Growth Hormone in a Patient with a Dominant-Negative GHR Mutation

Protocol Number: STUDY00000211

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.3 and throughout	Added in schedule of activities for extension phase as well as criteria for entry into extension phase	Subject is having a positive response to therapy and would like to continue into extension phase of study.

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STATEMENT OF COMPLIANCE

(1) The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Growth Hormone in a Patient with a Dominant-Negative GHR Mutation
Study Description:	This is a prospective interventional study designed for a single patient with a dominant-negative mutation in the growth hormone receptor gene (GHR) which results in increased levels of growth hormone binding protein (GHBP). The patient will receive escalating doses of growth hormone titrated to achieve an IGF-1 level above the mean and then growth response to therapy will be monitored.
Objectives:	Primary Objective: To determine whether increasing doses of growth hormone can normalize IGF-1 levels in a patient with a specific dominant-negative GHR mutation

	Secondary Objectives: To determine if normalizing IGF-1 levels in this specific patient will result in improved growth as measured by height velocity and height standard deviation score (SDS).
Endpoints:	Primary Endpoint: Dose of growth hormone required in mg/kg/day to achieve an IGF-1 level above the mean (adjusted for age and Tanner stage) Secondary Endpoints: Growth velocity during 1st year of growth hormone treatment; Change in height SDS over the course of the 1st year of treatment with growth hormone
Study Population:	This study is designed for a single male patient who is currently 9 years old.
Accrual Ceiling:	1
Phase:	II
Description of Sites/Facilities Enrolling Participants:	This study will be conducted at Children's National Hospital in Washington, DC.
Description of Study Intervention:	The subject will receive daily growth hormone via subcutaneous injection at a starting dose of 50 micrograms/kg/day. The dose of growth hormone will be increased by an increment of 50 micrograms/kg/day every 2 weeks until an IGF-1 level above the mean (adjusted for age and Tanner stage) is achieved. The subject will then remain on that dose for 1 year of treatment (inclusive of titration period). If the subject is responding to treatment, he will have the option of entering an extension phase which will continue the same dose/kg until the cessation of growth.
Study Duration:	18 months
Participant Duration:	12 months for initial study. There are 5 visits each lasting 2-3 hours. If the subject has a positive response, he will have the option to continue in the extension stage until the cessation of growth (estimated to be a total of 5-7 years of treatment depending on pubertal timing).

1.2 SCHEMA

Dose Escalation Schedule	
Dose Level	Dose of Growth Hormone
Level 1	50 mcg/kg/day
Level 2	100 mcg/kg/day
Level 3	150 mcg/kg/day

Level 4	200 mcg/kg/day
Level 5	250 mcg/kg/day
Dose level will be increased every 2 weeks in order to achieve an IGF-1 level above the mean and below +2 SD. If increasing to the next dose level results in an IGF-1 level above +2 SD, then the dose will be decreased to mid-way between the two dose levels.	

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Baseline Visit	Dose Escalation Period (Phone calls ~q2weeks)[g]	Dose Stable Period (Monthly phone calls)[h]	3 month visit (+/- 2 weeks)	6 month visit (+/- 2 weeks)	9 month visit (+/- 2 weeks)	12 month visit (+/- 2 weeks)	Early termination
Informed consent	X							
Medical History	X							
Parental anthropometrics[a]	X							
Physical examination	X			X	X	X	X	X
Tanner stage	X			X	X	X	X	X
Vital signs[b]	X			X	X	X	X	X
Anthropometric measurements[c]	X			X	X	X	X	X
Clinical labs[d]	X			X	X	X	X	X
Bone Age X-ray	X						X	X
Health events reviews		X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Study drug administration review		X	X	X	X	X	X	X
Adverse event reviews	X	X	X	X	X	X	X	X
Education in GH use	X							
Fasting glucose and IGF-1 Level[e]		X	X	X				
Dose Adjustment[f]		X						
Cortisol level		X[i]						

[a] Both parents heights should be measured if available.

