Treatment of Overdose

Not applicable - post-treatment observational study.

7 Study Procedures and Assessments

7.1 Schedule of Assessments

This is an observational study. Therefore, no study-specific visits are scheduled in the protocol.

Investigators (i.e., paediatricians and/or endocrinologists) who treat at their clinics short children who were born SGA will be responsible for screening and enrolling subjects. Eligible subjects (see also section 5.3.1) include subjects who completed or permanently discontinued treatment with Saizen® or other r-hGH products within 5 years prior to enrolment in the study. Subjects may have been enrolled in previous sponsored clinical studies with r-hGH in the SGA indication or may have received r-hGH products in a post-marketing setting. In any case, subjects (with parents/guardian as applicable) will need to attend first a screening visit in order to sign the ICF and enrol in the study.

During the course of the study, subjects are not required to visit the study Investigator. Subjects may go to their GP or other treating physician for their routine medical visits. Only information gathered by the treating physician/GP from procedures performed as part of the routine clinical practice may be available for the study. The medical data of interest (see Table 1) for this study (when/if available) will be collected by the investigator from the patient's treating physician/GP. Since the treating physician/GP will document the subject's routine medical data considered necessary for the patient's standard medical care, not all the data of interest described in Table 1 may be available to the study Investigator.

In order to minimize the subject loss to follow-up and to maintain subject motivation during the 10 years of the follow-up study, the CRO's dedicated PMC will contact the subjects once a year to update/confirm subjects' and treating physicians' contact information in order to send them the "Yearly Subject and Investigator SALTO kits", and to identify any change in health status/medical history. If any relevant change is identified by the PMC, the PMC will notify the investigator, who will gather the pertinent information from the treating physician/GP. The detailed content of the "Yearly Subject SALTO kit" is addressed in section 10.1.

In order to ensure adequate collection of the post-treatment medical data of interest, the following activities will be performed:

1. After every yearly call from the PMC, the PMC will update the contact information of the subject and subject's treating physician in the appropriate databases, and send the "Yearly Subject SALTO kit" to the subject/contact person. In addition, the PMC will identify any relevant change on the subject's health status, and will contact the Investigator who will obtain the relevant medical data from the subject's treating physician as previously described.

2. The subject can request a copy of his/her medical history/laboratory results from the treating physician/GP and send it to the Investigator who will enter the information into the electronic case report form (eCRF).

3. The Investigator will call the subject 5 and 10 years after r-hGH discontinuation to obtain any additional available relevant medical information.

Data collection will start once subjects have entered the study and will continue for a maximum of 10 years after discontinuation of treatment with Saizen® or other r-hGH products. Prior to collecting any data, the Investigator (i.e. paediatrician/endocrinologist) will ensure that the subject has provided a signed, written ICF according to the procedure described in section 9.2.

For subjects who have entered the study within the 5-year period after r-hGH treatment discontinuation, any data of interest occurring from the time of permanent cessation of r-hGH therapy up to the signature of the ICF will be retrospectively collected and recorded into the eCRF by the Investigator.

Data reporting is allowed at any time if a subject or his/her Investigator reports an adverse event related to changes in glucose metabolism parameters or to malignancy or to any Serious Adverse Event related to r-hGH treatment.

During subsequent follow-up visits, the Investigator or subject's treating physician/GP (when applicable) will ensure that the subject is informed and updated on the study.

Method of Reporting AEs of Interest

At the time of obtaining Informed Consent, the Investigator will explain the process of reporting an AE to the subject. The subject will be provided with a leaflet containing information on the AEs of interest (i.e., type 2 diabetes mellitus, metabolic syndrome and/or changes in glucose metabolism parameters, fasting insulin levels, HbA_{1c}, 2-hour OGTT results, blood pressure, lipid parameters, and parameters related to malignancies) and key message/information of the Company's post-approval commitment (PAC).

