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Protocol Number 14VR4

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

Statistical Analysis Plan

Version 1.2

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By signing, I attest I have reviewed this document and that it meets my approval.

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5 SEP 17
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5 Sept 2017
Date

ResearchPoint Global

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List of Abbreviations and Definitions

ADA	anti-drug antibody
AE	adverse event
ALS	acid labile subunit
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical Classification
BA/CA	bone age relative to chronological age
BMI	body mass index
BUN	blood urea nitrogen
CDC	Center for Disease Control
CI	confidence interval
CM	concomitant medications
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	data and safety monitoring board
ECG	electrocardiogram
ePRO	electronic patient-reported outcome
GGT	gamma glutamyl transferase
GHBP	growth hormone binding protein
GHD	growth hormone deficiency
hGH	human growth hormone
HT-SDS	height standard deviation score
HV	height velocity
ICH	International Conference on Harmonisation
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
ITT	Intention to Treat
K	potassium
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
Na	sodium
NAb	neutralizing antibody
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetic
PP	per protocol

PT	preferred term
rhGH	recombinant human growth hormone
ROW	rest of world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCFE	Slipped capital femoral epiphyses
SD	standard deviation
SDS	standard deviation score
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	System Organ Class
TEAE	treatment emergent event
TLFs	tables, listings, and figures
TSH	thyroid stimulating hormone
VELOCITY	Versartis Long-Acting Growth Hormone in Children compared to Daily rhGH
WHO	World Health Organization
XTEN	proprietary sequences of hydrophilic amino acids

1. INTRODUCTION/BACKGROUND

This statistical analysis plan (SAP) describes the data analysis specifications for Protocol 14VR4 entitled "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," Version 4, 5 April 2017.

This SAP follows the International Conference on Harmonisation (ICH) Guidelines E3 and E9. All statistical analyses will be performed using SAS®, Version 9.4 or higher. In cases in which the analyses in this SAP differ from those in the study protocol, the analyses in the SAP supersede those in the protocol. Should differences exist, these will be described in Section 6.2 of this document.

This protocol is a randomized, multi-center, open-label, non-inferiority study for pre-pubertal naïve to treatment children with growth hormone deficiency (GHD). Subjects will be randomized to receive 3.5 mg/kg somavaratan twice-monthly or daily treatment with rhGH. Safety and efficacy of these treatments over the course of one year will be evaluated along with 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 (BMI), height standard deviation scores (HT-SDS), and anti-drug antibody (ADA) responses.

Somavaratan is a fusion protein consisting of recombinant human growth hormone (rhGH) and two sequences (XTEN) of hydrophilic amino acids, designed to maintain active drug levels for a longer period of time than currently available therapies. It is being developed for treatment of GHD in adults and children and as a long-acting alternative to daily rhGH injections, which is currently the only approved treatment in the United States for adults and children with growth hormone deficiency.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare the safety and efficacy of subcutaneous (SC) somavaratan and daily rhGH during 12 months of treatment.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to evaluate and compare changes in pharmacodynamic responses (IGF-I, IGFBP-3, GHBP and ALS), bone age, weight, body mass index, and height standard deviation scores. The presence of anti-drug antibody (ADA) will be determined, and the responses will be explored.

3. STUDY DESIGN

3.1 OVERVIEW AND LENGTH OF STUDY

The study will be conducted at approximately 70 pediatric endocrinology centers in the United States, Canada, and Europe and will include up to 136 subjects. The duration of subject participation for this study is approximately 13 months.

3.2 STUDY SCHEDULE

3.2.1 Schedule of Events – Somavaratan (VRS-317) 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[5]	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 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 (ADA)
13. Per inclusion criteria (Section 4.2 of the protocol).
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, thyroid stimulating hormone (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.

3.2.2 Schedule of Events – 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 (ADA)

11 Per inclusion criteria (Section 4.2 of the protocol).

12 Complete blood count and differential.

13 Includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, GGT, glucose, electrolytes potassium (K) and sodium (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.

3.3 STUDY DRUG ADMINISTRATION AND EXTENT OF EXPOSURE

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

The selected somavaratan dose, which was chosen using results obtained from other protocols, 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 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 dosing arm and the daily rhGH dosing arm, 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.