[b]Vital signs include: body temperature in degrees Celsius (°C), heart rate, BP, and respiratory rate.
[c] Anthropometric measurements include standing height and weight. Standing height should be measured 5 times using a calibrated stadiometer. Weight should be measured on a digital scale.
[d] Clinical labs include: TSH, free T4, IGF-I, IGFBP-3, fasting glucose, Growth hormone binding protein and anti-GH antibodies. All labs will be obtained through the clinical lab at Children's National Hospital. IGF-1 levels will be sent to Quest Diagnostics.
[e] Fasting glucose and IGF-1 level will be drawn at a local Quest Diagnostics every 14 days +/- 2 days after dose escalation. Once a stable dose is established, fasting glucose and IGF-1 will be obtained monthly for the remainder of the 12-month study.
[f] Growth hormone dose will be escalated as per the Dose Escalation Schedule after the receipt of the IGF-1 result
[g] Phone calls will occur approximately every 2 weeks during the dose escalation period in order to adjust the growth hormone dose and assess for adverse events.
[h]Once the subject is on a stable dose of GH, monthly phone calls will be made to assess for adverse events. These will continue for the duration of the 12-month study.
[i]A morning cortisol level will be drawn once at the first lab draw after initiation of growth hormone to ensure that adrenal insufficiency has not been unmasked. This level will be sent to Quest Diagnostics along with the IGF-1 and fasting glucose level.

Extension Phase Schedule of Activities

Procedure	Telephone visits occurring every 6 months (+/- 2 weeks) starting at Month 15 (i.e. Months 15, 21, 27, 33, etc…)	In person visits occurring every 6 months (+/- 2 weeks) starting at Month 18 (i.e. Months 18, 24, 30, 36, etc…)	Early termination
Physical examination		X	X
Tanner stage		X	X
Vital signs [a]		X	X
Anthropometric measurements [b]		X	X
Clinical labs [c]		X	X
Bone Age X-ray [d]		X*	X
Health events reviews	X	X	X
Concomitant medications	X	X	X
Study drug administration review	X	X	X
Adverse event reviews	X	X	X
Fasting glucose and IGF-1 Level [e]	X		
Dose Adjustment [f]		X	

[a] Vital signs include: body temperature in degrees Celsius (°C), heart rate, BP, and respiratory rate.
[b] Anthropometric measurements include standing height and weight. Standing height should be measured 5 times using a calibrated stadiometer. Weight should be measured on a digital scale.

[c] Clinical labs include: TSH, free T4, IGF-I, IGFBP-3, fasting glucose, hemoglobin A1c, Growth hormone binding protein and anti-GH antibodies. All labs will be obtained through the clinical lab at Children's National Hospital. IGF-1 levels will be sent to Quest Diagnostics.
[d] A bone age X-ray will be done every 12 months starting at Month 24 in the extension phase of the study.
[e] Fasting glucose and IGF-1 level will be drawn at a local Quest Diagnostics during the same time window as the Telephone Visits during the extension phase.
[f] Growth hormone dose will be continued at a dose of 250 micrograms/kg/day and will be adjusted based on the subject's weight at each in-person visit.

2 INTRODUCTION

2.1 STUDY RATIONALE

This study is designed for a single patient with a dominant-negative mutation in *GHR* (the growth hormone receptor gene) which results in elevated levels of growth hormone binding protein (GHBP). Given our understanding of the mechanism of short stature in this patient, we hypothesize that high doses of growth hormone will be able to overcome the growth hormone resistance, normalize IGF-1 levels, and improve growth.

2.2 BACKGROUND

The subject is currently a 9-year-old male. He first presented at age 4 years to a pediatric endocrinologist who noted that his height had been less than the 3rd percentile since age 2 years. His birth weight was normal at 7 lbs 3 ounces. Per the endocrinologist's note, the father's height is 60" and mother's height is 63". He was followed clinically, and then at age 8 years, he was evaluated by a geneticist who performed a short stature panel which identified that he carried a heterozygous pathogenic variant in GHR, c.757del (p.Gln253Argfs*2), which he inherited from his father. This variant is located in exon 7 in the extracellular domain of GHR just above the junction with the transmembrane domain. Therefore, it is predicted to truncate the protein and result in increased release of growth hormone binding protein (GHBP) which is made from the extracellular domain of GHR.

He underwent growth hormone stimulation testing at age 8 years 7 months which showed a peak growth hormone level of 26.4 ng/ml. His IGF-1 level at that time was 61 ng/ml (normal range 59-275). The high growth hormone peak with a relatively low IGF-1 level is consistent with a degree of growth hormone resistance. A repeat IGF-1 done at age 8 years 9 months was 54 ng/ml (-1.9 SD for Tanner 1). At his most recent visit to the endocrinologist at age 9 years 0 months, he had a height of -3.34 SDS. A GHBP level done at age 9 years 2 months was 45 ng/ml (normal 11-26). The subject's baseline growth velocity is approximately 6 cm/year based on the measurements available in the record.

