

Official Title: A Phase IV, Multicenter, Open-Label Study of the Immunogenicity of Nutropin AQ® V1.1 [Somatropin (rDNA Origin) Injection] Administered Daily to Naïve Growth Hormone-Deficient Children (iSTUDY)

NCT Number: NCT02311894

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PROTOCOL

TITLE: A PHASE IV, MULTICENTER, OPEN-LABEL STUDY OF THE IMMUNOGENICITY OF NUTROPIN AQ[®] V1.1 [SOMATROPIN (rDNA ORIGIN) INJECTION] ADMINISTERED DAILY TO NAÏVE GROWTH HORMONE-DEFICIENT CHILDREN (*iSTUDY*)

PROTOCOL NUMBER: ML29543

VERSION NUMBER: 2

EUDRACT NUMBER: Not applicable

IND NUMBER: BB IND 39,305

TEST PRODUCT: Nutropin AQ[®] (Somatropin [rDNA origin] injection) (RO6823852)

MEDICAL MONITOR: [REDACTED], M.D.

SPONSOR: Genentech, Inc.

DATE FINAL: 8 October 2014

DATES AMENDED: Version 2: See date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name

[REDACTED]

Title

Company Signatory

Date and Time (UTC)

22-Apr-2015 00:08:54

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PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol ML29543 has been amended to include optional tests at screening, Month 6, and Month 12. These tests include a serum sample to test CBC at screening (if results are not available within 12 months prior to informed consent) and serum samples for insulin growth factor-1 (IGF-1), which can be drawn at the discretion of the investigator at Month 6 and 12. Optional tests also include X-ray to determine bone age eligibility at screening only if results are not available within 12 months prior to the enrollment date.

Screening specifications were updated to allow patients who do not meet eligibility criteria to be re-screened once. However, it was clarified that patients who have an abnormal CBC may have a repeat test done at the discretion of the investigator and may be enrolled if the investigator deems the results and clinical presentation of the patient are normal.

In addition to change in body weight, change in IGF-1 was added as a reason for dose adjustment of study drug at Month 6 to be consistent with real-world standard clinical practice.

Study assessments were updated to include clarification on CBC and bone age testing at screening. Specifically, if a patient does not have on record a CBC and bone age result within 12 months prior to informed consent date (for CBC) and enrollment date (for bone age), they will be asked to undergo a blood draw and an X-ray for determination of bone age.

Additional changes to the protocol included updates to the inclusion and exclusion criteria as follows:

- The inclusion criterion regarding bone age for females ≤ 9 years and males ≤ 11 years, as determined by X-ray of the left hand and wrist using Greulich and Pyle method, was changed to reflect that this can now be obtained up to 12 months prior to enrollment instead of up to 6 months prior to enrollment.
- The inclusion criterion regarding normal CBC within 6 months was changed to within 12 months prior to informed consent/assent.
- The exclusion criterion stating that patients with multiple pituitary hormone deficiencies (secondary/tertiary hypothyroidism, central adrenal insufficiency, diabetes insipidus) not associated with an intracranial tumor or central nervous system irradiation must be controlled on replacement medications for ≥ 6 months prior to study entry was updated to specify that hormonal treatments, such as androgens and estrogens to initiate puberty, are not permitted during the study.

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The protocol has also been updated to reflect the most current Genentech model document changes. Reference to safety reporting requirements for events, such as drug-induced liver injury and neutropenia (Section 5) reflect new template language requirements for all Genentech protocols, and do not necessarily reflect events known to be related to treatment with growth hormone therapy.

Additional minor changes have been made to improve clarity and consistency, and to adhere to protocol template standards. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

1.1 BACKGROUND ON GROWTH HORMONE DEFICIENCY

Human growth hormone (hGH) is the most abundant and one of the most extensively studied pituitary hormones. ~~Because hGH, and later recombinant human growth hormones (rhGH) have been available for use in humans for more than 40 years~~ *decades, and therefore much is known about their* physiology and mechanism of action (Franklin and Geffner 2009). ...

1.3 STUDY RATIONALE

Nutropin was approved by the FDA in 1994 for the treatment of GHD. In the ensuing ~~20~~-years, many technical advances have been made in large-scale manufacturing methods for recombinant DNA products.

3.1 DESCRIPTION OF STUDY

... Approximately 80 patients will be enrolled at approximately 30 sites in the U.S. and will be treated with daily SC injections of Nutropin AQ v1.1 at a dose of *up to* 0.043 mg/kg/day (*0.3 mg/kg/week, which is the approved and indicated dosage for pediatric GHD*; refer to the USPI for Nutropin AQ) for 12 months. Dose adjustments ~~for weight~~ *may be made at the Month 6 visit for changes in weight and insulin growth factor-1 (IGF-1) levels, if measured.*

Screening will be performed within 28 days prior to Day 1 unless otherwise specified, after which eligible patients will initiate study treatment. *Patients who do not meet eligibility criteria may be re-screened once for this study. If during screening a subject is found to have an abnormal CBC, this test may be repeated within the same screening period at the discretion of the investigator and the subject may be enrolled if the second result is found to be normal per investigator assessment.*

... Study assessments will be scheduled at 3-month intervals following the baseline visit with an additional visit for the Month 1 blood draw, *which can be conducted at home with the help of a home health nurse.* ...

Patients who discontinue from the study early will be asked to return to the clinic within 28 days (± 3 days) after the last dose of study drug for an early discontinuation visit, which will include the collection of serum samples for serum drug concentration and immunogenicity assessments.

... The annualized 6- and 12-month growth velocities for prepubertal patients ~~who are anti-GH antibody positive~~ will be analyzed. ...

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3.3.2 Rationale for Patient Population

The prepubertal GHD population was chosen for this study because healthy, prepubertal GHD children have well-characterized growth responses to rhGH. Other pediatric populations for which Nutropin AQ is approved (Turner syndrome, chronic kidney disease, and idiopathic short stature) may show variant responses due to co-existing conditions and concomitant medications. ~~Since there is almost no difference in the responses between prepubertal girls and boys, stratification for gender was not considered.~~

3.3.3 Rationale for Antibody Assay Assessments

As with all therapeutic proteins, there is potential for immunogenicity. In the case of GH, antibodies with GH binding capacities below 2 mg/L have not been associated with growth attenuation (*refer to the USPI for Nutropin AQ*). ... In clinical studies of pediatric patients who were treated with Nutropin or Nutropin AQ for the first time, antibodies with binding capacities ≥ 2 mg/L were not observed in any patients at 6 months ~~and~~ or 15 months for Nutropin and Nutropin AQ, respectively (refer to the USPI for Nutropin AQ).

... Any samples positive for anti-GH antibody with a titer >2.4 mg/L will ~~also~~ then be analyzed in an anti-GH neutralizing antibody assay and an anti-GH antibody binding capacity assay. ...

3.4.1 Primary Outcome Measure

The primary outcome measure for this study is the occurrence of anti-GH antibodies in rhGH-naïve, prepubertal GHD children treated with Nutropin AQ v1.1.

3.4.2 Secondary Outcome Measures

~~The occurrence of anti-GH antibodies during this study will be compared to historical data from earlier studies (L0368g and L2762g).~~

4.1.1 Inclusion Criteria

- Male or female *patients* age ≥ 3 years and ≤ 14 years. *The patient may be 14 years old exactly on the day of the first dose of study treatment.*
- Bone age ≤ 9 years (females) or ≤ 11 years (males) as determined by X-ray of the left hand and wrist using Greulich and Pyle method and obtained within the 6-12 months prior to enrollment
- Normal CBC within the 126 months prior to informed consent/assent

4.1.2 Exclusion Criteria

- Short stature etiologies other than GHD (e.g., untreated hypothyroidism, short stature associated with GH encoding gene mutations, chromosomal defect associated with short stature)
 - Patients with multiple pituitary hormone deficiencies (secondary/tertiary hypothyroidism, central adrenal insufficiency, diabetes insipidus) not associated

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with an intracranial tumor or CNS irradiation must be controlled on replacement medications for ≥ 6 months prior to study entry. *Hormonal treatments, such as androgens and estrogens to initiate puberty, are not permitted during the study.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is unblinded, open-label, single-arm study. After written informed consent/assent has been obtained and eligibility has been established, the study site will obtain the patient's unique identification number. Approximately 80 patients will be enrolled in this unblinded, open label, single arm study.

