Clinical Trial Protocol: 14VR4

	Date
Version 4:	5 Apr 2017
Version 3:	17 Jul 2015
Version 2:	15 Dec 2014
Version 1:	6 Nov 2014

Study Title:	Comparison of Somavaratan (VRS-317), a Long-acting Human Growth Hormone, to Daily rhGH in a Phase 3, Randomized, One-year, Open-label, Multi-center, Non-inferiority Trial in Pre-pubertal Children with Growth Hormone Deficiency. The VELOCITY Study: Versartis Long-Acting Growth Hormone in Children compared to Daily rhGH
Study Number:	14VR4
Study Phase:	3
Product Name:	Somavaratan (VRS-317)
IND Number:	108471
EudraCT Number	2014-004525-41
Indication:	Pediatric Growth Hormone Deficiency
Investigators:	Multicenter
Sponsor:	Versartis, Inc. (Versartis)
Sponsor Contact:	[redacted] [redacted] Versartis
Sponsor's Legal Representative:	[redacted] [redacted] Versartis
Medical Monitor:	[redacted] [redacted] Versartis
Global Project Manager	[redacted] [redacted] ResearchPoint Global
Study Statistician	[redacted] [redacted] ResearchPoint Global

APPROVAL/SIGNATURE PAGE: SPONSOR AND CONTRACT RESEARCH ORGANIZATION

Sponsor:

Versartis, Inc.
4200 Bohannon Drive, Suite 250
Menlo Park, CA 94025

Medical Monitor:

[redacted]
Versar[redacted]

Signature: _____

Date: 5 APR 17

Clinical Operations:

[redacted]
Versartis

Signature: _____

Date: 5th Apul, 2017

Contract Research Organization:

ResearchPoint Global (RPG)
5301 Southwest Parkway
Suite 100
Austin, TX 78735

Project Manager:

[redacted]
ResearchPoint Global

Signature: _____

Date: 10 Apr 2017

Project Statistician:

[redacted]
ResearchPoint Global

Signature: _____

Date: 10 Apr 2017

SUMMARY OF CHANGES IN VERSION 4

Rationale: Changes were made to align this protocol with other somavaratan pediatric GHD study protocols, all of which are intended to enhance safety of subjects. The primary change is the removal of an interim analysis.

1. **Administrative changes**

   - Updated personnel and personnel titles
   - Updated synopsis to reflect changes
   - Removal of new acronyms in abbreviations and definitions
   - Corrected typographical errors

2. **Introduction**

   - **Section 1.1.2 and 1.1.3**

     Updated to include information on the:

     (i) Phase 2/3 study in Japanese GHD children (Protocol J14VR5).

     (ii) Open label Safety Study (Protocol 13VR3). Information added includes details of the dosing, safety, efficacy, and immunogenicity for subjects with 18 months of continuous somavaratan exposure.

3. **Stopping Rules**

   - **Section 3.5.2 *Stopping Rules***

     Clarification of stopping criteria.

4. **Planned Statistical Analysis**

   - **Section 9.1 and 9.8**

     Removal of interim analysis

5. **References**

   - **Section 11 References**

     Updated references.

SYNOPSIS: PROTOCOL 14VR4

SPONSOR:
Versartis, Inc.

NAME OF FINISHED PRODUCT:
Somavaratan (VRS-317)

NAME OF ACTIVE INGREDIENT:
Somavaratan (VRS-317)

STUDY TITLE:
Comparison of Somavaratan (VRS-317), a Long-acting Human Growth Hormone, to Daily rhGH in a Phase 3, Randomized, One-year, Open-label, Multi-center, Non-inferiority Trial in Pre-pubertal Children with Growth Hormone Deficiency.

The VELOCITY Study: Versartis Long-Acting Growth Hormone in Children compared to Daily rhGH

STUDY NUMBER:
14VR4

PHASE OF DEVELOPMENT:
Phase 3

Objective(s):

- *Primary:* Compare the safety and efficacy of subcutaneous somavaratan and daily rhGH during 12 months of treatment
- *Secondary:* Evaluate and compare changes in pharmacodynamic responses (IGF-I, IGF binding protein-3 (IGFBP-3), growth hormone binding protein (GHBP) and acid labile subunit (ALS)), bone age, weight, body mass index, height standard deviation scores, pubertal development, and anti-drug antibody (ADA), responses

STUDY DESIGN:

General
The trial will compare a twice-monthly somavaratan dosing regimen for non-inferiority of treatment effect against daily injections of rhGH. This is an open-label study. Primary data analysis will occur at 12 months. The Sponsor and Investigators will be blinded to the aggregate height velocity data during the trial. An independent statistical consulting group will conduct sample size re-estimation procedures based on the observed variance in height velocity to determine if *a priori* assumptions for the non-inferiority tests were valid and notify the Sponsor if the total sample size should be increased to ensure valid statistical analyses with adequate power.

Safety
Subjects will be monitored for safety throughout their participation in the study. Safety will be monitored by physical examination, fundoscopy inspection of injection sites, vital signs, 12-lead ECGs, and clinical laboratory determinations. Adverse events (AEs) and concomitant medications (CMs) will be captured. AEs will be graded using the Common

Terminology Criteria for Adverse Events (CTCAE v 4.0). AEs will be coded using the MedDRA dictionary and CMs using the WHO Drug dictionary.

A Data and Safety Monitoring Board (DSMB) meeting will be utilized for the Phase 3 study. A DSMB meeting will be held when a minimum of 50 subjects have completed 6 months of active treatment. All available safety, PD, and immunogenicity data will be provided to DSMB members by the contract research organization (CRO). DSMB members will review data for any potential risk to subjects and determine if any protocol-specified stopping criteria have been met. DSMB members will be independent of the Sponsor and will include 3 pediatric endocrinologists with expertise in the diagnosis and management of children with GHD and a representative of the independent pharmacovigilance organization. At the DSMB meetings, members will determine if stopping criteria have been met for the somavaratan treatment arm.

Subjects meeting individual Stopping Criteria will be withdrawn from the trial. These include:

1. The Principal Investigator and/or Medical Monitor conclude it is unsafe for the subject to continue.
2. A new diagnosis of a significant medical condition or initiation of a new treatment if such a condition or the new treatment can influence the response to study drug (e.g., diabetes, renal failure).
3. Individual subjects with a change in HT-SDS ≤ 0 in the past 6 months may be withdrawn from treatment at the discretion of the PI and Medical Monitor

For subjects with IGF-I SDS ≥ 3, a repeat peak IGF-I sample should be obtained. For subjects with consecutive IGF-I SDS ≥ 3, the PI and Medical Monitor will determine if the subject may proceed with a dose reduction or be removed from the study.

The Stopping Criteria for the somavaratan arm include:

1. The determination is made that it is unsafe to continue because of unexpected adverse events.
2. A high frequency or unusual severity of expected events such as intracranial hypertension (IH), slipped capital femoral epiphyses (SCFE), progression of scoliosis or other.

Pharmacokinetics (PK) and Pharmacodynamics (PD)

The PK parameters will be assessed for the somavaratan treatment cohort only. The PD parameters are IGF-I and IGFBP-3 concentrations (GHBP and ALS as exploratory PD parameters). Sample collection for peak values of PK/PD parameters in the somavaratan treatment cohort will occur 3 ± 1 days after somavaratan dosing at 1, 3 and 9 months. Sample collection for trough values of PK/PD parameters in the somavaratan treatment cohort will occur within 3 days prior to somavaratan dosing at 6 months (sample collection prior to dosing) and at the end of the dosing interval at 12 months. Sample collection for PD parameters in the daily rhGH group will occur at each in-clinic visit (Day 1, and at 1, 3, 6, 9, and 12 months).

Descriptive PK parameters (somavaratan concentrations) and PD parameters (IGF-I, IGFBP-3, GHBP and ALS) will be determined. For each subject, IGF-I C_{max} and change from baseline will also be compared to age-and gender specific normative data and expressed as both concentrations and standard deviation scores (SDS).

Efficacy

The primary efficacy endpoint for this study is annual height velocity (cm/yr) in the first year (12 months) of treatment.

Secondary efficacy endpoints include: changes in height standard deviation score, bone age relative to chronological age (BA/CA), body mass index, body weight, IGF-I, IGFBP-3 and pubertal staging.

Study Population:

The study population will consist of naïve to treatment, pre-pubertal children with growth hormone deficiency (GHD). A 3:1 randomization ratio will be used for the somavaratan treatment cohort and the daily rhGH treatment cohort, respectively. Screening and randomizations will continue until a minimum of approximately 84 subjects have been enrolled or enrollment has been completed based on the sample size re-estimation procedure.

CRITERIA FOR INCLUSION AND EXCLUSION

Inclusion Criteria:

1. Chronological Age ≥ 3.0 years and ≤ 10.0 (girls) and ≤ 11.0 (boys).
2. Pre-pubertal status: Absent breast development in girls, testicular volume <4.0 mL in boys.
3. Diagnosis of GHD as documented two or more GH stimulation test results ≤ 10.0 ng/mL. The use of prior GH stimulation test results is permitted providing the

stimulatory agents, GH assay and test result are approved in writing by the medical monitor.

4. Height SDS ≤ -2.0 at screening.
5. Weight for Stature ≥ 10th percentile.
6. IGF-I SD score ≤ -1.0 at screening.
7. Delayed bone age (≥ 6 months as determined by the central reader). Left hand X-Ray must be obtained within 90 days of screening visit or during screening.
8. Normal thyroid function test results at screening visit (or a minimum of four weeks of thyroxine replacement therapy prior to study drug administration).
9. Available adrenal function test results at screening visit (or in the preceding 6 months) in all subjects without a minimum of four weeks glucocorticoid replacement therapy prior to study drug administration. The following interpretive guidelines will be used:
    a. Morning cortisol (06:00-09:00 hr):
        i. Normal >10.0 µg/dL
        ii. Intermediate 6.0-9.99 µg/dL
        iii. Low <6.0 µg/dL ***or***
    b. ACTH, Glucagon, Insulin or other Stimulation test:
        i. Normal >20.0 µg/dL
        ii. Intermediate 15.0-19.9 µg/dL
        iii. Low < 15.0 µg/dL

    Subjects with low cortisol values must receive glucocorticoid treatment for a minimum of 4 weeks before study drug administration. Subjects with intermediate cortisol values should receive temporary stress doses of glucocorticoid at the discretion of the Investigator.
10. Pathology relating to cause of GH deficiency must be stable for at least 6 months prior to screening.
11. Legally authorized representatives must be willing and able to give informed consent.

Exclusion Criteria:

1. Prior treatment with any growth promoting agent (e.g., GH, IGF-I, GH releasing hormone (GHRH), gonadotrophins, sex steroids). Up to 10 day exposures to a

growth promoting agent for diagnostic purposes are permitted if administered 30 or more days prior to screening.

2. Documented history of, or current, significant disease (e.g., diabetes, cystic fibrosis, renal insufficiency). In all cases of concurrent disease, screening must be approved in writing by the medical monitor.
3. Chromosomal aneuploidy, significant gene mutations (other than those that cause GHD) or confirmed diagnosis of a named syndrome (e.g., Russell Silver, Prader Willi, Turner, etc.).
4. Birth weight and/or birth length less than 5th percentile for gestational age using gestational age growth charts.
5. A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), use of ADHD medications or a likelihood of starting ADHD medications during study participation.
6. Daily use of anti-inflammatory doses of glucocorticoid.
7. Prior history of leukemia, lymphoma, sarcoma or cancer.
8. Treatment with an investigational drug in the 30 days prior to screening.
9. Known allergy to constituents of the study drug formulation.
10. Ocular findings suggestive of increased intracranial pressure and/or retinopathy at screening.
11. Significant spinal abnormalities including scoliosis, kyphosis and spina bifida variants.
12. Significant abnormality in screening laboratory studies (as assessed by PI ***and*** medical monitor).
13. Current social conditions which would prevent completion of study activities (e.g., planned family move to a distant location).
14. History of pancreatitis or undiagnosed chronic abdominal pain.
15. History of spinal or total body irradiation.
16. Subjects with other pituitary hormone deficiency who are not treated properly.
17. Unwillingness to provide consent for participation in all trial activities.
18. Unwillingness to accept dose assignments.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Somavaratan will be administered as subcutaneous bolus injection(s) in the thigh, abdomen, upper arms or buttocks. Injection sites will be rotated. rhGH will be administered as a subcutaneous bolus injection per instructions in the Dosage and Administration section of the Prescribing Information. The first dose of study drug (somavaratan or rhGH) will be administered at the investigators site and thereafter by a trained parent/guardian or a designated health care professional.

The dosing regimen for the somavaratan treatment cohort is 3.5 mg/kg twice-monthly (twice per month; every 15 days ± 2 days). The dose for the daily rhGH comparator group is 34 µg rhGH/kg per day (or 0.24 mg rhGH/kg/week).

DURATION OF TREATMENT:

Subjects will be treated with somavaratan or daily rhGH treatment for 12 months and may then elect to enroll in the long-term safety study and continue or start somavaratan treatment (Protocol 13VR3).