If the subject experiences an AE of interest (see definition of AE of interest in section 7.4.1.1) or a serious adverse event (SAE) of interest, the subject or his/her parents/guardians will be asked to call the PMC on the toll-free phone number that is enclosed in the yearly Subject SALTO Kit. The subject will inform the PMC of the AE/SAE details and the contact information of the treating physician. Upon receipt of the information, the PMC will immediately forward the received information to the corresponding Investigator. The Investigator may follow up with the subject and the subject's physician to confirm the received medical information, and determine if the AE/SAE is relevant for this study. This will be followed by reporting the AE/SAE of interest to the CRO/Sponsor by completing an eCRF and an SAE Report Form in case of SAE.

The timelines and methods for reporting these AEs/SAEs of interest by the Investigator are described in section 7.4.1.2.

Table 1 Summary of Data to be Collected*

Time points	Baseline	At any time over 10 years	At year 5	At year 10
Demographic characteristics and r-hGH treatment history	X			
Medical history/relevant change in medical history	X	X	X	X
Familial medical history/ relevant change in familial medical history	X	X	X	X
Anthropometric parameters				
Height (cm)	X	X	X	X
Weight (kg)	X	X	X	X
Waist circumference (cm)	X	X	X	X
Hip measurement (cm)	X	X	X	X
Occurrence of type 2 diabetes/ glucose metabolism disorders/ metabolic syndrome	X	X	X	X
Occurrence of malignancies (type, histological result, histological result, location, size, grading, severity, treatment, outcome)	X	X	X	X
Metabolic parameters				
Fasting Plasma insulin	X	X	X	X
Fasting Plasma glucose	X	X	X	X
$HbA1_c$ (%)	X	X	X	X
2 hour OGTT	X	X	X	X
Plasma triglycerides	X	X	X	X
HDL-cholesterol	X	X	X	X
LDL-cholesterol	X	X	X	X
Total cholesterol	X	X	X	X
Blood pressure	X	X	X	X
Urinary albumin excretion rate	X	X	X	X
Urinary Albumin:creatinine ratio	X	X	X	X
Concomitant medications (Only relevant concomitant medications are to be collected as per the Investigator's judgement)	X	X	X	X

*** Data to be collected by the Investigator only if available during routine medical care performed by the treating physician/GP**

7.2 Demographic and Other Baseline Characteristics

Demographics, subject's medical history (including age at starting treatment with r-hGH, r-hGH product(s) used, start and stop dates for each r-hGH product used, age at treatment end/permanent discontinuation of r-hGH treatment, duration of r-hGH treatment, maximum dose, clinically significant AEs experienced during r-hGH treatment) and subject's familial medical history will be collected for all subjects and entered into the eCRF by the investigator. For subjects who have

entered the study within the 5-year period after r-hGH treatment discontinuation, baseline characteristics will be comprised of the demographics, subjects' medical history and familial medical history corresponding to the end of r-hGH treatment.

Additional measurements at baseline for this study are as described in section 7.1.

7.3 Assessment of Efficacy

No efficacy parameters are being assessed during this study.

7.4 Assessment of Safety

Safety will be assessed through the recording, reporting and analysis of AEs. Specific safety endpoints (i.e., AEs of interest) will be measured as per study's primary and secondary objectives described in section 4.

The Investigator should report any AE of interest (that may be serious or non-serious, related or unrelated to r-hGH treatment) as described in section 7.4.1.1, whether observed by the Investigator or subject's physician or reported by the subject. Serious Adverse Events of interest and other SAEs assessed as related to r-hGH treatment by the investigator should be reported to the Sponsor as described in section 7.4.1.2 and 7.4.1.4.

The methods of reporting, recording and assessing AEs of interest are described in section 7.4.1.2. The reporting period for the AEs of interest is described in section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Investigational Medicinal Product (IMP), whether or not considered related to the IMP**.**

In this particular study, the following AEs of interest should be reported to the sponsor:

- Type 2 diabetes mellitus, glucose metabolism disorders other than overt type 2 diabetes mellitus, such as abnormal fasting or postprandial glycaemia, abnormal 2-hour OGTT or increased insulin levels or any other component of metabolic syndrome defined by the WHO as insulin resistance + at least two of the following criteria: a) High blood pressure (>=140 mm Hg systolic or >=90 mm Hg diastolic) or taking blood pressure medication, b) Plasma triglycerides >=150 mg/dL (>=1.7 mmol/L); c) HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women; d) BMI greater than 30 and/or waist:hip ratio >0.9 in men, >0.85 in women; e) Urinary albumin excretion rate >=20 µg/min or albumin:creatinine ratio >=30 mg/g (18).