Our group previously reported a patient with a similar mutation, p.Trp267*, which truncated the transmembrane domain and resulted in elevated GHBP levels.[1] In a cellular model, we demonstrated that this mutation did lead to elevated levels of secreted GHBP, and that these high levels of GHBP were responsible for the dominant-negative effect of the mutation through interference with GH binding to its receptor. Furthermore, we were able to show in vitro that administering high doses of GH resulted in normalization of downstream GHR signaling. This suggests that high dose GH administered to the patient may be able to overcome the GH resistance and normalize IGF-1 levels and improve growth. The patient reported in the prior study declined further treatment. The subject of this protocol has a mutation that appears to work via the same mechanism and is interested in pursuing treatment. To my

knowledge, there have not been any prior studies attempting to overcome growth hormone resistance with high doses of growth hormone.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Recombinant human growth hormone is FDA approved for a number of indications. It has a well-described safety profile and has been used in millions of children. In this study, GH will be used at doses above the currently approved dose although the subject has growth hormone resistance and thus should be at lower risks for side effects. The adverse events listed in the GH prescribing information are as follows (please see attached prescribing information[2] for details):

- Increased mortality in patients with acute critical illness *[see* Warnings and Precautions (5.1)*]*
- Fatalities in children with Prader-Willi syndrome *[see* Warnings and Precautions (5.2)*]*
- Neoplasms *[see* Warnings and Precautions (5.3)*]*
- Glucose intolerance and diabetes mellitus *[see* Warnings and Precautions (5.4)*]*
- Intracranial hypertension *[see* Warnings and Precautions (5.5)*]*
- Severe hypersensitivity *[see* Warnings and Precautions (5.6)*]*
- Fluid retention *[see* Warnings and Precautions (5.7)*]*
- Hypoadrenalism *[see* Warnings and Precautions (5.8)*]*
- Hypothyroidism *[see* Warnings and Precautions (5.9)*]*
- Slipped capital femoral epiphysis in pediatric patients *[see* Warnings and Precautions (5.10)*]*
- Progression of preexisting scoliosis in pediatric patients *[see* Warnings and Precautions (5.11)*]*
- Otitis media and cardiovascular disorders in patients with Turner syndrome *[see* Warnings and Precautions (5.12)*]*
- Lipoatrophy *[see* Warnings and Precautions (5.13)*]*
- Pancreatitis *[see* Warnings and Precautions (5.15)*]*

2.3.2 KNOWN POTENTIAL BENEFITS

If this treatment is successful, the subject could have improved growth and potentially reach a height within the normal range.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Patients routinely use growth hormone with the know risks for the indication of idiopathic short stature. The current subject and his family are highly interested in pursuing treatment to improve his growth and understand the attendant risks. IGF-1 levels will be monitored to prevent excessive GH stimulation as the dose will be titrated downward if the IGF-1 level is above +2 SD. The subject's other option is to pursue treatment with recombinant IGF-1 therapy, but this has not been approved as his IGF-1 is not below -3 SD (a requirement for approval). Additionally, recombinant IGF-1 has a higher rate of adverse events compared to GH and is generally less efficacious.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether increasing doses of growth hormone can normalize IGF-1 levels in a patient with a specific dominant-negative GHR mutation	Dose of growth hormone required in mg/kg/day to achieve an IGF-1 level above the mean (adjusted for age and Tanner stage)	This endpoint will determine the dose for ongoing treatment and will demonstrate proof of principle that the GH resistance can be overcome.
Secondary:		
To determine if normalizing IGF-1 levels in this specific patient will result in improved growth as measured by height velocity and height standard deviation score (SDS).	Growth velocity during 1st year of growth hormone treatment; Change in height SDS over the course of the 1st year of treatment with growth hormone During the extension phase, the endpoints will be growth velocity during each year of treatment and change in height SDS during each year of treatment as well as cumulative change in height SDS since initiation of treatment.	This endpoint will demonstrate efficacy of high dose GH treatment in this single subject.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective interventional study designed for a single patient with a dominant-negative mutation in the growth hormone receptor gene (GHR) which results in increased levels of growth hormone binding protein (GHBP). The patient will receive escalating doses of growth hormone titrated to achieve an IGF-1 level above the mean and then growth response to therapy will be monitored over the course of 1 year.
If the subject has a good response to therapy, he will be offered to continue on treatment until cessation of growth.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a single-arm study as the goal is to treat this single subject and achieve a normal IGF-1 and improved growth. Historical growth data is available for this subject to be used as a comparison. See background (2.2) for explanation of scientific rationale.