CRITERIA FOR EVALUATION – SAFETY

The following evaluations will be performed to assess study eligibility and safety:

Physical examination including injection site(s) evaluation

Vital signs including sitting blood pressure, pulse rate, temperature and respiratory rate

Laboratory tests: complete blood count, chemistry, hemoglobin A1c, thyroid function tests (Free T4 and TSH), urinalysis, 12-lead ECGs, and antibodies to somavaratan and hGH.

Adverse events (AEs)

Ocular fundoscopy (North America)

Concomitant medications

CRITERIA FOR EVALUATION – PHARMACOKINETICS AND PHARMACODYNAMICS

Descriptive pharmacokinetic (PK) parameters include treatment group specific peak and trough values for somavaratan concentrations. Pharmacodynamic (PD) parameters include peak and trough values of IGF-I and IGFBP-3 (GHBP and ALS as exploratory PD parameters).

CRITERIA FOR EVALUATION – EFFICACY

Standing height (by stadiometer, in triplicate and without shoes)

Body weight (in light clothing and without shoes)

Bone Age as assessed by central reader at Enrollment and at 12 months

STATISTICAL METHODS:

Summaries of subject disposition, demographics, disease characteristics and response to dosing of study medication will be provided for each treatment group. All summaries of continuous data will be presented as means (SD), and/or with medians with min/max as appropriate. Count data will be presented as number within each treatment group and % of subjects within each group.

Summaries of all adverse events (AEs), serious adverse events (SAEs) and Suspected, Unexpected Serious Adverse Reactions (SUSARs) will be reported. The incidence of CTCAE Grade 3 or 4 adverse events will be classified according to severity and relationship to study drug.

The study is open-label. The Sponsor and Investigators will be blinded to aggregate height velocity data throughout the trial.

Study sites will be pooled into two Regions: North America and Europe. The randomization will be stratified by Region, age (above and below anticipated median age of 7.5 years) and baseline IGF-I SDS (above and below anticipated median of -1.7). Randomization tables will be prepared by the CRO. The subjects will be randomized upon notification of subject eligibility by the medical monitor.

An intention to treat (ITT) population will be used for the primary evaluation of efficacy. The Primary endpoint will be the non-inferiority of somavaratan treatment height velocity compared to daily rhGH after 12 months on treatment. For subjects completing less than the 12 months of treatment, missing height at 12 months will be imputed from the last available height SDS, with a reduction of 2 cm/yr for subjects in the somavaratan group. This imputation calculates the height at 12 months from the height SDS observed at study exit. This is equivalent to a subject not having gained any more height relative to the age specific height (i.e., no treatment response) since study exit. The reduction of 2 cm/yr, the non-inferiority margin, only for the somavaratan imputed value avoids imputing to a common mean.[31] Multiple imputation technique will also be used to further evaluate role of missing data.

For the growth and bone age endpoints, the least squares means and confidence interval of the treatment groups from an ANCOVA model will be used to determine non-inferiority. The ANCOVA model will use the endpoint (e.g., height velocity) as the dependent variable, with treatment and region as fixed effects, and include age, baseline IGF-I SDS as covariates. Other covariates will be considered as appropriate. A per protocol analysis for subjects completing 12 months of treatment with <10% missed or incorrect dosing will also be performed.

The gender, age, height and weight of subjects entering puberty at one year will be described. Onset of puberty is defined as the appearance of Tanner stage 2 breast development in girls and a testicular volume ≥ 4 mL in boys.

Potential treatment differences in IGF-I and IGFBP-3 responses will be evaluated with ANCOVA models, with treatment and region as fixed effects and other covariates as appropriate.

An exploratory analysis will be conducted to determine if IGF-I responses and ADA status correlate to height velocity outcomes.

Sample size estimates are derived from considerations for non-inferiority testing of twice-monthly somavaratan versus daily rhGH. The somavaratan arm will be tested against daily rhGH using a one-sided test procedure. Assuming a 3:1 somavaratan to daily rhGH subject ratio, a standard deviation of ≤ 3.0 cm/yr in annual height velocity, an alpha of 0.05 and a non-inferiority limit for difference in mean height velocity of 2.0 cm/yr, a total of 76 subjects are required: 57 for the somavaratan dosing arm and 19 for the daily rhGH arm. The total number of planned subjects is 84 (76 plus 8 for potential drop-outs). An independent statistical consulting group will conduct sample size re-estimation using the observed variance in height velocity to determine if *a priori* assumptions were valid and notify the Sponsor if the total sample size should be increased to ensure statistical analyses with adequate power.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AGHD	adult growth hormone deficiency
ALT	alanine aminotransferase (SGPT)
ALS	acid labile subunit
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
AUC	area under curve
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CM	concomitant medications
C_{max}	maximum plasma concentration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DP	drug product (somavaratan)
DSMB	data and safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	electronic patient-reported outcome

ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GHD	growth hormone deficiency
GHBP	growth hormone binding protein
GHRH	growth hormone releasing hormone
GLP	Good Laboratory Practice
Hct	hematocrit
HCF	health care facility
Hgb	hemoglobin
hGH	human growth hormone
HIPAA	Health Information Portability and Accountability Act
HPA	hypothalamic-pituitary-adrenal
HT-SDS	height standard deviation score
HV	height velocity
ICH	International Conference on Harmonisation
ICF	informed consent form
IEC	independent ethics committee
IGF-I	insulin-like growth factor-I
IGF-I SDS	insulin-like growth factor-I standard deviation score
IGFBP-3	insulin-like growth factor-binding protein 3
IH	Intracranial hypertension
IND	Investigational New Drug
INN	International Nonproprietary Name
IRB	Institutional Review Board
ITT	Intention to Treat
LDH	lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

NOAEL	no observed adverse effect level
PD	pharmacodynamics
PGHD	pediatric growth hormone deficiency
PI	principal investigator
PK	pharmacokinetic
QP	qualified person
RBC	red blood cell (count)
RPG	ResearchPoint Global
rhGH	recombinant human growth hormone
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOP	standard operating procedure
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half life
T_{max}	time to maximum plasma concentration
TMF	trial master file
TSE	transmissible spongiform encephalopathy
TSH	thyroid stimulating hormone
US	United States
WBC	white blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

Somavaratan (VRS-317) is an investigational recombinant human growth hormone (rhGH) product intended for the treatment of growth hormone deficiency (GHD) in children and adults. Somavaratan is designed to maintain active drug levels for longer periods of time than currently available rhGH therapies. Somavaratan is a novel fusion protein (M.W. 119 kDa) consisting of recombinant human growth hormone (rhGH) and two sequences (XTEN) of hydrophilic amino acids: one sequence attached to the N- and one to the C-terminus of rhGH. The XTEN sequences serve to increase the hydrodynamic diameter of rhGH and delay its clearance by the growth hormone receptor (GHR). [1,2] The somavaratan development program is designed to test whether prolongation of study drug exposures with a reduced frequency of administration can provide similar responses to those seen with daily administration of rhGH. Daily rhGH is currently the only available treatment in North America and Europe for adults and children with growth hormone deficiency. Somavaratan is being developed for twice-monthly administration to children and adults with GHD. It is expected to offer a safe and effective alternative to the current daily injections. An rhGH product administered less frequently than daily rhGH therapy may provide greater adherence and therefore better long-term treatment outcomes for GHD children and adults.

Human growth hormone (hGH) is naturally secreted from the human anterior pituitary as intermittent pulses lasting from minutes to hours, typically occurring during sleep. To promote anabolic and growth processes, hGH binds to the hGH receptor initiating signaling processes involving the STAT (signal transducer and activator of transcription), the MAPK (mitogen-activated protein kinase) and the PI3K (phosphoinositide-3 kinase) pathways. Insulin-like growth factor-I (IGF-I) gene expression is activated from hGH receptor signaling resulting in secretion of IGF-I into the circulation. Although hGH retains unique biological actions, IGF-I is the primary mediator for the growth promoting effects of hGH.[3, 26] As such, IGF-I also serves as the primary pharmacodynamic marker for response to rhGH administration. In the circulation, IGF-I forms a complex with insulin-like growth factor binding protein-3 (IGFBP-3) and the acid labile subunit (ALS). Both IGFBP-3 and ALS expression are also regulated by hGH receptor activation.

GHD in children results from a variety of genetic, neoplastic, inflammatory, post-traumatic and iatrogenic causes.[4] Subjects with untreated childhood onset GHD will have significant growth failure with attainment of adult heights significantly less than five feet in many instances.[6] In addition, there is abnormal body composition with decreased bone mineralization, decreased lean body mass and increased fat mass. Treatment with exogenous rhGH initiates a period of accelerated or “catch-up” growth that when begun at an early age allows attainment of normal adult height and body composition.[5, 6, 7, 8, 9]

Daily rhGH administration does not mimic the normal endogenous pulses of hGH in non-GHD children, but nevertheless results in significant age- and dose-dependent increases in growth with typical first year responses averaging 9.5–11 cm/yr in pre-pubertal children.[10, 11, 12] Alternative pharmacokinetic profiles for rhGH delivery can also be beneficial. Clinical studies of continuous infusion of rhGH with a pump demonstrated comparable growth velocity and IGF-I levels to those achieved with daily rhGH injections.[13, 14, 15] Therefore, continuous, as well as pulsatile, administration of rhGH is efficacious.

Beginning in 1985, national health authorities have approved several rhGH products for daily, long-term administration to children with GHD.[16, 17, 18, 19, 20, 21] Compliance with daily injections for the period of years required to complete childhood and pubertal growth can be a challenge. A lack of compliance with daily rhGH administration is commonplace and can lead to loss of treatment effects.[22, 23, 24] Long-acting rhGH offers the possibilities of many fewer injections, enhanced compliance and attainment of improved treatment outcomes.

In this protocol (14VR4), long term safety, pharmacodynamics (PD), and efficacy of somavaratan will be compared to that of daily rhGH in pre-pubertal, naïve to treatment children with GHD.

1.1 Clinical Experience

1.1.1 Adult Growth Hormone Deficiency

The first in humans study of somavaratan was a randomized, placebo controlled, single ascending dose study of 5 active dosing groups in 50 adult subjects with documented GHD (Protocol 11VR1.1). Somavaratan doses of 0.05, 0.10, 0.20, 0.40 or 0.80 mg/kg were given as a single subcutaneous (SC) dose.[25] Each of the five dosing arms consisted of 8 subjects randomized to active drug and 2 subjects to placebo. Blood samples for PK/PD determinations were obtained at 21 time points over 30 days. Safety monitoring was carried out for 60 days post-dose. Stopping rules were pre-specified by protocol. The membership and activities of the Safety Review Committee (SRC) were specified in the SRC Charter, developed prior to study onset. Safety Review Committee meetings were successfully concluded prior to each dose escalation; no stopping criteria were met at any time point.

In adults with GHD, single dose somavaratan in the specified dose range was safe and well tolerated. There were no serious or unexpected AEs. There was no lipoatrophy or nodule formation at the injection sites. There were no laboratory safety signals. All subjects completed the study.

Single somavaratan doses safely increased the amplitude and duration of IGF-I in a dose-dependent manner. The pharmacokinetics and pharmacodynamics combined with the

observed safety profile indicate the potential to achieve a prolonged clinical response in a safe and effective manner.[25]

1.1.2 Pediatric Growth Hormone Deficiency

1.1.2.1 Protocol 12VR2

The safety and efficacy of somavaratan in naïve to treatment, pre-pubertal subjects with GHD was demonstrated in the Phase 1b/2a study (Protocol 12VR2) with results from this study published in 2016.[27] In that study, somavaratan was safe and well tolerated with an overall safety profile similar to daily rhGH. The IGF-I responses were maintained over each of the dosing intervals studied (1.15 mg/kg weekly, 2.5 mg/kg twice-monthly, or 5 mg/kg once-monthly for six months). No significant overexposure to IGF-I occurred. Over six months, substantial improvements were noted in height standard deviation scores and mean annualized six-month height velocities were similar to annual height velocities for published age-matched historical controls for less severe GHD children receiving 33 µg/kg rhGH daily[13]. There was no undue advancement of skeletal age (bone age). No treatment related serious AEs were reported (subject [redacted] experienced the unrelated SAE of appendicitis). Most treatment related AEs were mild in intensity, but three moderate AEs were reported in two subjects (transient urticaria and arthralgia in subject [redacted] and headache in subject [redacted] Subject [redacted] saw an ophthalmologist who ruled out intracranial hypertension. There were no laboratory safety signals. No nodule formation or lipoatrophy at injection sites were reported.

1.1.2.2 Protocol 13VR3

All subjects completing a somavaratan clinical study are offered participation in a Long-Term Safety Study, Protocol 13VR3. Of 63 subjects who completed Phase 2a, 60 have enrolled in the 13VR3 study. A Safety Review Committee (SRC) reviewed data against the protocol-specified stopping criteria at six month intervals. Four SRC meetings have been held (January and July, 2015, and January and July, 2016) with the conclusion that the study was safe to continue and that no protocol-specified stopping rules have been met. Forty-eight subjects have completed 24 months in the Study (30 months total somavaratan exposure with the most recent 18 months at the Phase 3 dose and schedule).