4.3.2 Dosage, Administration, and Compliance

Nutropin AQ v1.1 will be provided to the patient and administered at a dose of up to 0.043 mg/kg/day (0.3 mg/kg/week). ~~and The dose may be adjusted at the Month 6 visit per investigator assessment for: 1) a change in body weight of at least ± 2 kg from baseline at the Month 6 study visit, if appropriate OR 2) a change in IGF-1 level (if tested and the investigator deems a change in dose is clinically indicated).~~

Missed doses or drug holidays are discouraged. *Information on study treatment discontinuation and adverse events that may lead to discontinuation of treatment* ~~Guidelines for dosage modification and treatment interruption or discontinuation are~~ provided in Sections 4.6.2 and 5.1.1, respectively.

... The solution may be used for SC administration for 28 days after initial use when stored in the pen device at 2–8°C/236–46°F (under refrigeration). ... *Once study drug is assigned and dispensed to patients, they will be provided with containers for transport of the drug from the investigative sites to their homes for refrigerated storage.*

... ~~If the solution is cloudy, the contents must not be injected.~~ *administered and the affected pens should be returned to the site.*

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (Nutropin AQ v1.1) will be provided by the Sponsor. The ~~investigational study~~ site will acknowledge receipt of IMPs, using the Interactive Voice and Web Response System (IXVRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

4.4 CONCOMITANT THERAPY

Careful monitoring is advisable when Nutropin AQ v1.1 is administered in combination with insulin or other hypoglycemic agents, other drugs metabolized by CYP450 liver enzymes, or other hormone replacement therapy.

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4.4.2 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements, ~~medications to manage multiple pituitary hormone deficits as well as other chronic medications~~) used by a patient from 7 days prior to dosing to the study completion/early discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Medications to manage multiple pituitary-hormone deficits or other chronic conditions should also be recorded as concomitant medications.

~~Careful monitoring is advisable when Nutropin AQ v1.1 is administered in combination with insulin or other hypoglycemic agents, other drugs metabolized by CYP450 liver enzymes, or other hormone replacement therapy.~~

4.5.1 Informed Consent Forms and Screening Log

If a patient does not have on record a CBC and bone age result within 12 months prior to informed consent (for CBC) or enrollment (for bone age), they will be asked to undergo a blood draw (to be analyzed at local laboratory for CBC) and an X-ray for determination of bone age to determine eligibility for the study.

Patients who fail screening may be re-screened once for this study. However, patients who are found to have an abnormal CBC may have a repeat test done within the same screening period at the discretion of the investigator and may be enrolled if the investigator deems the results and clinical presentation of the patient are normal.

4.5.5 Laboratory Assessments

At screening, patients may be required to provide a blood sample to check for CBC, which will be analyzed at the local laboratory.

At Month 6 and 12 study visits, optional samples may be drawn to check IGF-1 levels, which will also be analyzed at the local laboratory.

For assessment of immunogenicity, samples will be drawn at each study visit. ~~The following laboratory tests are to be performed during the study, according to the schedule of assessments (see Appendix 1) and will be sent to the central laboratory to assess the following:~~

- ~~Samples for s~~Serum drug concentration. ~~and immunogenicity assessments will be collected at specified study visits.~~ GH concentration levels are necessary to interpret anti-GH antibody status and titers.
- Immunogenicity, ~~will be assessed utilizing the following assays, which will test for the presence of specific antibodies in patient serum:~~
 - anti-GH antibody screening assay
 - anti-GH neutralizing antibody assay

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- anti-GH antibody binding capacity assay

During the study treatment period, blood samples *for immunogenicity* should be drawn at least 12 hours after the last administration of Nutropin AQ v1.1 and prior to the next scheduled dose.

The last blood sample *for immunogenicity* at Month 12 must be drawn at least 12 hours after the last dose of Nutropin AQ v1.1. ...

4.6.3 Study and Site Discontinuation

- *No study activity (i.e., all patients have completed and all obligations have been fulfilled)*

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)*

5.3.1 Adverse Event Reporting Period

... After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection reaction") on the Adverse Event eCRF. ~~If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF.~~

If a patient experiences both a local and systemic reaction (e.g., generalized injection reaction and localized injection site reaction) to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, ~~with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.~~

5.3.5.3 Adverse Events That Are Secondary to Other Events

- *If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.*

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- *Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$*
- *Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with clinical jaundice*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.11 Adverse Events in Individuals Not Enrolled in the Study

~~If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., injury to the healthcare provider or caregiver during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to Roche or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.~~

5.4.4 Reporting Requirements for NuSpin Device Complaints

In this study, NuSpin is considered a medical device. The investigator must report all NuSpin device complaints to the Sponsor. The investigator should document as much information as possible on the ~~Device Complaint eCRF~~ IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the site pharmacy manual for further details). ~~and expiration date.~~ If the medical device complaint results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. ~~the Complaint eCRF must be completed and submitted through the EDC immediately (i.e., no more than 24 hours after learning of the event).~~ The adverse event must be reported on the Adverse Event eCRF. If the event is serious, the Adverse Event eCRF must be completed and submitted through the EDC immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2. ~~If the medical device results in an adverse event to an individual other than the study patient, the event should be reported as described in Section 0.~~

6.3 OUTCOMES ANALYSES

Descriptive statistics and graphic displays will be provided to summarize data from this study. There are no formal statistical hypothesis tests ~~to be performed~~ planned.

6.3.1 Primary Endpoint

The primary endpoint for this study is the proportion of patients who develop anti-GH antibodies after *initiating* treatment with Nutropin AQ v1.1.

6.3.2 Secondary Endpoints

The secondary endpoints for this study are as follows:

- Proportion of patients with neutralizing antibody among those who had positive anti-GH antibody
 - This analysis will be summarized by visit, as well as ~~collectively~~ *cumulatively*, for patients who had ~~at least one episode of~~ detectable anti-GH antibody at any post-baseline visit, as well as those who *remained negative throughout the study* ~~never developed antibody~~.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's *Informed Assent Form* or Home Nursing Caregiver's Informed Consent Form, if applicable) will be provided to each site. ...

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, a member of the Roche group, and will be managed by Genentech and a CRO. The CRO will provide clinical operations management, *project management, monitor study conduct, data management, patient enrollment and discontinuation*, and medical monitoring *for the duration of the study*.

An ~~IXRS~~-IWRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and shipments.

APPENDIX 1: Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM AND SAMPLE INFORMED ASSENT FORM

The sample Informed Consent Form and the sample Informed Assent Form have been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A PHASE IV, MULTICENTER, OPEN-LABEL STUDY
OF THE IMMUNOGENICITY OF NUTROPIN AQ®
V1.1 [SOMATROPIN (rDNA ORIGIN) INJECTION]
ADMINISTERED DAILY TO NAÏVE GROWTH
HORMONE-DEFICIENT CHILDREN (*iSTUDY*)

PROTOCOL NUMBER: ML29543

VERSION NUMBER: 2

EUDRACT NUMBER: Not applicable

IND NUMBER: BB IND 39,305

TEST PRODUCT: Nutropin AQ® (Somatropin [rDNA origin] injection)
(RO6823852)

MEDICAL MONITOR: [REDACTED], M.D.

