CLINICAL STUDY PROTOCOL

PRODUCT NAME/NUMBER:	Lonapegsomatropin
PROTOCOL NUMBER:	TCH-306
IND / EudraCT NUMBER:	IND: 126053 EudraCT: 2020-000929-42
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	foresiGHt: A multicenter, randomized, parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency
PROTOCOL DATE:	02 June 2022
VERSION NUMBER:	4.0
SPONSORED BY:	Ascendis Pharma Endocrinology Division A/S Tuborg Boulevard 12, DK-2900 Hellerup, Denmark
Sponsor Medical Monitors (Medical Monitors)	[redacted] MD [redacted] Ascendis Pharma A/S Cell: [redacted] email: [redacted] [redacted] MD [redacted] Ascendis Pharma, Inc. Cell: [redacted] email: [redacted]

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the following:

- The Protocol and protocol referenced documents
- Declaration of Helsinki (2013)
- Good Clinical Practice (GCP) as outlined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH E6 (R2)) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations

1. APPROVAL SIGNATURES

1.1. SPONSOR

CLINICAL TRIAL TITLE:

foresiGHt: A multicenter, randomized, parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency

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Date

2. SYNOPSIS

PRODUCT NAME/NUMBER	Lonapegsomatropin
PROTOCOL NUMBER	TCH-306
IND / EudraCT NUMBER	IND: 126053 EudraCT: 2020-000929-42
DEVELOPMENT PHASE	3 (pivotal)
PROTOCOL TITLE	foresiGHt: A multicenter, randomized, parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with once-weekly placebo and a daily somatropin product in adults with growth hormone deficiency
INDICATION	Adult Growth Hormone Deficiency (AGHD)
OBJECTIVES	**Primary:** To evaluate the efficacy of once-weekly lonapegsomatropin compared to placebo at 38 weeks in adults with growth hormone deficiency (GHD). **Secondary:** 1. To evaluate the safety and tolerability of once-weekly lonapegsomatropin in adults with GHD 2. To evaluate the pharmacokinetics (PK) of once-weekly lonapegsomatropin in adults with GHD 3. To evaluate the pharmacodynamics (PD) of once-weekly lonapegsomatropin in adults with GHD **Tertiary:** [redacted]
ENDPOINTS	**Primary Efficacy Endpoint:** Change from baseline in trunk percent fat (as assessed by dual-energy x-ray absorptiometry [DXA]) at Week 38. **Secondary Efficacy Endpoints:** • Change from baseline in trunk fat mass at Week 38 (as assessed by DXA) • Change from baseline in total body lean mass at Week 38 (as assessed by DXA)

	Exploratory Efficacy Endpoints: [redacted] **Safety Endpoints:** Safety endpoints as measured throughout the 38 weeks of treatment include: • Incidence of adverse events (AEs) • Laboratory values • Vital signs • Incidences of anti-drug antibodies (ADA) and neutralizing antibodies against hGH • Electrocardiograms (ECGs) • Fundoscopy **Pharmacokinetic/Pharmacodynamic Endpoints:** • hGH levels • Lonapegsomatropin levels • mPEG levels • IGF-1 levels and IGF-1 SDS • IGFBP-3 levels and IGFBP-3 SDS
PLANNED TRIAL SITES	Approximately 120 sites in North America, Europe, Asia, including Japan, and Oceania.
PLANNED NUMBER OF SUBJECTS	Approximately 240, however, for local regulatory requirements recruitment may be kept open in some countries after having this number reached for the global study.

TRIAL POPULATION	Adults with GHD (male and female), either treatment-naïve or not having received growth hormone (GH) therapy for at least 12 months prior to screening will be enrolled. Subjects will be randomized to 1 of 3 treatment arms in a 1:1:1 ratio: • Approximately 80 subjects will be randomized to once-weekly lonapegsomatropin • Approximately 80 subjects will be randomized to once-weekly placebo • Approximately 80 subjects will be randomized to daily somatropin product
TRIAL ENTRY CRITERIA	**Inclusion Criteria** 1. Age between 23 and 80 years, inclusive, at screening. 2. AGHD Diagnosis Criteria For adult-onset AGHD: documented history of structural hypothalamic-pituitary disease, hypothalamic-pituitary surgery, cranial irradiation, 1-4 non-GH pituitary hormone deficiencies, a proven genetic cause of GHD, or traumatic brain injury (TBI). Subjects with childhood-onset GHD must have had GH axis re-assessed at final height. In subjects with TBI as a cause of GHD, GHD must be confirmed by GH -stimulation testing performed at least 12 months after the injury. For all subjects, documentation of test results must be available before randomization. Stimulation test protocols and results are subject to review and approval by the Medical Monitor. *A. For all countries except Japan*: Subjects must satisfy at least one of the following criteria: a. Insulin tolerance test: peak GH ≤5 ng/mL b. Glucagon stimulation test according to body mass index (BMI) i. BMI ≤30 kg/m^2: peak GH ≤3 ng/mL ii. BMI >30 kg/m^2: peak GH ≤1 ng/mL c. Three or four pituitary axis deficiencies (ie, adrenal, thyroid, gonadal, and/or vasopressin; not including GH) with IGF-1 SDS ≤ -2.0 at screening as measured by central laboratory d. Macimorelin test: peak GH ≤2.8 ng/mL e. Growth hormone-releasing hormone (GHRH) + arginine test according to BMI: i. BMI <25 kg/m2, peak GH <11 ng/mL ii. BMI ≥25–≤30 kg/m2, peak GH <8 ng/mL iii. BMI >30 kg/m^2, peak GH <4 ng/mL

	B. For Japan only: Subjects with GHD and deficiency of at least one non-GH pituitary hormone need to satisfy one of the following GH stimulation tests. Subjects with GHD and without additional non-GH pituitary hormone deficiencies with or without evidence of intracranial structure disorder need to satisfy at least 2 of the following stimulation tests a. Insulin tolerance test: peak GH ≤1.8 ng/mL b. Glucagon test: peak GH ≤1.8 ng/mL c. Growth Hormone-Releasing Peptide-2 (GHRP-2) tolerance test: peak GH ≤9 ng/mL 3. IGF-1 SDS ≤ -1.0 at screening as measured by central laboratory. 4. hGH treatment-naïve or no exposure to hGH therapy or GH secretagogue for at least 12 months prior to screening. ***Note:*** GH secretagogue product used in connection with stimulation tests for diagnosis of GHD is permitted (eg, macimorelin). 5. For subjects on hormone replacement therapies for any hormone deficiencies other than GH (eg, adrenal, thyroid, estrogen, testosterone) must be on adequate and stable doses for ≥6 weeks prior to and throughout screening. ***Note:*** Short-term increases in glucocorticoid doses taken on an as -needed basis for adrenal insufficiency are permitted ("stress dose" allowance: duration up to 5 days up to 2 times in 6 weeks, the maximum dose may reach 3 times the stable dose). One-time dose increases for diagnostic or other medical procedures are allowed. ***Note:*** For subjects receiving oral estrogen or estrogen-containing therapy, subjects must intend to maintain the same dose and route of estrogen administration throughout the trial. For subjects receiving non-oral estrogen or estrogen-containing therapy, the dose may be adjusted as required, however subjects must intend to maintain the same route of administration throughout the trial. 6. For subjects not on glucocorticoid replacement therapy, documentation of adequate adrenal function at screening defined as: morning (6:00-10:00AM) serum cortisol >15.0 µg/dL (measured at central laboratory) and/or Adrenocorticotrophic Hormone (ACTH) stimulation test or ITT with serum cortisol >18.0 µg/dL at or within 90 days prior to screening. Stimulation test protocols and results are subject to review and approval by the Medical Monitor. 7. For males not on testosterone replacement therapy: morning (6:00-10:00AM) total testosterone within normal limits for age as measured by the central laboratory at screening.

	8. On a stable diet and exercise regime at screening with no intention to modify diet or exercise pattern during the trial, ie, no weight reduction program intended during the trial or within the last 90 days prior to or through screening. 9. No plans to undergo bariatric surgery during the trial. 10. Fundoscopy at screening without signs/symptoms of intracranial hypertension or diabetic retinopathy stage 2 / moderate or above or any other retinal disease contraindicated to growth hormone therapy. For subjects with a diagnosis of diabetes mellitus at screening, this must be documented with a fundus photograph. 11. Able and willing to provide a written Informed Consent Form (ICF) and authorization for protected health information (PHI) disclosure in accordance with Good Clinical Practice (GCP). 12. Serum fT4 in the normal range at screening as measured by central laboratory. **Exclusion Criteria** 1. Known Prader-Willi Syndrome and/or other genetic diseases that may have an impact on an endpoint. 2. Diabetes mellitus at screening if any of the following criteria are met: a. Poorly controlled diabetes, defined as HbA_{1c} >7.5% at screening according to central laboratory b. Diabetes mellitus (defined as HbA_{1c} ≥6.5% and/or fasting plasma glucose ≥126 mg/dL and/or plasma glucose ≥200 mg/dL two hours after oral glucose tolerance test) diagnosed <26 weeks prior to screening c. Change in diabetes regimen (includes dose adjustment) within <90 days prior and throughout screening d. Use of any diabetes drugs other than metformin and/or DPP-4 inhibitors for a cumulative duration of greater than 4 weeks within 12 months prior to screening e. Diabetes-related complications at screening (ie, nephropathy as judged by the investigator, neuropathy requiring pharmacological treatment, retinopathy stage 2 / moderate and above within 90 days prior to screening or during screening) 3. Active malignant disease or history of malignancy. Exceptions to this exclusion criterion: a. Resection of in situ carcinoma of the cervix uteri b. Complete eradication of squamous cell or basal cell carcinoma of the skin c. Subjects with GHD attributed to treatment of intracranial malignant tumors or leukemia, provided that a recurrence-free survival period of at least 5 years prior to screening is

	documented in the subject's file (based on a Magnetic Resonance Imaging (MRI) result for intracranial malignant tumors) 4. Evidence of growth of pituitary adenoma or other benign intracranial tumor within the last 12 months before screening. ***Note:*** Absence of tumor growth is determined by comparison of two MRI or Computed Tomography (CT) scans; the most recent MRI or CT scan must be performed within 6 months prior to screening, and the interval between the two assessments must be at least 9 months. If MRI/CT scan within 6 months prior to screening is not available, it can be performed during screening. ***Note:*** In subjects with no evidence of residual tumor or no prior history of intracranial tumor, one MRI/CT scan performed within 6 months prior to screening or during screening will suffice to confirm tumor absence. 5. Subjects with acromegaly without remission / with documented remission less than 24 months prior to screening. 6. Subjects with Cushing's disease without remission / with documented remission less than 24 months prior to screening. 7. Subjects with prior cranial irradiation or hypothalamic-pituitary surgery: the procedure took place less than 12 months prior to screening. 8. eGFR <60 mL/min/1.73m^2 determined based on Modification of Diet in Renal Disease (MDRD) equation using serum creatinine from the central laboratory at screening. 9. Hepatic transaminases (ie, AST or ALT) >3 times the upper limit of normal according to the central laboratory at screening. 10. Heart failure NYHA class 3 or greater (NYHA 1994). 11. QTcF ≥ 451 milliseconds on 12-lead ECG at screening ***Note:*** If the initial measurement is out of range, the assessment should be repeated 2 more times and the average QTcF value should be used to determine the subject's eligibility. 12. Poorly controlled hypertension, defined as supine systolic blood pressure >159 mmHg and/or supine diastolic blood pressure >95 mmHg at screening ***Note:*** if the initial measurement is out of range, may be repeated 2 more times after 15 min and exclusion will be based on the average of the three measurements. 13. Cerebrovascular accident within 5 years prior to screening. 14. Anabolic steroids (other than gonadal steroid replacement therapy) or oral/intravenous/intramuscular corticosteroids (other

	than in replacement or stress doses as described in Inclusion Criterion No.5) within 90 days prior to or throughout screening. ***Note:*** Stable doses of inhaled, intra-articular, or topical corticosteroids are permitted. 15. Currently using or have used within 26 weeks prior to screening any weight-loss or appetite-suppressive medications including orlistat, zonisamide, lorcaserin, bupropion, topiramate, sibutramine, stimulants (eg, phentermine or ADHD medications such as methylphenidate or amphetamines), glucagon-like peptide-1 (GLP-1) receptor agonists (eg, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide), sodium-glucose cotransporter-2 (SGLT-2) inhibitors (eg, canagliflozin, dapagliflozin, empagliflozin, sotagliflozin) or medications that affects IGF-1 or GH measurements including cabergoline at doses above 0.5 mg weekly or bromocriptine at doses above 20 mg weekly ***Note:*** if it can be documented that no weight-loss occurred with these drugs, a 90-day withdrawal period prior to screening is sufficient. 16. Known history of hypersensitivity and/or idiosyncrasy to any of the test compounds (somatropin) or excipients employed in this trial. 17. Known history of neutralizing anti-hGH antibodies 18. Inability to undergo scanning by DXA or a non-interpretable DXA scan at screening 19. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) and not using adequate contraceptive methods • Acceptable highly effective methods of contraception include intrauterine device (IUD); intrauterine system (IUS); bilateral tubal occlusion (must be documented); combined or progestogen-only hormonal contraception associated with inhibition of ovulation; vasectomized partner (must be documented); or sexual abstinence (only when it is the usual and preferred lifestyle of the subject) • Clinically acceptable methods of birth control include male or female condom with or without spermicide; progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; or cap, diaphragm, or sponge with spermicide. • Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