Adverse events (Grade 2) considered related to somavaratan treatment have been infrequent with four subjects reporting moderate treatment-related AEs of any type. One subject reported moderate headaches on two occasions, both resolved within 24 hours. The subject was evaluated by a neurologist and an ophthalmologist and had a cranial MRI study. There was no evidence for intracranial hypertension. One subject reported moderate headache/migraine on two occasions and was sent home from school. One subject reported

moderate injection site pain. One subject reported moderate obstructive sleep apnea (this subject was later diagnosed with [redacted] and withdrawn from the study).

An intention to treat analysis of the Year 1 and Year 2 height velocities (HV) in the 64 subjects who enrolled in the Phase 1b/2a study (Protocol 12VR2) and 57 subjects who entered year 2 of somavaratan treatment demonstrated that HV was consistent over two years of treatment. Mean HV in cm/yr (SD) was 7.93 (2.34) for 0-12 months and 7.83 (2.27) for 12-24 months. The lack of expected decline in second year HV is attributed to the dose increase to 3.5mg/kg twice monthly, but also illustrates continued efficacy.

1.1.2.3 Protocol J14VR5

A Phase 2/3 study in Japanese GHD children was initiated in Japan in August 2015 (Protocol J14VR5). This study has three stages. The Phase 2 stage will compare the PK/PD profile of up to 24 subjects after receiving single dose somavaratan at 3 dose levels to the same 3 doses studied in the Phase 1b stage of Protocol 12VR2. All subjects completing the single dose Phase 2 stage are offered immediate enrollment into the Phase 2 extension stage where they receive somavaratan twice monthly at the intended Phase 3 dose of 3.5 mg/kg. In the Phase 3 stage, Japanese GHD children will receive open-label somavaratan for 12 months. Approximately 48 children will participate in this study. As of October 1, 2016, three of 20 (15%) have experienced somavaratan related adverse events of any type. Most reported AEs have been mild to moderate and transient. One subject experienced unrelated serious AEs of infection of a congenital cystic adenomatoid malformation and associated lung abscess. One subject experience a serious AE considered possibly related to study drug: a [redacted] year old [redacted] was admitted with status epilepticus and lactic acidosis. Work-up revealed an underlying mitochondrial abnormality. The Phase 2 stage of this study has completed enrollment and preliminary data indicate no meaningful differences between the PK/PD profiles of Japanese children when compared to Western children. Based on these findings, the Phase 3 stage of the study began enrolling in October, 2016.

1.1.3 Summary of Clinical Experience

The safety, tolerability, and PK/PD profiles of somavaratan when administered to GHD adults and children has been initially characterized in Phase 1 and 2 studies, and continues in ongoing long-term safety and Phase 3 studies. Somavaratan is intended for use as a long acting rhGH with twice-monthly dosing. The somavaratan dose ranges studied have provided a comprehensive view of somavaratan safety and efficacy and support the current dose of 3.5 mg/kg twice-monthly in all pediatric GHD subjects. Somavaratan has been safe to administer at all tested doses and frequencies. Reference Safety Information has been established based on overall exposure (including up to 36 months of treatment in Protocols 12VR2/13VR3). Events considered expected for the purposes of regulatory reporting include

injection site pain and headache in adults and children with GHD. Lipoatrophy has been identified as a safety signal but is considered to be low risk due to the fact that it can be mitigated by injection site rotation and preliminary data suggests that it is transient in the majority of cases (recent cases require further follow-up). In adults as well as children, drug exposure parameters (C_{max} and AUC) were proportional to dose.

In the pediatric somavaratan clinical program, normalization of IGF-I exposures did not come at the expense of initial overexposure to IGF-I. Some subjects experienced transient IGF-I SDS levels above the normal range (> 2 SDS), but no clinical or laboratory adverse events that were suspected to be associated with elevated IGF-I levels were reported in the subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

Compare the safety and efficacy of subcutaneous somavaratan and daily rhGH during 12 months of treatment.

2.2 Secondary Objective

Evaluate and compare changes in pharmacodynamic responses (IGF-I, IGF binding protein-3 (IGFBP-3), growth hormone binding protein (GHBP) and acid labile subunit (ALS)), bone age, weight, body mass index, height standard deviation scores, and anti-drug antibody (ADA) responses.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is designed as a pivotal study to compare the safety and efficacy of a selected dose regimen of somavaratan to daily rhGH. The study is a randomized, multi-center, open label study of 12 months duration. The primary endpoint is height velocity at 12 months and will be analyzed by ANCOVA with a test of non-inferiority to compare somavaratan and daily rhGH treatment effects. The Sponsor and Investigators will be blinded to aggregate height data until the study is completed. Up to 136 children will be enrolled from pediatric endocrinology practices participating in Versartis clinical trials in the United States, Canada, and Europe.

Subjects will be monitored for safety throughout their participation in the study. Safety will be monitored by physical examination, inspection of injection sites, vital signs, 12-lead ECGs, and clinical laboratory determinations. Adverse events (AEs) and concomitant medications (CMs) will be captured. AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE v 4.0). AEs will be coded using the MedDRA dictionary and CMs using the WHO Drug dictionary.

3.2 Rationale for Study Design and Control Group

There are currently no preventative treatments for GHD in children or adults. The only approved treatment is daily rhGH. Somavaratan is initially being developed for twice-monthly dosing in GHD children to provide a simpler alternative than daily dosing that may avoid the compliance problems and attendant loss of treatment effect seen with daily rhGH therapy. Accordingly, the pivotal trial for somavaratan is a direct comparison to daily rhGH using a non-inferiority test of hypothesis. Age and IGF-I SDS at baseline are known to affect the primary efficacy endpoint (height velocity). Therefore, subjects will be randomized to receive either somavaratan or daily rhGH. The treatment arms will be balanced for baseline age and IGF-I SDS.

3.3 Rationale for Dose Selection

In Versartis protocols 12VR2 and 13VR3, prepubertal children with GHD have received somavaratan in doses up to 7.0 mg/kg per month. These doses proved safe and effective to increase height velocity and height standard deviation scores. These doses result in a dose-dependent increase in IGF-I SDS without a significant incidence of individual IGF-SDS above the normal range (IGF-I SDS > 2.0) and overall mean of peak and trough IGF-I SDS for individual subjects at or near the middle of the normal range for children (IGF-I SDS = 0). For this study, the selected somavaratan dose is chosen from these previous exposures and is 3.5 mg/kg administered twice-monthly.

The selected daily rhGH dose is 34 µg/kg, the highest dose approved for GHD children in all regions where this study will be conducted.

3.4 Study Duration and Dates

The subjects completing the study will participate for approximately 13 months.

3.5 Safety Reviews and Stopping Rules

A Data and Safety Monitoring Board (DSMB) meeting will be utilized for the Phase 3 study. A DSMB meeting will be held when a minimum of 50 subjects have completed 6 months of active treatment. All available safety, PD, and immunogenicity data will be provided to DSMB members by the contract research organization (CRO). DSMB members will review data for any potential risk to subjects and determine if any protocol-specified stopping criteria have been met.

3.5.1 Data and Safety Monitoring Board Membership

DSMB members will be independent of the Sponsor and include 3 pediatric endocrinologists with expertise in the diagnosis and management of children with GHD and a representative of the independent pharmacovigilance organization.

3.5.2 Stopping Rules

3.5.2.1 Individual Subjects

Subjects meeting individual Stopping Criteria will be withdrawn from the study. These include:

1. The Principal Investigator and/or Medical Monitor conclude it is unsafe for the subject to continue.
2. A new diagnosis of a significant medical condition or initiation of a new treatment if such a condition or the new treatment can influence the response to study drug (e.g., diabetes, renal failure).
3. Individual subjects with a change in HT-SDS ≤ 0 in the past 6 months may be withdrawn from treatment at the discretion of the PI and Medical Monitor.

For subjects with IGF-I SDS ≥ 3, a repeat peak IGF-I sample should be obtained. For subjects with consecutive IGF-I SDS $\geqq 3$, the PI and Medical Monitor will determine if the subject may proceed with a dose reduction or be removed from the study.

3.5.2.2 Somavaratan Treatment Cohort

The Stopping Criteria for the somavaratan treatment arm include:

1. The determination is made that it is unsafe to continue because of unexpected adverse events.
2. A high frequency or unusual severity of expected events such as intracranial hypertension (IH), slipped capital femoral epiphyses (SCFE), progression of scoliosis or other.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population is naïve-to-treatment, pre-pubertal children with documented Growth Hormone Deficiency (GHD). Up to 136 subjects will be enrolled in a 3:1 randomization to somavaratan or daily rhGH treatment cohorts, respectively (up to 102 somavaratan and up to 34 daily rhGH subjects).

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Chronological Age ≥ 3.0 years and ≤ 10.0 (girls) and ≤ 11.0 (boys).
2. Pre-pubertal status: Absent breast development in girls, testicular volume < 4.0 mL in boys.
3. Diagnosis of GHD as documented by two or more GH stimulation test results ≤ 10.0 ng/mL. The use of prior GH stimulation test results is permitted providing the stimulatory agents, GH assay and test results are approved in writing by the medical monitor.
4. Height SD score ≤ -2.0 at screening.
5. Weight for Stature ≥ 10^{th} percentile.
6. IGF-I SD score ≤ -1.0 at screening.
7. Delayed bone age (≥ 6 months as determined by the central reader). Left hand X-Ray must be obtained within 90 days of screening visit or during screening.
8. Normal thyroid function test results at screening visit (or a minimum of four weeks of thyroxine replacement therapy prior to study drug administration).
9. Available adrenal function test results at screening visit (or in the preceding 6 months) in all subjects without a minimum of four weeks glucocorticoid replacement therapy prior to study drug administration. The following interpretive guidelines will be used:

   Morning cortisol (06:00-09:00 hr):

   - Normal > 10.0 µg/dL
   - Intermediate 6.0-9.99 µg/dL
   - Low < 6.0 µg/dL ***or***

   ACTH, Glucagon, Insulin or other Stimulation test:

   - Normal > 20.0 µg/dL

- Intermediate 15.0-19.9 µg/dL
- Low < 15.0 µg/dL

Subjects with low cortisol values must receive glucocorticoid treatment for a minimum of 4 weeks before study drug administration. Subjects with intermediate cortisol values should receive temporary stress doses of glucocorticoid at the discretion of the Investigator.

10. Pathology relating to cause of GH deficiency must be stable for at least 6 months prior to screening.
11. Legally authorized representatives must be willing and able to give informed consent.

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Prior treatment with any growth promoting agent (e.g., GH, IGF-I, GH releasing hormone (GHRH), gonadotrophins, sex steroids). Up to 10 day exposures to a growth promoting agent for diagnostic purposes are permitted if administered 30 or more days prior to screening.
2. Documented history of, or current, significant disease (e.g., diabetes, cystic fibrosis, renal insufficiency). In all cases of concurrent disease, screening must be approved in writing by the medical monitor.
3. Chromosomal aneuploidy, significant gene mutations (other than those that cause GHD) or confirmed diagnosis of a named syndrome (e.g., Russell Silver, Prader Willi, Turners, etc.).
4. Birth weight and/or birth length less than 5th percentile for gestational age using gestational age growth charts.
5. A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), use of ADHD medications or a likelihood of starting ADHD medications during study participation.
6. Daily use of anti-inflammatory doses of glucocorticoid.
7. Prior history of leukemia, lymphoma, sarcoma or cancer.
8. Treatment with an investigational drug in the 30 days prior to screening.
9. Known allergy to constituents of the study drug formulation.
10. Ocular findings suggestive of increased intracranial pressure and/or retinopathy at screening.
11. Significant spinal abnormalities including scoliosis, kyphosis and spina bifida variants.

12. Significant abnormality in screening laboratory studies (as assessed by PI ***and*** medical monitor).
13. Current social conditions which would prevent completion of study activities (e.g., planned family move to a distant location).
14. History of pancreatitis or undiagnosed chronic abdominal pain.
15. History of spinal or total body irradiation.
16. Subjects with other pituitary hormone deficiency that are not properly treated.
17. Unwillingness to provide consent for participation in all trial activities.
18. Unwillingness to accept dose assignments.

4.4 Subject Withdrawals and Replacements

Consent may be withdrawn at any time for any reason by subject or subject caregiver without prejudice to future treatment. The investigators or medical monitor may withdraw a subject if it is judged to be in the best interest of the subject or if it is clear the subject cannot comply with the protocol. For early withdrawals, the tests and evaluations listed for the Month 12 visit should be completed, if possible.

Subjects that develop a new significant medical condition at any point during the trial may be withdrawn.