SPONSOR: Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

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PROTOCOL SYNOPSIS

TITLE: A PHASE IV, MULTICENTER, OPEN-LABEL STUDY OF THE IMMUNOGENICITY OF NUTROPIN AQ® V1.1 [SOMATROPIN (rDNA ORIGIN) INJECTION] ADMINISTERED DAILY TO NAÏVE GROWTH HORMONE-DEFICIENT CHILDREN (*iSTUDY*)

PROTOCOL NUMBER: ML29543

VERSION NUMBER: 2

EUDRACT NUMBER: Not applicable

IND NUMBER: BB IND 39,305

TEST PRODUCT: Nutropin AQ® (Somatropin [rDNA origin] injection) (RO6823852)

PHASE: IV

INDICATION: Somatropin-naïve prepubertal growth hormone-deficient children

SPONSOR: Genentech, Inc.

Objectives

The primary objective for this study is to characterize the immunogenicity profile of Nutropin AQ v1.1 when administered as a daily subcutaneous (SC) injection for 12 months (per the U.S. Prescribing Information [USPI] for Nutropin AQ).

The clinical impact of immunogenicity will also be assessed during the course of the study by evaluating patients for functional growth attenuation in association with the development of anti-growth hormone (GH) antibodies.

Study Design

Description of Study

This is a Phase IV, multicenter, open-label, single-arm study of somatropin (rDNA origin) (Nutropin AQ v1.1) in naïve prepubertal children with growth hormone deficiency (GHD). Approximately 80 patients will be enrolled at approximately 30 sites in the U.S. and will be treated with daily SC injections of Nutropin AQ v1.1 at a dose of *up to 0.043 mg/kg/day (0.3 mg/kg/week, which is the approved and indicated dosage for pediatric GHD; refer to the USPI for Nutropin AQ) for 12 months. Dose adjustments may be made at the Month 6 visit for changes in weight and insulin growth factor-1 (IGF-1) levels, if measured.*

Screening will be performed within 28 days prior to Day 1 unless otherwise specified, after which eligible patients will initiate study treatment. *Patients who do not meet eligibility criteria may be re-screened once for this study. If during screening a subject is found to have an abnormal CBC, this test may be repeated within the same screening period at the discretion of the investigator and the subject may be enrolled if the second result is found to be normal per investigator assessment.*

Historical laboratory and radiographic tests will be reviewed prior to obtaining informed consent and initiation of study drug. Study assessments will be scheduled at 3-month intervals following the baseline visit with an additional visit for the Month 1 blood draw, *which can be conducted at home with the help of a home health nurse.* Study assessments will include physical examinations, height and weight measurements, assessment of pubertal status, and collection of serum samples for study-specific laboratory assessments (serum drug concentration and immunogenicity assessments). Patients will otherwise be treated and followed as determined by their health care provider.

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Patients who complete the Month 12 visit will be considered to have completed the study. Patients will be contacted by phone 28 (± 3) days after the Month 12 visit to collect adverse events.

Patients who discontinue from the study early will be asked to return to the clinic within 28 (± 3 days) days after the last dose of study drug for an early discontinuation visit, which will include the collection of serum samples for serum drug concentration and immunogenicity assessments.

Growth response will be monitored throughout the study. The annualized 6- and 12-month growth velocities for prepubertal patients will be analyzed. Growth velocities of patients who enter puberty during the study will not be included in the 6- and 12-month velocity analyses. However, these patients will remain in the study and their antibody data will be assessed.

Safety assessments will consist of monitoring and recording of all serious and non-serious adverse events as outlined in Section 5.2.

Please see Appendix 1 for the schedule of assessments performed during the study.

Number of Patients

Approximately 80 patients will be enrolled at approximately 30 sites in the study in the U.S.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent/Assent Form
 - The parent(s)/guardian(s) must be willing to give written informed consent; and
 - The child may be required to give written informed assent (if able, and dependent on state/Institutional Review Board requirements).
- Willing to adhere to the visit schedules and meet study requirements
 - For patients below the legal age of consent, both child and parent must be able to adhere to dose and visit schedules and meet study requirements.
- Ability to comply with study assessments for the full duration of the study (1 year)
- Male or female *patients* age ≥ 3 years and < 14 years. *The patient may be 14 years old exactly on the day of the first dose of study treatment.*
- Bone age ≤ 9 years (females) or ≤ 11 years (males) as determined by X-ray of the left hand and wrist using Greulich and Pyle method and obtained within the 12 months prior to enrollment
- Prepubertal (Tanner I) males and females by physical exam
- Diagnosis of GHD (stimulated GH < 10 ng/mL) by two standard pharmacologic tests obtained up to 12 months prior to informed consent/assent
 - Acceptable GH stimulation tests include: insulin tolerance test (considered two tests if done sequentially with arginine); arginine stimulation test (considered two tests if done sequentially with insulin); glucagon stimulation test; clonidine stimulation test; L-dopa stimulation test; L-dopa + inderal stimulation test (considered one test if done together).
- Normal thyroid function test within the 12 months prior to informed consent/assent
- Normal CBC within the 12 months prior to informed consent/assent
- Documentation of prior height and weight measurements, with height standard deviation score (SDS) ≤ -1.5 (≤ 5 th percentile) for idiopathic isolated GHD patients

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any previous rhGH treatment
- Short stature etiologies other than GHD (e.g., untreated hypothyroidism, short stature associated with GH encoding gene mutations, chromosomal defect associated with short stature)

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- Patients with multiple pituitary hormone deficiencies (secondary/tertiary hypothyroidism, central adrenal insufficiency, diabetes insipidus) not associated with an intracranial tumor or central nervous system irradiation must be controlled on replacement medications for ≥ 6 months prior to study entry. *Hormonal treatments, such as androgens and estrogens to initiate puberty, are not permitted during the study.*
- Acute critical illness or uncontrolled chronic illness, which in the opinion of the investigator and Medical Monitor, would interfere with participation in this study, interpretation of the data, or pose a risk to patient safety
- Chronic illnesses such as inflammatory bowel disease, celiac disease, heart disease, and diabetes
- Bone diseases such as achondroplasia or hypochondroplasia, intracranial tumor, irradiation, and traumatic brain injury
- Patients receiving oral or inhaled chronic corticosteroid therapy (> 3 months) for other medical conditions other than central adrenal insufficiency
- Patients who require higher ($2\times$ or greater than maintenance) doses of corticosteroids for more than 5 days in the 6 months prior to enrollment in the study
- Patients with active malignancy or any other condition that the investigator believes would pose a significant hazard to the patient if recombinant human growth hormone (rhGH) were initiated
- Females with Turner syndrome (documented with a karyotype or short stature homeobox [SHOX] analysis at any time prior to informed consent/assent), regardless of their GH status
- Prader-Willi syndrome regardless of GH status
- Born small for gestational age regardless of GH status
- Presence of scoliosis requiring monitoring
- Previous participation in another clinical trial or investigation of GH, treatment for growth failure, or treatment with a biologic agent
- Patients with closed epiphyses
- Patients with a known hypersensitivity to somatropin, excipients, or diluent

Length of Study/End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 12 months after the last patient is enrolled and receives the first Nutropin AQ v1.1 injection.

Outcome Measures

Primary Outcome Measure

The primary outcome measure for this study is the occurrence of anti-GH antibodies in *rhGH*-naïve, prepubertal GHD children treated with Nutropin AQ v1.1.