	Note: Females of childbearing potential must accept to use the above-mentioned methods of contraception from the beginning of screening to the last trial visit ***Note:*** Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. ***Note:*** For subjects using oral combined hormonal contraception (ie, containing estrogen), the dose and route must be stable for ≥6 weeks prior to screening and throughout the trial 20. Male subjects must use a condom, or his female partner of childbearing potential must use an effective form of contraception as described above, from the beginning of screening to the last trial visit. 21. Known substance abuse or known (or previous) eating disorders, including anorexia nervosa, bulimia and severe gastrointestinal disease affecting normal eating (as judged by the investigator). 22. Any disease or condition that, in the judgement of the investigator, may make the subject unlikely to comply with the requirements of the trial or any condition that presents undue risk from the investigational product or procedures. 23. Participation in another interventional clinical trial involving an investigational compound within 26 weeks prior to screening or in parallel to this trial. 24. Currently using or have used within the last 3 days prior to screening: biotin >0.03 mg/day from supplements 25. Known history of positive results of tests for human immunodeficiency virus (HIV) antibodies or hepatitis B and/or C (exceptions if vaccinated towards Hepatitis B virus and Hepatitis C virus). 26. Any of the following: acute critical illness and complications following open heart surgery, abdominal surgery, multiple accidental traumas, acute respiratory failure, or similar conditions within 180 days prior to screening. ***Note:*** For France, all categories of protected persons specified in the Public Health Code are excluded from participation.

TRIAL DESIGN	This is a randomized, parallel-arm, placebo-controlled, active-controlled trial and designed to evaluate efficacy of lonapegsomatropin versus placebo. The daily somatropin product arm is included as a calibration arm to assist clinical judgement on the trial results. The trial will consist of: • Screening Period – up to approx. 6 weeks to establish eligibility (including up to one week between randomization and the first dose to allow for logistics and shipment as needed) • Treatment Period – (38 weeks in total), consisting of: – Dose Titration Period – 12 weeks of dose titration, scheduled dose titration visits will occur at Week 4, Week 8, and Week 12 – Dose Maintenance Period – 26 weeks of maintenance treatment, trial visits will occur at Week 17, Week 28, and Week 38 – All patients completing the treatment period will be offered to participate in an open-label extension study on once-weekly lonapegsomatropin treatment • Follow-up Period – (4 weeks in total), treatment free period, AEs/SAEs will be collected via phone 2 weeks after Week 38 (Week 40), an ADA sample will be taken 4 weeks after Week 38 (Week 42). The treatment free follow-up Period is not applicable for subjects participating in the extension trial. Due to the different hGH dose requirements, depending on subject's age and receipt of concomitant oral estrogen, this trial will have three dosing groups per arm: • Subjects receiving concomitant oral estrogen (any age) or subjects being <30 years old at start of screening • Subjects being ≥30 to ≤60 years old at start of screening and do not require oral estrogen • Subjects being >60 years old at start of screening and do not require oral estrogen Once all data and results determining the subject eligibility are available and confirmed by the Investigator and Medical Monitor, the subject will be centrally randomized to 1 of 3 treatment arms: either once-weekly lonapegsomatropin (N = 80), once-weekly placebo (N = 80) or daily somatropin product (N = 80), in a 1:1:1 ratio.

	In all regions except Japan, the following randomization stratifications will be applied: 1. Dosing group. 2. In the "≥30 to ≤60 years old (no oral estrogen)" dosing group, randomization will be further stratified by sex. 3. Diabetes mellitus status. In Japan, randomization will be stratified by dosing group only. All subjects' visits should be performed in the morning to ensure fasting status. Also, DXA assessments should be performed in a similar setting (time and hydration status) at each visit, using the same approved DXA machine throughout the trial. **Screening Period** Prior to any protocol-related activities or evaluations, informed consent will be obtained from each potential subject in accordance with ICH GCP and regional regulatory requirements. The screening period will be used to collect clinical data to establish the subject's eligibility for the trial. Within the screening period, still missing assessments for inclusion /exclusion may be conducted. The following assessments will be performed, and appropriate data collected: • Demography, including sex, age, childbearing potential, oral estrogen intake, ethnicity and race • Medical history, including a description of pituitary deficiencies • Currently and previously taken relevant medications (for the 12 months prior to screening) • Vital signs measurements • Height and weight • Physical examination • Blood collection for the following laboratory assessments (fasting required, central analysis): – Routine chemistry and hematology – Hormone status: TSH, fT4, fT3, and morning cortisol – Glycemic status: HbA1c, fasting insulin and fasting plasma glucose. In case of suspected glucose intolerance, a 2-hour oral glucose tolerance test should be performed – Fasting lipid panel – Females: Serum human chorionic gonadotropin (hCG) – Males: morning (6:00-10:00AM) serum total testosterone – IGF-1 and IGFBP-3

	– ADA: ▪ The ADA analyses may only be conducted after enrollment and are not required for eligibility verification. These data will be used to support evaluation of post-dose antibody detection ▪ Blood samples for immunogenicity assessment will be retained for up to 5 years following trial finalization for possible further characterization if requested by the authorities of a potential anti-drug antibody responses • 12-lead ECG, local reading • Fundoscopy • DXA scan (central reading) • MRI / CT scan: A pituitary MRI scan is required at screening if an MR|I scan from within 6 months prior to screening is not available. A CT scan can be used if MRI scan is contraindicated. Screening shall be stopped at any point in case any of the eligibility criteria not being met, such cases will be classified as screening failures. All results will be reviewed by the Medical Monitor to verify eligibility of each subject prior to randomization. Randomization happens after screening is complete, and subject is confirmed to be eligible. **Treatment Period** Randomized subjects will receive the study drug as assigned according to randomization and dosing group. The trial procedures are indicated in the Schedule of Events (Section 18.2) and Section 10.2.2; Visit 3 may be conducted via phone call per investigator's discretion. **Visit Schedule of Weekly Treatment Arms (Lonapegsomatropin/Placebo)** • Visit 1 will be performed on the day of the 1st dose (Week 1, Day 1) and all assessments will be done pre-dose, except for the injection site reaction assessment. The first dose will be given on site. • Visit 2 (Week 4) and Visit 3 (Week 8) will be conducted approx. 4 - 5 days post-dose (96-120 h post-dose +/- 3 hours) to be able to assess the average IGF-1 level (IGF-1 SDS) to support dose titration. • Visit 4 (Week 12) will be conducted approx. 4 - 5 days post-dose (96-120 h post-dose +/- 3 hours) to be able to assess the average IGF-1 level (IGF-1 SDS) to support dose titration. Subjects will be assigned their fixed dose for the next 26 weeks.

	• Visit 5 (Week 17, +/- 1 week) will be conducted on the day of the 17th dose (+/- 1 dose) to have a steady-state trough value and the upcoming dose given on site (144 – 168 h after the prior dose +/- 3 hours). All assessments (except for injection site reaction assessment) are suggested to be done pre-dose. • Visit 6 (Week 28, +/- 1 week) will be conducted 1-3 days post-dose (24-72 h post-dose +/- 3 hours) to have a maintenance phase sampling at approximate peak hGH and peak IGF-1 (IGF-1 SDS). • Visit 7 (Week 38, + 1 week, end of trial) will be conducted approx. 4 - 5 days post-dose (96-120 h post-dose +/- 3 hours) to be able to assess the average IGF-1 level (IGF-1 SDS) at the end of the trial. • For subjects not participating in the extension trial: A phone call will be conducted up to 2 weeks after this visit to assess if ongoing AEs are closed. A sample for ADA and pregnancy testing will be collected approximately at least 30 days after the last study drug dose. **Visit Schedule of Daily Somatropin Treatment Arm** • Visit 1 will be performed on the day of the 1st dose (Week 1, Day 1) and all assessments will be done pre-dose, except for the injection site reaction assessment. The first dose will be given on site. • Visit 2 (Week 4) and Visit 3 (Week 8) will be conducted at any day of the week. • Visit 4 (Week 12) will be conducted at any day of the week. Subjects will be assigned their fixed dose for the next 26 weeks. This dose may be given on site or at the subject's home. • Visit 5 (Week 17, +/- 1 week) and Visit 6 (Week 28, +/- 1 week) will be conducted at any day of the week. • Visit 7 (Week 38, + 1 week, end of trial) will be conducted the day after the 26^{th} week (or 27^{th} week) of fixed dosing is completed. • For subjects not participating in the extension trial: A phone call will be conducted up to 2 weeks after this visit to assess if ongoing AEs are closed. A sample for ADA and pregnancy testing will be collected approximately at least 30 days after the last study drug dose.

Dose Adjustment Parameters:

Individual doses may be adjusted based on AEs and IGF-1 SDS as outlined in Figure 3 and Figure 4 (Section 9.6.1) and according to the dose levels indicated in Table 3 and Table 4.

Dose Reduction and Possible Stopping:

The investigator may stop or reduce the dose of the study drug for an individual subject as per the dosing algorithms shown in Figure 3 and Figure 4, as well as at any time during the trial for the following reasons:

- HbA_{1c} levels:
  - Subjects without diabetes diagnosis at trial start: In case the HbA1c level is > 6.5 % and / or has an absolute increase of 0.8 % from the prior visit HbA1c: Confirmation of HbA1c level is required. Once confirmed, the study drug dose (lonapegsomatropin/placebo or daily somatropin product) may be decreased to the next lower dose level (see Table 3 and Table 4) or a diet / nutritional counseling and / or diabetes medication may be added per investigator judgement. If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional lonapegsomatropin dose adjustments may be appropriate
  - Subjects with diabetes diagnosis at trial start: additional diabetes medication may be added as considered appropriate by the investigator
  - Severe hGH-related AEs

Required Stopping

The investigator **must** stop the study drug for an individual subject at any time during the trial in the presence of the following:

- Evidence of severe hypersensitivity to the study drug
- Confirmed neutralizing anti-hGH antibodies
- Evidence of tumor growth or new onset malignancy
- Evidence of progression or new onset retinopathy
- Pregnancy

If in any case treatment should be discontinued, all subsequent visits and assessments should continue as planned. If the only option for the subject is to drop-out of the trial, the subject may also be offered to only attend the final Visit 7.

For subjects who discontinue the study drug for reasons related to safety, unblinding of the treatment assignment for the subject may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the subject.