3.5 SAMPLE SIZE CALCULATION/JUSTIFICATION

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 (one-tailed 0.025) 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 Versartis, Inc. if the total sample size should be increased to ensure statistical analyses with adequate power. Assuming the SD (standard deviation) is not greater than 3.5, the sample size should be no greater than 136 subjects.

3.6 RANDOMIZATION SCHEME

The randomization will be stratified by region (North America and Europe), age (above and below anticipated median age of 7.5 years) and baseline IGF-I SDS (above and below anticipated median of -1.7) in a 3:1 ratio of either VRS-317 or daily rhGH treatment, respectively.

4. ANALYSIS SETS

4.1 PRIMARY ANALYSIS POPULATION AND MODIFIED INTENT TO TREAT (MITT)

The primary analysis population (ITT, Intent-To-Treat) will be based on all randomized subjects. In addition, a mITT population, defined as all subjects completing at least one month of dosing with completed efficacy assessments at the Month 1 visit will also be created. Subjects completing less than one month of treatment or without a post-treatment height measurement will not be included in the mITT population. Based on previous studies with somavaratan, the expectation is that very few subjects who randomize will not be able to complete at least 1 month of treatment and evaluations.

4.2 PER PROTOCOL (PP)

The PP population is defined as subjects completing one year of treatment, without missing 10% or more of the assigned doses. Subjects with other major protocol violations/deviations will be excluded.

A major protocol violation/deviation is defined as an action which would render the data incomparable due to compromising the effect of the study medication. A reason for

exclusion may include, but would not be limited to, taking contraindicated concomitant medications (CM). Subjects excluded from the PP analysis due to a major protocol violation/deviation will be identified in formal notes to file signed by the study director/medical monitor prior to data base lock.

4.3 PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) POPULATION

The PK/PD population is defined as 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.

4.4 SAFETY POPULATION

The safety population will consist of all subjects receiving any amount of study drug.

4.5 OTHER ANALYSIS POPULATIONS (INCLUDING SUBGROUPS)

Subjects entering puberty after one year will be grouped and analyzed.

Other populations and analyses may be conducted at the discretion of Versartis, Inc. to supplement the results or for research purposes.

4.6 TREATMENT MISALLOCATIONS

As this is an open-label study, should any treatment misallocations occur, all subjects will also be analyzed in the "As Treated" treatment group for the primary endpoint instead of "As Randomized." A listing will be provided to display any subjects with treatment misallocations, should they occur.

4.7 PROTOCOL DEVIATIONS

All protocol deviations will be documented in the study files, and any significant deviations will be included in the study report. If any deviation is considered to have resulted in changes in treatment or data collected, separate analyses may be conducted to determine the impact of the deviation.

5. ENDPOINTS AND COVARIATES

5.1 PRIMARY ENDPOINTS

The primary efficacy endpoint for this study is annual height velocity (cm/yr) in the first year (12 months) of treatment and will be analyzed by a non-inferiority test of the somavaratan treatment height velocity compared to daily rhGH.

5.2 SECONDARY ENDPOINTS

The following secondary efficacy endpoints will be analyzed in hierarchical order:

- Change in height SDS (Height SDS based on Center for Disease Control (CDC) Clinical Growth Charts; 2000)
- 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.

5.3 COVARIATES

The adjusted (least squares) mean and SE (standard error) from an analysis of covariance will be used to determine non-inferiority. The ANCOVA model will include treatment group, region and gender as fixed effects, with baseline age and baseline IGF-I SDS as covariates. Baseline height may also be included as a covariate if found to be significant at $p<0.10$. Other covariates may be considered for exploratory purposes.

6. STATISTICAL METHODOLOGY AND ANALYSES

6.1 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, and 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.

Analyses outside of this SAP may be performed to supplement results or for research purposes at the discretion of Versartis, Inc.

6.2 CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Changes to the protocol may result in changes to the planned analyses, and may change the defined analysis endpoints and methods. Any changes to analysis as a result of changes to the protocol will be documented as an amendment to this SAP. Other than transformations or modeling needed to address the structure and distribution of the resulting data, additional analyses will be for exploratory purposes only.