Secondary Outcome Measures

The secondary outcome measures for this study are to assess:

- The occurrence of functional growth impairment in association with positive antibody formation in patients treated with Nutropin AQ v1.1
This will be considered in any patient who demonstrates an initial growth response greater than pretreatment velocity after treatment with Nutropin AQ v1.1, but then slows to below pretreatment velocity in the ensuing 6- to 12-month period (or reaches ≤ 2 cm per year)
- The difference between the annualized 6- and 12-month growth velocities for patients who were anti-GH antibody-positive at any post-baseline visit and those who were anti-GH antibody-negative at all visits (including baseline)
- The formation of neutralizing antibodies, and the association between the presence of neutralizing anti-GH antibodies and growth attenuation

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Safety Outcome Measures

No specific safety assessments are planned for this study. However, analysis of all safety events will be performed (see Section 6.4).

Investigational Medicinal Product

Test Product

Nutropin AQ v1.1 will be supplied by the Sponsor as labeled study drug using the Nutropin AQ v1.1 NuSpin™ 10 device for the 1-year duration of this study. For information on the formulation, packaging, and handling of Nutropin AQ v1.1, see the pharmacy manual and the USPI for Nutropin AQ.

Nutropin AQ v1.1 will be provided to the patient and administered at a dose of *up to* 0.043 mg/kg/day (0.3 mg/kg/week). *The dose may be adjusted at the Month 6 visit per investigator assessment for: 1) a change in body weight of at least ± 2 kg from baseline OR 2) a change in IGF-1 level (if tested and the investigator deems a change in dose is clinically indicated).* The dose of Nutropin AQ v1.1 will be administered via SC injections by the patient or caregiver.

Statistical Methods

Outcomes Analysis

Primary Endpoint

The primary endpoint for this study is the proportion of patients who develop anti-GH antibodies after *initiating* treatment with Nutropin AQ v1.1.

Secondary Endpoints

The secondary endpoints for this study are as follows:

- Proportion of patients who exhibit growth attenuation (defined as initial growth response greater than pretreatment velocity followed by reduction in growth response to below the pretreatment velocity in the subsequent 6- to 12-month treatment period or reaching ≤ 2 cm per year)
 - Cross tabulation between growth attenuation status (i.e., with or without) and anti-GH antibody status (i.e., positive or negative) will be provided for any antibody and for neutralizing anti-GH antibody, respectively, at each visit. Similar tables will also be provided for patients who had at least one positive anti-GH antibody (anti-GH antibody and neutralizing antibody, respectively) at any follow-up visit against those who never developed antibody after treatment.
- Proportion of patients with neutralizing antibody among those who had positive anti-GH antibody
 - This analysis will be summarized by visit, as well as *cumulatively*, for patients who had detectable anti-GH antibody at any post-baseline visit, as well as those who *remained negative throughout the study*.
- Annualized 6- and 12-month growth velocities and height SDS will be summarized separately for patients who were anti-GH antibody-positive at any post-baseline follow-up visit and those who were anti-GH antibody-negative at all visits (including baseline). Graphic displays of the individual patient growth patterns along with the longitudinal antibody profile over the course of the study will be prepared. Patients who enter puberty during the study period will be included up to the last visit at which they were determined to be prepubertal.

Additional analyses deemed appropriate for assessing immunogenicity will be described in the Statistical Analysis Plan.

Safety Analysis

Safety analyses will include all patients who received at least one dose of study drug.

Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. Summaries (or listings, if appropriate), including investigator assessments of relationship to study drug, will also be produced for each of the following:

- Serious adverse events

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- All events leading to the withdrawal of treatment
- All events by severity
- All events possibly indicative of hypersensitivity

Determination of Sample Size

A target enrollment of 80 patients was chosen to allow for a projected 10–15% dropout rate and exclusion of growth data for an estimated 10% of patients who might enter puberty during the study period and leave sufficient patient numbers to compare to previous studies of immunogenicity. This target enrollment was based on enrollment in a previous study (L0368) which planned to enroll 60 patients for the assessment of growth rate and change in height SDS. An initial sample size was chosen to ensure that at least 50 patients would complete the study (L0368 FR 30SEP97; Sec 4.8.4).

This study is expected to yield a minimum of 50 evaluable patients. Given a sample size of 50, and an assumed 50% of patients developing anti-GH antibodies, the 95% confidence interval around this proportion will be (35.53%, 64.47%). This interval was calculated using Clopper-Pearson methodology. Fluctuations in the proportion of patients developing anti-GH antibodies and the increase of evaluable patients will result in more precise confidence intervals. The exact confidence intervals for the scenarios for sample size of 50 and 60 in combination with the proportion of patients who are anti-GH antibody positive of 50% and 20% are listed in the table below.

N	Proportion of Patients Who Are Anti-GH Antibody Positive	95% Confidence Interval (Lower Limit)	95% Confidence Interval (Upper Limit)
50	0.5	0.3553	0.6447
60	0.5	0.3681	0.6319
50	0.2	0.1003	0.3372
60	0.2	0.1078	0.3230

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AVN	avascular necrosis
CNS	central nervous system
CRO	contract research organization
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
hGH	human growth hormone
ICH	International Conference on Harmonisation
<i>IGF-1</i>	<i>insulin growth factor-1</i>
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LPLV	last patient, last visit
rhGH	recombinant human growth hormone
SC	subcutaneous
SCFE	slipped capital femoral epiphysis
SDS	standard deviation score
SHOX	short stature homeobox
ULN	upper limit of normal
USPI	U.S. Prescribing Information

1. BACKGROUND

1.1 BACKGROUND ON GROWTH HORMONE DEFICIENCY

Human growth hormone (hGH) is the most abundant and one of the most extensively studied pituitary hormones. hGH and recombinant human growth hormones (rhGH) have been available for use in humans for *decades, and therefore* much is known about *the* physiology and mechanism of action ([Franklin and Geffner 2009](#)). This knowledge base has been further enhanced by the study of the naturally occurring clinical syndromes of growth hormone deficiency (GHD) and excess.

GHD, as defined by inadequate endogenous secretion of hGH, results in proportionate dwarfism in children, who are usually more than two standard deviations below average height. The etiologies can be genetic or developmental and present from birth or manifested during growth; organic from central nervous system (CNS) tumors, head trauma, radiation, and infection; or idiopathic ([Procter et al. 1998](#)). The development of sensitive immunoassays to measure hGH in blood has enabled physicians to diagnose this syndrome in children whose serum hGH level does not increase substantially after administration of arginine, L-dopa, clonidine, glucagon, or the induction of hypoglycemia.

When given a growth hormone-releasing hormone (GHRH), many patients with idiopathic GHD release hGH. This indicates that in some patients the fundamental abnormality lies not in the pituitary itself, but rather in the inability of the hypothalamus and higher centers to induce normal hGH release ([Procter et al. 1998](#)).

Treatment with exogenous GH began in the 1960s and 1970s with human pituitary extracted GH injected intramuscularly three times a week, and progressed to rhGH in the mid-1980s, first with subcutaneous (SC) injections three times a week, and then with daily SC injections.

1.2 BACKGROUND ON NUTROPIN AQ® [SOMATROPIN (rDNA ORIGIN) INJECTION]

Nutropin [somatropin (rDNA origin) for injection] is a lyophilized form of hGH produced by recombinant DNA technology. Nutropin has 191 amino acid residues and a molecular weight of 22,125 Daltons. The amino acid sequence of the product is identical to that of pituitary-derived 22kD hGH. Nutropin AQ [somatropin (rDNA origin) injection] is a liquid formulation with the chemical structure of somatropin identical to lyophilized Nutropin.

In vitro and in vivo nonclinical and clinical testing has demonstrated that Nutropin is therapeutically equivalent to pituitary-derived hGH.