	The Medical Monitor will review all safety information on an ongoing basis.
INVESTIGATIONAL PRODUCT	Name: Lonapegsomatropin drug product. Lonapegsomatropin is a long-acting prodrug of somatropin, such that the growth hormone released maintains the same mode of action, including receptor-binding affinity, as daily GH; the difference is that it delivers a pharmacodynamically optimized hGH exposure profile over the course of a week. Lonapegsomatropin consists of a parent drug, somatropin, that is transiently bound to a methoxypolyethylene glycol carrier (4 x 10 kDa mPEG) via a proprietary TransCon Linker. The carrier extends the duration of somatropin in the systemic circulation through a shielding effect that minimizes renal excretion and receptor-mediated clearance. At physiologic pH and temperature, lonapegsomatropin releases fully active, unmodified somatropin via autocleavage of the TransCon Linker in a controlled manner that follows first-order kinetics. Lonapegsomatropin will be provided as a lyophilized powder in single-use glass vials requiring reconstitution with 1 mL sterile water for injection (sWFI) and administered by subcutaneous (SC) injection via syringe and needle. Lonapegsomatropin will be supplied in 2 vial presentations that, after reconstitution, will result in 2 solutions with two concentrations: 1. 12.1 mg hGH/vial ([redacted]mg hGH/mL after reconstitution). 2. 24.2 mg hGH/vial ([redacted]mg hGH/mL after reconstitution).
REFERENCE PRODUCT(S)	**Placebo for Lonapegsomatropin drug product, weekly administration** The placebo for lonapegsomatropin drug product will contain the same excipients as lonapegsomatropin drug product but does not contain lonapegsomatropin itself. It will be provided in vials.
TREATMENT REGIMENS	Due to the different hGH dose requirements, depending on subject's age and concomitant use of oral estrogen, this trial will have three dosing groups per arm. Subjects will be initiated on a low dose, and the dose will slowly be increased to avoid adverse reactions as much as possible (Dose Titration Period) until the target maintenance dose is reached (Dose Maintenance Period). All treatments will be administered by the site staff, or subject. The relevant dosing regimens for once-weekly treatment arms (lonapegsomatropin and placebo) and for daily somatropin treatment arm are displayed in the tables below.

Dosing Table for Once-Weekly Treatment Arms (lonapegsomatropin and placebo)

Week		Dose Group 1 (oral estrogen intake [any age] or <30 years old)	Dose Group 2 (≥30 to ≤60 years old; no oral estrogen intake)	Dose Group 3 (>60 years old; no oral estrogen intake)
Weeks 1-4	[redacted]			
Weeks 5-8				
Weeks 9-12				
Weeks 13-38 (Dose Maintenance Period)				

Dosing Table for Daily Somatropin Treatment Arm

Week		Dose Group 1 (oral estrogen intake [any age] or <30 years old)	Dose Group 2 (≥30 to ≤60 years old; no oral estrogen intake)	Dose Group 3 (>60 years old; no oral estrogen intake)
Weeks 1-4	[redacted]			

	[redacted]
	Individual doses may be adjusted based on AEs and IGF-1 SDS as outlined in Figure 3 and Figure 4 (Section 9.6.1) and according to the dose levels indicated in tables below. **Dose Levels for Dose Titration for Once-Weekly Treatment Arms (lonapegsomatropin and placebo)** [redacted] **Dose Levels for Dose Titration for Daily Somatropin Treatment Arm** [redacted]
BLINDING	The once-weekly lonapegsomatropin and once-weekly placebo treatment arms will be double-blinded, whereas the daily somatropin product treatment arm will be open-label.

	To maintain the double-blind between the once-weekly lonapegsomatropin and once-weekly placebo treatment arm, subjects in the once-weekly placebo treatment arm will receive the same dose volume as if they would have been randomized to once-weekly lonapegsomatropin. The placebo will look similar to lonapegsomatropin: the same vials, cap color and diluent will be used, and a blinding shell cover the glass vial. For dose adjustments due to IGF-1 that is required for the lonapegsomatropin arm, a sham titration will be initiated for a subject in the placebo arm, in a pattern that follows the dose modifications of the lonapegsomatropin arm. In case of high IGF-1 values, a dose titration/reduction recommendation based on a predetermined algorithm will be provided by the unblinded CRO team member. Blinding of a weekly study drug (lonapegsomatropin or placebo) versus daily comparator (daily somatropin product) is not considered feasible. However, critical assessors (selected Sponsor team members, central vendors and other personnel as appropriate and feasible) will be kept blinded to all treatment assignments to minimize bias prior to database lock and trial unblinding. The central reader for DXA scans will be blinded to the treatment arm throughout the trial.
TRIAL AND TREATMENT DURATION	The total duration of the trial for an individual subject is up to approximately 48 weeks (up to 6 weeks for screening + 12 weeks dose titration + 26 weeks stable treatment + 4 weeks of follow-up treatment free period; The timelines may include approx. 1 week between screening and treatment period to allow for logistics and shipments). The treatment free follow-up period is not applicable for subjects continuing into the extension trial. End of trial is defined as the last subject last visit.
STATISTICAL METHODS	The efficacy analyses will be conducted using an Intent-To-Treat population defined as all randomized subjects who have received any amount of the study drug and subjects will be analyzed by treatment arm as randomized. The Safety Analysis Set will include all randomized subjects who have received at least one dose of the study drug, subjects will be analyzed by treatment arm as treated. The PK/PD Analysis set will include all randomized subjects who have received at least one dose of the study drug and have post-randomization PK/PD data, subjects will be analyzed by treatment arm as treated. In general, data from clinical assessments will be summarized using descriptive statistics.

	Categorical data will be presented using counts and percentages of subjects. Continuous variables will be presented using number of subjects, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. The ANCOVA model will include treatment arm and dose group as factors, baseline trunk percent fat as a covariate and additional factors that may include region (Japan vs. all regions except Japan), baseline age group, sex, concomitant oral estrogen at screening (yes vs. no), diabetes mellitus (yes vs. no), and AGHD onset (adult vs. childhood). The daily somatropin product arm will be included in the ANCOVA model, but no formal statistical testing will be performed on this arm. The 95% confidence intervals will be calculated for the mean treatment differences between lonapegsomatropin vs. placebo and lonapegsomatropin vs. daily somatropin. Similar ANCOVA models with multiple imputation will be applied to analyze secondary efficacy endpoints, with corresponding baseline value as a covariate. To control familywise error rate at level of 0.05, the secondary endpoints will be adjusted by Hochberg procedure only if the test for the primary endpoint (lonapegsomatropin vs. placebo) is statistically significant. Reporting of the safety data will be descriptive. The safety parameters include AEs, clinical laboratory, immunogenicity data, vital signs, ECG parameters, and other safety parameters. Details of statistical methods will be provided in the Statistical Analysis Plan (SAP).
SAMPLE SIZE DETERMINATION	This trial is powered for the efficacy comparison of lonapegsomatropin versus placebo. The daily somatropin product arm is included as a calibration arm and not powered for formal comparison. Approximately 240 subjects will be randomized in a 1:1:1 ratio to once-weekly lonapegsomatropin, once-weekly placebo, or daily somatropin product. A sample size of 80 subjects per arm in the lonapegsomatropin and placebo arms will provide 90% power to detect a treatment difference of 1.9% between once-weekly lonapegsomatropin and placebo for the primary endpoint of change from baseline in trunk percent fat at Week 38 at the 2 sided 5% significance level, with the assumption of a common SD of 3.7%.

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[redacted]

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4. LIST OF ABBREVIATIONS

µg	Microgram
ACP-001	TransCon PEG80 hGH
ACP-011	TransCon PEG40 hGH, Lonapegsomatropin
ACTH	adrenocorticotrophic hormone
ADA	anti-drug antibodies
AE	adverse event
AGHD	adult growth hormone deficiency
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AUEC	area under the effect curve
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CRO	Contract Research Organization
CT	Computed Tomography
d	Day
DCC	dual chamber cartridge
DPP-4	dipeptidyl peptidase-4
DXA	dual-energy x-ray absorptiometry
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
E_{max}	maximum observed effect
EOT	end of trial
[redacted]	
FDA	Food and Drug Administration
fT3	free triiodothyronine
fT4	free thyroxine
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone-releasing hormone

GHRP-2	growth hormone-releasing peptide 2
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide 1
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
hGH	human growth hormone
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH	International Council on Harmonization
ICF	informed consent form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor binding protein-3
IMP	Investigational Medicinal Product
IND	investigational new drug
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
kDa	Kilodalton
kg	Kilogram
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	Doctor of Medicine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency

mL	Milliliter
mPEG	methoxypolyethylene glycol
MRI	Magnetic Resonance Imaging
ng	Nanogram
NYHA	New York Heart Association
PD	Pharmacodynamics
PEG	polyethylene glycol
[redacted]	
pH	power of hydrogen
PK	Pharmacokinetics
[redacted]	
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
SDS	standard deviation score
SE	standard error
SGLT-2	sodium-glucose cotransporter-2
SIV	site initiation visit
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
TBI	traumatic brain injury
[redacted]	
TSH	thyroid stimulating hormone
VLDL	very low-density lipoprotein
WHO	World Health Organization

5. INTRODUCTION

5.1. ADULT GROWTH HORMONE DEFICIENCY

Growth hormone (GH; somatotropin) is a product of endocrine secretion of the pituitary gland and targets many tissues to control metabolism in adults via its direct and indirect (via IGF-1) effects. In adipose tissue, GH is lipolytic and protects against hypoglycemia, and opposes the effects of IGF-1 (lipogenesis and reduced blood sugar). Growth hormone also has direct effects and indirect effects on bone metabolism, including on osteoblast proliferation and bone mineral density/bone accumulation (Olney 2003). New research continues to reveal other potential roles of GH, including regulation of cardiac and immune function, mental agility, and aging.

Adult growth hormone deficiency (AGHD) results from insufficient GH secretion from the anterior pituitary gland and may represent either a continuation of childhood-onset GHD or GHD acquired during adulthood. The primary etiology for adult-onset GHD is damage to the hypothalamic-pituitary region from tumors or treatment with surgery and radiation (Yuen 2019). Severe GHD has also been reported following treatment for acromegaly (Ronchi 2009) or Cushing's disease (Hughes 1999).

Clinically, AGHD is associated with central adiposity, diminished lean muscle mass, decreased bone mass, and reduced quality of life (Melmed 2019). Additional clinical features of untreated GHD include dyslipidemia, insulin resistance, and hepatic steatosis, which predispose this patient population to metabolic syndrome (Attanasio 2010) and significantly increase their cardiovascular morbidity and mortality (Gazzaruso 2014).

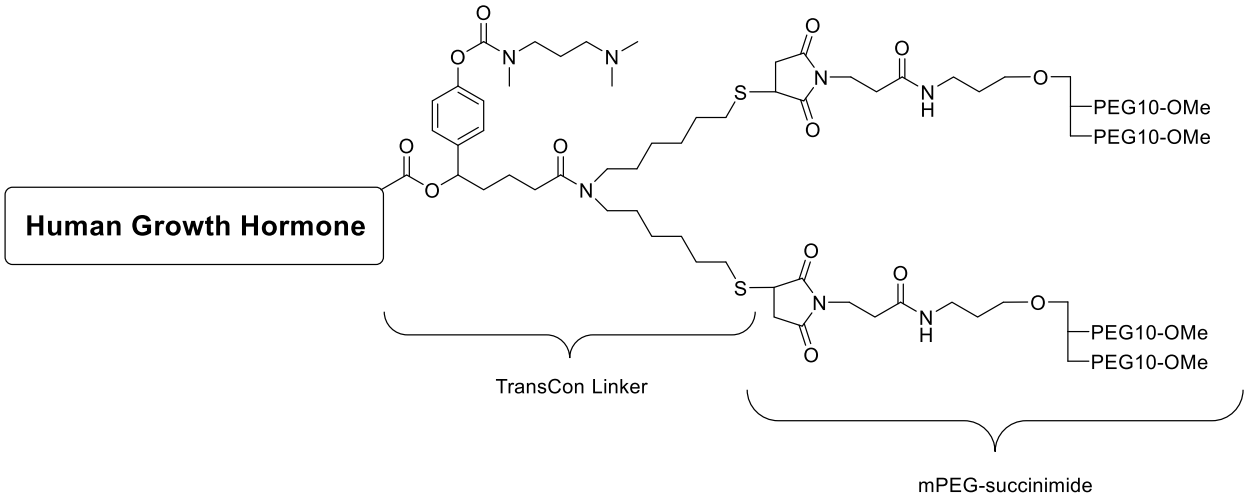
GH replacement therapy represents standard of care treatment that addresses multiple aspects of the condition (Ho 2007, Molitch 2011, Japan Endocrine Society 2019, Yuen 2019, Kim 2020). In particular, the lipolytic and anabolic actions of GH have been shown to confer beneficial effects on body composition across multiple trials (Møller 2009, Newman 2015). GH has also demonstrated important effects on bone mineral density (Snyder 2007) in longer term studies. Finally, quality of life improvements have been noted by patients' partners following initiation of GH therapy (Burman 1995).