4.3 JUSTIFICATION FOR DOSE

The starting dose of recombinant human growth hormone of 50 mcg/kg/day was chosen as a common dose used in non-GH deficient indications (such as Turner syndrome, SHOX deficiency or idiopathic short stature). The 50 mcg/kg/day increment for dose increases was chosen arbitrarily as it is difficult to

extrapolate from the *in vitro* work to know what dose will be required to have an effect *in vivo*. However, if this increment proves to be too high, the dose will be down titrated to an intermediate dose which maintains an IGF-1 between the mean and +2 SD. The maximum dose given will be 250 mcg/kg/day. Based on the subject's current weight, the starting dose will be ~1 mg/day and the maximum dose would be ~ 5 mg/day.

4.4 END OF STUDY DEFINITION

The participant is considered to have completed the study when he has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

If the subject is demonstrating a positive response to therapy, he will be offered enrollment into the extension phase. A good response to growth hormone treatment is an increase in height SDS of 0.4 or greater over the course of 1 year. The extension phase will end when the subject has an annualized growth velocity of <2 cm/year in the preceding 6 months.

5 STUDY POPULATION

This study is designed for a specific single subject. He will be the only one in the study. If this study is successful and other subjects with similar mutations are identified, a protocol amendment will be submitted to include those subjects.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Be the specific subject with the *c*.757del (p.Gln253Argfs*2) mutation in GHR who is described in the Background section.

To be eligible for the extension phase of the study, the subject must have had an increase in height SDS of 0.4 or greater during the first year of therapy.

5.2 EXCLUSION CRITERIA

There are no exclusion criteria for this study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Not applicable

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The individual subject for whom this study is designed is interested in participating. I am in contact with the subject's mother. Once the protocol is approved, I will contact the mother and the family will travel to Children's National for the Baseline Visit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

For this study, we will be using the Genotropin brand of recombinant human growth hormone. We intend to use a pen formulation. The exact formulation will depend on the drug availability from Pfizer.

GENOTROPIN lyophilized powder contains somatropin, which is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). GENOTROPIN is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. GENOTROPIN is a sterile white lyophilized powder intended for subcutaneous injection.

GENOTROPIN 5 mg is dispensed in a two-chamber cartridge. The front chamber contains recombinant somatropin 5.8 mg, glycine 2.2 mg, mannitol 1.8 mg, sodium dihydrogen phosphate anhydrous 0.32 mg, and disodium phosphate anhydrous 0.31 mg; the rear chamber contains 0.3% m-Cresol (as a preservative) and mannitol 45 mg in 1.14 mL water for injection. The GENOTROPIN 5 mg two-chambered cartridge contains 5.8 mg of somatropin. The reconstituted concentration is 5 mg/mL. The cartridge contains overfill to allow for delivery of 1ml containing the stated amount of GENOTROPIN – 5 mg.

GENOTROPIN 12 mg is dispensed in a two-chamber cartridge. The front chamber contains recombinant somatropin 13.8 mg, glycine 2.3 mg, mannitol 14.0 mg, sodium dihydrogen phosphate anhydrous 0.47 mg, and disodium phosphate anhydrous 0.46 mg; the rear chamber contains 0.3% m-Cresol (as a preservative) and mannitol 32 mg in 1.13 mL water for injection. The GENOTROPIN 12 mg two-chambered cartridge contains 13.8 mg of somatropin. The reconstituted concentration is 12 mg/ml. The cartridge contains overfill to allow for delivery of 1ml containing the stated amount of GENOTROPIN – 12 mg.