The changes from the protocol specified analyses are:

1. Growth Hormone Binding Protein (GHBP) and Acid Labile Subunits (ALS) will be summarized but not analyzed as secondary endpoints.
2. Inclusion of Levine's test for homogeneity of variance
3. Inclusion of Welch's t-test if there is unequal variance
4. Replaced multiple imputation for missing data with tipping point analysis

6.3 STUDY HYPOTHESES

The primary comparison of the annualized height velocity between somavaratan and daily rhGH is based on the null hypothesis that the difference is less than or equal to -2.0 cm/yr, the non-inferiority margin.

6.4 HANDLING OF MISSING VALUES AND OUTLIERS

Because of subject privacy limitations, birth dates may only be reported by month and year in certain locations. Where the specific birth day is not available, the day of month will be imputed as the 15th.

For the primary endpoint in the ITT population, missing height at 12 months will be imputed from the last available height. This imputation assumes no growth after the last available measurement observed at study exit. This is an extremely conservative approach. For example, a [redacted] year old [redacted] subject who discontinued at month 6 with annualized HV of 6 cm/yr (Day 1 height of [redacted] cm and Month 6 height of [redacted]) will have the height at 12 months imputed to [redacted] cm, resulting in an annual HV of 3 cm/yr.

For the sensitivity analysis of the effect of missing data on the primary endpoint, height velocity at Month 12, a tipping point approach will be used. The missing data will be imputed as follows:

For the control group:

1. All subjects to the control group mean (calculated without subjects missing endpoint)
2. 50% to the group mean, 50% to the HV associated with each subjects last reported height (no additional gain in height)
3. Each subject's HV imputed based on its own last reported height

For the somavaratan group:

1. All subjects to the somavaratan group mean (calculated without subjects missing endpoint)
2. 50% to the group mean, 50% to the HV associated with each subjects last reported height (no additional gain in height)
3. Each subject's HV based on its own last reported height
4. Each subject imputed to HV based on last reported height, minus 1 cm.
5. Each subject imputed to HV based on last reported height, minus 2 cm (the non-inferiority margin, to avoid imputing to a common mean).

The reduction of the imputed HV by -1 and -2 cm will be limited to a minimum 0 HV, as negative HV is not possible. This will result in a total of 15 comparisons which should cover the range of plausible results for the subjects who are not able to provide Month 12 height velocity, and accounts for combinations where the somavaratan drop outs will have worse outcomes than drop outs in the control group (e.g., control group imputation 1 versus somavaratan imputations 2 to 5).

No imputations will be considered for the PP populations.

All data collected under this protocol will be included in the assessment of safety. Any AEs missing the relationship to study treatment after repeated query attempts will be assigned as "unknown." Missing or incomplete start dates will be imputed to the date of first dose. Outliers that may have undue influence on the analysis and results will be discussed, but the

results will not be based on any exclusion. No other imputation is planned for the safety population.

Based on the validated assay performed at the central laboratory, the IGF-I values have a lower limit of quantitation (LLOQ) of 16.0 ng/mL and a lower limit of detection (LLOD) of 2.5 ng/mL. As subjects are expected to have growth hormone deficiency, IGF-I values may occasionally fall below the LLOQ. In these cases, the IGF-I value will be assigned to the value midway between the LLOQ and the LLOD, which is 9.25 ng/mL.

Adjustments to the safety laboratory data (blood chemistry, hematology) and IGFBP-3 due to values being below a quantifiable level will be made to indicate a value as one-hundredth (0.01) less than or higher than the limit value (e.g. < 5.0 will be adjusted and summarized as 4.99, > 12.5 will be adjusted and summarized as 12.51).

Adjustments to the PK data due to missing values or for values being below a quantifiable level may be performed, but those will be described in a separate PK report.

6.5 INTERIM ANALYSES, FINAL ANALYSES, AND UNBLINDING

This is an unblinded study; however, Versartis, Inc. and Investigators will be blinded to the aggregate height velocity data during the trial.

Sample size re-estimation will be conducted by an independent statistical consulting group not directly affiliated with the study. This group will use the observed variance in height velocity to determine if *a priori* assumptions are valid, and will notify the sponsor if the sample size needs to be increased (up to 136 total subjects) to ensure appropriate statistical power.