To achieve the planned sample size for analysis, additional subjects will be enrolled as needed to account for subjects who withdraw prior to completing one month of treatment and Month 1 height evaluations.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Somavaratan Treatment Cohort

All subjects randomized to receive the long-acting investigational drug during the study will receive somavaratan. Somavaratan is a fusion protein consisting of recombinant human growth hormone (rhGH) and two XTEN sequences containing natural amino acids. The XTEN sequences are attached to the N- and C-termini of rhGH. The molecular mass of somavaratan is 119 kDa.

Somavaratan is formulated at a nominal concentration of 100 mg/mL in 20 mM histidine, 154 mM sodium chloride, pH 5.5.

5.1.2 Recombinant Human Growth Hormone Treatment Cohort

All subjects randomized to receive daily recombinant human growth hormone (rhGH) will receive commercially available rhGH indicated for treatment of children with growth failure due to growth hormone deficiency. The Sponsor will procure and supply all rhGH for use in the study. Daily rhGH used in the study will be commercially available product supplied by the Sponsor.

5.2 Treatments Administered

Somavaratan and daily rhGH doses will be calculated using the subjects' body weight obtained at the screening visit (or a body weight obtained within the previous 30 days before baseline dosing if available). Somavaratan and daily rhGH doses will be recalculated based on subject weight at each clinic visit. Somavaratan and daily rhGH doses will be administered subcutaneously by a health care professional or parent/guardian.

The study drug dosing and number of doses in each cohort of the study will be as follows:

Table 1 Study Drug Dosing Information

Cohorts	Study Dose	Frequency of Administration	Duration of Treatment	Total Number of Assigned Study Doses
Somavaratan	3.5 mg/kg	Twice-Monthly[1]	12 months	24
Daily rhGH	34 µg/kg/day[2]	Daily	12 months	365

1: Allowable dosing window is every 15 days ± 2 days
2: Mean dose

Subject body weight and assigned doses will be updated at each clinic visit. Weight-based dose adjustments will not be made in between clinic visits.

5.3 Selection and Timing of Dose for Each Subject

The medical monitor will review results of all available medical history and screening activities and notify the HCF investigator and CRO if the subject may be enrolled in the study.

Subjects completing all screening activities and signing informed consent (and Assent if required) will be randomized in a 3:1 ratio to either somavaratan or daily rhGH treatment, respectively.

Subjects will be dosed on Day 1 and then at twice-monthly intervals (every 15 days ± 2 days) if randomized to the somavaratan treatment cohort or once daily if randomized to the daily rhGH cohort. Study dosing will continue for a total of 12 months.

5.4 Method of Assigning Subjects to Treatment Groups and Subject Number Assignments

Randomization into the study will be based on the order of appearance of subjects successfully completing screening activities with approval by the Medical Monitor. The randomization will be in a 3:1 ratio of somavaratan to daily rhGH, and be stratified by region, subject age and IGF-SDS to assure that the two treatments are not grossly imbalanced for factors that may influence treatment outcomes. A unique Subject Number will be sequentially assigned to each subject. (Table 2).

Table 2 Assignment of Subject Numbers

Cohort	Subject Numbers
Somavaratan	[redacted]
Daily rhGH	[redacted]

Note: All subject numbers may not be allocated.

To achieve the planned sample size for analysis, additional subjects will be enrolled as needed to account for subjects who withdraw prior to completing one month of treatment and Month 1 height evaluations. Subject numbers will not be re-assigned.

The statistician at the CRO will be responsible to implement the randomization. This is an open label study. Subjects, study sites, and the CRO will be informed of the treatment assignment, after randomization.

5.5 Concomitant Therapy

Restrictions on prior and concomitant therapy are provided in the Inclusion and Exclusion Criteria (Sections 4.2 and 4.3). At screening, subjects must be naïve to any form of chronic

growth promoting therapies. Other known pituitary hormone deficiencies must have been treated for a minimum of four weeks prior to study dosing. Adjustments to these medications (thyroid, glucocorticoid and antidiuretic hormones) are permitted during the protocol as required by standard medical practice. The initiation of prohibited medications described in Sections 4.2 and 4.3 is cause for subject withdrawal.

The status of the hypothalamic-pituitary-adrenal (HPA) axis of all subjects will be documented by the PI and verified by the medical monitor before subject entry into a treatment cohort is approved. Subjects with documented adrenocortical trophic hormone (ACTH) deficiency must be maintained on glucocorticoid treatment during participation in this trial. The use of stress doses of glucocorticoid during illness or injury will occur per the standards of current medical practice (refer to Inclusion Criteria, Section 4.2). Sufficiency of the HPA axis may be confirmed by normal cortisol responses during insulin-hypoglycemia, ACTH stimulation, glucagon stimulation, or diurnal variation tests. Such tests must occur within 6 months prior to screening. If no test of HPA axis is available it may be done as part of screening activities.

5.6 Restrictions

There are no restrictions on diet or exercise for these subjects. No fasting is required for blood sample collections.

5.7 Treatment Compliance

Administration of all somavaratan or daily rhGH doses will be performed by health care professionals or parent/guardian. The time, date, dose volume and site of administration will be recorded directly into a study-specific electronic patient-reported outcome (ePRO) solution. Failure to receive all scheduled doses may be cause for withdrawal.

Efforts should be made to complete all protocol specified activities within the allotted time frame. Failure to adhere to the schedule for PK/PD and safety data sample collection may be cause for withdrawal.

5.8 Packaging and Labeling

5.8.1 Somavaratan

Somavaratan Drug Product (DP, study medication) will be provided by the Sponsor, Versartis, Inc. along with batch numbers, TSE statements and Certificates of Analysis. DP will be supplied as sterile vials by Versartis to Catalent, Inc. (Catalent). Catalent will label the DP and distribute a sufficient quantity of single-unit dose containers of DP with tamper evident seal to the participating Investigational Pharmacy at each site. The DP will be

provided as labeled 2 mL glass vials with a rubber stopper and a crimp seal with flip top lid. DP vials are designed to allow for withdrawal of 1.0 mL (100 mg) of medication.

5.8.1.1 Assembly and Labeling of Unit Doses

Dispensing of the unit doses into syringes for subject administration in the clinic will be the responsibility of each principle investigator in compliance with the site practices and local regulatory requirements. Dose administration will be performed by a health care professional or trained parent/guardian.

Dispensing of the unit doses into syringes for subject administration for doses administered outside of the clinic by parent/guardian will be the responsibility of each subject's parent/guardian. Dose administration by parent/guardian will be allowed only after adequate training and documentation of demonstrated understanding by parent/guardian. Dose administration outside of the clinic will be performed by a health care professional or trained parents/guardians only.

5.8.2 Recombinant Human Growth Hormone

rhGH (study medication) will be procured from commercially available sources and provided by the Sponsor with original package labeling. rhGH will be supplied by Myoderm USA or Myoderm Limited.

Dispensing of the correct assigned doses for subject administration for doses administered by parent/guardian will be the responsibility of each subject's parent/guardian. Dose administration by parent/guardian will be allowed only after adequate training and documentation of demonstrated understanding by parent/guardian. Dose administration will be performed by healthcare professional or trained parents/guardians only.

5.9 Storage and Accountability

5.9.1 Somavaratan

The DP will be stored at 2–8° C at the investigational pharmacy. DP storage at investigational pharmacy will have restricted access. The DP will be removed from cold storage and allowed to equilibrate to room temperature for a minimum of 30 minutes before subject administration. No special procedures are required for the safe handling of the DP, however, it must be handled gently (e.g., no shaking, agitating, heating under warm water, etc.). The DP will remain stable for up to 8 hours at ambient temperature. Directions for use and administration will be provided. Documentation of somavaratan doses administered will be entered directly by the person administering the doses (parent/guardian or health care professional) into the ePRO solution provided by Versartis.

5.9.2 Recombinant Human Growth Hormone

rhGH will be stored and handled as per instructions provided by the manufacturer. Documentation of rhGH doses administered will be entered directly by the person administering the doses (parent/guardian or health care professional) into the ePRO solution provided by Versartis.

5.10 Investigational Product Retention at Study Site

Records will be maintained showing the receipt and disposition of all DP, rhGH, and other study supplies (if applicable). The Sponsor and/or its designee will routinely monitor and audit the records of DP and rhGH receipt, supplies, storage, dosage preparation procedures, and records at the investigational pharmacy. For all used DP, the empty used unit dose containers will be discarded upon satisfactory completion of accountability procedures. Any unused DP will be retained until completion of the study. Unused commercial rhGH will be returned for inspection and completion of accountability procedures.

Following completion of the clinical phase of the study and Sponsor review of accountability, all unused DP and study supplies will either be returned to the Sponsor (together with the accountability records) or will be destroyed at the clinical site and Certificates of Destruction (or equivalent) provided to the Sponsor.

Somavaratan Drug Product and rhGH must be controlled and accounted for by the study investigator or the designee; however, the study investigator retains primary responsibility for its use and documentation of use. No persons other than those designated as qualified study participants may receive study medication. The study investigator or physician sub-investigators are the only persons authorized to provide medication orders or prescribe study treatments.

The study investigator must ensure that DP and rhGH are stored under the specified conditions and in a secure location with access limited to those involved in the study or other appropriate study site personnel. Additionally, the study investigator must allow access to the Sponsor, Clinical Research Associates (CRAs), auditors and regulatory authorities for inspection of records and investigational product supplies.

6 STUDY PROCEDURES

6.1 Informed Consent

Informed consent for each subject must be provided by the legally authorized representative prior to any study activity. Where required, subjects should provide a completed Assent form.

6.2 Medical History

A complete medical history will be obtained as part of enrollment activities during the screening visit.

6.3 Physical Examination

A physical examination will be performed during Screening and at Months 6 and 12. Brief physical examinations are directed at reported health complaints and will be performed at Day 1 and Months 1, 3, and 9. Injection sites will be examined at all in clinic visits.

Pubertal staging will be performed during Screening and at Months 6 and 12. The method of Tanner and Marshall will be used to assess breast and pubic hair development.[28,29] For males, testicular volume will be estimated by palpation with reference to a Prader orchidometer.

Ocular fundoscopy through undilated pupil by the PI, sub-investigator, or ophthalmologist will be conducted to detect signs of intracranial hypertension or retinopathy at Screening. At all sites same day fundoscopy is required as clinically indicated if the subject exhibits signs and symptoms of intracranial hypertension (e.g., severe or prolonged headache lasting more than 12 hours or visual disturbances lasting more than 2 hours). Immediate medical attention is required for subjects who develop signs and symptoms of intracranial hypertension.

6.4 Vital Signs

Vital signs, height and weight are measured at the beginning of all in clinic visits.

Pulse rate, respiration rate, body temperature, and systolic/diastolic blood pressure will be measured with the subject sitting quietly for at least five minutes.

Height will be measured, in triplicate, using a wall-based stadiometer. The stadiometer should be calibrated just prior to use. The subject will be measured without shoes. Required precision of repeat height measurements is 0.2 cm (2 mm).

Weight will be measured with subject wearing light clothing and without shoes.

6.5 Electrocardiograms (ECGs)

ECGs will be conducted using 12-lead ECG equipment at Screening and repeated at Month 3 (at the expected time of somavaratan C_{max}). Triplicate tracings required.

6.6 Clinical Laboratory Tests

6.6.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Urine tests will be performed locally. Clinical laboratory tests will be conducted by a central laboratory to be identified by the Sponsor and include the following:

Table 3 List of Laboratory Tests

Hematology: – Red blood cell (RBC) count – White blood cell (WBC) with differential – Platelet count – Hemoglobin (Hgb) – Hematocrit (Hct) – Mean corpuscular hemoglobin (MCH) – Mean corpuscular hemoglobin concentration (MCHC) – Mean corpuscular volume (MCV)	Serum Chemistry: – Albumin (ALB) – Alkaline phosphatase (ALK-P) – Alanine aminotransferase (ALT; SGPT) – Aspartate aminotransferase (AST; SGOT) – Blood urea nitrogen (BUN) – Calcium (Ca) – Creatinine – Gamma-glutamyl transpeptidase (GGT) – Phosphate – Potassium (K) – Sodium (Na) – Total protein
Urinalysis: Performed locally by Urine Multistix® (or similar) – Bilirubin – Glucose – Ketones – Nitrite – Occult blood – pH – Protein – Urobilinogen	Pharmacodynamics: – IGF-I – IGFBP-3 – GHBP – ALS Immunogenicity: – Anti-drug antibodies (ADA) detection and characterization
Endocrine: – Glucose – HbA1c – Free T4 – TSH – Cortisol[1]	Pharmacokinetics: – somavaratan plasma concentration

1: Repeat adrenal testing in symptomatic/suspicious subjects as needed

6.6.2 Sample Collection, Storage, and Shipping

The safety, pharmacokinetic and pharmacodynamics assessments require blood samples to be collected during the study. The total blood volume required to be collected over the course of the study including the screening visit has been minimized and is provided in Table 4.