GENOTROPIN MINIQUICK® is dispensed as a single-use syringe device containing a two-chamber cartridge. GENOTROPIN MINIQUICK is available as individual doses of 0.2 mg to 2.0 mg in 0.2 mg increments. The front chamber contains recombinant somatropin 0.22 to 2.2 mg, glycine 0.23 mg, mannitol 1.14 mg, sodium dihydrogen phosphate 0.05 mg, and disodium phosphate anhydrous 0.027 mg; the rear chamber contains mannitol 12.6 mg in water for injection 0.275 mL. The reconstituted GENOTROPIN MINIQUICK two-chamber cartridge contains overfill to allow for delivery of 0.25 ml containing the stated amount of GENOTROPIN.

6.1.2 DOSING AND ADMINISTRATION

The study participant will start at a dose of 50 micrograms/kg/day given as a daily subcutaneous injection. An IGF-1 level will be obtained 2 weeks after initiation of growth hormone. The PI, Dr. Dauber, will review the IGF-1 level and will increase the dose as per the table below with the goal of achieving an IGF-1 between the mean and +2 SD. Repeat IGF-1 levels will be obtained 2 weeks after every dose change and Dr. Dauber will continue to titrate the dose as indicated until the desired IGF-1 is obtained. We will not exceed a dose of 250 mcg/kg/day. If the subject does not achieve and IGF-1 level above 0 SD at a dose of 250 mcg/kg/day, then the trial will be discontinued. If an increase in dose results in an IGF-1 level above +2 SD, the dose will be decreased to midway between the current dose and the prior dose which resulted in an IGF-1 below the mean and a repeat IGF-1 will be drawn in 2 weeks. Dr. Dauber will personally speak with the subject's parents to review all dose changes and will verify understanding of the appropriate dose to be given using closed-loop communication. Once the target IGF-1 level is achieved, IGF-1 levels will be checked monthly to ensure that the level stays within the target range.

Dose Escalation Schedule	
Dose Level	Dose of Growth Hormone
Level 1	50 mcg/kg/day
Level 2	100 mcg/kg/day
Level 3	150 mcg/kg/day
Level 4	200 mcg/kg/day
Level 5	250 mcg/kg/day
Dose level will be increased every 2 weeks in order to achieve an IGF-1 level above the mean and below +2 SD. If increasing to the next dose level results in an IGF-1 level above +2 SD, then the dose will be decreased to mid-way between the two dose levels.	

For the extension phase of the study, the subject will continue on the dose required to achieve the target IGF-1 level. The same dose level will then be used for the entirety of the extension study, but the actual dose will be adjusted based on weight at all in-person visits.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigational pharmacy will distribute 3 month supplies of medication at each in person visit during the initial phase of the study and 6 month supplies of medication during the extension phase of the study. The subject will be asked to return all study medication at the next in person visit for drug accountability. At each study visit, used (empty) and unused study drug will be returned to the investigational pharmacy for disposal. At the conclusion of the entire study, unused drug will either be returned to Pfizer or destroyed as per standard operating procedure of the investigational pharmacy.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Genotropin will be used in its pen form, either the 5 mg or 12 mg pen depending on the dose. Formulation details are noted above in section 6.1.1. The boxes of Genotropin pens will have a label stating “Caution: New Drug--Limited by Federal (or United States) law to investigational use."

6.2.3 PRODUCT STORAGE AND STABILITY

The 5 mg and 12 mg cartridges of GENOTROPIN contain a diluent with a preservative. Thus, after reconstitution, they may be stored under refrigeration for up to 28 days.

6.2.4 PREPARATION

See attached prescribing information for detailed instructions on use of Genotropin pen. In brief, a cartridge is inserted into the pen device and mixed. Then, a daily dose of medication is dialed up in the pen and given as a subcutaneous injection.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable. This is an open label study in a single subject.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol will be monitored in two ways. First, we will have periodic telephone calls with the subjects during which medication adherence will be reviewed (See Schedule of Activities, **Section 1.3**). Second, subjects will be asked to bring all remaining medication to each study visits. We will calculate the dose used to assess for compliance.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications. Concomitant therapy will be monitored at all study visits as outlined in the Schedule of Activities, **Section 1.3**. Concomitant medications prohibited during this study include recombinant IGF-1. All other concomitant medications are allowed.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from growth hormone will result in discontinuation from the study, as there is only 1 subject in the study. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation are outlined in the Early Termination visit in the Schedule of Activities, **Section 1.3**.

Growth hormone will be discontinued if the subject experiences a Grade 3 or higher adverse event that is related to the study medication or any of the specific AEs noted in the next section. This will result in discontinuation of the entire study. Additionally, if the subject does not achieve and IGF-1 level above 0 SD at a dose of 250 mcg/kg/day, then the trial will be discontinued.