Compliance with daily somatropin products in adults with GHD has been reported to be suboptimal. Based on survey data for 158 adults with GHD, the rate of non-compliance with GH therapy has been estimated to be 65% (Rosenfeld 2008).

5.2. LONAPEGSOMATROPIN

Lonapegsomatropin (ACP-011, TransCon hGH) is a long-acting prodrug of somatropin (hGH), designed to maintain the same mode of action and distribution as daily somatropin products, but with a once-weekly injection. Lonapegsomatropin consists of a parent drug, somatropin, that is transiently conjugated to a methoxypolyethylene glycol (mPEG) carrier (4 × 10 kDa mPEG) via a proprietary TransCon Linker (Figure 1). The carrier has a shielding effect that minimizes renal excretion and receptor-mediated clearance of lonapegsomatropin. At physiologic pH and temperature, lonapegsomatropin releases fully active, unmodified hGH via autocleavage of the TransCon Linker in a controlled manner that follows first-order kinetics.

Figure 1: Structure of Lonapegsomatropin (ACP-011)



Abbreviations: PEG10-OMe: 10 kDa methoxypolyethylene chain.

Human GH released from lonapegsomatropin has the same mode of action, volume of distribution, and cellular signaling as endogenous GH. The advantage of lonapegsomatropin in comparison to daily hGH, is the sustained exposure to hGH during the weekly dosing interval, which enhances delivery of hGH into target tissues and is important for optimal efficacy. Upon linker cleavage and release of hGH, a small molecular weight molecule, [redacted] is also liberated but has shown to be rapidly cleared from systemic circulation. After release of hGH, the remainder of the linker remains covalently bound to mPEG and is cleared from the body primarily through renal clearance, as known for other high molecular weight molecules.

A predecessor molecule to lonapegsomatropin, ACP-001, contained a 4 x 20 kDa branched-chain mPEG moiety as the inactive carrier in the prodrug. Early clinical (Phase 1 and Phase 2) trials have been completed with this predecessor molecule. Subsequently, a change in the molecular weight (decrease) of the inactive branched-chain mPEG carrier molecule was introduced to generate lonapegsomatropin (ACP-011), the current version in development. This molecule contains the same hGH and TransCon Linker moieties as those incorporated into ACP-001. The only difference between the molecules is limited to the molecular weight of the inactive branched-chain mPEG carrier molecule, which is 80 kDa in ACP-001 and 40 kDa in lonapegsomatropin. The reduction in mPEG size was done to reduce the viscosity of the drug product; an extensive nonclinical and clinical program demonstrated biologic comparability of ACP-001 and lonapegsomatropin.

5.3. RELEVANT FINDINGS FROM NONCLINICAL STUDIES

Nonclinical pharmacology and toxicology studies have been conducted to support the clinical development program involving weekly subcutaneously administration of lonapegsomatropin (ACP-011) in adults with growth hormone deficiency. All pivotal nonclinical safety studies either have been or are being conducted in compliance with Good Laboratory Practices (GLP) and the program as a whole followed recommendations provided by ICH guidance and product specific guidance from health authorities. The nonclinical program has assessed both the parent prodrug and the products of autocleavage (hGH, the remainder mPEG-linker, and [redacted] as well as IGF-1, a biomarker for hGH.

Please refer to the current Investigator's Brochure for detailed information pertaining to the nonclinical program supporting conduct of this clinical trial.

5.4. CLINICAL EXPERIENCE

The clinical development program for lonapegsomatropin and its predecessor molecule, ACP-001, includes a total of 8 completed clinical trials: four Phase 1 trials, two Phase 2 trials, and two Phase 3 trials. The Phase 3 trials (TransCon hGH CT-301, TransCon hGH CT-301EXT, TransCon hGH CT-302) evaluated lonapegsomatropin for pediatric GHD. Please refer to the current Investigator's Brochure for detailed information pertaining to these trials.

In adults with GHD, a Phase 2, randomized, open-label, active-controlled trial of three different doses (ACP-001 0.02 mg hGH/kg, 0.04 mg hGH/kg and 0.08 mg hGH/kg) of ACP-001 administered weekly was compared to a daily hGH (Omnitrope 0.04 mg hGH/kg/week divided into 7 equal daily doses) over a period of 4 weeks. A total of 37 subjects were randomized and dosed. ACP-001 was safe and well-tolerated at all 3 doses administered during the study. There was no marked difference in the number of AEs (AEs) and injection site reactions experienced by patients treated with ACP-001 compared to those reported by the patients treated with Omnitrope, including no reported lipoatrophy or nodule formation at the injection site. Additionally, once-weekly administration of ACP-001 over a period of 4 weeks stimulated a dose-proportional response of IGF-1 at all 3 dose levels investigated in this study. Finally, treatment with ACP-001 0.04 mg hGH/kg/week, stimulated a similar IGF-1 response (AUEC) after 4 weeks of treatment to the corresponding dose of daily hGH (Omnitrope) given in this study, indicating that ACP-001 is as potent as daily hGH on corresponding weekly dose levels. Additional results for this trial may be found in the Investigator's Brochure and have been published (Höybye 2017).

In healthy adults, two Phase 1 clinical trials (ACP-011 CT-101 and TransCon hGH CT-102) have been completed with lonapegsomatropin. ACP-011 CT-101 demonstrated bioequivalence between ACP-001 and lonapegsomatropin. In TransCon hGH CT-102, lonapegsomatropin was bioequivalent in terms of hGH PK (C_{max} and AUC) and IGF-1 PD (E_{max} and AUEC) response when administered via GH Auto-Injector vs. syringe and needle.

In children with GHD, two Phase 3 clinical trials have been completed with lonapegsomatropin. The pivotal Phase 3 trial (TransCon hGH CT-301, heiGHt) in treatment-naïve prepubertal children with GHD demonstrated once-weekly lonapegsomatropin (0.24 mg hGH/kg/week) was superior to daily hGH (Genotropin 0.24 mg hGH/kg/week divided into 7 equal daily doses) for the primary endpoint of annualized height velocity (AHV) at 52 weeks.

No serious adverse event (SAEs) related to study drug were observed in either arm. No treatment-emergent adverse events (TEAEs) leading to discontinuation of study drug were observed in either arm. A low incidence of low-titer non-neutralizing antibodies was observed, comparable to that seen with daily somatropin therapies.

The single-arm Phase 3 trial (TransCon hGH CT-302, fliGHt) in predominantly treatment-experienced prepubertal children with GHD demonstrated safety and efficacy when switching from a daily hGH product to once-weekly lonapegsomatropin (0.24 mg hGH/kg/week). No drug-related discontinuations or drug-related SAEs were observed. A low incidence of low-titer non-neutralizing antibodies was observed. For both TransCon hGH CT-301 and TransCon hGH CT-302, the AE profile of lonapegsomatropin was similar to the published safety profile of daily GH therapies.

The open-label, single-arm Phase 3 extension trial (TransCon hGH CT-301EXT, enliGHten) is investigating the long-term safety and efficacy in children from the Phase 3 heiGHt and fliGHt trials receiving lonapegsomatropin. Subject retention has been high, and no safety signals have been detected to date. The study is ongoing.

Overall Clinical Summary:

Across lonapegsomatropin and ACP-001 clinical trials conducted in children and adults, there have been no AEs that led to discontinuation of the study drug, no suspected unexpected serious adverse reactions (SUSARS), and no neutralizing anti-hGH antibodies detected. The general safety and tolerability profile have been consistent with that seen with daily-administered somatropin products. Injection site reactions have generally been mild and transient and have been observed at a rate similar to that for daily somatropin. Maximum hGH serum concentrations have been comparable between equivalent weekly hGH doses of lonapegsomatropin and daily somatropin.

5.5. TRIAL RATIONALE

The primary objective of this trial is to assess the efficacy of once-weekly lonapegsomatropin compared to placebo in adults with GHD. The daily somatropin product arm is included to provide a concurrent assessment of standard of care in this patient population. GHD in adults is associated with central adiposity, diminished lean muscle mass, decreased bone mass, and reduced quality of life (Melmed 2019), and GH replacement therapy represents standard of care treatment that addresses multiple aspects of the condition (Ho 2007, Molitch 2011, Japan Endocrine Society 2019, Yuen 2019, Kim 2020). Changes in body composition are therefore an objective and sensitive endpoint that reflects biologic activity of GH and clinical efficacy. In similar placebo-controlled trials reporting trunk percent fat over a six-month period in patients with AGHD, the observed treatment effect for somatropin products has varied from -1.53% to -3.50% (Norditropin US PI, Saizen US PI, Zomacton US PI, Omnitrope US PI and Genotropin US PI). Although there is no consensus guideline to suggest a minimally important reduction for trunk percent fat (Hamdy 2006), a change from baseline in trunk percent fat of 1.9% will be clinically meaningful as it represents a significant reduction in the key visceral adipose compartment that is metabolically important.

In addition to assessing efficacy, a treatment duration of approx. 9 months is considered adequate to assess safety and is supported by the well-characterized safety of daily somatropin products for AGHD and extensive clinical experience for lonapegsomatropin for pediatric GHD at higher doses (approximately 2-6 fold based on weight) than used in AGHD.

To assess long-term safety and efficacy, an open-label extension trial is planned. During the extension trial, all subjects will receive lonapegsomatropin.

5.6. POTENTIAL RISKS AND BENEFITS

Lonapegsomatropin is an investigational medicinal hGH prodrug product with a proposed once-weekly dosing regimen designed to overcome the inconvenience and suboptimal compliance of daily hGH injections. The safety and efficacy profile are anticipated to be comparable to currently approved daily hGH products, while maintaining exposure (C_{max} and AUC) in the optimal therapeutic range. Moreover, the exposure to hGH during the weekly dosing interval is anticipated to enhance delivery of hGH into target tissues and optimize efficacy. Obviating the need for daily injections should increase compliance and therefore long-term efficacy, which would be of great benefit to adult patients with GHD.

The safety of the subjects will be monitored by the investigators as well as the medical monitors. Stop rules have been defined in the protocol. There are no high risk procedures required and the measurement of the endpoint by dual-x-ray-absorptiometry (DXA) can be considered standard of care and is only associated with very low x-ray exposure.

In conclusion, the risk-benefit assessment for this trial is considered to be acceptable based on nonclinical, already gained clinical experience and safety data in the pediatric populations, the fact that no harming study procedures are implemented, and the fact that somatropin has been approved and used for over 30 years.

5.6.1. Risks Associated with Placebo

The objective of the study is to evaluate the efficacy of lonapegsomatropin versus placebo regarding percent change trunk fat. This placebo comparison is needed to demonstrate superiority versus no treatment, the shortest timeframe for this being 6 months maintenance (final stable dose) treatment which is commonly considered acceptable and follows similar recent clinical development programs. In addition, a double-blinded study can only be conducted using weekly administered placebo/comparator as lonapegsomatropin is administered weekly.