- Any malignancy.

In this particular study only the AEs of interest, which can be assessed by the investigator as related or unrelated to the previously received r-hGH treatment, should be reported to the Sponsor.

It is important to remark that the pre-defined AEs of interest for safety monitoring of this study are defined as the primary and secondary objectives which are described in section 4 (see also Table 1).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity/intensity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (publication date: 9 August 2006). This is a descriptive terminology that can be used for AE reporting.

If a particular AE's severity/intensity is not specifically graded by the guidance document, the Investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death related to AE

Note: Death (Grade 5 as defined by NCI-CTCAE version 3.0) is mainly regarded as an *outcome*, to be documented as described below.

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the treating physician must also report the event as an SAE (see definition below) as per section 7.4.1.4.

The Investigator must also systematically assess the causal relationship of AEs of interest in relation to previous r-hGH treatment, by using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the IMP):

Probable: A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the Investigational Medicinal Product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the Investigational Medicinal Product.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an electrocardiogram [ECG] trace) should not be reported as AEs unless they are associated with clinical signs and symptoms or are considered otherwise medically important by the Investigator or general practitioner. If an abnormality fulfils these criteria, the identified medical condition (e.g. anaemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events (SAEs)

In this particular study, the SAEs assessed by the Investigator as related to the previously received r-hGH treatment, and the SAEs of interest, should be reported to the sponsor.

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product is also considered a serious adverse reaction and all such cases should be reported in an expedited manner as described in section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Hospitalisation for routine check-up should not be reported as a SAE. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at study start, that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

Complete, accurate and consistent data on all SAEs and AEs of interest (serious or non-serious, related or unrelated to previous r-hGH treatment) experienced at any time during the reporting period (defined in section 7.4.1.3) will be documented by the Investigator in the appropriate section of the eCRF. All serious AEs must be additionally documented and reported using an SAE Report Form as described in section 7.4.1.4.

The CRO, PPD, will check legibility, consistency and plausibility of all AE reports and will forward all these reports to the Sponsor (Merck KGaA) within 24 hours. Furthermore, PPD will serve as an interface between the Sponsor and the site/Investigators, and will ensure that queries and follow-up information are managed accordingly.

It is important that each AE report (in the eCRF/SAE Report Form) includes a description of the event, its duration (onset/start and resolution/end dates), its severity, its relationship with the previous r-hGH treatment, any other potential causal factors, any treatment given or other action taken, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance is defined as the 10-year period after cessation of r-hGH treatment (i.e., during the 10 years after the date of last r-hGH administration).

7.4.1.4 Procedure for Reporting Serious Adverse Events

In the event of any new SAE related to the previous r-hGH treatment or any SAE of interest (related and not related) occurring during the reporting period, the Investigator must immediately (i.e. within a maximum **24 HOURS** after becoming aware of the event) inform the CRO, PPD , by phone, fax or by email. Non-serious AEs of interest (related and not related) are sent to the CRO within one week. The reports have to be sent by phone, fax or by email to the contact details below:

Email: PPD

Fax: PPD

Safety Hotline: PPD

The CRO, PPD , will check legibility, consistency and plausibility of all AE reports and will forward all these AE reports to the Sponsor (Merck KGaA) within 24 hours. Furthermore, PPD will serve as an interface between the Sponsor and the site/Investigators, and will ensure that queries and follow-up information are managed accordingly.

When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or email, in the format of a SAE Report Form.

Reporting procedures and timelines are the same for any new information on a previously reported SAE related to r-hGH treatment or SAE of interest (= follow-up).

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the SAE Report Form or the protocol, or as applicable, in a specific document including Sponsor contact details.

All written reports on SAEs should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions. Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). In all cases, the information provided in the SAE Report Form must be consistent with the data on the event that are recorded in the corresponding sections of the eCRF.