6.5.1 Safety Reviews

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. DSMB members will review data for any potential risk to subjects and determine if any protocol-specified stopping criteria have been met.

6.5.2 Stopping Rules

The Stopping Criteria for individual subjects include:

- The Principal Investigator and/or Medical Monitor conclude it is unsafe for the subject to continue.
- A new diagnosis of a significant medical condition or initiation of a new treatment if such condition or new treatment can influence the response to study drug (e.g., diabetes, renal failure).
- 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 individual subjects with 2 consecutive IGF-I SDS $\geq$ 3.0, 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 treatment arm include:

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

6.6 ADJUSTMENT FOR MULTIPLE COMPARISONS

Multiple comparisons of key endpoints are not planned. Any additional comparisons will be for exploratory purposes and definition of a significance level will not be done.

6.7 POOLING OF SITES

Because of the relatively small sample size for each treatment group, all sites will be pooled into one of two Regions: North America and Europe (Rest of World - ROW).

6.8 EXTENT OF EXPOSURE AND 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. Compliance will be summarized and listed, and will be used to determine the Per Protocol population.

6.9 SUBJECT DISPOSITION

The number of subjects enrolled, treated, and discontinued before study end will be summarized by count and percentage for each treatment group.

6.10 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and Baseline characteristics will be presented for all subjects and for each analysis population as total enrolled and by treatment group. Gender, race, and ethnicity will be summarized by count and percentage. Age, height, height SDS, body weight, BMI, bone age, IGF-I, IGF-I SDS and IGF-BP3 will be presented with numeric descriptive statistics. Pubertal staging will be summarized by count and percentage for pubic hair and breast development and with numeric descriptive statistics for testicular volume. In addition, age will be summarized into two quantiles using the median.

The subject's age is calculated as the number of years from the subject's date of birth to the date the Informed Consent signed (because of privacy limitation at some sites, the date of birth may only be collected as month and year, and in these cases the date will be imputed as the 15^{th}):

Age = [Date Informed Consent Signed - Date of Birth] / 365.25

Other Demographic and Baseline characteristics to be summarized with numeric descriptive statistics, where available, are maternal and paternal heights, birth weights, lengths, and

gestational ages, prior height velocities, growth hormone stimulation tests results, and adrenal function tests results.

Demographic and Baseline Characteristics will be summarized for the ITT, PP, and safety populations, should these populations be different.

6.11 EFFICACY ANALYSES

The primary efficacy analyses will be done using the All Randomized population, and will also be done using the mITT and PP populations.

6.11.1 Primary Efficacy Endpoint

Annual height velocity will be calculated using the formula below:

$$Height\ Velocity\ \left(\frac{cm}{year}\right) = \left[\frac{Month\ X\ Height\ (cm) - \ Baseline\ Height\ (cm)}{Month\ X\ date - Baseline\ date}\right] * 365.25$$

The primary analysis will be the comparison of the annual height velocity between somavaratan and daily rhGH, with null hypothesis that the difference is less than or equal to -2 cm/year, the non-inferiority margin. An Analysis of Covariance (ANCOVA) model will be used to determine the adjusted (least squares) means and SE to determine the confidence interval (CI) of the difference. The model fixed effects are treatment group, region and gender, with baseline age, baseline IGF-I SDS, and baseline height as covariates. The ANCOVA is used to adjust for the influence of these covariates, and not to determine if these covariates themselves are statistically significant factors. A reduced model removing covariates with $p>0.10$ may also be considered for exploratory purposes. The randomization stratification should result in balance between the two treatments in terms of the factors. Levene's will be used to determine if the variances is equal between the two treatment groups. If there is evidence of unequal variance, a Welch test on the treatment main effects will be performed with null hypothesis of somavaratan HV - daily rGH HV <= -2 cm. Rejection of this null hypothesis will be evidence of non-inferiority of somavaratan to daily rGH.