AGHD is caused by insufficient production of endogenous GH. The reasons for this insufficient production of GH include and are not limited to structural, infiltrative or degenerative disease in the hypothalamus / pituitary gland, hypothalamic-pituitary surgery, radiation after brain tumor, genetic disorder or traumatic brain injury (TBI). AGHD is not an acute condition, and in contrast to cortisol and thyroid hormone deficiencies not life threatening. Symptoms of AGHD are nonspecific (e.g. decrease in lean body mass and bone mineral density), metabolism and quality of life are negatively affected and establishing the diagnosis is challenging and complex.

Standard treatment of AGHD is replacement therapy (substitution) with GH, injected on a daily basis. Depending on the underlying cause, treatment mostly starts with quite some distance from the “event” (e.g. TBI, surgery, or radiation) and diagnosis to ensure stable replacement of other pituitary hormones and sufficient monitoring for tumor regrowth or tumor residual.

Based on the above, treatment initiation can take months to years. Since patients for this study must have received no GH treatment for at least 12 months prior to screening, the trial period will be a continuum of the treatment-free time for patients randomized into the placebo arm. It is to be noted that patients currently treated with GH are not eligible and no patient is asked to discontinue their GH treatment to participate in this study, only GH treatment-naïve patients or patients who have discontinued GH treatment for reasons unrelated to the study can be enrolled.

The up to 48-week treatment-free period (up to 6 weeks screening, 38 weeks treatment on placebo, and 4 weeks follow-up) is not considered to be harmful for the patients or causing significant deterioration of the condition or affecting effects of future GH treatment. The clinical manifestations of GHD are mainly of a metabolic nature: increased fat mass, decrease in muscle mass and bone mineral density, decrease in muscle strength, hypercholesterolemia, decrease in basal metabolic rate, sleep disturbances, and psychological disturbances. These clinical manifestations do not affect patient safety and are reversible under GH treatment, hence not considered causing any longer-term harm for patients. This was also concluded in a recently published study by Swedish and Dutch authors (Postma 2020).

Furthermore, during the study, the patients will be closely monitored by the investigator and the sponsors medical monitors for any signs of safety risk.

All patients completing this study will be offered to participate in an open-label extension study on once-weekly lonapegsomatropin treatment.

In conclusion, the placebo arm is needed and justified to conduct a double-blinded study and to demonstrate a robust treatment effect for lonapegsomatropin. The placebo arm is considered standard in AGHD studies without causing long-term harm to patients, diminishing future GH treatment effects, or posing a safety risk. None of the subjects are supposed to discontinue GH treatment as the study only includes subjects not treated with GH for the last 12 months or newly diagnosed with AGHD.

5.6.2. Risks Associated with the COVID-19 Pandemic

Lonapegsomatropin is a long-acting prodrug that liberates somatropin and is believed not to cause immunosuppression. Therefore, the risk of subjects being exposed to SARS-CoV-2 or suffering from COVID-19 due to treatment with lonapegsomatropin, placebo or the daily somatropin product will be similar to that of the general population. Subjects and site staff involved in this trial are expected to act according to local guidelines, recommendations, national laws, local restrictions, and hospital procedures related to COVID-19, and hereby ensure keeping the risk of viral infection low. Decisions to adjust the trial conduct will be based on the risk assessment performed by the Sponsor. The risk assessment will, as applicable, include a risk assessment of each individual trial participant. In case of local COVID-19 outbreaks several mitigating actions can be applied to ensure patient safety and data integrity: Recruitment and randomization can be postponed. For subjects already included in the study, site visits can be replaced by remote contacts as phone calls or virtual meetings, safety lab and assessments can be done locally, and study medication can be sent directly to the home of the subjects.

6. OBJECTIVES

6.1. PRIMARY OBJECTIVE

To evaluate the efficacy of once-weekly lonapegsomatropin compared to placebo at 38 weeks in adults with GHD.

6.2. SECONDARY OBJECTIVES

1. To evaluate the safety and tolerability of once-weekly lonapegsomatropin in adults with GHD.
2. To evaluate the PK of once-weekly lonapegsomatropin in adults with GHD.
3. To evaluate the PD of once-weekly lonapegsomatropin in adults with GHD.

6.3. TERTIARY OBJECTIVE

[redacted]

7. TRIAL DESIGN

7.1. OVERALL TRIAL DESIGN AND PLAN

7.1.1. Trial Design

This is a randomized, parallel-arm, placebo-controlled, active-controlled trial, designed to evaluate efficacy of lonapegsomatropin versus placebo. The daily somatropin product arm is included as a calibration arm to assist clinical judgement on the trial results.

Subjects will be randomized to 1 of 3 treatment arms in a 1:1:1 ratio:

- Approximately 80 subjects will be randomized to once-weekly lonapegsomatropin
- Approximately 80 subjects will be randomized to once-weekly placebo
- Approximately 80 subjects will be randomized to daily somatropin product

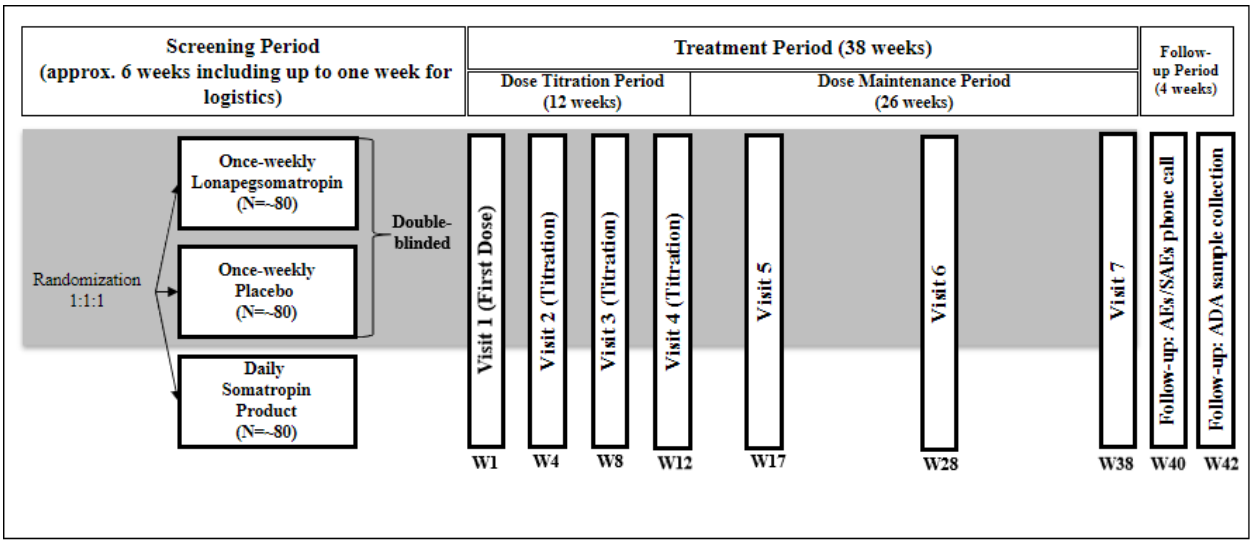
The trial will consist of:

- Screening Period – up to approx. 6 weeks to establish eligibility (including up to one week between randomization and the first dose to allow for logistics and shipment as needed)
- Treatment Period – (38 weeks in total), consisting of:
  - Dose Titration Period – 12 weeks of dose titration, scheduled dose titration visits will occur at Week 4, Week 8, and Week 12
  - Dose Maintenance Period – 26 weeks of maintenance treatment, trial visits will occur at Week 17, Week 28, and Week 38
  - All patients completing the treatment period will be offered to participate in an open-label extension study on once-weekly lonapegsomatropin treatment.

- Follow-up Period – (4 weeks in total), treatment free period, AEs/SAEs will be collected via phone 2 weeks after Week 38 (Week 40), an ADA sample will be taken 4 weeks after Week 38 (Week 42) The treatment free follow-up period is not applicable for subjects participating in the extension trial.

The overall trial design is shown in Figure 2, a Schedule of Events can be seen in Section 18.2.

Figure 2: Trial Design



W = Week; N = Number;

7.1.2. Measures Taken to Minimize Bias

Once all data and results determining the subject eligibility are available and reviewed by the Investigator and Medical Monitor, the subject will be centrally randomized to 1 of 3 treatment arms: either once-weekly lonapegsomatropin, (N = 80), once-weekly placebo (N = 80) or daily somatropin product (N = 80), in a 1:1:1 ratio. In all regions except Japan, the following stratifications will be applied:

1. Dosing group.
2. In the "≥30 to ≤60 years old (no oral estrogen)" dosing group, randomization will be further stratified by sex.
3. Diabetes mellitus status.

In Japan, randomization will be stratified by dosing group only.

All subjects' visits should be performed in the morning to ensure fasting status. Also, DXA assessments should be performed in a similar setting (time and hydration status) at each visit, using the same approved DXA machine throughout the trial.

Additionally, all efforts will be made to keep missing data to a minimum, including the following:

1. Investigators will be trained about the importance of subject retention.
2. Investigators will be instructed to encourage subjects to complete all trial visits, until they complete the trial.

3. Investigators will be trained to collect the reason for missing data when it does occur.
4. The Informed Consent Form (ICF) will include a statement educating subjects about the scientific importance of their data, even if they discontinue study drug.
5. Special efforts will be made to provide assistance to subjects who might discontinue due to travel or cost barriers, such as offers of transportation to the clinic.
6. Visit windows allow flexibility for clinic attendance (see Section 10.2.2.1 and Section 10.2.2.2.
7. Every effort will be made to contact subjects/caregivers or other family members to maintain contact with the clinic.

Subjects will be identified by a Subject Number (allocated at screening) consisting of 5 digits to indicate the site and 3 digits specific for the subject.

For more details on risk-based monitoring, please refer to Section 15.5.1.

7.1.2.1. Blinding and Emergency Unblinding

The once-weekly lonapegsomatropin and once-weekly placebo treatment arms will be double-blinded, whereas the daily somatropin product treatment arm will be open-label.

In case of medical emergency where knowledge of the actual treatment could influence treatment of the subject, the investigator will have direct access to unblinding of treatment assignment through the interactive response technology (IRT).

To maintain the double-blind between the once-weekly lonapegsomatropin and once-weekly placebo treatment arms, subjects in the once-weekly placebo treatment arm will receive the same dose volume as if they would have been randomized to once-weekly lonapegsomatropin. The placebo will look similar to lonapegsomatropin: the same vials, cap color and diluent will be used, and a blinding shell cover the glass vial.

For dose adjustments due to IGF-1 that is required for the lonapegsomatropin arm, a sham titration will be initiated for a subject in the placebo arm in a pattern that follows the dose modifications of the lonapegsomatropin arm. In case of high IGF-1 values, a dose titration/reduction recommendation based on a predetermined algorithm will be provided by the unblinded CRO team member.

Blinding of a weekly study drug (lonapegsomatropin or placebo) versus daily somatropin product is not considered feasible. However, critical assessors (selected Sponsor team members, central vendors and other personnel as appropriate and feasible) will be kept blinded to all treatment assignments to minimize bias prior to database lock and trial unblinding.

The central reader for DXA scans will be blinded to the treatment arm throughout the trial.

7.2. TRIAL SITES

The trial will be conducted at approximately 120 sites in North America, Europe, Asia, including Japan, and Oceania. All centers will be experienced endocrinology centers.

7.3. TERMINATION RULES

7.3.1. Early Termination of Subjects

The reason for early termination of a subject should be collected, including:

- AE
- Non-compliance with the study drug
- Withdrawal of consent by the subject
- Use of prohibited concomitant medication (protocol deviation) and subsequent decision to withdraw the subject from the trial (Section 9.9.2.2)
- If the investigator and / or Sponsor considers that withdrawal from the trial is necessary, eg, due to subject's
  - Protocol deviation, or
  - Non-compliance with the trial schedule and / or procedures.
- Subject is lost-to-follow-up
- Death
- Trial terminated by the Sponsor

For procedures to be performed for subjects discontinuing trial participation, refer to Section 8.2.