Table 4 Maximum Blood Volumes Required

Sample Type	Blood Volume (mL) per Sample	Collection Schedule							Total Number of Occasions	Total Per Subject (mL)
		Screening	**Day 1**	**M1**	**M3**	**M6**	**M9**	**M12**		
Hematology	2.0	X		X		X		X	**4**	8.0
Chemistry	4.0	X		X		X		X	**4**	16.0
PD[1]	4.0	X	X	X	X	X	X	X	**7**	28.0
PK[2]	2.0		X	X	X	X	X	X	**6**	12.0
Antibodies	3.0	X		X	X	X	X	X	**6**	18.0
HbA1c	2.0	X		X		X		X	**4**	8.0
Total Blood Volume (mL) Required For Study										**90.0**

1: May include IGF-I, IGFBP-3, GHBP and ALS (refer to Appendix 1)
2: PK collected in the somavaratan treatment cohort only

To ensure subject safety, no more than 17 mL (and not to exceed 2 mL/kg) of blood will be collected from individual subjects at any specific time point and will not exceed 4 mL/kg in any 30-day blood collection period.

6.7 Dispensing Study Drug

6.7.1 At the Study Site

The study investigator must maintain adequate records of receipt, dispensing and return/destruction of all DP and rhGH. Shipments of DP and rhGH will be reviewed upon receipt and contents verified with notification sent to the Sponsor or its designee. Exact records of dispensation and return from investigational pharmacy must be maintained including the following information:

- Identification of study subject by study number and initials
- Date of dispensation
- Subject weight (kg) used to calculate dose
- Quantity of DP or rhGH dispensed (primary container)

- Signature and date of dispensing pharmacist or other trained/authorized personnel
- Date used/unused DP or rhGH containers are returned to HCF

An Investigational Product Accountability Log will be provided by the Sponsor or its designee. Institution-required logs/documents may be used provided they contain the study-required elements and are approved by the Sponsor or its designee.

All used and partially used DP or rhGH will be returned to HCF for drug accountability reconciliation. After verification by the Study Monitor, the unused somavaratan DP and other study supplies may be destroyed or returned to the Sponsor's designated investigational product storage facility. Details for destruction and/or return are provided in the Pharmacy Manual.

6.7.2 At the Subject's Home

The study investigator must provide records for dispensation of all DP and rhGH to parent/guardian including the following information:

- Identification of study subject by study number and initials
- Schedule of required dosing events, including specific dates for somavaratan administration
- Subject weight (kg) used to calculate dose
- Total required volume of somavaratan or rhGH to be administered at each dose

An Investigational Product Dose Request Log will be provided by the Sponsor or its designee. Institution-required logs/documents may be used provided they contain the study-required elements and are approved by the Sponsor or its designee.

All used and partially used DP or rhGH will be returned to HCF for drug accountability reconciliation. Other study supplies may be discarded by the parent/guardian. Safety containers will be provided to parent/guardian for safe disposal of used needles and syringes.

6.8 Adverse Events Assessments

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

AEs may include increases in intensity or frequency of conditions or diseases that were pre-existing prior to study participation. Examples might include a subject in whom routine headaches become more severe or begin to occur more frequently.

Medical or surgical procedures are not in and of themselves considered AEs, but if a condition or disease led to the procedure, the condition or disease would be considered an AE unless it was present prior to entering the study and did not worsen after entering the study.

When possible, AEs will be reported using the terms in the current version of the CTCAE. A copy will be supplied in the Study Manual, and it can be found online at http://evs.nci.nih.gov/ftp1/CTCAE and http://safetyprofiler-ctep.nci.nih.gov/ctc/ctc.aspx.

Subjects entering the trial with ongoing baseline medical conditions should have their signs/symptoms graded according to CTCAE criteria. Increases in CTCAE grading from baseline conditions (e.g., Grade 1 to Grade 2) will be considered adverse events.

A non-serious AE is any AE that does not meet the definition of a serious adverse event below.

6.8.1 Performing Adverse Events Assessments

AEs will be collected at each visit to the health care facility.

6.8.2 Timing

AEs noted at Screening through Day 1 and prior to initial study drug administration are pre-existing medical conditions and part of medical history. AEs occurring after study drug administration are treatment emergent AEs.

6.8.3 Severity

AEs will be assessed for severity (intensity) according to the clinical description provided in the CTCAE (Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5). If an AE cannot be classified using CTCAE terminology, severity will be assessed using the following definitions listed in Table 5.

Table 5 Adverse Event Severity

Grade 1	**Mild**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.[1]
Grade 3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living.[2]
Grade 4	**Life-threatening**	Life-threatening consequences; urgent intervention indicated.
Grade 5	**Death**	Death related to the AE.

[1] Examples of instrumental activities of daily living include: Watching television, using a computer, playing video games, attending school, playing outside, using the telephone, etc.

[2] Examples of self-care activities of daily living are: bathing, dressing and undressing, feeding self, using the toilet, taking medications, etc.

6.8.4 Relationship

For each AE, the PI is required to assess the causal relationship (relatedness) between the administration of the study drug and the occurrence of the AE. The PI should use his or her clinical judgment and the following definitions listed in Table 6 to determine relatedness.

Table 6 Adverse Event Relationship

Definitely	An AE that follows a reasonable temporal sequence from study drug administration, AND follows a known response pattern to the use of the study drug, AND either recurs with re-challenge, and/or is improved by stopping study drug administration (dechallenge). The response to dechallenge should be clinically plausible. The event cannot be explained by the subject's clinical state including concurrent disease or other modes of therapy administered to the subject.
Probably	An AE that follows a reasonable temporal sequence from study drug administration, AND follows a known response pattern to the use of the study drug, AND could not be reasonably explained by the known characteristics of the subject's clinical state including concurrent disease or other modes of therapy administered to the subject.
Possibly	An AE that follows a reasonable temporal sequence from study drug administration, AND follows a known response pattern to the use of the study drug, BUT could have been produced by the subject's clinical state including concurrent disease or other modes of therapy administered to the subject.
Unlikely	An AE occurring after study drug exposure whose relationship to study drug cannot be entirely ruled out but cannot be reasonably explained from known characteristics of the study drug.
Unrelated	An AE that is known, beyond all reasonable doubt, to be caused by a concurrent illness, a concomitant medication, or other means, and not study drug. By definition, AE that occur prior to study drug administration are unrelated to study drug.

6.8.5 Expected Adverse Events

Adverse events associated with somavaratan administration have been generally mild and transient and have been similar to those typically observed when rhGH is introduced in GHD patients. The frequency of related adverse events decreased during each successive 6 month

treatment period. During the first 6 months (Phase 1b/2a; Protocol 12VR2), 34 of 64 subjects (53.1%) reported a related AE. In the second 6 months (Protocol 13VR3), 9 of 56 (16.1%) reported a related AE and in the third 6 months (months 12-18 in Protocol 13VR3) 7 of 56 subjects (12.5%) reported a related AE. In GHD children, related adverse events in 68 children exposed to at least one and up to 18 months of continuous repeat dose somavaratan treatment are listed in Table 7.

Table 7 Somavaratan Related Adverse Events in Pediatric GHD (n = 68)

Adverse Event	**Subjects Reporting Event (%)**
Subjects with at least one related AE	45 (66.2)
Injection site pain	39 (57.4)
Injection site erythema	8 (11.8)
Headache	8 (11.8)
Pain in extremity	5 (7.4)
Arthralgia	5 (7.4)
Injection site discomfort	3 (4.4)
Injection site reaction	2 (2.9)
Injection site anesthesia	1 (1.5)
Injection site hematoma	1 (1.5)
Injection site hemorrhage	1 (1.5)
Hunger	1 (1.5)
Increased appetite	1 (1.5)
Urticaria	1 (1.5)
Rash maculo-papular	1 (1.5)
Dizziness	1 (1.5)
Migraine	1 (1.5)
Presyncope	1 (1.5)
Sleep apnea syndrome	1 (1.5)
Back pain	1 (1.5)
Bone pain	1 (1.5)

Muscle Spasms	1 (1.5)
Musculoskeletal pain	1 (1.5)
Myalgia	1 (1.5)
Increased blood glucose	1 (1.5)
Decreased Free Thyroxine	1 (1.5)

6.8.6 Vital Signs, Physical Examination and Clinical Laboratory Adverse Events

Laboratory abnormalities and changes in vital signs or physical examination/findings are considered AEs only if they are determined to be clinically significant by the PI, result in withdrawal from the study, necessitate therapeutic intervention, or for some other reason the PI considers them clinically important. However, if any of these changes in laboratory, vital signs or physical examinations is attributable to a new disease or condition or a worsening of a condition pre-existing study enrollment, the disease or condition itself shall be the reported AE, not the change in laboratory, vital sign or physical examination.

6.8.7 Serious Adverse Events

6.8.7.1 Definition

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

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

6.8.7.2 Reporting Serious Adverse Events

SAEs must be reported to the Sponsor and Sponsor's contracted pharmacovigilance vendor, using the SAE reporting form provided within 24 hours of occurrence of event (or knowledge of the SAE). Complete reconciliation of SAEs often require follow up and review of medications, terminology, treatments administered, start and stop dates, and subject

discharge records. The study investigator has ultimate responsibility to ensure complete review and reconciliation of SAEs as required.

6.9 Concomitant Medication Assessments

All concomitant medications reported during the study period (screening visit through Month 12 visit or early termination visit) will be recorded and assessed for all subjects.

6.10 Removal of Subjects from the Trial or Study Drug

The subject may be withdrawn from the study for any of the following reasons:

- A protocol violation occurs
- A serious or intolerable adverse event occurs
- A clinically significant change in a laboratory parameter occurs
- The subject does not adhere to dosing schedules or omits specified evaluations by the PI
- The Sponsor or investigator terminates the study
- The subject or subject parent/guardian requests to be discontinued from the study

6.11 Other Study Procedures

An x-ray of the left hand and wrist will be performed during screening and at Month 12 to assess bone age delay at enrollment and the appropriateness of skeletal maturation during treatment. This schedule is consistent with medical practice in subjects with growth hormone deficiency. Subjects with historical x-rays taken within 90 days of screening activities and provided to the central reader are not required to repeat x-ray during screening.

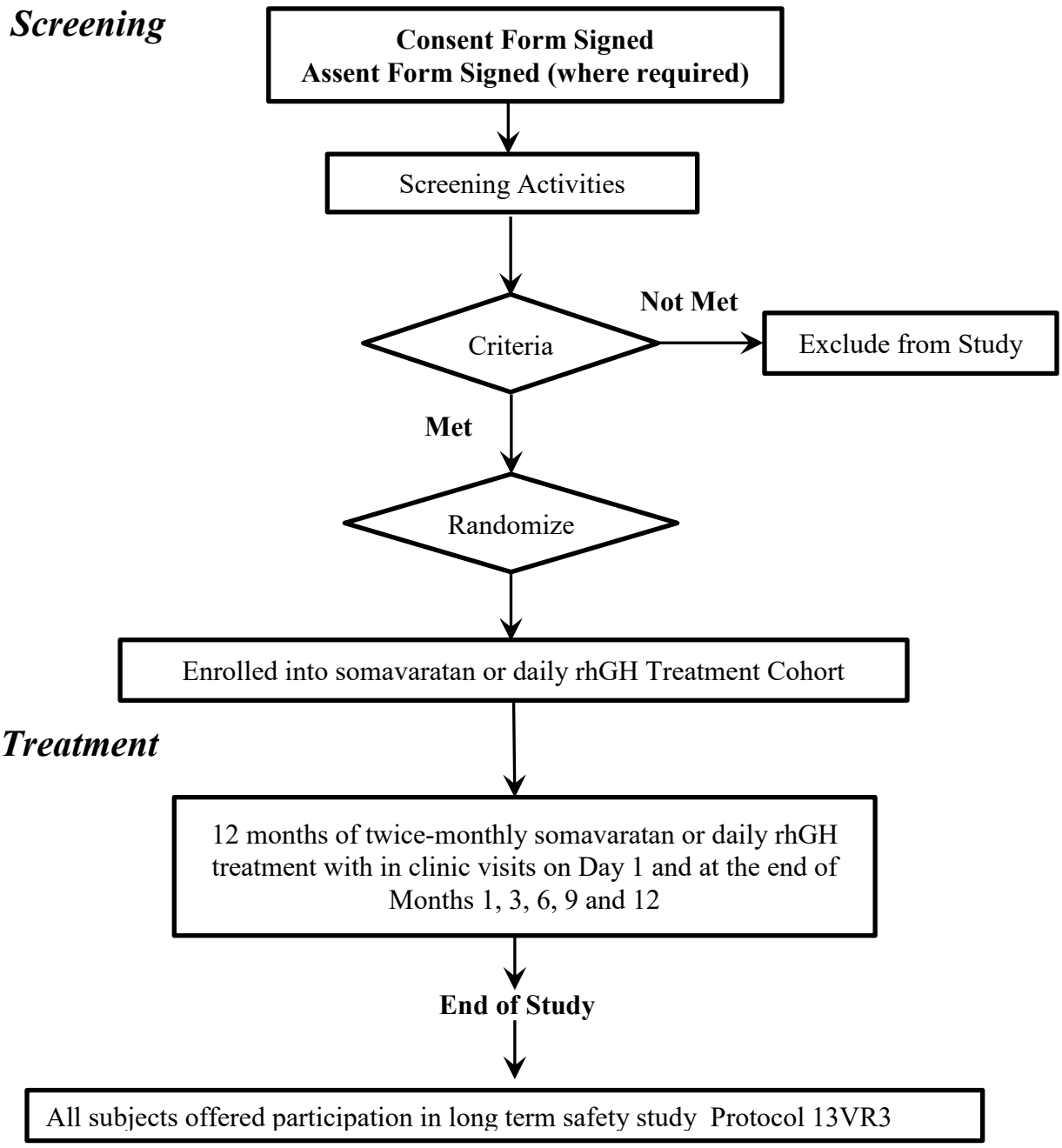
6.12 Appropriateness of Measurements

The PK/PD, safety and efficacy assessments are standard in clinical trials of growth promoting agents in children.