The extension phase of the study will be completed when the subject has an annualized growth velocity of <2 cm/year in the preceding 6 months.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects (or their legally authorized representative) have the right to withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out.

Reasons for which a subject may be withdrawn from the study or from study treatment by the Investigator include but are not limited to the following:

- Subject experiences a serious or intolerable AE
  - Specifically, if the subjects develops any of the following AEs, then the subject will be withdrawn from the study:
    - Increased intracranial pressure
    - Slipped capital femoral epiphysis
    - A new malignancy
    - Hypersensitivity to growth hormone
    - Clinically significant worsening of scoliosis as determined by an orthopedic physician
    - New onset diabetes of any type
    - Persistent fasting hyperglycemia of greater than 100 mg/dl on 2 consecutive blood draws
- Subject develops a clinically significant laboratory abnormality
- Subject requires medication or medical procedure prohibited by the protocol
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

Non-adherence to study medication administration will be monitored via review of the amount of medication returned at each visit. The subject will be encouraged to have 100% compliance with study drug administration.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Termination Visit Case Report Form.

7.3 LOST TO FOLLOW-UP

The participant will be considered lost to follow-up if he fails to return for any in-person scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if the participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

Demographic Data and Medical History

Demographic data and a detailed medical history will be obtained at the Baseline visit. This medical history should elicit all major illnesses, diagnoses, and surgeries that the subject has ever had, and any prior or existing medical conditions that might interfere with study participation or safety.

Parental Anthropometrics

The standing height of the participant's biological parents will be assessed if they agree to participate. Both parents should be measured if available. If unavailable, report of the parents' heights will be recorded.

Subject Anthropometrics

Anthropometric measurements include standing height and weight. Standing height should be measured 5 times using a calibrated stadiometer. The average of the 5 measurements will be used as the outcome measure. All measurements will be done in the Clinical Research Center at Children's National Hospital and will be performed by the PI. Weight should be measured on a digital scale.

Height Outcome Measures

Efficacy will be assessed as the annualized growth velocity and the change in height SDSD from the baseline visit to the 12 Month visit.

8.1 SAFETY AND OTHER ASSESSMENTS

Health events

Health events (medical issues that result in a hospital admission or trip to the emergency department, other significant medical issues, and changes in the participant's health status including changes to prescription medications) will be reviewed at the time points indicated in the Schedule of Activities (**Section 1.3**) and recorded on a case report form (CRF). Updates to concomitant medications will be captured on the appropriate CRF. Should the occurrence of an adverse event (AE) or serious adverse event (SAE) come to the attention of study personnel during review of heath events, it will be captured on the appropriate CRF.

Physical Examination and Tanner Staging

Physical examination will include assessment of general appearance; cardiovascular; dermatologic; head, eyes, ears, nose, and throat; lymphatic; respiratory; GI; musculoskeletal; and neurological/psychological and genitourinary. Tanner stage will also be assessed. All physical examinations will include a detailed hip and spine examination as well as a funduscopic exam. The Baseline Visit results will be the baseline values and clinically significant changes from baseline will be recorded as an AE or SAE as appropriate. A qualified medical provider (either physician or NP) will perform the physical examination.

Vital Signs
All treatment visits have pre-dose vital sign assessments. Vital signs include: body temperature in degrees Celsius (°C), heart rate, blood pressure, and respiratory rate.

Concomitant Medication Assessment
A list of all medications will be assessed at the time points indicated in the Schedule of Activities (**Section 1.3**). The names of the medications will be recorded in a case report form.

Clinical Labs
Clinical labs include: TSH, free T4, fasting glucose, IGF-I, IGFBP-3, anti-GH antibody levels, and Growth hormone binding protein. During the extension phase of the study, a hemoglobin A1c will be added to the clinical labs. All labs will be obtained through the clinical lab at Children's National Hospital. IGF-1 levels will be sent to Quest Diagnostics. Clinical labs and IGF-1 levels will be performed at the time points indicated in the Schedule of Activities (**Section 1.3**). A cortisol level will be checked at the first lab draw post-initiation of GH therapy.

Bone Age X-rays
Bone age X-rays will be performed using routine clinical protocols. The bone age X-rays will be done at an interval similar to routine clinical care but are being done for the research purposes and costs will be covered by the study.