7.3.2. Early Termination of the Trial

End of trial is defined as the last subject last visit. The Sponsor reserves the right to discontinue or suspend the trial at any time in the event of any of the following:

- Inefficacy of the study drug
- Occurrence of AEs unknown to date with respect to their nature, severity, and duration, or an unexpected incidence of known AEs such that the Sponsor has determined that continued treatment with lonapegsomatropin presents an unreasonable and significant risk of illness or injury
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the subject recruitment
- Cancellation of the drug development

The Sponsor reserves the right to discontinue or suspend the trial for any reason, in which case subjects will be offered daily hGH treatment until they are switched over to standard hGH treatment per local practice or until 9 months, whichever comes first.

The Sponsor may stop this trial at a particular site for any of the following reasons:

- The site cannot include an adequate number of subjects
- Serious and/or persistent non-compliance with the protocol or clinical trial conduct

- Careless or premeditated false documentation in the electronic case report form (eCRF)
- Inadequate cooperation between the investigator and Sponsor
- Non-compliance with ICH GCP and/or regulatory requirements
- The investigator requests discontinuation

8. SUBJECT POPULATION

Adults with GHD (male and female), either treatment-naïve or not having received GH therapy for at least 12 months prior to screening will be enrolled.

8.1. TRIAL ENTRY CRITERIA

At the discretion of the investigator, blood samples can be re-drawn for re-analysis at the central laboratory for one or more of the following analytes: fT4, testosterone, cortisol, or creatinine. Re-analysis is allowed once for each parameter. Any result, of the initial or subsequent blood-draws, being within protocol defined ranges is considered satisfactory to fulfill the inclusion/exclusion criteria for these parameters.

8.1.1. Inclusion Criteria

1. Age between 23 and 80 years, inclusive, at screening.

2. AGHD Diagnosis Criteria

   For adult-onset AGHD: documented history of structural hypothalamic-pituitary disease, hypothalamic-pituitary surgery, cranial irradiation, 1-4 non-GH pituitary hormone deficiencies, a proven genetic cause of GHD, or traumatic brain injury (TBI).

   Subjects with childhood-onset GHD must have had GH axis re-assessed at final height.

   In subjects with TBI as a cause of GHD, GHD must be confirmed by GH stimulation testing performed at least 12 months after the injury.

   For all subjects, documentation of test results must be available before randomization. Stimulation test protocols and results are subject to review and approval by the Medical Monitor.

   A. For all countries except Japan: Subjects must satisfy at least one of the following criteria:

   a. Insulin tolerance test: peak GH ≤5 ng/mL
   b. Glucagon stimulation test according to body mass index (BMI)
      i. BMI ≤30 kg/m^2: peak GH ≤3 ng/mL
      ii. BMI >30 kg/m^2: peak GH ≤1 ng/mL
   c. Three or four pituitary axis deficiencies (ie, adrenal, thyroid, gonadal, and/or vasopressin; not including GH) with IGF-1 SDS ≤ -2.0 at screening as measured by central laboratory
   d. Macimorelin test: peak GH ≤2.8 ng/mL
   e. Growth hormone-releasing hormone (GHRH) + arginine test according to BMI:
      i. BMI <25 kg/m^2, peak GH <11 ng/mL
      ii. BMI ≥25–≤30 kg/m^2, peak GH <8 ng/mL

iii. BMI >30 kg/m^2, peak GH <4 ng/mL

B. For Japan only: Subjects with GHD and deficiency of at least one non-GH pituitary hormone need to satisfy one of the following GH stimulation tests. Subjects with GHD and without additional non-GH pituitary hormone deficiencies with or without evidence of intracranial structure disorder need to satisfy at least 2 of the following stimulation tests

a. Insulin tolerance test: peak GH ≤1.8 ng/mL
b. Glucagon test: peak GH ≤1.8 ng/mL
c. GHRP-2 tolerance test: peak GH ≤9 ng/mL

3. IGF-1 SDS ≤ -1.0 at screening as measured by central laboratory.
4. hGH treatment-naïve or no exposure to hGH therapy or GH secretagogue for at least 12 months prior to screening.

   Note: GH secretagogue product used in connection with stimulation tests for diagnosis of GHD is permitted (eg, macimorelin).
5. For subjects on hormone replacement therapies for any hormone deficiencies other than GH (eg, adrenal, thyroid, estrogen, testosterone) must be on adequate and stable doses for ≥6 weeks prior to and throughout screening.

   Note: Short-term increases in glucocorticoid doses taken on an as -needed basis for adrenal insufficiency are permitted ("stress dose" allowance: duration up to 5 days up to 2 times in 6 weeks, the maximum dose may reach 3 times the stable dose). One-time dose increases for diagnostic or other medical procedures are allowed.

   Note: For subjects receiving oral estrogen or estrogen-containing therapy, subjects must intend to maintain the same dose and route of estrogen administration throughout the trial. For subjects receiving non-oral estrogen or estrogen-containing therapy, the dose may be adjusted as required, however subjects must intend to maintain the same route of administration throughout the trial.
6. For subjects not on glucocorticoid replacement therapy, documentation of adequate adrenal function at screening defined as: morning (6:00-10:00AM) serum cortisol >15.0 µg/dL (measured at central laboratory) and/or Adrenocorticotrophic Hormone (ACTH) stimulation test or ITT with serum cortisol >18.0 µg/dL at or within 90 days prior to screening. Stimulation test protocols and results are subject to review and approval by the Medical Monitor.
7. For males not on testosterone replacement therapy: morning (6:00-10:00AM) total testosterone within normal limits for age as measured by the central laboratory at screening.
8. On a stable diet and exercise regime at screening with no intention to modify diet or exercise pattern during the trial, ie, no weight reduction program intended during the trial or within the last 90 days prior to or through screening.
9. No plans to undergo bariatric surgery during the trial.
10. Fundoscopy at screening without signs/symptoms of intracranial hypertension or diabetic retinopathy stage 2 / moderate or above or any other retinal disease contraindicated to growth hormone therapy. For subjects with a diagnosis of diabetes mellitus at screening, this must be documented with a fundus photograph.

11. Able and willing to provide a written ICF and authorization for protected health information (PHI) disclosure in accordance with Good Clinical Practice (GCP).
12. Serum fT4 in the normal range at screening as measured by central laboratory.

8.1.2. Exclusion Criteria

1. Known Prader-Willi Syndrome and/or other genetic diseases that may have an impact on an endpoint.
2. Diabetes mellitus at screening if any of the following criteria are met:
   a. Poorly controlled diabetes, defined as HbA1c >7.5% at screening according to central laboratory
   b. Diabetes mellitus (defined as HbA1c ≥6.5% and/or fasting plasma glucose ≥126 mg/dL and/or plasma glucose ≥200 mg/dL two hours after oral glucose tolerance test) diagnosed <26 weeks prior to screening
   c. Change in diabetes regimen (includes dose adjustment) within <90 days prior and throughout screening
   d. Use of any diabetes drugs other than metformin and/or DPP-4 inhibitors for a cumulative duration of greater than 4 weeks within 12 months prior to screening
   e. Diabetes-related complications at screening (ie, nephropathy as judged by the investigator, neuropathy requiring pharmacological treatment, retinopathy stage 2 / moderate and above within 90 days prior to screening or during screening)
3. Active malignant disease or history of malignancy. Exceptions to this exclusion criterion:
   a. Resection of in situ carcinoma of the cervix uteri
   b. Complete eradication of squamous cell or basal cell carcinoma of the skin
   c. Subjects with GHD attributed to treatment of intracranial malignant tumors or leukemia, provided that a recurrence-free survival period of at least 5 years prior to screening is documented in the subject's file based on a Magnetic Resonance Imaging (MRI) result for intracranial malignant tumors
4. Evidence of growth of pituitary adenoma or other benign intracranial tumor within the last 12 months before screening.

   Note: Absence of tumor growth is determined by comparison of two MRI or Computed Tomography (CT) scans; the most recent MRI or CT scan must be performed within 6 months prior to screening, and the interval between the two assessments must be at least 9 months. If MRI/CT scan within 6 months prior to screening is not available, it can be performed during screening.

   Note: In subjects with no evidence of residual tumor or no prior history of intracranial tumor, one MRI/CT scan performed within 6 months prior to screening or during screening will suffice to confirm tumor absence.
5. Subjects with acromegaly without remission / with documented remission less than 24 months prior to screening.
6. Subjects with Cushing's disease without remission / with documented remission less than 24 months prior to screening.

7. Subjects with prior cranial irradiation or hypothalamic-pituitary surgery: the procedure took place less than 12 months prior to screening.
8. eGFR <60 mL/min/1.73m^2 determined based on Modification of Diet in Renal Disease (MDRD) equation using serum creatinine from the central laboratory at screening.
9. Hepatic transaminases (ie, AST or ALT) >3 times the upper limit of normal according to the central laboratory at screening.
10. Heart failure NYHA class 3 or greater (NYHA 1994).
11. QTcF ≥ 451 milliseconds on 12-lead ECG at screening.

    Note: If the initial measurement is out of range, the assessment should be repeated 2 more times and the average QTcF value should be used to determine the subject's eligibility.
12. Poorly controlled hypertension, defined as supine systolic blood pressure >159 mmHg and/or supine diastolic blood pressure >95 mmHg at screening

    Note: if the initial measurement is out of range, may be repeated 2 more times after 15 min and exclusion will be based on the average of the three measurements.
13. Cerebrovascular accident within 5 years prior to screening.
14. Anabolic steroids (other than gonadal steroid replacement therapy) or oral/intravenous/intramuscular corticosteroids (other than in replacement or stress doses as described in Inclusion Criterion No.5) within 90 days prior to or throughout screening.

    Note: Stable doses of inhaled, intra-articular, or topical corticosteroids are permitted.
15. Currently using or have used within 26 weeks prior to screening any weight-loss or appetite-suppressive medications including orlistat, zonisamide, lorcaserin, bupropion, topiramate, sibutramine, stimulants (eg, phentermine or ADHD medications such as methylphenidate or amphetamines), GLP-1 receptor agonists (eg, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide), SGLT-2 inhibitors (eg, canagliflozin, dapagliflozin, empagliflozin, sotagliflozin) or medications that affects IGF-1 or GH measurements including cabergoline at doses above 0.5 mg weekly or bromocriptine at doses above 20 mg weekly.

    Note: if it can be documented that no weight-loss occurred with these drugs, a 90-day withdrawal period prior to screening is sufficient.
16. Known history of hypersensitivity and/or idiosyncrasy to any of the test compounds (somatropin) or excipients employed in this trial.
17. Known history of neutralizing anti-hGH antibodies.
18. Inability to undergo scanning by DXA or a non-interpretable DXA scan at screening.

19. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) and not using adequate contraceptive methods

    - Acceptable highly effective methods of contraception include intrauterine device (IUD); intrauterine system (IUS); bilateral tubal occlusion (must be documented); combined or progestogen-only hormonal contraception associated with inhibition of ovulation; vasectomized partner (must be documented); or sexual abstinence (only when it is the usual and preferred lifestyle of the subject).
    - Clinically acceptable methods of birth control include male or female condom with or without spermicide; progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; or cap, diaphragm, or sponge with spermicide.
    - Permanent sterilization includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    Note: Females of childbearing potential must accept to use the above-mentioned methods of contraception from the beginning of screening to the last trial visit.

    Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Note**:** For subjects using oral combined hormonal contraception (ie containing estrogen), the dose and route must be stable for ≥6 weeks prior to screening and throughout the trial

20. Male subjects must use a condom, or his female partner of childbearing potential must use an effective form of contraception as described above, from the beginning of screening to the last trial visit.
21. Known substance abuse or known (or previous) eating disorders, including anorexia nervosa, bulimia and severe gastrointestinal disease affecting normal eating (as judged by the investigator).
22. Any disease or condition that, in the judgement of the investigator, may make the subject unlikely to comply with the requirements of the trial or any condition that presents undue risk from the investigational product or procedures.
23. Participation in another interventional clinical trial involving an investigational compound within 26 weeks prior to screening or in parallel to this trial.
24. Currently using or have used within the last 3 days prior to screening: biotin >0.03 mg/day from supplements
25. Known history of positive results of tests for human immunodeficiency virus (HIV) antibodies or hepatitis B and/or C (exceptions if vaccinated towards Hepatitis B virus and Hepatitis C virus)

26. Any of the following: acute critical illness, and complications following open heart surgery, abdominal surgery, multiple accidental traumas, acute respiratory failure, or similar conditions within 180 days prior to screening.