6.11.2 Secondary Efficacy Endpoints

Secondary endpoints will be summarized with descriptive statistics, and as appropriate, comparisons with t-test or ANCOVA, or non-parametric methods if assumptions of normality are not met. Pubertal staging will be with categorical methods showing count and %. The change from baseline for the secondary endpoints will also be presented. For any comparisons performed, the null hypothesis for the test is that the two groups are equal at $p<0.05$. There is no intent to show non-inferiority for the secondary endpoints, as the sample size was not determined to be sufficient to show non-inferiority for these secondary endpoints.

The main intent of ANCOVA will be to explore the influence of the covariates on the outcome of the secondary endpoint. Differences between treatment groups are not expected,

so there is no plan to adjust the alpha level of each comparison. The primary covariates will be those used for the primary endpoint, plus the baseline value of the secondary endpoint being analyzed.

6.12 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

6.12.1 Pharmacokinetic Analyses

Calculation of PK parameters and the PK analysis and interpretation will be presented in a separate report.

6.12.2 Pharmacodynamic Analyses

IGF I and IGF I SDS.

The peak and trough levels of IGF I and IGF SDS will be summarized by each time point sampled. The change from baseline to last peak and last trough level will be calculated and summarized.

An exploratory analysis of the relationship of IGF-I, IGF SDS and IGFBP-3 to height velocity will be done with ANCOVA. The model used for the primary endpoint will be the starting point, with IGF results added.

The molar ratio between IGF-I and IGFBP-3 will be calculated and summarized over time. A molecular mass of 7,649 Da (Daltons) will be used for IGF-I and a molecular mass of 43,000 Da (Daltons) will be used for IGFBP-3. Assuming 1 Da equals 1 g/mole, then the molarity of IGF-I and IGFBP-3, respectively, will be calculated using the following formulas:

$$Molarity\ of\ IGF-I\ \left(\frac{nmol}{mL}\right) = \frac{IGF-I\ value\ in \frac{ng}{ml}}{7{,}649}$$

and

$$Molarity\ of\ IGFBP-3\ \left(\frac{nmol}{mL}\right) = \frac{\left(IGFBP-3\ value\ in \frac{mg}{L}\right) * 1000}{43{,}000}$$

Once derived, the molar ratio will be calculated by dividing the moles of IGF-I by the moles of IGFBP-3.

6.12.3 Immunogenicity/Antibodies

Immunogenicity of somavaratan and daily rhGH will be assessed by measurement of anti-drug antibodies (ADAs) in serum samples. ADAs to both somavaratan and daily rhGH will be determined following a tiered approach consisting of screen, confirmation, titration and additional characterization. The additional characterization of somavaratan ADAs includes measurement of ADA specificity to rhGH and XTEN and neutralization capacity in an *in*

vitro cell bioassay. A summary of the ADA results will be described in detail in a separate immunogenicity analysis report included in the Integrated Summary of Immunogenicity (ISI).

The effect of ADAs on height velocity (HV) and safety will be evaluated for both treatment groups. An analysis of variance (ANOVA) model of HV as dependent variable with treatment and ADA classification (e.g., positive/negative status (c.f., Shankar et al., 2014); based on titer, etc.) as factors will be used as the first step in this evaluation. Comparisons of somavaratan PK, IGF-I and IGF-SDS between the ADA classification groups will also be performed. The additional characterization data will also be assessed for relevance to HV.

6.13 SAFETY ANALYSES

Safety analyses will be based on the Safety population consisting of all subjects receiving any amount of somavaratan or rhGH.

6.13.1 Adverse Events

Analysis of adverse events will be based on Treatment Emergent events. A Treatment Emergent Adverse Event (TEAE) is any sign, symptom, or abnormal laboratory finding after the first drug administration, or an increase in the severity or frequency of a condition existing at the time of enrollment. Procedures will not be included as an adverse event, but any condition not present at enrollment, or change in condition, leading to the procedure should be classified as an adverse event.

AEs will be reported by the Investigator and coded using the MedDRA dictionary. AE severity will be determined using the CTCAE v4.0 definitions. Severity of AEs that are not classified using CTCAE will be assigned scores based on the following:

Severity of Adverse Events

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.