Adverse Events
The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 8.3. Assessments of AEs will occur at the time points shown in the Schedule of Activities (Section 1.3).

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The Investigator will determine the severity of each AE using the version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE)[3]. Adverse events that do not have a corresponding CTCAE term will be assessed according to the following guidelines:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.2.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the

training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.5 ADVERSE EVENT REPORTING

Subjects will be encouraged to notify the study team immediately should any adverse event occur. Formal review of adverse events will occur at each visit and telephone call as detailed in the Schedule of Activities (**Section 1.3**). The PI or a qualified co-investigator will review all adverse events within 48 hours and serious adverse events within 24 hours of becoming aware of the event or as soon as possible if clinical treatment or dose reduction may be necessary. An adverse event log will be maintained. Reports of all AEs will be provided to the external study safety monitor after completion of the Month 6 Visit and the Month 12 Visit. The study team will comply with all local legal, regulatory, and IRB requirements with regards to adverse events.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

All study personnel will immediately report to the sponsor investigator any serious adverse event (SAE), whether or not considered study intervention related, including those listed in the protocol or prescribing information and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. The PI will report all SAEs to Pfizer within 24 hours of being made aware of an occurrence using the Pfizer Investigator Sponsored Research or Clinical Research Collaboration Interventional Serious Adverse Event Report Form.

All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable.

The study sponsor/PI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor investigator must notify FDA and Pfizer must notify all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor investigator determines that the information qualifies for reporting. The IND safety report will be submitted to the FDA using Form 3500A as per FDA regulations and will follow the appropriate FDA guidance (see https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-

reports) and to Pfizer using the Pfizer Investigator Sponsored Research or Clinical Research Collaboration Interventional Serious Adverse Event Report Form.

8.2.7 REPORTING EVENTS TO PARTICIPANTS

As there is only 1 participant in this study, he will be aware of any AE that occurs.

8.2.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.2.9 REPORTING OF PREGNANCY

Not applicable. This single subject in this study is a male.

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

UPs will be promptly reported to the IRB of record and to the DCC/study sponsor in accordance with policy and regulatory requirements. As Children's National serves as the IRB of record, UPs

should be reported to the IRB within 7 business days of the investigator becoming aware of the UP.

8.3.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

As there is only 1 participant in this study, he will be aware of any UP that occurs.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This is a pilot study in a single subject. There will be no formal statistical analysis.

9.2 SAMPLE SIZE DETERMINATION

Not applicable

9.3 POPULATIONS FOR ANALYSES

Not applicable

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This will be a descriptive study where the outcome measures will simply be reported with no further statistical analysis.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint will be reported as the dose of growth hormone in mg/kg/day needed to maintain an IGF-1 between the mean and + 2 SD.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The annualized growth velocity will be described as cm/year and the change in height SDS will be calculated using the CDC growth charts.

9.4.4 SAFETY ANALYSES

The end-of-study safety analysis will be descriptive.

All AEs will be categorized and classified for severity as described above based on the original terms entered on the CRF. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment, and severity. All AEs, including AEs that lead to dose interruption/hold, permanent discontinuation from the study and from study treatment and SAEs, will be listed.

All other safety measures including laboratory tests, vital signs, and concomitant medication data will also be summarized descriptively. Laboratory tests will also be summarized by absolute and percent change from baseline and listed by significant values.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics include height, height SDS, weight, weight SDS, BMI, BMI SDS, baseline growth velocity (based on historical medical record data), baseline bone age and Tanner stage.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

Not applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant date will be listed for each measure and time point.

9.4.9 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: Consent form for subject to be completed by guardian which will include a verbal assent form.

A written consent addendum will be used for the extension phase of the protocol and will be obtained at the Month 12 visit. A written assent form will be used at the first in-person after the subject reaches 12 years of age.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent forms will be Institutional Review Board (IRB)-approved and the participant/legally authorized representative (LAR) will be asked to read and review the document. The principal investigator will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room. Assent will be conducted. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants/families/LAR will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants/family/LAR should have the opportunity to discuss the study with their family or surrogates, or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants/families/LAR must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants/families/LAR for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the PI to study participant, Pfizer, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and Pfizer and will provide the reason(s) for the termination or suspension. Study participant will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Loss of funding and/or support from Pfizer

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB, DSMB, Pfizer and/or Food and Drug Administration (FDA) as necessary.