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE of interest within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Merck KGaA personnel, although in exceptional circumstances the Global Patient Safety department may contact the treating physician directly to obtain clarification or to discuss a particularly critical event.

7.4.1.5 Safety Reporting to Regulatory Authorities, Investigators and Ethics Committees

The Sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable specific requirements related to the reporting of SAEs involving his/her subjects to the Ethics Committee (EC) that approved the study.

The Sponsor will inform the Investigator or general practitioner of findings that could adversely affect the safety of subjects in accordance with applicable laws and regulations.

The Investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety reports directly to the concerned lead EC and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned EC of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

7.4.1.6 Monitoring of Subjects with Adverse Events

Type 2 diabetes mellitus, metabolic syndrome and/or changes in glucose metabolism parameters (glycaemia parameters- fasting blood glucose and postprandial glucose, fasting insulin levels, HbA_{1c}, 2-hour OGTT results, blood pressure, lipid parameters) and any malignancy that occurs during the course of the study and any SAE that is considered to be probably or possibly related to previous r-hGH treatment. Correlation of type 2 diabetes mellitus and/or malignancy will be established against blood pressure, body mass index, lipid parameters, medical history and familial inheritance.

Safety reports submitted to Global Patient Safety (related SAEs, AEs and SAEs of interest) will be followed up. Reasonable attempts to obtain this information must be made and documented. It is the responsibility of the subject's medical care provider to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Not applicable. Subjects are not exposed to drug during this observational study. Nevertheless, any SAE in a pregnant women or the newborn assessed as related to the previously received r-hGH treatment should be reported as described in section 7.4.1.4.

7.4.3 Laboratory Assessments

No scheduled laboratory assessments are required by protocol. Nevertheless, laboratory data of interest related to glucose metabolism, metabolic syndrome or any malignancy (see Table 1)

deemed necessary and requested by the treating physician/GP as part of the subject's standard medical care, will be, when available, recorded into the eCRF by the Investigator (see section 7.1).

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Blood pressure, height, weight and waist circumference will be collected when available.

7.5 Pharmacokinetics

Not applicable.

7.6 Biomarkers/Pharmacogenetics (PGX)

Not applicable.

7.7 Other Assessments

Not applicable.

8 Statistics

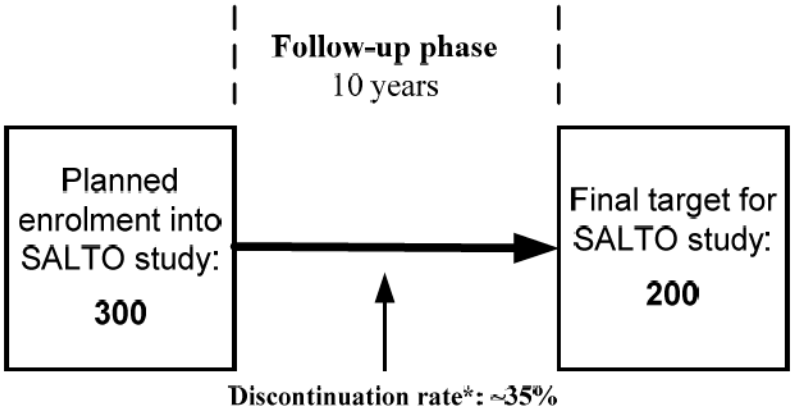
8.1 Sample Size

It has been agreed with the Health Authorities to organize an observational study to have follow-up data on a minimum of 200 subjects born SGA for 10 years after cessation of Saizen® or other r-hGH therapies.

It has been estimated that up to 35% of subjects are likely to be lost or will drop out during the 10-year study duration (which can be due to withdrawal of consent, lost to follow-up, or death). Therefore, it was decided to recruit approximately 300 subjects in the SALTO study to have the 200 subjects for the final analysis at 10 years of follow-up. The sample size of 300 subjects represents 150% of the 200 subjects completing the study, as requested by the Health Authorities.

While recruitment is still open, the Sponsor will closely monitor the subject dropout rate to determine the need to recruit additional subjects. If the attrition rate is anticipated to be greater than 35%, additional subjects may be recruited to maximize the probability that 200 patients will have completed the study.