7 STUDY ACTIVITIES

Figure 1 demonstrates subject flow through the study from screening to study completion visits.

Figure 1 Subject Study Activity Flow Diagram



7.1 Screening Visit(s)

Subjects will sign the study-specific assent form (where required) and parents/legal guardians will authorize subject participation and acknowledge understanding of study procedures by providing written informed consent in the presence of a study research health care professional familiar with the protocol and the process of providing informed consent. Subjects may undergo study specific screening activities only after assent/consent are provided and up to 30 days prior to enrollment (Day 1) in the study. Subjects are considered enrolled in the study after providing written informed consent/assent, fulfillment of the inclusion/exclusion criteria and assignment of a treatment cohort (randomization). During the screening period subjects will have the following procedures and activities performed:

1. Informed consent and assent (where required).
2. Verification of inclusion/exclusion criteria.
3. Medical history including documentation of baseline signs and symptoms (ongoing observations documented using CTCAE scale).
4. Physical exam.
5. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI, sub-investigator, or opthalmologist).
6. Tanner staging of pubic hair for boys and girls, breast development for girls and estimated testicular volume by orchidometer for boys.
7. Vital signs including respiratory rate, body temperature, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
8. 12-lead ECG (triplicate tracings).
9. Height measured without shoes in triplicate by stadiometer.
10. Body weight measured in light clothing and without shoes.
11. Collection of blood samples for PD (IGF-I) and immunogenicity.
12. Collection of blood for adrenal function tests (if needed).
13. Collection of blood samples for hematology, serum chemistry, HbA1c, Free T4 and TSH.
14. Urinalysis by urine Multistix®.
15. An x-ray of the left hand and wrist (may be obtained within 90 days of screening).
16. Recording of all concomitant medications.

It is expected that the screening activities will take up to 2-4 hours to complete. Fasting is not required. Meals and/or snacks may be provided to the subject during the Screening visit(s).

7.2 Treatment Period (Day 1 to Month 12)

7.2.1 Visit Day 1 Procedures

Subjects may undergo study specific Day 1 activities only after assent/consent are provided and randomization to a treatment cohort is completed (subject number is assigned). Assessments on Visit Day 1 include:

1. Brief physical exam (ongoing observations documented using CTCAE scale).
2. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI or sub-investigator). North America sites only.
3. Vital signs including respiration, body temperature, pulse rate and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
4. Height measured without shoes in triplicate by stadiometer.
5. Collection of blood samples for PK (somavaratan concentration in the somavaratan treatment cohort only) and PD (IGF-I, IGFBP-3, GHBP and ALS).
6. Body weight measured in light clothing and without shoes.
7. Recording of AEs using the CTCAE grading scale.
8. Recording of all concomitant medications.
9. Training of dose preparation and study drug administration.
10. Training, downloading, programming (based on subject weight) and distribution of ePRO solution to parent/guardian.
11. Somavaratan or rhGH dose administration (may be administered by parent/guardian to demonstrate ability to administer study drug).
12. Distribution of DP and ancillary supplies to parent/guardian that will be required for at home dosing events.
13. Training on process for storage of study medication at home.
14. Scheduling of study doses and next clinic visit.
15. Reminder that used and partially used somavaratan DP vials or daily rhGH DP must be returned to clinic at all visits.

It is expected that the Day 1 visit activities will take up to 2 hours to complete. Fasting is not required.

7.2.2 Visit Month 1 Procedures

All subjects will return to the clinic at the end of Month 1 for an assessment and collection of blood samples. For subjects in the somavaratan treatment cohort, this visit will occur 3 ± 1 days after somavaratan dosing (peak sample collection). Assessments on Visit Month 1 include:

1. Brief physical exam (brief, problem-specific exam may be performed for any reported AE at the discretion of the investigator).
2. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI or sub-investigator). North America sites only.
3. Vital signs including respiratory rate, body temperature, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
4. Height measured without shoes in triplicate by stadiometer.
5. Body weight measured in light clothing and without shoes.
6. Collection of blood samples for PK (somavaratan concentration in somavaratan treatment cohort only).
7. Collection of blood samples for PD (IGF-I, IGFBP-3, GHBP and ALS), and immunogenicity.
8. Collection of blood samples for hematology, serum chemistry, HbA1c, Free T4 and TSH.
9. Urinalysis by urine Multistix®
10. Recording of AEs using the CTCAE grading scale.
11. Recording of all concomitant medications
12. Scheduling of study doses and next clinic visit. Distribution of DP and ancillary supplies to parent/guardian that will be required for at home dosing events.
13. Reminder that used and partially used somavaratan DP vials or daily rhGH DP must be returned to clinic at next visit.
14. Dose programming (based on subject weight) of ePRO solution and review of dosing documentation instructions with parent/guardian.
15. Return of used and partially used vials by parent/guardian for accountability.

7.2.3 Visit Month 3 Procedures

All subjects will return to the clinic at the end of Month 3 for an assessment and collection of blood samples. For subjects in the somavaratan treatment cohort, this visit will occur 3 ± 1 days after somavaratan dosing (peak sample collection). Assessments on Visit Month 3 include:

1. Brief physical exam (brief, problem-specific exam may be performed for any reported AE at the discretion of the investigator).
2. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI or sub-investigator). North America sites only.
3. Vital signs including respiratory rate, body temperature, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
4. 12-lead ECG (triplicate tracings).
5. Height measured without shoes in triplicate by stadiometer.
6. Body weight measured in light clothing and without shoes.
7. Collection of blood samples for PK (somavaratan concentration in somavaratan treatment cohort only).
8. Collection of blood samples for PD (IGF-I, IGFBP-3) and immunogenicity.
9. Recording of AEs using the CTCAE grading scale.
10. Recording of all concomitant medications
11. Scheduling of study doses and next clinic visit. Distribution of DP and ancillary supplies to parent/guardian that will be required for at home dosing events.
12. Reminder that used and partially used somavaratan DP vials or daily rhGH DP must be returned to clinic at next visit.
13. Dose programming (based on subject weight) of ePRO solution and review of dosing documentation instructions with parent/guardian.
14. Return of used and partially used vials by parent/guardian for accountability.

7.2.4 Visit Month 6 Procedures

All subjects will return to the clinic at the end of Month 6 for an assessment and collection of blood samples. For subjects in the somavaratan treatment cohort, this visit will occur 15 ± 1 days after somavaratan dosing (trough sample collection). Assessments on Visit Month 6 include:

1. Physical exam.

2. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI or sub-investigator). North America sites only.
3. Tanner staging of pubic hair for boys and girls, breast development for girls and estimated testicular volume by orchidometer for boys.
4. Vital signs including respiratory rate, body temperature, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
5. Height measured without shoes in triplicate by stadiometer.
6. Body weight measured in light clothing and without shoes.
7. Collection of blood samples for PD (IGF-I, IGFBP-3, GHBP and ALS), PK, (somavaratan concentration in the somavaratan treatment cohort only) and immunogenicity.
8. Collection of blood samples for hematology, serum chemistry, HbA1c, Free T4 and TSH.
9. Urinalysis by urine Multistix®
10. Recording of AEs using the CTCAE grading scale.
11. Recording of all concomitant medications.
12. Scheduling of study doses and next clinic visit. Distribution of DP and ancillary supplies to parent/guardian that will be required for at home dosing events.
13. Reminder that used and partially used somavaratan DP vials or daily rhGH DP must be returned to clinic at next visit.
14. Dose programming (based on subject weight) of ePRO solution and review of dosing documentation instructions with parent/guardian.
15. Optional: In clinic dosing of somavaratan or daily rhGH after blood sample collection.
16. Return of used and partially used vials by parent/guardian for accountability.

7.2.5 Visit Month 9 Procedures

All subjects will return to the clinic at the end of Month 9 for an assessment and blood sample collection. For subjects in the somavaratan treatment cohort, this visit will occur 3 ± 1 days after somavaratan dosing (peak sample collection). Assessments on Visit Month 9 include:

1. Brief physical exam (brief, problem-specific exam may be performed for any reported AE at the discretion of the investigator).
2. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI or sub-investigator). North America sites only.
3. Vital signs including respiratory rate, body temperature, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
4. Height measured without shoes in triplicate by stadiometer.
5. Body weight measured in light clothing and without shoes.
6. Collection of blood samples for PD (IGF-I, IGFBP-3), PK, (somavaratan concentration in the somavaratan treatment cohort only) and immunogenicity.
7. Recording of AEs using the CTCAE grading scale.
8. Recording of all concomitant medications.
9. Scheduling of study doses and next clinic visit. Distribution of DP and ancillary supplies to parent/guardian that will be required for at home dosing events.
10. Reminder that used and partially used somavaratan DP vials or daily rhGH DP must be returned to clinic at next visit.
11. Dose programming (based on subject weight) of ePRO solution and review of dosing documentation instructions with parent/guardian.
12. Return of used and partially used vials by parent/guardian for accountability.

7.2.6 Visit Month 12 Procedures

All subjects will return to the clinic at the end of Month 12 for an assessment and collection of blood samples. For subjects in the somavaratan treatment cohort, this visit will occur 15 ± 1 days after the last somavaratan dosing (trough sample collection). Assessments on Visit Month 12 include:

1. Physical exam.
2. Ocular fundoscopy through undilated pupils to detect signs of intracranial hypertension or retinopathy (may be conducted by the PI or sub-investigator). North America sites only.
3. Tanner staging of pubic hair for boys and girls, breast development for girls and estimated testicular volume by orchidometer for boys.
4. Vital signs including respiratory rate, body temperature, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.

5. Height measured without shoes in triplicate by stadiometer.
6. Body weight measured in light clothing and without shoes.
7. Collection of blood samples for PD (IGF-I, IGFBP-3, GHBP and ALS), PK, (somavaratan concentration in the somavaratan treatment cohort only) and immunogenicity.
8. Collection of blood samples for hematology, serum chemistry, HbA1c, Free T4 and TSH.
9. Urinalysis by urine Multistix®.
10. An x-ray of the left hand and wrist.
11. Recording of AEs using the CTCAE grading scale.
12. Recording of all concomitant medications.
13. Return of used and partially used vials by parent/guardian for accountability.

7.3 Study Completion

Visit Month 12 is the final study visit. Subjects who discontinue the study for any reason at any time should complete all activities associated with the Month 12 visit.

All subjects that complete the Month 12 visit in this study will be offered participation in the long term safety study, Protocol 13VR3. Subjects enrolled in the somavaratan treatment cohort in this study may continue dosing with somavaratan and subjects enrolled in the daily rhGH treatment cohort may transition to dosing with somavaratan in Protocol 13VR3.

8 QUALITY CONTROL AND ASSURANCE

This study will be conducted in accordance with the GCP/ICH consolidated guideline (April 2011). These guidelines include:

- 21 CFR parts 11, 50, 54, 56, 312 and 314
- ICH E2a & ICH E6 (R1)

8.1 Adherence to the Protocol

The principal investigator and all personnel involved with the conduct of the study agree to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the investigator(s). All such deviations will be documented in the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the clinical study report and provided in a timely manner to the Sponsor, Sponsor's designee and research site IRB per IRB guidelines.

Quality assurance audits of the clinic and study practices/procedures may occur. Any findings from quality assurance audits related to the study will be reported to the Sponsor.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Summaries of subject disposition, demographics, disease characteristics and response to dosing of study medication will be provided for each treatment group. All summaries of continuous data will be presented as means (SD), and/or with medians with min/max as appropriate. Count data will be presented as number within each treatment group and % of subjects within each group.

Summaries of all adverse events (AEs), serious adverse events (SAEs) and Suspected, Unexpected Serious Adverse Reactions (SUSARs) will be reported. The incidence of CTCAE Grade 3 or 4 adverse events will be classified according to severity and relationship to study drug. Standard statistical methods will be employed to analyze all data. It is anticipated that the following techniques may be used: descriptive statistics, t-test, paired t-test, McNemar's/Bowker's test, ANOVA, ANCOVA, and graphical displays. Assumptions of normality and homogeneity of variance will be tested with the Shapiro-Wilks test. If the normality distributional assumptions are violated, non-parametric techniques, such as Wilcoxon's Rank-Sum test and the Kruskal-Wallis test, will be employed as appropriate.