Nutropin AQ is approved by the U.S. Food and Drug Administration (FDA) and is indicated for:

- Pediatric patients: Treatment of children with growth failure due to GHD, idiopathic short stature, Turner syndrome, and chronic kidney disease up to the time of renal transplantation
- Adult patients: Treatment of adults with either childhood-onset or adult-onset GHD

See the Nutropin AQ Investigator's Brochure and the U.S. Prescribing Information (USPI) for Nutropin AQ for details on nonclinical and clinical studies, dosage, and safety profile.

1.3 STUDY RATIONALE

Nutropin was approved by the FDA in 1994 for the treatment of GHD. In the ensuing years, many technical advances have been made in large-scale manufacturing methods for recombinant DNA products.

To use the most advanced methodology and equipment to ensure a continued supply of Nutropin AQ, Genentech has updated its manufacturing process while continuing to use the same *Escherichia coli* GH production system. Chemical and biological characterization (including potency) has demonstrated comparability of drug substance produced by the original and updated manufacturing processes and, based on this, the new manufacturing process that is used to produce Nutropin AQ v1.1 has been approved by FDA.

This study, performed in children with GHD, will assess the immunogenicity profile of Nutropin AQ produced by the new manufacturing process.

2. OBJECTIVES

The primary objective for this study is to characterize the immunogenicity profile of Nutropin AQ v1.1 when administered as a daily SC injection for 12 months (per the USPI for [Nutropin AQ](#)).

The clinical impact of immunogenicity will also be assessed during the course of the study by evaluating patients for functional growth attenuation in association with the development of anti-GH antibodies.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase IV, multicenter, open-label, single-arm study of somatropin (rDNA origin) (Nutropin AQ v1.1) in naïve prepubertal children with GHD. Approximately 80 patients will be enrolled at approximately 30 sites in the U.S. and will be treated with daily SC injections of Nutropin AQ v1.1 at a dose of *up to* 0.043 mg/kg/day (*0.3 mg/kg/week, which is the approved and indicated dosage for pediatric GHD*; refer to the USPI for [Nutropin AQ](#)) for 12 months. Dose adjustments may be made at the Month 6 visit *for changes in weight and insulin growth factor-1 (IGF-1) levels, if measured*.

Screening will be performed within 28 days prior to Day 1 unless otherwise specified, after which eligible patients will initiate study treatment. *Patients who do not meet eligibility criteria may be re-screened once for this study. If during screening a subject is found to have an abnormal CBC, this test may be repeated within the same screening period at the discretion of the investigator and the subject may be enrolled if the second result is found to be normal per investigator assessment.*

Historical laboratory and radiographic tests will be reviewed prior to obtaining informed consent and initiation of study drug. Study assessments will be scheduled at 3-month intervals following the baseline visit with an additional visit for the Month 1 blood draw, *which can be conducted at home with the help of a home health nurse*. Study assessments will include physical examinations, height and weight measurements, assessment of pubertal status, and collection of serum samples for study-specific laboratory assessments (serum drug concentration and immunogenicity assessments). Patients will otherwise be treated and followed as determined by their health care provider.

Patients who complete the Month 12 visit will be considered to have completed the study. Patients will be contacted by phone 28 ± 3 days after the Month 12 visit to collect adverse events.

Patients who discontinue from the study early will be asked to return to the clinic within 28 days (± 3 days) after the last dose of study drug for an early discontinuation visit, which will include the collection of serum samples for serum drug concentration and immunogenicity assessments.

Growth response will be monitored throughout the study. The annualized 6- and 12-month growth velocities for prepubertal patients will be analyzed. Growth velocities of patients who enter puberty during the study will not be included in the 6- and 12-month velocity analyses. However, these patients will remain in the study and their antibody data will be assessed.

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Safety assessments will consist of monitoring and recording of all serious and non-serious adverse events as outlined in Section 5.2.

Please see [Appendix 1](#) for the schedule of assessments performed during the study.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 12 months after the last patient is enrolled and receives the first Nutropin AQ v1.1 injection.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Nutropin AQ v1.1 Dose and Schedule

The Nutropin AQ v1.1 treatment route, dose, and dosing regimen used in this study are consistent with what is approved for treatment of children with GHD (refer to the USPI for [Nutropin AQ](#)).

3.3.2 Rationale for Patient Population

The prepubertal GHD population was chosen for this study because healthy, prepubertal GHD children have well-characterized growth responses to rhGH. Other pediatric populations for which Nutropin AQ is approved (Turner syndrome, chronic kidney disease, and idiopathic short stature) may show variant responses due to co-existing conditions and concomitant medications.

3.3.3 Rationale for Antibody Assay Assessments

As with all therapeutic proteins, there is potential for immunogenicity. In the case of GH, antibodies with GH binding capacities below 2 mg/L have not been associated with growth attenuation (*refer to the USPI for [Nutropin AQ](#)*). In a very small number of patients treated with Nutropin AQ, where binding capacity was above 2 mg/L, interference with growth response was observed. In clinical studies of pediatric patients who were treated with Nutropin or Nutropin AQ for the first time, antibodies with binding capacities ≥ 2 mg/L were not observed in any patients at 6 months *or* 15 months for Nutropin and Nutropin AQ, respectively (*refer to the USPI for Nutropin AQ*).

In this study, all serum samples taken for immunogenicity assessments will be analyzed in an anti-GH antibody screening assay. Any samples positive for anti-GH antibody with a titer > 2.4 mg/L will *then* be analyzed in an anti-GH neutralizing antibody assay and an anti-GH antibody binding capacity assay. Neutralizing antibody assays are an additional method for assessing anti-therapeutic antibodies that can result in changes in the toxicology, pharmacokinetics, and efficacy of biotechnology-derived pharmaceuticals. Growth attenuation due to the development of neutralizing anti-GH antibodies is rare and, when reported, usually occurs in patients with mutations in the GH encoding gene ([Schwarz et al. 1987](#); [Cogan and Phillips 2006](#)). When this rare event occurs, the growth response in the first 3–6 months is followed by a rapid decline in annualized

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growth velocity to below pretreatment rates. Conversely, in those patients without a genetic mutation who develop antibodies, the binding capacity is usually low, and a functional effect on growth has very rarely been detected (Buzi et al. 1989; Pirazzoli et al. 1995). GH-1 mutation testing may be performed at the discretion of the investigator and will not be conducted as part of the protocol. Data from this study will be used to determine if the immunogenicity profile of Nutropin AQ v1.1 produced by the new manufacturing process is different from the original product. This study will also include outcome measures to evaluate the growth of GHD children being treated with Nutropin AQ v1.1 to determine if any variations in growth are associated with antibody development.

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measure

The primary outcome measure for this study is the occurrence of anti-GH antibodies in *rhGH*-naïve, prepubertal GHD children treated with Nutropin AQ v1.1.

3.4.2 Secondary Outcome Measures

The secondary outcome measures for this study are to assess:

- The occurrence of functional growth attenuation in association with positive antibody formation in patients treated with Nutropin AQ v1.1
This will be considered in any patient who demonstrates an initial growth response greater than pretreatment velocity after treatment with Nutropin AQ v1.1, but then slows to below pretreatment velocity in the ensuing 6- to 12-month period (or reaches ≤ 2 cm per year).
- The difference between the annualized 6- and 12-month growth velocities for patients who were anti-GH antibody-positive at any post-baseline visit and those who were anti-GH antibody-negative at all visits (including baseline)
- The formation of neutralizing antibodies, and the association between the presence of neutralizing anti-GH antibodies and growth attenuation

3.4.3 Safety Outcome Measures

No specific safety assessments are planned for this study. However, analysis of all safety events will be performed (see Section 6.4).