Figure 2 **Determination of planned sample size.**



*Discontinuation includes: Lost to FU, protocol deviation, non-compliance, AEs, patient decision and other reasons.

8.2 Randomization

This is an observational study, therefore randomization is not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

The number and proportion of subjects diagnosed at any time during the 10-year follow-up will be tabulated for the two primary endpoints:

- Type 2 diabetes mellitus
- Any malignancy

8.3.2 Secondary Endpoints

- Metabolic syndrome and/or changes in glucose metabolism parameters as per
  - Glycaemia parameters, fasting plasma glucose and postprandial glucose, and/or fasting plasma insulin levels
  - HbA1c
  - 2-hour OGTT results
  - Blood pressure
  - Lipid parameters.
- Malignancies (including typology, size and location, as applicable, grading, severity, treatment, outcome)
- Correlation of type 2 diabetes mellitus and/or malignancies will be established against

- Blood pressure (BP)
- Body Mass Index (BMI)
- Lipid parameters
- Medical history
- Familial inheritance

8.3.3 Efficacy Endpoint(s)

Not applicable

8.3.4 Further Endpoints of Interest

Not applicable.

8.4 Analysis Sets

The **safety population** will be defined as all subjects having been included in the present study and have received r-hGH at least once for treatment of short stature due to SGA.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

No statistical significance testing will be performed. The study will contribute to the estimation of the incidence of type 2 diabetes mellitus and the incidence of any malignancy among study participants. Detailed information on statistical analyses and the minimum available data points required to calculate correlations will be specified in the statistical analysis plan (SAP).

8.5.2 Analysis of Primary Safety Endpoints

For primary endpoints, details for each subject of the safety population will be listed and will include at least; time on follow-up, onset date(s) of event(s) and description of event(s).

In parallel with numbers and proportions of subjects experiencing the events, the incidence rate per subject-years of follow-up will be calculated during the 10-year follow-up. The subject-time of follow-up will be defined as the time between the day of last r-hGH treatment and the end of the 10-year period. Furthermore, an analysis of association of the primary endpoints with subject characteristics (e.g., age, sex, blood pressure, BMI, family history) and possible confounding factors of the diseases (e.g., concomitant treatment, medical history, environmental factors) will be conducted. Exploratory analysis will be performed by each brand of r-hGH product if permitted by sample size per brand.

Further details will be provided in the SAP.

8.5.3 Analysis of Secondary Safety Endpoint(s)

All secondary endpoints will be analysed using appropriate statistics. For quantitative variables, statistics are the number of non-missing values (N), number of missing values, mean, standard deviation (SD), minimum (Min), first quartile (Q1), median, third quartile (Q3) and maximum (Max). For qualitative variables, statistics within categories are number of non-missing values (N), number of missing values and percentages of subjects.

Further details will be provided in the SAP.

8.5.4 Efficacy Analyses

Not applicable.

8.5.5 Analysis of Further Endpoints

Not applicable.

8.6 Interim Analysis

All the analyses described above (primary and secondary safety endpoints) for the 10-year final analysis will also be performed at 5 years after cessation of r-hGH treatment.

The 5-year interim analysis will be performed when 200 subjects enrolled in the study will have completed the 5-year study period after discontinuation of r-hGH treatment, and will include the available clinical data from 5 years after discontinuation of r-hGH treatment.

Further details will be provided in the SAP.

8.7 Imputation of missing data

Imputation of missing data will be performed for the analyses performed at the 5- and 10-year time points. An example is given as follows:

- If a subject experienced an event after 3 years and then dropped-out at 4 years, then this subject will be incorporated into the 5- and 10-year analyses as having had the event.
- If a subject dropped-out at a given time *t* without having experienced an event, this subject will not be included in subsequent analyses (after time t).

This imputation of missing data will not be applied to analyses of "subject-years".

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

Investigators are responsible for screening and enrolling subjects into the study, for informing subjects of study process, for collecting subjects' demographic and medical data, for contacting the treating physician/GP when medical data is available, for following-up with the subjects at year 5 and 10 as well as for entering the relevant information into the eCRF for each subject.