The study is open-label. The Sponsor and Investigators will be blinded to-aggregate height velocity data throughout the trial.

Study sites will be pooled into two Regions: North America and Europe. The randomization will be stratified by Region, age (above and below anticipated median age of 7.5 years) and for baseline IGF-I SDS (above and below anticipated median of -1.7). Randomization tables will be prepared by the CRO. Randomization assignments will be made upon approval of subject eligibility by the medical monitor.

An intention to treat (ITT) population will be used for the primary evaluation of efficacy. The primary endpoint will be the non-inferiority of somavaratan treatment height velocity compared to daily rhGH after 12 months on treatment. For subjects completing less than the 12 months of treatment, missing height at 12 months will be imputed from the last available height SDS, with a reduction of 2 cm/yr for subjects in the somavaratan group. This imputation calculates the height at 12 months from the height SDS observed at study exit. This is equivalent to a subject not having gained any more height relative to the age specific height (i.e., no treatment response) since study exit. The reduction of 2 cm/yr, the non-inferiority margin, only for the somavaratan imputed value avoids imputing to a common mean.[31] A sensitivity analysis using multiple imputation technique, assuming missing at random, will also be conducted. Baseline characteristics of these dropped subjects will be reported. A per protocol analysis for subjects completing 12 months of treatment with <10% missed or

incorrect dosing will also be performed. No imputations will be considered for the PP populations.

For the growth and bone age endpoints, the least squares means and confidence interval of the treatment groups from an ANCOVA model will be used to determine non-inferiority. The ANCOVA model will use the endpoint (e.g., height velocity) as the dependent variable, with treatment and region as fixed effects, and include age, baseline IGF-I SDS as covariates. Other covariates will be considered as appropriate. The potential treatment differences in IGF-I and IGFBP-3 responses will be evaluated with ANCOVA, with treatment and region as fixed effects, and baseline characteristics as covariates as appropriate.

The gender, age, height and weight of subjects entering puberty at one year will be described. Onset of puberty is defined as the appearance of Tanner stage 2 breast development in girls and a testicular volume ≥ 4 mL in boys.

An exploratory analysis will be conducted to determine if IGF-I responses correlate to height velocity outcomes.

Mean values and mean change from baseline for safety laboratory data will be summarized by visit and treatment group. If applicable, appropriate statistical methods may be employed to look for trends in safety variables. No formal tests of hypotheses are planned for safety parameters and no corrections for multiple comparisons will be made.

A detailed Statistical Analysis Plan will be developed before the first subject begins study drug.

Version 9.4 or higher of the SAS® statistical software package will be used to provide all statistical analyses.

9.2 Determination of Sample Size

Between 84 and 136 subjects are expected to complete the study. Sample size estimates are derived from considerations for non-inferiority testing of twice-monthly somavaratan versus daily rhGH. The somavaratan treatment cohort will be tested against the daily rhGH treatment cohort using a one-sided test procedure. Assuming a 3:1 somavaratan to daily rhGH subject ratio for each comparison, a standard deviation of ≤ 3.0 cm/yr. in annual height velocity, an alpha of 0.05 and a non-inferiority limit for difference in mean height velocity of 2.0 cm/yr., a total of 76 subjects are required: 57 for the somavaratan treatment cohort and 19 for the daily rhGH treatment cohort. The total number of planned subjects is 84 (76 plus 8 for potential drop-outs).

A non-inferiority margin of -2.0 cm/yr is chosen for analysis of the primary endpoint. This margin was used for the approval of Valtropin®. The margin is considered conservative when compared to the distribution of first year height velocities for children with similar degrees of GHD and treated with daily rhGH in a dose similar to the daily rhGH treatment cohort of this study. For children with moderate ("less severe") GHD, ages 4 to 10, the differences between the 3rd and 50th percentile for the first year height velocity is approximately 3–4.5 cm/yr.

An independent statistical consulting group will conduct sample size re-estimation using the observed variance in height velocity to determine if *a priori* assumptions were valid and notify the Sponsor if the total sample size should be increased to ensure statistical analyses with adequate power. If the assumption of variance in height velocity has been underestimated as determined in the sample size re-estimation procedure, the sample size may be increased up to 136 subjects.

9.3 Analysis Populations

9.3.1 Safety Population

The safety population will consist of all subjects completing a screening evaluation and receiving any amount of study drug.

9.3.2 PK/PD Population

The PK/PD analysis population will consist of all subjects receiving study drug and having at least one post-treatment PK/PD assessment. A PK/PD per protocol subset will include all subjects with complete PK/PD assessments and no missed doses in the dosing interval prior to a PK/PD assessment.

9.3.3 Intent-to-Treat Population

The intention to treat analysis (ITT) will be the primary analysis population. The ITT population will consist of all subjects completing at least one month of dosing with completed efficacy assessments at the Month 1 Visit. For subjects completing less than the 12 months of treatment, the height velocity at 12 months will be imputed from the change from baseline of last measurement of HT-SDS. With this procedure, a 12 month height velocity measurement will be available for all subjects in the ITT.

Baseline characteristics of the excluded subjects will be reported. In the event that numerous imputations are required, comparisons of subject that completed versus those who dropped and required imputation will be done.

9.3.4 Per Protocol Population

A per protocol analysis will be used to evaluate efficacy parameters. All subjects completing one year of continuous study dosing with efficacy assessments at Month 12 will be included. Patients with major dosing deviations (≥ 10% of total assigned doses missed) will be excluded from per protocol analysis. Missing data for the per protocol population will not be imputed.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics to be collected include:

Gender

Race/Ethnicity

Measured maternal and paternal heights (where available)

Birth history (weight, length, gestational age at birth)

Prior height velocity assessed from 6 or more months observation (where available)

Bone age results and date of examination

GH stimulation tests (date, agents used, maximal GH response)

Adrenal test results (morning cortisol or stimulation test). If stimulation test, specify date test agent used and maximal cortisol response

9.5 Primary Endpoints

The primary efficacy endpoint is:

- Annual height velocity after 12 months continuous treatment with either somavaratan or daily rhGH

9.6 Secondary Endpoints

The secondary efficacy endpoints are:

- Change in height SDS
- Change in bone age relative to chronological age (BA/CA)
- Change in Body Mass Index
- Change in body weight

- IGF-I and IGFBP-3 responses to study drug administration and their relationship to height velocity will be evaluated.

9.7 Retention of Data

All primary data generated in the study and described by RPG (or copies thereof [e.g., laboratory records, data sheets, correspondence, photographs and computer records]), which are a result of the original observations and activities of the clinical study, and are necessary for the reconstruction and evaluation of the study report, will be retained in the RPG archive for a period of 5 years after issue of the final report. At this time, the Sponsor will be contacted to determine whether the data should be returned, retained or destroyed on their behalf. No data will be destroyed without the agreement of the Sponsor.

All study-related records must be retained until 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will inform the PI/Institution when the documents no longer need to be retained. The PI must obtain approval in writing from the Sponsor prior to destruction of any records. Typically, these records will be held in the PI's archives. If the PI is unable to meet this obligation, the PI must obtain permission from the Sponsor to make alternative arrangements. Details of these arrangements must be documented in writing to the Sponsor.

Specimens requiring frozen storage are specifically excluded from the above. These will be retained for as long as the quality of the material permits evaluation but for no longer than 6 months after completion of the study (defined as issuance of Clinical Study Report). The Sponsor will be notified of the intent to destroy samples and any financial implications before specimens are destroyed on their behalf.

9.8 Interim Analysis

No interim analysis is planned.

9.9 Other Analyses

Estimation of PK and PD parameters (e.g., C_{max}, average concentration) will be performed using non-compartmental methods. Post hoc PK/PD models of IGF-I response to somavaratan and rhGH may be evaluated using appropriate methods.

Pubertal development will be described. Findings from 12-lead ECGs will be described.

In addition, the relationship of the presence of ADAs will be explored. The subjects will be classified as ADA negative, transient or persistent based on Shankar et al., and the relationship of this ADA classification with PK, PD and clinical endpoints will be evaluated.[30]

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Versartis has an agreement with a contract research organization (CRO) to provide project management oversight for this protocol. RPG has been assigned many study oversight responsibilities for the protocol conduct. A formal transfer of obligations document outlines the activities assigned to RPG.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The principal investigator will initiate and enroll subjects only after IRB/IEC approval of the protocol and the informed consent documents have been received. All recruiting materials used in the study must have IRB/IEC approval. Progress reports regarding the study will be submitted to the IRB/IEC in accordance with institutional and regulatory guidelines.

10.3 Ethical Conduct of the Study

The study will be performed in compliance the Food & Drug Administration Code of Federal Regulations for Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) Regulations. These procedures ensure the protection of the rights and the integrity of the subjects, adequate and correct conduct of all study procedures, adequate data collection, adequate documentation and adequate data verification. The SOPs relevant in the context of the study are available at the RPG.

10.4 Subject Information and Consent

Before being enrolled, subjects must be provided informed consent to participate and their legal guardian must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained. A copy of the consent document must be given to the subject. The original signed consent document will be retained by the Principal Investigator (PI). Subject assent will be provided and obtained from subjects where required.

10.5 Subject Confidentiality

Subject confidentiality will be maintained throughout the study according to applicable guidelines, regulations and IRB requirements. All samples, study clinical data, and reports of results will de-identify individual subjects. Subjects will be identified by initials, date of birth, gender and subject number only for use in data collection. Published data will provide subject numbers only if needed for clarity of presentation (e.g., in individual event listings).

10.6 Study Monitoring

All investigational sites will receive on site visits from the Sponsor and/or Sponsor designee, RPG. Site visits may be conducted with representatives from both the Sponsor and RPG in attendance. All sites will receive at a minimum a pre-study qualification visit and a site initiation visit. All sites that enroll subjects into the study will receive routine monitoring visits where source data verification will be conducted by the monitor.

All activated sites will receive study close-out visits by the Study Monitor upon closure of the study.

RPG will develop a monitoring plan that will be approved by Versartis and followed for the duration of the study. All study sites must allow direct access to all pertinent study documentation and medical records for enrolled subjects.

10.7 Case Report Forms and Study Records

Source documents must be maintained for each subject during the course of the study. The documents must demonstrate in writing that informed consent was obtained prior to subject participation. Source documents include the signed original ICFs, medical records including physician notes, nursing flow sheets, and hospital charts. They include documentation of all procedures conducted for the study and are the primary original source for all study data except where otherwise specified.

Electronic Case Report Forms (eCRFs) will be used in this study and must be completed for each enrolled subject.

All protocol-required information collected during the study must be entered by the investigator or the designee in the eCRF. CRF completion and correction will be performed in accordance with the study eCRF guidlines.

The investigator or designee should complete the eCRF pages as soon as possible after the study information is obtained. An explanation should be given for all missing data.

The completed eCRF must be reviewed and signed by the principal investigator.

10.8 Protocol Violations/Deviations

Protocol-specified events, visits, tests, and procedures should be followed without exception. In situations where protocol deviations (e.g., missed visits or tests) occur due to unforeseen circumstances, documentation of the reason should be made in the source document and documented by the CRA for inclusion in the CSR.

10.9 Access to Source Documentation

All study data entered into the electronic CRF must be verifiable to the source data. Versartis and its delegated representative study monitors and auditors must have access to all original recordings, laboratory reports and enrolled subject's medical records.

10.10 Data Generation and Analysis

RPG (the CRO) will perform the data analysis. The results of the study will be reported together in one clinical study report. A detailed Statistical Analysis Plan describing the methodology to be used will be finalized prior to study enrollment and may be modified as needed and documented prior to database lock.

RPG and Sponsor will prepare an integrated clinical, pharmacodynamics and pharmacokinetic report. Prior to issuing the final clinical study report, RPG will prepare a draft report for approval by the Sponsor. The report will be in accordance with the International Conference on Harmonisation (ICH) Note for Guidance on Structure and Content of Clinical Study Reports. The draft report may be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

10.11 Financial Disclosure

A completed financial disclosure document is required for all principal investigators participating in this study.

10.12 Publication and Disclosure Policy

The Sponsor holds all publication rights to the aggregate data obtained from this study. Study investigators will submit any planned publication of individual site data to Sponsor for review and approval at least 60 days prior to submission to the publisher.

11 REFERENCES

1. Schellenberger, V., Wang, C. W., Geething, N. C., Spink, B. J., Campbell, A., To, W., Scholle, M. D., Yin, Y., Yao, Y., Bogin, O., Cleland, J. L., Silverman, J. & Stemmer, W. P. (2009). A recombinant polypeptide extends the in vivo half-life of peptides and proteins in a tunable manner. *Nat Biotechnol* **27**, 1186-90.

2. Cleland, J. L., Geething, N. C., Moore, J. A., Rogers, B. C., Spink, B. J., Wang, C. W., Alters, S. E., Stemmer, W. P. & Schellenberger, V. (2012). A novel long-acting human growth hormone fusion protein (VRS-317): enhanced in vivo potency and half-life. *J Pharm Sci* **101**, 2744-54.