4. MATERIALS AND METHODS

4.1 PATIENTS

Only prepubertal *rhGH*-naïve patients who meet the inclusion/exclusion criteria specified below will be enrolled. Approximately 80 patients will be enrolled in the study in the U.S. Investigators must keep a record of all patients who are screened.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent/Assent Form
 - The parent(s)/guardian(s) must be willing to give written informed consent; and
 - The child may be required to give written informed assent (if able, and dependent on state/Institutional Review Board [IRB] requirements)
- Willing to adhere to the visit schedules and meet study requirements
 - For patients below the legal age of consent, both child and parent must be able to adhere to dose and visit schedules and meet study requirements.
- Ability to comply with study assessments for the full duration of the study (1 year)
- Male or female *patients* age ≥ 3 years and < 14 years. *The patient may be 14 years old exactly on the day of the first dose of study treatment.*
- Bone age ≤ 9 years (females) or ≤ 11 years (males) as determined by X-ray of the left hand and wrist using Greulich and Pyle method and obtained within the 12 months prior to enrollment
- Prepubertal (Tanner I) males and females by physical exam
- Diagnosis of GHD (stimulated GH < 10 ng/mL) by two standard pharmacologic tests obtained up to 12 months prior to informed consent/assent.
 - Acceptable GH stimulation tests include: insulin tolerance test (considered two tests if done sequentially with arginine); arginine stimulation test (considered two tests if done sequentially with insulin); glucagon stimulation test; clonidine stimulation test; L-dopa stimulation test; L-dopa + inderal stimulation test (considered one test if done together).
- Normal thyroid function test within the 12 months prior to informed consent/assent
- Normal CBC within the 12 months prior to informed consent/assent
- Documentation of prior height and weight measurements, with height standard deviation score (SDS) ≤ -1.5 (≤ 5 th percentile) for idiopathic isolated GHD patients

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any previous rhGH treatment
- Short stature etiologies other than GHD (e.g., untreated hypothyroidism, short stature associated with GH encoding gene mutations, chromosomal defect associated with short stature)
 - Patients with multiple pituitary hormone deficiencies (secondary/tertiary hypothyroidism, central adrenal insufficiency, diabetes insipidus) not associated with an intracranial tumor or CNS irradiation must be controlled on replacement medications for ≥ 6 months prior to study entry. *Hormonal treatments, such as androgens and estrogens to initiate puberty, are not permitted during the study.*

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- Acute critical illness or uncontrolled chronic illness, which in the opinion of the investigator and Medical Monitor, would interfere with participation in this study, interpretation of the data, or pose a risk to patient safety
- Chronic illnesses such as inflammatory bowel disease, celiac disease, heart disease, and diabetes
- Bone diseases such as achondroplasia or hypochondroplasia, intracranial tumor, irradiation, and traumatic brain injury
- Patients receiving oral or inhaled chronic corticosteroid therapy (> 3 months) for other medical conditions other than central adrenal insufficiency
- Patients who require higher (2× or greater than maintenance) doses of corticosteroids for more than 5 days in the 6 months prior to enrollment in the study
- Patients with active malignancy or any other condition that the investigator believes would pose a significant hazard to the patient if rhGH were initiated
- Females with Turner syndrome (documented with a karyotype or short stature homeobox [SHOX] analysis at any time prior to informed consent/assent), regardless of their GH status
- Prader-Willi syndrome regardless of GH status
- Born small for gestational age regardless of GH status
- Presence of scoliosis requiring monitoring
- Previous participation in another clinical trial or investigation of GH, treatment for growth failure, or treatment with a biologic agent
- Patients with closed epiphyses
- Patients with a known hypersensitivity to somatropin, excipients, or diluent

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is unblinded, open-label, single-arm study. After written informed consent/assent has been obtained and eligibility has been established, the study site will obtain the patient's unique identification number.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Nutropin AQ v1.1 will be supplied by the Sponsor as labeled study drug using the Nutropin AQ v1.1 NuSpin™ 10 device for the 1-year duration of this study. For information on the formulation, packaging, and handling of Nutropin AQ v1.1, see the pharmacy manual and the USPI for Nutropin AQ.

4.3.2 Dosage, Administration, and Compliance

Nutropin AQ v1.1 will be provided to the patient and administered at a dose of *up to* 0.043 mg/kg/day (0.3 mg/kg/week). The dose may be adjusted at the Month 6 visit per investigator assessment for: 1) a change in body weight of *at least* ± 2 kg from baseline

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OR 2) a change in IGF-1 level (if tested and the investigator deems a change in dose is clinically indicated).

The dose of Nutropin AQ v1.1 will be administered via SC injections by the patient or caregiver. Instructions and training on Nutropin AQ v1.1 administration with the NuSpin device will be provided by a trained study nurse coordinator.

Administration of the first dose of Nutropin AQ v1.1 (Day 1, baseline visit) should occur after the patient receives dosing administration instruction in the clinic and after the initial blood sample is drawn.

Blood samples scheduled after baseline (Months 1, 3, 6, 9, and Month 12 or early discontinuation) should be taken at least 12 hours after the last dose of Nutropin AQ v1.1 and prior to the next dose.

Missed doses or drug holidays are discouraged. *Information on study treatment discontinuation and adverse events that may lead to discontinuation of treatment is provided in Sections 4.6.2 and 5.1.1, respectively.*

The Nutropin AQ v1.1 solution contained within the NuSpin device contains a phenol preservative. The solution may be used for SC administration for 28 days after initial use when stored in the pen device at 2–8°C/36–46°F (under refrigeration). Avoid freezing the contents of the NuSpin device. The Nutropin AQ v1.1 contained within the device is light sensitive and should be protected from light. Store the NuSpin device refrigerated in a dark place when it is not in use. *Once study drug is assigned and dispensed to patients, they will be provided with containers for transport of the drug from the investigative sites to their homes for refrigerated storage.*

The solution in the device should be clear immediately after removal from the refrigerator. Allow the pen cartridge to come to room temperature and gently swirl. If the solution is cloudy, the contents must not be *administered and the affected pens should be returned to the site.*

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. Section 5.3.5.11 summarizes available safety data related to overdosing of Nutropin AQ.

4.3.3 Investigational Medicinal Product Accountability

Study drug will be shipped to the investigator site, logged into the appropriate forms, and dispensed at the baseline visit and at each 3-month visit.

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All investigational medicinal products (IMPs) required for completion of this study (*Nutropin AQ v1.1*) will be provided by the Sponsor. The *study* site will acknowledge receipt of IMPs, using the Interactive Web Response System (IWRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

Unused, returned, or expired IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT THERAPY

Careful monitoring is advisable when Nutropin AQ v1.1 is administered in combination with insulin or other hypoglycemic agents, other drugs metabolized by CYP450 liver enzymes, or other hormone replacement therapy.

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to dosing to the study completion/early discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Medications to manage multiple pituitary-hormone deficits or other chronic conditions should also be recorded as concomitant medications.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Any type of investigational therapy
- Other rhGH therapy
- Estrogen or androgens
- Immunosuppressive drugs other than maintenance corticosteroids as described above

Notify the Medical Monitor immediately if high dose (> 2 times replacement therapy) oral or systemic corticosteroids are prescribed. Patients who require high dose oral or systemic corticosteroids for more than 5 days in any 6-month period will be terminated from the study.

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The above list of medications is not necessarily comprehensive. The investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

Please see [Appendix 1](#) for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent from the parent(s) or a legally authorized representative of the child, and patient assent, if applicable, for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms and Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study drug. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a patient does not have on record a CBC and bone age result within 12 months prior to informed consent (for CBC) or enrollment (for bone age), they will be asked to undergo a blood draw (to be analyzed at local laboratory for CBC) and an X-ray for determination of bone age to determine eligibility for the study.

Patients who fail screening may be re-screened once for this study. However, patients who are found to have an abnormal CBC may have a repeat test done within the same screening period at the discretion of the investigator and may be enrolled if the investigator deems the results and clinical presentation of the patient are normal.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, prior height and weight measurements, and all prescription medications used by the patient in the 30 days prior to the screening visit.