Investigators will enrol subjects who have received Saizen® or other r-hGH products for the treatment of short stature due to SGA, as part of clinical studies or the post-marketing setting. Furthermore, Investigators will be encouraged to inform subjects who are still under r-hGH treatment about the EMR 200098_008/ SALTO study.

Even though patients will sign an ICF and enter into the study once r-hGH therapy is completed or permanently discontinued, the investigator will ask the subjects to provide a CICF while still on therapy, in order to allow the CRO's PMC to contact the subject and track subject contact information. The signature of the CICF is optional and will not limit the patient's participation in the SALTO study once eligibility criteria are met (see section 9.2).

As soon as the subjects complete or permanently discontinue treatment with Saizen® or other r-hGH products, the Investigators will be able to invite the subjects to participate in this observational study. At Sponsor's request he/she should obtain the written informed consent from the subject if he/she is an adult and also from the two parents or the legal guardian if he/she is minor. When minors reach the legal age, the Investigator will request written informed consent again. The Investigators will ensure that the subject's ICF will not be signed before these subjects have completed or have permanently discontinued or withdraw from r-hGH treatment (see also section 9.2).

Investigators will be also encouraged to re-contact or call back patients from their clinic who have permanently discontinued r-hGH treatment within a maximum of 5 years previously, in order to obtain consent to be enrolled into the study.

During the course of the SALTO study, subjects may no longer be required to visit their Investigator. Therefore, to ensure adequate collection of the post-treatment data, Investigators will obtain medical information through the subject's treating physician or GP. In addition, Investigators will contact subjects 5 and 10 years after discontinuation of r-hGH treatment to inform them of study development and to obtain any additional available relevant medical data for the study (see section 7.1).

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation/enrolment in the study is his/her written informed consent. The subject's written informed consent to participate in the study must be given before any data collection activities are started. The subject may sign the ICF and be enrolled the day after his/her last r-hGH dose and up to 5 years after permanent cessation of treatment.

Even though patients will sign the ICF and will enter into the study once r-hGH therapy is completed or permanently discontinued, subjects will be asked to provide a CICF while still in therapy in order to allow the CRO's PMC to contact the subject and track subject contact information. The signature of the CICF is optional and will not limit the patient's participation in the SALTO study once eligibility criteria are met.

A subject information sheet in the local language will be prepared and provided by the Sponsor or Sponsor's representative to obtain informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject verbally of all pertinent aspects of the study. The language used in doing so must be chosen so that the information can be fully and readily understood by laypersons. The informed consent process will follow the national regulations and hospital procedures.

In the particular case where the subject is minor, the Investigator should also give adequate information to his/her parents or his/her legal guardian about the purpose of the observational study before obtaining their written informed consents. When minors reach the legal age, written informed consent will be obtained again.

The ICF must be signed and personally dated by the Investigator, the subject and his/her parents or legal guardian. The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent form should be provided to the subject and his/her parents or guardian prior to participation.

In addition, the parents, legal guardian or the subject will be asked to complete a specific document to identify two adult members of the family to be the contact of the Investigator or the CRO during the study period. One of these people will be the main study contact and the second nominated person will be a backup if there is a problem contacting the main person. The main contact person may possibly be the subject him/herself. Name, address and phone number of the two contacts in the family will be collected and recorded in a specific and independent database which will be only used to reach this person.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained.

A PPD subject numbering convention as shown in Table 2 will be used. This convention will ensure the subject numbering in the database (and all subsequent data reporting to authorities) is matching the protocol number. The subject numbering will be as follows:

PPD

This number will serve as the subject's identifier in the study as well as in the clinical study database. All subject's data collected in the study will be stored under this number.

Data protection and privacy regulations will be observed during transfer, processing and storage of subject's data. Subject will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

The CRO will use two separate databases in this study to capture the data.

The first type of database will serve to store subject contact details in order to maintain contact with the participating subjects during the 10-year study period. This database will be updated according to the provided data from the yearly Subject SALTO Kit and from the yearly call from the PMC.