3. Le Roith, D., Bondy, C., Yakar, S., Liu, J. L. & Butler, A. (2001). The somatomedin hypothesis: 2001. *Endocr Rev* **22**, 53-74.

4. Vance, M. L. & Mauras, N. (1999). Growth hormone therapy in adults and children. *N Engl J Med* **341**, 1206-16.

5. Wit, J. M., Kamp, G. A. & Rikken, B. (1996). Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. *Pediatr Res* **39**, 295-302.

6. Tanner, J. M., Whitehouse, R. H., Hughes, P. C. & Vince, F. P. (1971). Effect of human growth hormone treatment for 1 to 7 years on growth of 100 children, with growth hormone deficiency, low birthweight, inherited smallness, Turner's syndrome, and other complaints. *Arch Dis Child* **46**, 745-82.

7. Reiter, E. O., Price, D. A., Wilton, P., Albertsson-Wikland, K. & Ranke, M. B. (2006). Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. *J Clin Endocrinol Metab* **91**, 2047-54.

8. Sas, T. C., de Ridder, M. A., Wit, J. M., Rotteveel, J., Oostdijk, W., Reeser, H. M., Otten, B. J. & de Muinck Keizer-Schrama, S. M. (2010). Adult height in children with growth hormone deficiency: a randomized, controlled, growth hormone dose-response trial. *Horm Res Paediatr* **74**, 172-81.

9. Carel, J. C., Ecosse, E., Nicolino, M., Tauber, M., Leger, J., Cabrol, S., Bastie-Sigeac, I., Chaussain, J. L. & Coste, J. (2002). Adult height after long term treatment with recombinant growth hormone for idiopathic isolated growth hormone deficiency: observational follow up study of the French population based registry. *BMJ* **325**, 70.

10. Bakker, B., Frane, J., Anhalt, H., Lippe, B. & Rosenfeld, R. G. (2008). Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *J Clin Endocrinol Metab* **93**, 352-7.

11. Cohen, P., Rogol, A. D., Howard, C. P., Bright, G. M., Kappelgaard, A. M., Rosenfeld, R. G. & American Norditropin Study, G. (2007). Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. *J Clin Endocrinol Metab* **92**, 2480-6.

12. Ranke, M. B., Lindberg, A. & Board, K. I. (2010). Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *J Clin Endocrinol Metab* **95**, 1229-37.

13. Jorgensen, J. O., Moller, N., Lauritzen, T. & Christiansen, J. S. (1990). Pulsatile versus continuous intravenous administration of growth hormone (GH) in GH-deficient patients: effects on circulating insulin-like growth factor-I and metabolic indices. *J Clin Endocrinol Metab* **70**, 1616-23.

14. Laursen, T., Jorgensen, J. O., Jakobsen, G., Hansen, B. L. & Christiansen, J. S. (1995). Continuous infusion versus daily injections of growth hormone (GH) for 4 weeks in GH-deficient patients. *J Clin Endocrinol Metab* **80**, 2410-8.

15. Tauber, M., De Bouet Du Portal, H., Sallerin-Caute, B., Rochiccioli, P. & Bastide, R. (1993). Differential regulation of serum growth hormone (GH)-binding protein during continuous infusion versus daily injection of recombinant human GH in GH-deficient children. *J Clin Endocrinol Metab* **76**, 1135-9.

16. NutropinDepot™. (1999). http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21075lbl.pdf.

17. NutropinAQ®. (2012). http://www.gene.com/gene/products/information/pdf/nutropin-aq-prescribing.pdf.

18. Humatrope®. (2011). http://pi.lilly.com/us/humatrope-cart-pi.pdf.

19. Genotropin®. (2011). http://www.labeling.pfizer.com/showlabeling.aspx?id=577.

20. Omnitrope®. (2011). http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=58d84ffa-4056-4e36-ad67-7bd4aef444a5, http://www.omnitrope.com/omnitrope/index.html.

21. Saizen®. (2012). http://www.emdserono.com/cmg.emdserono_us/en/images/saizen.ce.pi_tcm115_19400.pdf?Version=.

22. Desrosiers, P., O'Brien, F. & Blethen, S. (2005). Patient outcomes in the GHMonitor: the effect of delivery device on compliance and growth. *Pediatr Endocrinol Rev* **2 Suppl 3**, 327-31.

23. Rosenfeld, R. G. & Bakker, B. (2008). Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract* **14**, 143-54.

24. Cutfield, W. S., Derraik, J. G., Gunn, A. J., Reid, K., Delany, T., Robinson, E. & Hofman, P. L. (2011). Non-compliance with growth hormone treatment in children is common and impairs linear growth. *PLoS One* **6**, e16223.

25. Yuen, K. C., Conway, G. S., Popovic, V., Merriam, G. R., Bailey, T., Hamrahian, A. H., Biller, B. M., Kipnes, M., Moore, J. A., Humphriss, E., Bright, G. M. & Cleland, J. L. (2013). A long-acting human growth hormone with delayed clearance (VRS-317): results of a double-blind, placebo-controlled, single ascending dose study in growth hormone-deficient adults. *J Clin Endocrinol Metab* **98**, 2595-603.

26. Green, H., Morikawa, M. & Nixon, T. (1985). A dual effector theory of growth-hormone action. Differentiation; research in biological diversity **29**, 195-198.

27. Moore, W.V., Nguyen, H. J., Kletter, G. B., Miller, B.S., Rogers, D., Ng, D., Moore, J.A., Humphriss, E., Cleland, J.L., & Bright, G.M (2016). A Randomized Safety and Efficacy Study of Somavaratan (VRS-317), a Long-Acting rhGH, in Pediatric Growth Hormone Deficiency. *J Clin Endocrinol Metab* **101(3)**, 1091-1097

28 Marshall, W. A. & Tanner, J. M. (1969). Variations in pattern of pubertal changes in girls. *Arch Dis Child* **44**, 291-303.

29. Marshall, W. A. & Tanner, J. M. (1970). Variations in the pattern of pubertal changes in boys. *Arch Dis Child* **45**, 13-23.

30. Shankar, G., Arkin, S., Cocea, L., Devanarayan, V., Kirshner, S., Kromminga, A., Quarmby, V., Richards, S., Schneider, C. K., Subramanyam, M., Swanson, S., Verthelyi, D., Yim, S. (2014). Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations. *The American Association of Pharmaceutical Scientists* **16**, 658-673.

31. Koch GG. Comments on 'Current issues in non-inferiority trials' by Thomas R. Fleming. *Statistics in Medicine, DOI*: 10.1002/sim.2855. Stat Med 2008: 27:333-342.

Appendix 1 Schedule of Events for Somavaratan Subjects

Activity/Assessment	Screening	Day 1	Month 1[1]	Month 3[1]	Month 6[1]	Month 9[1]	Month 12[2]
Informed Consent/Assent[3]	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Physical Exam	X				X		X
Brief Physical Exam[4]		X	X	X		X	
Fundoscopy	X	X	X	X	X	X	X
Pubertal Staging[6]	X				X		X
Vital Signs[7]	X	X	X	X	X	X	X
12-lead ECG[8]	X			X			
Height[9], Weight[10]	X	X	X	X	X	X	X
PK/PD Samples[11]	X	X	X	X	X	X	X
GHBP and ALS		X	X		X		X
Antibody Samples[12]	X		X	X	X	X	X
Adrenal Assessment[13]	X						
Hematology[14]	X		X		X		X
Chemistry[15]	X		X		X		X
Hemoglobin A1c	X		X		X		X
Free T4, TSH	X		X		X		X
Urinalysis[16]	X		X		X		X
Bone Age[17]	X						X
Adverse Events[18]		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Somavaratan Dosing[19]		X					

1. For Month 1, 3 and 9, the visits will occur 3 ± 1 days after a somavaratan dose (peak sample collection). For Month 6, the visit will occur 15 ± 1 days after somavaratan dosing (trough sample collection).
2. Should occur after the end of the last dosing interval and approximately 12 months after the Day 1 visit.
3. Informed consent to be completed by duly authorized subject representative. Assent provided by subject, where required.
4. A directed physical exam to address health complaints and to examine injection sites.
5. Ocular fundoscopy through undilated pupil will be conducted by the PI, sub-investigator, or ophthalmologist to detect signs of intracranial hypertension or retinopathy. In sites outside North America, protocol-required fundoscopy will be conducted at screening. At all sites same day fundoscopy is required as clinically indicated if the subject exhibits signs and symptoms of intracranial hypertension (e.g., severe or prolonged headache lasting more than 12 hours or visual disturbances lasting more than 2 hours). Immediate medical attention is required for subjects who develop signs and symptoms of intracranial hypertension.
6. Tanner staging of pubertal hair (boys and girls), breast development (girls) and estimated testicular volume by orchidometer (boys).
7. Includes temperature, respiratory rate, pulse rate and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
8. All subjects will receive 12-lead ECGs (triplicate tracings) at Screening and Month 3.
9. Heights to be measured without shoes in triplicate by stadiometer. Stadiometer should be calibrated just before use. Required precision ≤ 0.2 cm.
10. Weights to be taken in light clothing and without shoes.
11. PK sample is somavaratan plasma concentration. PD samples include IGF-I and IGFBP-3. At Screening, only IGF-I is collected to determine eligibility.
12. Serum samples will be collected for immunogenicity
13. Per inclusion criteria (Section 4.2).
14. Complete blood count and differential.
15. Includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, GGT, glucose, electrolytes (K, Na), phosphate, total protein. Free T4, TSH.
16. Random sample tested by urine Multistix®.
17. A radiograph of the left hand and wrist to be submitted to the central reader.
18. AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.
19. Somavaratan dosing commences on Day 1 with dose administered in clinic by a qualified healthcare professional in conjunction with training of parent/guardian. All other somavaratan doses will be administered twice-monthly (2 times per month; every 15 days ± 2 days) by a properly instructed parent/guardian or by a qualified health care professional.

Appendix 2 Schedule of Events for Daily rhGH Subjects

Activity/Assessment	Screening	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12
Informed Consent/Assent[1]	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Physical Exam	X				X		X
Brief Physical Exam[2]		X	X	X		X	
Fundoscopy[3]	X	X	X	X	X	X	X
Pubertal Staging[4]	X				X		X
Vital Signs[5]	X	X	X	X	X	X	X
12-lead ECG[6]	X			X			
Height[7], Weight[8]	X	X	X	X	X	X	X
PD Samples[9]	X	X	X	X	X	X	X
GHBP and ALS		X	X		X		X
Antibody Samples[10]	X		X	X	X	X	X
Adrenal Assessment[11]	X						
Hematology[12]	X		X		X		X
Chemistry[13]	X		X		X		X
Hemoglobin A1c	X		X		X		X
Free T4, TSH	X		X		X		X
Urinalysis[14]	X		X		X		X
Bone Age[15]	X						X
Adverse Events[16]		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Daily rhGH Dosing[17]		X					

1 Informed consent to be completed by duly authorized subject representative. Assent provided by subject, where required.

2 A directed physical exam to address health complaints and to examine injection sites.

3 Ocular fundoscopy through undilated pupil will be conducted by the PI, sub-investigator, or ophthalmologist to detect signs of intracranial hypertension or retinopathy. In sites outside North America, protocol-required fundoscopy will be conducted at screening. At all sites same day fundoscopy is required as clinically indicated if the subject exhibits signs and symptoms of intracranial hypertension (e.g., severe or prolonged headache lasting more than 12 hours or visual disturbances lasting more than 2 hours). Immediate medical attention is required for subjects who develop signs and symptoms of intracranial hypertension.

4 Tanner staging of pubertal hair (boys and girls), breast development (girls) and estimated testicular volume by orchidometer (boys).

5 Includes temperature, respiratory rate, pulse rate and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.

6 All subjects will receive 12-lead ECG (triplicate tracings) at Screening and Month 3.

7 Heights to be measured without shoes in triplicate by stadiometer. Stadiometer should be calibrated just before use. Required precision ≤ 0.2 cm.

8 Weights to be taken in light clothing and without shoes.

9 PD samples include IGF-I and IGFBP-3. At Screening, only IGF-I is collected to determine eligibility.

10 Serum samples will be collected for immunogenicity.

11 Per inclusion criteria (Section 4.2).

12 Complete blood count and differential.

13 Includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, GGT, glucose, electrolytes (K, Na), phosphate, total protein, Free T4, TSH.

14 Random sample tested by urine Multistix®.

15 A radiograph of the left hand and wrist to be submitted to the central reader.

16 AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

17 Daily rhGH dosing commences on Day 1 with dose administered in clinic by a qualified health care professional in conjunction with training of parent /guardian. Daily dosing continues with doses administered by properly instructed parent/guardian or by a qualified health care professional.

Appendix 3 Approval and Signature Page: Principal Investigator

I have read Protocol 14VR4 and agree to conduct the study as outlined. In addition, I agree to conduct the study in compliance with Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) Regulations and all guidelines as stated in the protocol and other information supplied to me.

Print Name:

Principal Investigator:

Signature: _____

Date: _____