Demographic data will include date of birth, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

Limited physical examinations should be performed as per the standard of care guidelines for a child with GHD undergoing GH therapy. Pubertal status and confirmation of prepubertal status, presence of hip or knee pain, appearance of spine (i.e., appearance of significant scoliosis), and routine fundoscopic examination for absence of signs of intracranial pressure must be recorded. New or worsened clinically significant abnormalities after baseline should be recorded as adverse events, if applicable.

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4.5.4 Height and Weight

Height (three measurements at the same visit with a stadiometer or equivalently fixed measuring device) and weight will be recorded.

4.5.5 Laboratory Assessments

At screening, patients may be required to provide a blood sample to check for CBC, which will be analyzed at the local laboratory.

At Month 6 and 12 study visits, optional samples may be drawn to check IGF-1 levels, which will also be analyzed at the local laboratory.

For assessment of immunogenicity, samples will be drawn at each study visit (see [Appendix 1](#)) and will be sent to the central laboratory to assess the following:

- Serum drug concentration. GH concentration levels are necessary to interpret anti-GH antibody status and titers.
- Immunogenicity, utilizing the following assays:
 - anti-GH antibody screening assay
 - anti-GH neutralizing antibody assay
 - anti-GH antibody binding capacity assay

During the study treatment period, blood samples *for immunogenicity* should be drawn at least 12 hours after the last administration of Nutropin AQ v1.1 and prior to the next scheduled dose.

The last blood sample *for immunogenicity* at Month 12 must be drawn at least 12 hours after the last dose of Nutropin AQ v1.1. In the event of early discontinuation, an early discontinuation visit should be scheduled within 28 days after the last dose of Nutropin AQ v1.1 and a blood sample will be collected for a final assessment of serum drug concentration and immunogenicity.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, specifically defined as: refusal to allow for serum draws for antibodies; failure to adhere to study visit schedule; failure to comply with GH administration by giving less than 85% of daily injections over each 3-month interval

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- Development of growth failure with velocity decrease to below pretreatment velocity

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed as part of the study for any reason after consent has been withdrawn. Patients who withdraw from the study prematurely will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients who experience a protocol-defined adverse event may be discontinued from treatment (see Section 5.1.1). Patients who discontinue study treatment prematurely will be asked to return to the clinic for an early discontinuation visit and may undergo final study assessments. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely may remain in the study and continue to be followed per the schedule of assessments for sample collection, reporting of adverse events, and height and weight measurements.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Recall or other unforeseen problems with the drug and/or device
- FDA or other government health and regulatory agencies request termination

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- *No study activity (i.e., all patients have completed and all obligations have been fulfilled)*

Sites that are closed may be replaced at the Sponsor's discretion.

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5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Patient safety will be monitored through physical exams and incidence or severity of adverse events and serious adverse events.

5.1.1 Adverse Events That May Lead to Discontinuation of Treatment with Nutropin AQ v1.1

Management of specific adverse events should follow the information provided in the USPI for Nutropin AQ, published guidelines, and standard of care practices in the monitoring of patients receiving rhGH therapy.

Events that may lead to discontinuation of Nutropin AQ v1.1 include, but are not limited to, the following:

- Papilledema by fundoscopy
- Somatropin-induced intracranial hypertension
- Evidence of recurrent or new malignancy
- New or recurrent event of slipped capital femoral epiphysis (SCFE) or avascular necrosis (AVN)
- Diabetes mellitus
- Pancreatitis
- New scoliosis or significant scoliosis progression
- Anaphylactic reactions/severe hypersensitivity
- Acute critical illness requiring intensive care hospitalization

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

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- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section [5.3.5.9](#)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
 - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section [5.3.5.10](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, severe, or life-threatening; see Section [5.3.3](#)); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#) for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Those adverse events of special interest for this study include the following:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)*
- Suspected transmission of an infectious agent by the study drug, as defined below
 - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all serious adverse events and non-serious adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug as provided in this study. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

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5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 1 provides guidance for assessing adverse event severity.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 2):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

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- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis on the Adverse Event eCRF.

If a patient experiences both a local and systemic reaction (e.g., generalized injection reaction and localized injection site reaction) to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events

based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult patient, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- *If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.*

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory abnormality observed during physician's caring for the patient should be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- *Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$*
- *Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with clinical jaundice*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

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5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
 - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
 - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Short-term overdose could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention.

Long-term overdose could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess GH.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (*see Sections 5.2.2 and 5.4.2 for further details*)
- Non-serious adverse events of special interest (*see Sections 5.2.3 and 5.4.2 for further details*)
- Pregnancies (*see Section 5.4.3 for further details*)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [REDACTED], M.D.

Telephone No: [REDACTED] (South San Francisco)

Alternate Telephone No: [REDACTED] (South San Francisco)

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events (see Section 5.2.2) and non-serious adverse events of special interest (see Section 5.2.3) will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee (Genentech) immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Genentech Drug Safety Fax No.: (650) 225-4682

Alternate Fax No: [REDACTED]

Genentech Drug Safety email: us_drug.safety@gene.com

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

Should patients enter puberty during the study and become pregnant, the following information will apply.

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee (Genentech) immediately (i.e., no more than 24 hours after learning of the

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pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 5.4.2. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.4 Reporting Requirements for NuSpin Device Complaints

In this study, NuSpin is considered a medical device. The investigator must report all NuSpin device complaints to the Sponsor. The investigator should document as much information as possible on the *IMP Deviation Form*, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the site pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche or its designee (Genentech), either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided in Section 5.4.2.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the USPI for Nutropin AQ.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A target enrollment of 80 patients was chosen to allow for a projected 10–15% dropout rate and exclusion of growth data for an estimated 10% of patients who might enter puberty during the study period and leave sufficient patient numbers to compare to previous studies of immunogenicity. This target enrollment was based on enrollment in a previous study (L0368) which planned to enroll 60 patients for the assessment of growth rate and change in height SDS. An initial sample size was chosen to ensure that at least 50 patients would complete the study (L0368 FR 30SEP97; Sec 4.8.4).

This study is expected to yield a minimum of 50 evaluable patients. Given a sample size of 50, and an assumed 50% of patients developing anti-GH antibodies, the 95% confidence interval around this proportion will be (35.53%, 64.47%). This interval was calculated using Clopper-Pearson methodology. Fluctuations in the proportion of

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patients developing anti-GH antibodies and the increase of evaluable patients will result in more precise confidence intervals. The exact confidence intervals for the scenarios for sample size of 50 and 60 in combination with the proportion of patients who are anti-GH antibody positive of 50% and 20% are listed in [Table 3](#).

Table 3 Clopper-Pearson 95% Confidence Intervals for the Proportion of Patients Who Are Anti-GH Antibody Positive Based on 50 and 60 Patients

N	Proportion of Patients Who Are Anti-GH Antibody Positive	95% Confidence Interval (Lower Limit)	95% Confidence Interval (Upper Limit)
50	0.5	0.3553	0.6447
60	0.5	0.3681	0.6319
50	0.2	0.1003	0.3372
60	0.2	0.1078	0.3230

6.2 SUMMARIES OF CONDUCT OF STUDY

Patients enrolled, visit completion, and reasons for study termination/study withdrawal will be summarized. The baseline variables for all enrolled patients to be summarized include, but are not limited to, demographic and physical characteristics (sex, height, and weight), pubertal status, historical laboratory test results, and all other entry criteria. Antibody status at baseline will also be summarized. All enrolled patients will be included in these summaries as the intent-to-treat population. The primary and secondary analyses will include all treated patients as described below, except as noted for patients who enter puberty.

6.3 OUTCOMES ANALYSES

Descriptive statistics and graphic displays will be provided to summarize data from this study. There are no formal statistical hypothesis tests *planned*.