The second database will contain the anonymous clinical subject data recorded. All clinical data will be validated prior to entry in the database. There will be no connection between the two databases because both will be hosted and maintained using two independent servers.

This data processing will be the responsibility of the CRO data management in accordance with the CRO's data management procedures. Database lock will occur once quality assurance procedures have been completed.

9.4 Emergency Medical Support and Subject Card

This study is a post-treatment observational study therefore no Emergency Medical Support will be needed for the subject.

9.5 Subject Insurance and Compensation to Subjects

This is a post-treatment observational study, therefore no Sponsor insurance coverage is required. Subjects will not be compensated.

9.6 Independent Ethics Committee

Before the commencement of the study, the protocol will be submitted for approval according to the regulations and requirements as appropriate for the participating countries.

9.7 Regulatory Authorities

Before the commencement of the study, the protocol will be submitted for approval according to the regulations and requirements as appropriate for the participating countries.

10 Study Management

10.1 Case Report Form Handling

The study will use an electronic Case Report Form (eCRF).

The main purpose of the eCRF is to obtain, when available, those data required by the study protocol in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents. The eCRFs are regulatory documents and must be suitable for authority inspections and submissions to the Health Authorities.

To collect subject's relevant medical data over the 10-year follow-up period after cessation of r-hGH treatment, Investigators will be asked to complete an eCRF document with the available data.

The Investigators must ensure that the eCRFs and any other associated documents forwarded to the CRO remain confidential.

To ensure the maximum data possible is collected during the study, the CRO's PMC will contact the subject or the main contact person every year to update/confirm the subject's and treating physician/GP's contact information to know where the "Yearly Subject SALTO Kit" should be sent.

The "Yearly Subject SALTO Kit" will contain but will not be limited to:

- Pre-stamped envelope including the CRO address.
- The CRO's toll-free phone number
- Subject card to complete and update personal and treating physician/GP information
- The information notice explaining the study for the treating physician/GP
- Pocket size leaflet including study summary and the post approval commitment (PAC)
- A printed copy of the eCRF page with the medical and laboratory data to be collected (to be given to the GP to fill up at the moment of a visit (optional)
- A release of information authorization to be provided to the treating physician/GP to allow the transfer of medical information from the treating physician/GP to the investigator
- Pocket size leaflet including general information about AE/SAEs of interest.

Simultaneously, the CRO will also send an Investigator-specific yearly package to all participating Investigators to keep them informed, motivated and increase their awareness of the study developments.

This will include, but may not be limited to;

- Subject's treating physician/GP contact information.
- Subject's personal contact information.
- Pocket size (inclusion and exclusion criteria)
- Pocket size PAC and information on AE of interest and SAE reporting procedure

In addition, Investigators will be updated on a regular basis with a newsletter.

10.2 Source Data and Subject Files

The Investigator will be requested to keep source data in accordance to his/her own routine practice and applicable local and regulatory requirements.

10.3 Investigator Site File and Archiving

The Investigators, who participate in EMR 200098_008 study, will be provided with an Investigator Site File upon initiation of the study. This file will contain all documents necessary for the conduct of the study and will be updated and completed throughout the study. It must be available for review by the Monitor, during and after the study, and must be safely archived for at least 15 years after the end of the study. The documents to be thus archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Authorities

Central remote monitoring will be conducted for this study. CRO monitors may conduct on-site visits to the sites for the purpose of monitoring various aspects of the study. Health Authority inspectors, Representatives of the Sponsor's Development Quality Assurance unit or a designated organization must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, and the subject's original medical records/files.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual clinical study report, will be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

10.5 Changes to the Protocol

Changes to the protocol will be documented in written Protocol Amendments and submitted for approval to the regulatory bodies as per the requirements.

Any amendment that could have an impact on the subject's agreement to participate in the study requires the subject's informed consent prior to implementation (see section 9.2).

The two previous protocol amendments were non substantial and administrative, and pertained to the change of medical responsible in the Company.