    Note: For France, all categories of protected persons specified in the Public Health Code are excluded from participation.

8.2. PREMATURE SUBJECT WITHDRAWAL

Early withdrawal occurs when an enrolled subject ceases participation in the trial, regardless of the circumstances, prior to the expected completion of the trial (= completion of Week 38). Additionally, the investigator may discontinue the treatment of a subject at any time if considered to be in the subject's best interest, see Section 7.3.1 for detailed definition.

If in any case treatment should be discontinued, all subsequent visits and assessments should continue as planned. If the only option for the subject is to drop-out of the trial, the subject may also be offered to only attend the final Visit 7.

If the subject withdraws from the trial prematurely, a Completion Visit/Early Termination Visit should be performed to collect data, particularly AE follow-up data (if applicable), and to collect blood for laboratory evaluations. This visit should contain all assessments from Visit 7 (Week 38, see Schedule of Events, Section 18.2) and will be documented in the eCRF together with the reason(s) for trial withdrawal. Individual assessments may be waived if the subject refuses to participate, if they have been done recently and/or or are not deemed appropriate or required. Such instances shall be discussed with the Medical Monitor. For subjects who discontinue the study drug for reasons related to safety, unblinding of the treatment assignment for the subject may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the subject.

8.3. SUBJECT REPLACEMENT CRITERIA

Subjects who have been randomized but not dosed may be replaced.

9. TREATMENTS

9.1. INVESTIGATIONAL PRODUCT

9.1.1. Once-Weekly Lonapegsomatropin / Placebo

Lonapegsomatropin/placebo will be provided as a lyophilized powder in single-use glass vials requiring reconstitution with 1 mL sterile water for injection (sWFI) and administered by subcutaneous (SC) injection via syringe and needle.

Lonapegsomatropin will be supplied in 2 vial presentations that, after reconstitution, will result in 2 solutions with two concentrations:

1. 12.1 mg hGH/vial [redacted] mg hGH/mL after reconstitution)
2. 24.2 mg hGH/vial [redacted] mg hGH/mL after reconstitution).

The placebo for lonapegsomatropin drug product will contain the same excipients as lonapegsomatropin drug product but does not contain lonapegsomatropin itself.

The following materials for the study drug reconstitution and administration will be provided to the investigational sites and distributed by the investigator to the subject:

- Instructions for Use (IFU)
- sWFI
- Syringes for administration
- Needles for reconstitution and administration
- Additional material as required (eg, bags for transportation, alcohol swabs, etc.)

Lonapegsomatropin / placebo will be dispensed to subjects in sufficient amounts to provide the subject with enough study drug until the next dispensing visit. Details will be described in the Pharmacy Manual/IMP (Investigational Medicinal Product) Manual.

9.1.2. Once-Weekly Placebo (Reference Product)

The placebo for lonapegsomatropin drug product will contain the same excipients as lonapegsomatropin drug product but does not contain lonapegsomatropin itself. It will be provided as a lyophilized powder in single-use glass vials requiring reconstitution with 1 mL sWFI. Following reconstitution, the placebo solution will be administered by SC injection via syringe and needle.

9.1.3. Daily Somatropin (Reference Product)

[redacted] (somatropin) 5 mg/1.5 mL will be provided as a commercially approved solution for injection in a pre-filled pen for daily SC administration.

In some countries, [redacted] (somatropin) 6 mg cartridge kit for injection may be provided with a commercially approved pen device for the daily SC administration as back-up instead of [redacted] In some countries, [redacted] 6 mg [redacted] 5 mg/1.5 mL may be provided by prescription with reimbursement by the Sponsor. Details will be described in the Pharmacy Manual/IMP Manual.

9.2. LABELING

All study drugs will be labeled according to Good Manufacturing Practice (GMP) and local requirements. The labels are trial-specific and carry unique identification pack numbers. Subjects will be provided with dosing and storage instructions. The study drug labels will comply with regulatory requirements of each country and will be printed in the local language.

Additionally, a blinding shell will cover the placebo and lonapegsomatropin.

9.3. TREATMENT ADMINISTERED

Due to the different hGH dose requirements, depending on subject's age and receipt of concomitant oral estrogen, this trial will have three dosing groups per arm:

1. Subjects receiving concomitant oral estrogen (any age), or subjects <30 years old at start of screening.
2. Subjects ≥30 to ≤60 years old at start of screening who do not require oral estrogen.
3. Subjects >60 years old at start of screening who do not require oral estrogen.

The first dose of study drug is administered in a healthcare setting. Subjects will be initiated on a low dose, and the dose will slowly be increased to avoid adverse reactions as much as possible (Dose Titration Period) until the target maintenance dose is reached (Dose Maintenance Period).

The starting doses, titration doses, and target doses for each treatment arm are shown in Table 1, Table 2, Table 3 and Table 4. Dose adjustments are described in Section 9.6.

All treatments will be administered by the site staff, or subject into the left or right buttock, left or right thigh, or left or right abdomen.

To minimize local side effects, it is recommended to rotate the 6 injection sites in a subsequent manner (eg, right thigh, right abdomen, right buttock, left thigh, left abdomen, left buttock).

For specific dosing instructions for each treatment arm, please refer to the IMP Manual and / or IFU.

9.3.1. Once-Weekly Lonapegsomatropin/Placebo

Table 1 shows the dosing groups, the preferred concentration to be used and the volume to be administered to the weekly treatment arms (lonapegsomatropin/placebo). It is imperative that investigators follow the chart and administer the exact volume of the given concentration as indicated.

The reason for administering the exact volume as per Table 1 is to match the dosing increments of an administration device (GH Auto-Injector) to be used with lonapegsomatropin drug product presented in dual chamber cartridges (DCCs). The DCC presentation and device is currently in development. Currently at least ten DCC dose strengths are being developed [redacted] mg hGH for adult GHD), and while DCCs are not anticipated to be used in this trial, the dosing is designed to match a future use of the GH Auto-Injector.

Please refer to the Investigator's Brochure for details on the composition and characteristics of lonapegsomatropin.

Table 1: Dosing Table for Once-Weekly Treatment Arms (Lonapegsomatropin and Placebo)

Week		Dose Group 1 (oral estrogen intake [any age] or <30 years old)	Dose Group 2 (≥30 to ≤60 years old; no oral estrogen intake)	Dose Group 3 (>60 years old; no oral estrogen intake)
Weeks 1-4	[redacted]			
Weeks 5-8				
Weeks 9-12				
Weeks 13-38 (Dose Maintenance Period)				

9.3.2. Daily Somatropin Product

Table 2 shows the dosing groups, the preferred concentration to be used and the volume to be administered to the daily treatment arm.

Table 2: Dosing Table for Daily Somatropin Treatment Arm

Week		**Dose Group 1** (oral estrogen intake [any age] or <30 years old)	**Dose Group 2** (≥30 to ≤60 years old; no oral estrogen intake)	**Dose Group 3** (>60 years old; no oral estrogen intake)
Weeks 1-4	[redacted]			
Weeks 5-8				
Weeks 9-12				
Weeks 13-38 (Dose Maintenance Period)				

9.4. DISPENSING AND STORAGE

All study drugs must be kept in a locked area with access limited to designated trial staff and stored according to its labeling. The sWFI supplied for reconstitution of lonapegsomatropin and placebo should also be stored according to its labeling. All products will be temperature-monitored, as appropriate.

All study drugs and sWFI will be dispensed by trial staff to the subjects to be stored according to its labeling. Under the special circumstances, and if allowed by local regulations, the study drug/sWFI may be shipped to a subject as site-to-subject shipment using a trusted courier service.

Further details are provided in the IMP Manual and IFU.

9.5. SELECTION OF TRIAL DOSES

Fixed, non-weight-based dosing will be used for the trial, hence not titration to a certain IGF-1 response. The starting doses, titration doses, and target doses for each treatment arm are shown in Table 1, Table 2, Table 3, and Table 4. Dose adjustments are described in Section 9.6.

The relationship between ACP-001 dose and IGF-1 generation in adults with GHD has been preliminarily characterized in a 4-week Phase 2 trial (ACP-001 CT-002). Dosed at the same weekly hGH dose (weight-based dosing; mg hGH/kg/week), ACP-001 produced a comparable IGF-1 exposure when compared with a daily somatropin product (Omnitrope, trademark owned by Sandoz). Therefore, to allow for maximal comparability between the clinical effects of lonapegsomatropin and the daily somatropin product, this trial will use the same fixed dose schedule for lonapegsomatropin and the daily somatropin product in terms of mg hGH/week.

Doses for this trial were selected based on clinical practice guidelines and published literature. Starting doses of 0.2-0.3 mg hGH/day are generally recommended for younger subjects, whereas lower doses (0.1-0.2 mg hGH/day) are recommended for older subjects (Ho 2007, Molitch 2011, Fleseriu 2016, Yuen 2019). Additionally, there is evidence showing that the GH requirements for subjects on concomitant oral estrogen and/or for those aged <30 years old may be higher (Cook 1999, Underwood 2003); these subjects have been grouped together in the interest of a simplified dosing table that can be implemented in a global registration trial.

Titration at 4-week intervals ensures stabilization of IGF-1 levels prior to each dose increase. A 12-week Titration Period was selected to allow a sufficiently gradual increase in dose. Dose levels were selected to align with the Sponsor's plans to use the GH Auto-Injector with fixed-dose DCCs at the time of lonapegsomatropin commercialization. Target maintenance doses were selected to ensure subjects would receive adequate dosing for efficacy based on age and concomitant oral estrogen intake, with the knowledge that dose reductions or a delay in dose escalation would be permitted in case of persistent AEs or other safety parameters attributable to GH effects, or in the event of elevated IGF-1 levels.

9.6. DOSE ADJUSTMENTS

9.6.1. Dose Adjustment Parameters

Any time during the trial, the study drug dose may be adjusted based on:

- Study drug tolerability (ie treatment related AEs) as assessed by the investigator, or
- IGF-1 SDS (average value over the course of a week for lonapegsomatropin) as measured by Central Lab – For all three treatment arms, IGF-1 results will be blinded to investigators/sites and blinded team members. There will be an unblinded team member to assess the IGF-1 results and report to the sites whether a dose titration is warranted. IGF-1 SDS >2.0 has been selected as a threshold to identify values that have exceeded the normal range of -2.0 to +2.0 SDS. For lonapegsomatropin, average IGF-1 level over the course of the week will be used to determine if dose adjustment is required. If the sample was drawn at a time corresponding to average IGF-1 level (96-120 h post-dose +/- 3 h; V2, V3, V4), the central laboratory value will be used for potential dose adjustment assessment. If the blood sample was drawn at a time corresponding to non-average IGF-1 level (at V5, V6 and potential Unscheduled Visits), a table based on a modeled PD curve will support the unblinded team member's decision making. For subjects in the arm with daily somatropin administration, central laboratory IGF-1 values will be used to determine if dose adjustment is required.

To maintain trial blind, for dose adjustments due to IGF-1 that are required for the lonapegsomatropin arm, a sham titration will be initiated for a subject in the placebo arm in a pattern that follows the dose modifications of the lonapegsomatropin arm.

Dose levels for dose titration in the trial are outlined in Table 3 for lonapegsomatropin and placebo treatment arms and in Table 4 for placebo treatment arm.