6.3.1 Primary Endpoint

The primary endpoint for this study is the proportion of patients who develop anti-GH antibodies after *initiating* treatment with Nutropin AQ v1.1.

6.3.2 Secondary Endpoints

The secondary endpoints for this study are as follows:

- Proportion of patients who exhibit growth attenuation (defined as initial growth response greater than pretreatment velocity followed by reduction in growth response to below the pretreatment velocity in the subsequent 6- to 12-month treatment period or reaching ≤ 2 cm per year)
 - Cross tabulation between growth attenuation status (i.e., with or without) and anti-GH antibody status (i.e., positive or negative) will be provided for any

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antibody and for neutralizing anti-GH antibody, respectively, at each visit. Similar tables will also be provided for patients who had at least one positive anti-GH antibody (anti-GH antibody and neutralizing antibody, respectively) at any follow-up visit against those who never developed antibody after treatment.

- Proportion of patients with neutralizing antibody among those who had positive anti-GH antibody
 - This analysis will be summarized by visit, as well as *cumulatively*, for patients who had detectible anti-GH antibody at any post-baseline visit, as well as those who *remained negative throughout the study*.
- Annualized 6- and 12-month growth velocities and height SDS will be summarized separately for patients who were anti-GH antibody-positive at any post-baseline follow-up visit and those who were anti-GH antibody-negative at all visits (including baseline). Graphic displays of the individual patient growth patterns along with the longitudinal antibody profile over the course of the study will be prepared. Patients who enter puberty during the study period will be included up to the last visit at which they were determined to be prepubertal.

Additional analyses deemed appropriate for assessing immunogenicity will be described in the Statistical Analysis Plan.

6.4 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study drug.

Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. Summaries (or listings, if appropriate), including investigator assessments of relationship to study drug, will also be produced for each of the following:

- Serious adverse events
- All events leading to the withdrawal of treatment
- All events by severity
- All events possibly indicative of hypersensitivity

6.5 HANDLING OF MISSING DATA

Missing data will not be imputed. All available assessments will be reported with associated number of observations. If a patient discontinues study drug before the end of the 1-year treatment period, growth rate will be computed for the last 3-month interval visit and used in the calculation of mean growth for that time interval only.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through

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use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the

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ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's *Informed Assent Form* or *Home Nursing* Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information

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under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

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Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, a member of the Roche group, and will be managed by Genentech and a CRO. The CRO will provide clinical operations management, *project management, monitor study conduct, patient enrollment and discontinuation*, and medical monitoring *for the duration of the study*.

An IWRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an EDC system using eCRFs (see Section [7.2](#)).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. **REFERENCES**

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Appendix 1 Schedule of Assessments

Assessment	Screening (Day –28 to Day –1)	Baseline (Day 1) ^a	Month 1 (±3 days)	Month 3 (±3 days)	Month 6 (±3 days)	Month 9 (±3 days)	Month 12 (±3 days) ^b	Safety Follow-Up (±3 days) ^c	Early Discontinuation ^d
Informed consent/assent	x ^e								
Medical history ^f	x								
Eligibility criteria ^g	x								
Demographic data ^h	x								
Limited physical examination ⁱ	x	x		x	x	x	x		x
Concomitant medications ^j	x	x		x	x	x	x		x
Height and weight	x	x		x	x	x	x		x
Serum sample for serum drug concentration and immunogenicity assessments ^k		x	x	x	x	x	x ^l		x ^l
<i>Optional tests ^m</i>	x				x		x		
NuSpin instruction/ training ⁿ		x							
Nutropin AQ v1.1 administration ^o		x	x	x	x	x	x		
Nutropin AQ v1.1 dose compliance ^p			x	x	x	x	x		x
Adverse events ^q	x	x	x	x	x	x	x	x	x

^a All baseline assessments should be performed before the first dose of study drug.

^b The Month 12 visit will serve as the study completion visit.

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Appendix 1 (cont.) Schedule of Assessments

- ^c The patient will be contacted by phone 28 ± 3 days after the Month 12 visit to collect adverse events.
- ^d Patients who discontinue from the study early will be asked to return to the clinic within 28 days after the last dose of study drug.
- ^e Written informed consent/assent must be obtained and documented before any study-specific screening procedure is performed.
- ^f Includes clinically significant diseases, surgeries, prior height and weight measurements, and all prescription medications used by the patient in the 30 days prior to the screening visit.
- ^g Historical laboratory tests include two GH stimulation tests with GH response < 10 ng/mL (obtained up to 12 months prior to informed consent/assent; see Section 4.1.1 for acceptable tests); thyroid function testing (obtained within 12 months prior to informed consent/assent); complete blood counts (obtained within 12 months prior to informed consent/assent); and for females, karyotype or SHOX analysis to exclude the diagnosis of Turner syndrome (obtained any time prior to informed consent/assent). Historical radiographic test includes bone age obtained within 12 months prior to enrollment. *If results are not available within a specified timeframe, the tests that may be done as part of the screening process are CBC and X-ray for bone age. All other tests should be done as part of standard care.*
- ^h Demographic data will include date of birth, sex, and self-reported race/ethnicity.
- ⁱ Limited physical examinations should be performed as per the standard of care guidelines for a child with GHD undergoing GH therapy. Pubertal status and confirmation of prepubertal status, presence of hip or knee pain, appearance of spine (i.e., appearance of significant scoliosis), and routine fundoscopic examination for absence of signs of intracranial pressure must be recorded. New or worsened clinically significant abnormalities after baseline should be recorded as adverse events, if applicable.
- ^j Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements, medications to manage multiple pituitary-hormone deficits as well as other chronic medications) used by a patient from 7 days prior to dosing to the study completion/early discontinuation visit.
- ^k A single blood sample will be collected at each visit during the treatment period *for immunogenicity and drug concentrations*. Process each sample for serum and split into four separate tubes for serum drug concentration and immunogenicity assessments (anti-GH antibody screening assay, anti-GH neutralizing antibody assay, and anti-GH antibody binding capacity assay). After baseline, blood samples *for immunogenicity and serum drug concentration* should be taken at least 12 hours after the last dose of Nutropin AQ v1.1 and prior to the next dose.
- ^l The last blood sample at Month 12 must be drawn at least 12 hours after the last dose of Nutropin AQ v1.1. In the event of early discontinuation, an early discontinuation visit should be scheduled within 28 days after the last dose of Nutropin AQ v1.1 and a blood sample will be collected for a final assessment of serum drug concentration and immunogenicity.
- ^m *Optional tests include a serum sample to test CBC at screening (if results are not available within 12 months prior to informed consent) and serum samples for IGF-1, which can be drawn at the discretion of the investigator at Month 6 and 12. All optional samples will be analyzed at the local laboratory. Optional tests also include an X-ray to determine bone age eligibility at screening only if the results are not available within 12 months prior to the enrollment date.*
- ⁿ Nutropin AQ v1.1 will be administered via daily SC injections by the patient or caregiver. Instruction and training on Nutropin AQ v1.1 administration with the NuSpin device will be provided by a trained study nurse coordinator.

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Appendix 1 (cont.) Schedule of Assessments

- ° The first dose (Day 1, baseline visit) should occur after the patient receives dosing administration instruction in the clinic and after the initial blood sample is drawn. Blood samples scheduled after baseline (Months 1, 3, 6, 9, and Month 12 or early discontinuation) should be taken at least 12 hours after the last dose of Nutropin v1.1 and prior to the next dose.
- p Assess compliance with daily dosing at each visit after baseline. Reinstruct patients and caregivers, as needed.
- q After initiation of study drug, all serious adverse events and non-serious adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug as provided in this study. After this period, the investigator should report any serious adverse events that are believed to be related to study drug. The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.