- Protocol Amendment No. 1: 15 April 2010
- Protocol Amendment No. 2: 17 November 2010
- Protocol Amendment No. 3: 17 November 2010
- Protocol Amendment No. 4: 25 February 2016
- Protocol Amendment No. 5: 23 April 2018

10.6 Study Report and Publication Policy

10.6.1 Study Report

The study Sponsor will prepare the 5-year interim study report and the final study report of 10-year follow-up. Both reports are planned to be completed within 12 months after the 5-year and 10-year follow-up periods.

10.6.2 Publication

All the results and data from this observational study are the property of the Sponsor. The Sponsor reserves the right to use the data of this study.

The Investigators will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the study or its results (abstracts, posters, oral presentations, manuscripts, etc.) in any venue, either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

Study results will be published under the responsibility of the Sponsor.

11 References

1. Industria Farmacéutica Serono Sp.A. List of post approval commitments: Saizen (somatropin, r-hGH); extension of indication: growth disturbance in short children born small for gestational age (SGA). IT/H/0025/002-006/II/49, 1-3. 2005. Rome, Italy
2. Clayton PE, Cianfarani S, Czernichov P, Johannsson G, Rapaport R, Rogol A. Consensus statement: management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endo Metab 2007; 92:804-10
3. Van Dijk M, Banninck EMN, van Pareren YK, Mulder PGH, Hokken-Koelega ACS. Risk factors for diabetes mellitus type 2 and metabolic syndrome are comparable for previously growth hormone-treated young adults born small for gestational age (SGA) and untreated short SGA controls. J Clin Endocrinol Metab 2007; 92:160-65
4. Lee PA, Kendig JW, Kerrigan JR. Persistent short stature, other potential outcomes, and the effect of growth hormone treatment in children who are born small for gestational age. Pediatrics 2003; 112:150-62
5. Merck Serono. Post-marketing surveillance commitment; extension of indication: Saizen in SGA. IT/H/0025/002-006/II/49, 1-7. 2006
6. Merck Serono. Saizen treatment in children with short stature who were born small for gestational age: analysis of final height data and long-term treatment efficacy and safety from combined phase III studies: summary report. 0900e0ef802afc6, 1-187 2006
7. Merck Serono. Saizen 8mg click.easy. 2006. Middlesex, UK
8. Merck Serono. Saizen®; [somatropin(rDNA origin) for injection]; for subcutaneous or intramuscular injection. 2007
9. Hokken-Koelega ACS, Sas T, van Pareren Y. Effects of long-term growth hormone treatment on body composition, carbohydrate metabolism, blood pressure and lipids in short children born small for gestational age. Horm Res 2003; 59(Suppl 1):138
10. Crabbé R, von Holtey M, Engrand P, Chatelain P. Recombinant human growth hormone for children born small for gestational age: meta-analysis confirms the consistent dose-effect relationship on catch-up growth. J Endorinol Invest 2008; 31:346-51
11. Bramnert M, Segerlantz M, Laurila E, Daugaard JR, Manhem P, Groop L. Growth hormone replacement therapy induces insulin resistance by activating the glucose-fatty acid cycle. J Clin Endo Metab 2003; 88:1455-63
12. Hokken-Koelega A, van Pareren Y, Arends N, Boonstra V. Efficacy and safety of long-term continuous growth hormone treatment of children born small for gestational age. Horm Res 2004; 62(suppl 3):149-54
13. De Schepper J, Thomas M, Beckers D, Craen M, Maes M, De Zegher F. Growth hormone treatment and fat redistribution in children born small for gestational age. J Pediatr 2008; 152(3):327-30

14. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH research society. J Clin Endocrinol Metab 2000; 85:3990-3

15. Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab 2006; 91:3494-8

16. Jenkins PJ, Mukherjee A, Shalet SM. Does growth hormone cause cancer? Clin Endocrinol 2006; 64:115-21

17. Thorner MO. Critical evaluation of the safety of recombinant human growth hormone administration: Statement from the growth hormone research society. The Journal of Clinical Endocrinology & Metabolism 2001; 86:1868-70

18. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. Geneva: World Health Organization 1999

19. Van der Steen M, Smeets CCJ, Kerkhof GF, et al. 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. Feb 2017; 5(2):106-16

12 Appendix: General organization for data processing