10.1.3 DATA CONFIDENTIALITY AND PARTICIPANT PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study safety monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.
The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored in the Division of Endocrinology at Children's National Hospital in a locked file cabinet or on a password protected research drive on the Children's National network. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number.

10.1.4 FUTURE USE OF STORED HUMAN SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in a password protected research drive on the Children's National server. No biological specimens will be stored.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Andrew Dauber, MD MMSc Chief of Endocrinology
Children's National Hospital
111 Michigan Ave NW, Washington, DC 20010
202-476-1241
adauber@childrensnational.org

An external study safety monitor will be identified prior to initiation of the study. The external monitor will be a pediatric endocrinologist with expertise in growth research outside of Children's National Hospital with no other involvement in the study.
Children's National Hospital will serve as the IRB of record for this single site trial.

10.1.6 SAFETY OVERSIGHT

As this is a trial of an approved medication in a single subject, Dr. Dauber will oversee the day-to-day safety events of the trial. We will appoint an external safety monitor who will receive reports of all AEs after the Month 6 and Month 12 visits. The external safety monitor will also be alerted of any treatment-related Grade 3 or higher AEs and all SAEs within 48 hours of the investigator team becoming aware. The external safety monitor will advise the PI on any adjustments to the study protocol or decisions to terminate the study.

10.1.7 CLINICAL MONITORING

No formal monitoring plan will be put in place as this is a single subject study with minimal data collection.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

We will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. As this is a very limited study with a single subject and minimal data collection, all CRFs will be completed on paper and scanned into the research drive. No separate research database will be created.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

Children's National Hospital will provide direct access to all trial related site, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. As this is a very limited study with a single subject and minimal data collection, all CRFs will be completed on paper and scanned into the research drive. No separate research database will be created.

Laboratory results and measurements taken at Children's National will be entered into the medical record.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the termination of the study. Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is defined by institutional policy. It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to Dr. Dauber. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. Protocol deviations and corrective actions must be sent to the Children's National IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This trial is registered at ClinicalTrials.gov (XXXX), and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals within 1 year of completion of the trial. Data from this study may be requested from other researchers after publication of the initial study results by contacting Dr. Dauber.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with Children's National Hospital has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

This is an investigator-initiated academic study which is being supported through provision of study drug by Pfizer. All decisions about study design, study conduct, data analysis, and publication of trial results will be made independently by the study team at Children's National Hospital. Pfizer will be provided with copies of the protocol, data, and planned publications. Pfizer may comment on these items but all decisions regarding these items will be made by Dr. Dauber and the study team. A clinical trial agreement outlining these terms will be in effect prior to study initiation.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	Growth hormone
GHBP	Growth hormone binding protein
GHR	Growth hormone receptor
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SC	Subcutaneous
SDS	Standard Deviation Score
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.2	June 2, 2022	**Clarified dose titration protocol and that dose titration will be performed by PI** **Clarified that the approach of giving high dose GH has not been previously trialed.** **Provided additional details about height assessment**	**Needed to make dose titration process more explicit.** **All height assessments will be done by the PI in the Clinical Research Center.**
1.3	**July 1, 2022**	**Increased in person visits to every 3 months and IGF-1 monitoring and safety phone calls to every month once dose is stable. Adding fasting glucose monitoring as well as monitoring of single cortisol value.** **Clarified specific AEs that would lead to study discontinuation.** **Added in details about SAE reporting to Pfizer**	**In discussion with FDA, it was decided that more frequent safety monitoring was indicated. FDA also requested clarifications about AEs.** **Reporting language added to comply with Pfizer reporting requirements**

11 REFERENCES

1. Rughani A, Zhang D, Vairamani K, Dauber A, Hwa V, Krishnan S. Severe growth failure associated with a novel heterozygous nonsense mutation in the *GHR* transmembrane domain leading to elevated growth hormone binding protein. *Clinical Endocrinology.* 2020;92(4):331-337.
2. Genotropin approved drug label, version 4/2019. Accessed from *https://labeling.pfizer.com/ShowLabeling.aspx?id=577* on May 11, 2022.
3. Common Terminology Criteria for Adverse Events (CTCAE) v5.0, accessed from the National Cancer Institute Division of Cancer Treatment and Diagnosis website, *https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60*.