For analysis purposes, all AEs will be classified to the appropriate MedDRA preferred term (PT) and system organ class. For each subject, multiple events that map to the same PT will only be counted once for the PT, and multiple PTs within a System Organ Class (SOC) will only be counted as one occurrence for that SOC to assess subject incidence of events. The count and percentage of subjects with each PT and SOC will be summarized for each treatment group.

Relationship and severity of adverse events will be summarized (subject count, % of subjects) for each treatment group. For these summaries, multiple occurrences of an event within a subject will be classified as a single observation with the strongest relationship and maximum severity ratings. In addition, frequency tables of all reported events with each associated relationship and severity will be presented.

A tabulation of the incidence of all Grade 3 and 4 treatment-emergent adverse events will be displayed, overall and those related to study drug. Furthermore, a tabulation of the incidence of all treatment-emergent injection site adverse events will be created including, but not limited to, events such as pain/tenderness, erythema, lipoatrophy, stinging, burning, itching, etc. A listing of the treatment-emergent injection site adverse events will supplement the tabulation and will contain dosing information including but not limited to, onset time since last dose, relationship to study drug, dose, grade, injection location, injection volume, number of injections received per dosing event, and duration.

Moreover, a listing of instances of headache reported as an adverse event will be presented which will include information about the event such as, but not limited to, onset time since last dose, relationship to study drug, dose, grade, and duration.

Serious Adverse Events (SAE) are defined as those events that are life threatening, require hospitalization or prolong existing hospitalization; or cause disability, incapacity, or death; or require intervention to prevent such outcomes. These events will be classified as SAEs by the Investigator and appropriate medical review and will be summarized by treatment group, as well as total subjects exposed.

A listing of SAE data will be provided to supplement the tabulated results.

6.13.2 Physical Exams

For the complete physical examinations performed, the proportion of subjects reporting results of “Normal”, “Abnormal, Not Clinically Significant,” and “Abnormal, Clinically Significant” will be calculated and presented for each scheduled time point, body system and treatment group. Any changes in physical examinations post-injection, including injection site findings, will be captured as an AE and will be presented in those tabulations and/or listings. The proportion of subjects that report changes in brief physical examination (e.g., change/no change) will be calculated and presented by treatment group across visits.

6.13.3 Vital Signs and ECG

Descriptive statistics of vital signs will be calculated at each scheduled time point and will include the raw change from Baseline. The summary of descriptive statistics at each time point will be displayed by treatment group.

A listing of all vital signs data will be provided to supplement the tabulated results.

ECG abnormalities from Screening and Month 3 will be listed. A count and percent of subjects with abnormal changes (normal at screening, abnormal findings at Month 3) will be presented.

6.13.4 Ocular Fundoscopy

For the fundoscopy examination, the proportion of subjects reporting abnormal results will be calculated and presented by treatment group. Abnormal findings will also be included as AEs for the AE summaries.

A listing of all fundoscopy data will be provided to supplement the tabulated results.

6.13.5 Laboratory Data

Laboratory data will be reported by analyte for each treatment group. There will not be any hypothesis testing. The laboratory results will be presented at each scheduled time point along with the raw change from Baseline for quantitative data. Presence/absence or normal/abnormal results will be summarized as count and percentage. In addition, shift tables summarizing changes from normal to out-of-normal range will be provided.

A listing of all laboratory data, including unscheduled and any follow up evaluations will be provided to supplement the tabulated results.

6.13.6 Medical History

Medical History data will not be tabulated but will be provided in a listing by treatment group and subject.

6.13.7 Concomitant Medications

Concomitant Medications will be coded using the World Health Organization (WHO) Drug dictionary, version as noted in the Data Management Plan, using Anatomical Therapeutic Chemical (ATC) classifications and WHO preferred terms. Concomitant Medications will not be tabulated but will be provided in a listing by treatment group and subject.

7. REFERENCES

Centers for Disease Control and Prevention, National Center for Health Statistics. Clinical Growth Charts: Percentile Data Files with LMS Values.
https://www.cdc.gov/growthcharts/percentile_data_files.htm

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8. TABLES, LISTINGS, AND FIGURES

The final list of Tables, Listings, and Figures (TLFs) used in the clinical study report will be provided outside of this SAP prior to database lock.

9. APPENDICES

None.