Table 3: Dose Levels for Dose Titration for Once-Weekly Treatment Arms (Lonapegsomatropin and Placebo)

[redacted]

Table 4: Dose Levels for Dose Titration for Daily Somatropin Treatment Arm

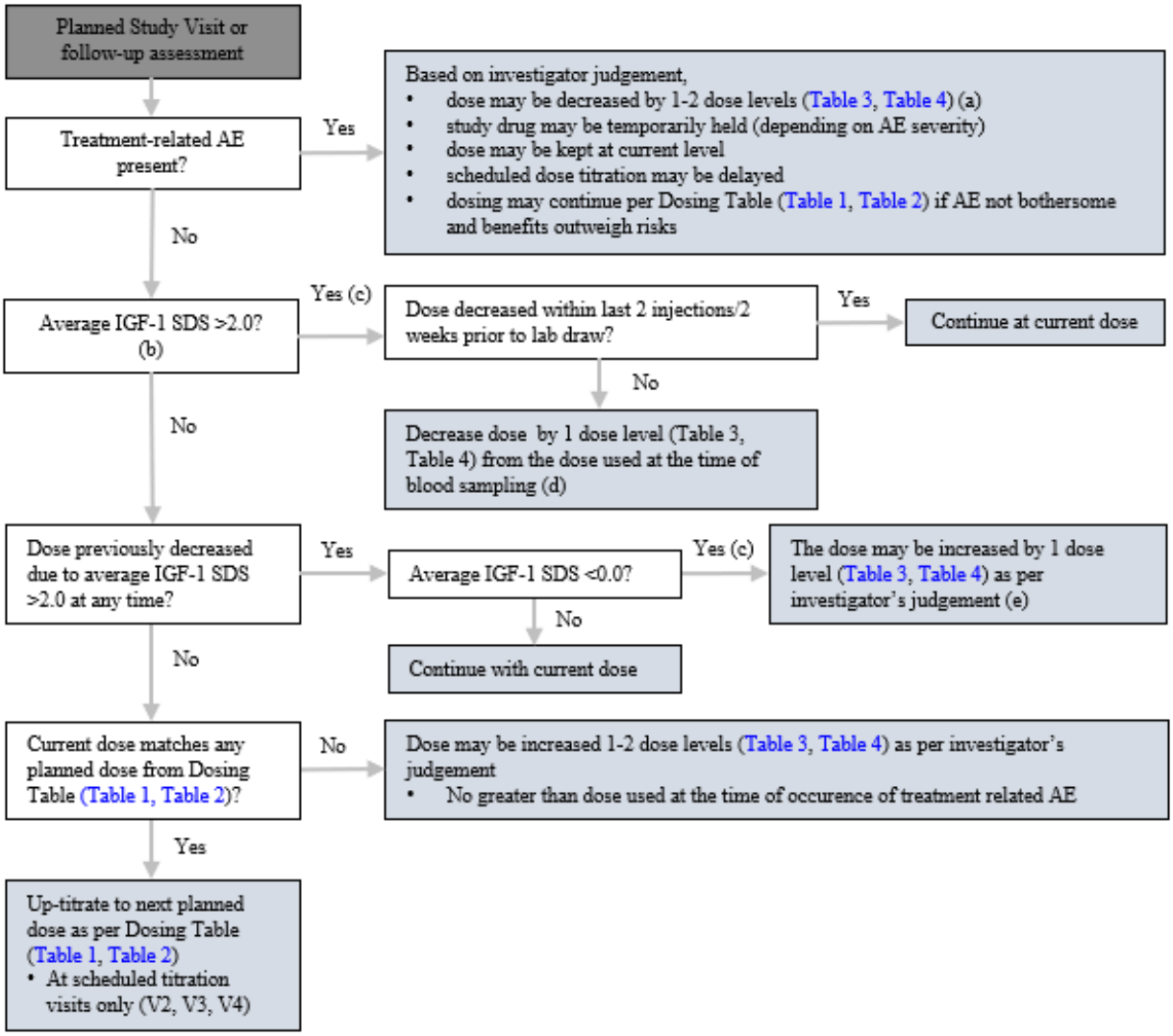
[redacted]

For each dosing group, the dose may not exceed the dose shown for Weeks 13-38 in Table 1 and Table 2 at any time during the trial. In addition, during the Dose Maintenance Period, the dose may not exceed the dose assigned at V4, which may differ from dosing tables (Table 1, Table 2) taking into consideration potential dose reductions during Titration Period due to tolerability or IGF-1 levels.

For all dose adjustments in all treatment arms, the site staff may inform the subject via phone or other communication methods about the new dose. The subject is not required to attend an additional in-person visit unless additional training on study drug administration is needed as determined by site staff or requested by the subject.

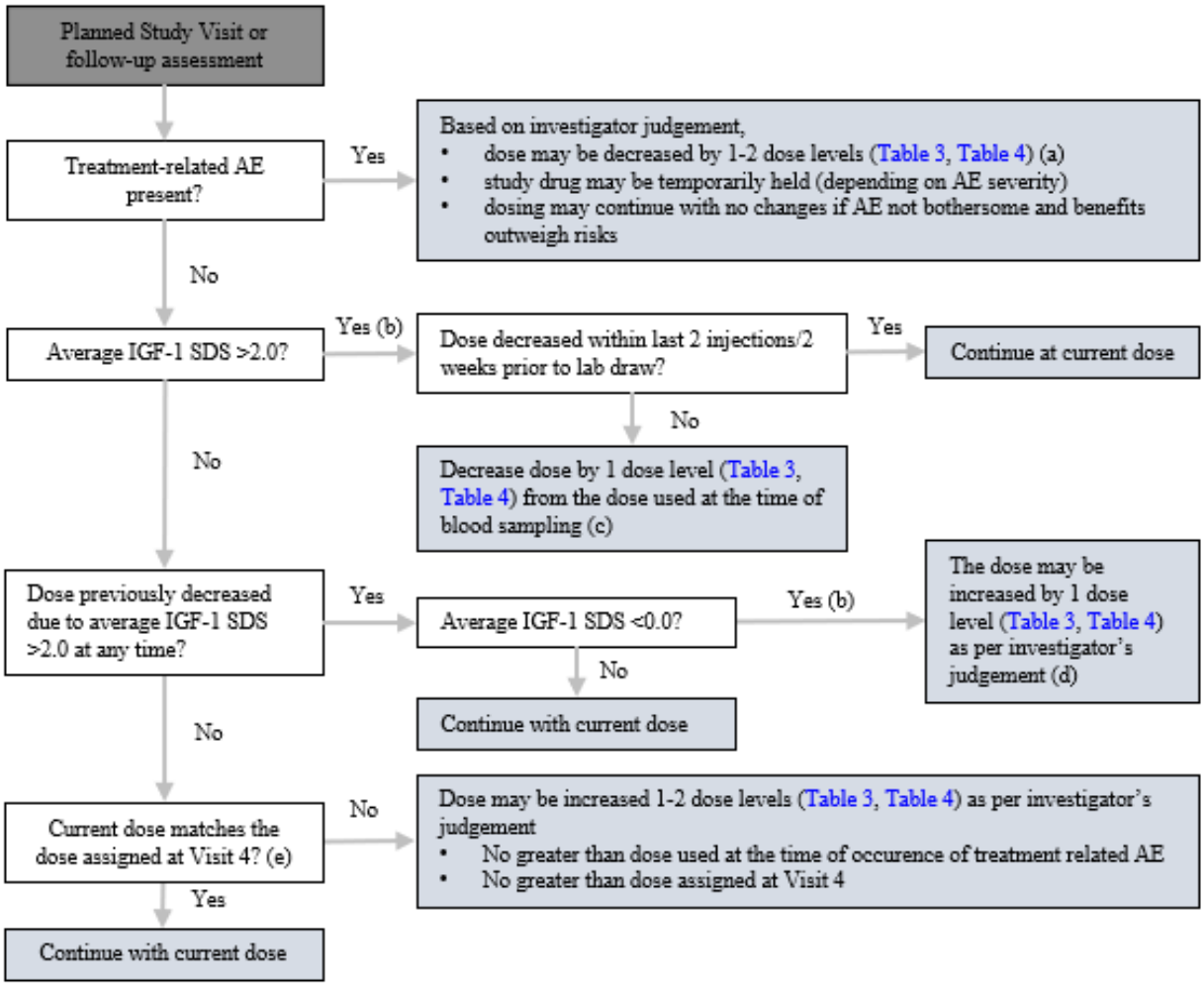
The trial will use dosing algorithms to ensure uniform trial design and consistent dose adjustments across (Figure 3 and Figure 4).

Figure 3: Dosing Algorithm – Titration Period



(a) For subjects on the lowest dose level ([redacted] mg hGH/week or [redacted] mg hGH/day), instead of dose decrease, the study drug may be temporarily held or discontinued based on investigator's judgement.
(b) Considering timelines for analysis and reporting of IGF-1 levels, protocol defined up-titrations will occur at Week 5, Week 9 and Week 13 based on safety and tolerability as judged by the investigator. Once the IGF-1 result is available, it will be assessed for whether a dose decrease is warranted (ie, if average IGF-1 > 2.0 SDS) and the site will be informed accordingly. This will be done in a blinded manner as described in Section 7.1.2.1.
(c) Investigator will be informed by the unblinded team member in case of average IGF-1 SDS > 2.0, or in case of average IGF-1 SDS < 0.0 for subjects who previously had a dose decrease due to average IGF-1 SDS > 2.0. This will be done in a blinded manner as described in Section 7.1.2.1.
(d) For subjects on the lowest dose level ([redacted] mg hGH/week or [redacted] mg hGH/day), study drug should be discontinued.
(e) Only 1 re-challenge is allowed for subjects who previously had a dose decrease due to average IGF-1 SDS > 2.0. In case average IGF-1 SDS would rise again > 2.0 after the re-challenge, the dose will be decreased for 1 dose level (Table 3, Table 4) and will not be further increased.

Figure 4: Dosing Algorithm – Maintenance Period



(a) For subjects on the lowest dose level ([redacted] mg hGH/week or [redacted] mg hGH/day), instead of dose decrease, the study drug may be temporarily held or discontinued based on investigator's judgement.
(b) Investigator will be informed by the unblinded team member in case of average IGF-1 SDS > 2.0, or in case of average IGF-1 SDS < 0.0 for subjects who previously had a dose decrease due to average IGF-1 SDS > 2.0. This will be done in a blinded manner as described in Section 7.1.2.1.
(c) For subjects on the lowest dose level ([redacted] mg hGH/week or [redacted] mg hGH/day), study drug should be discontinued.
(d) Only 1 re-challenge is allowed for subjects who previously had a dose decrease due to average IGF-1 SDS > 2.0. In case average IGF-1 SDS would rise again > 2.0 after the re-challenge, the dose will be decreased for 1 dose level (Table 3, Table 4) and will not be further increased.
(e) The dose assigned at V4 may differ from dosing tables (Table 1, Table 2), taking into consideration potential dose decreases during Titration Period due to tolerability or IGF-1.

In case of occurrence of treatment related AE, study drug dosing may continue as planned and as per Dosing Table (Table 1, Table 2) if AE is not bothersome and benefits outweigh risks as determined by the investigator. However, based on investigator's judgement the study drug dose may be:

- Reduced by 1-2 dose levels as per Table 3 or Table 4 (depending on subject's treatment arm assignment, weekly lonapegsomatropin/placebo vs. daily somatropin product)
- Temporarily interrupted, or
- Study drug dose may be kept at current level with delayed scheduled up-titration (Dose Titration Period only)

For subjects on the lowest dose level ([redacted] mg hGH/week or [redacted] mg hGH/day), instead of dose decrease the study drug may be temporarily held or discontinued based on investigator's judgement.

Once treatment related AE is resolved or not bothersome with favorable risk-benefit ratio as judged by the investigator, the study drug dose may be increased by 1-2 dose levels (Table 3, Table 4), but not greater than dose used at the time of occurrence of treatment related AE.

In case of weekly average IGF-1 SDS > 2.0, investigator will be informed accordingly by unblinded team member and the study drug dose will be reduced by 1 dose level from the dose used at the time of blood sampling (Table 3, Table 4), unless the dose was already reduced for any reason within 2 injections/2 weeks prior to corresponding lab draw. In such case, the study drug dose will not be reduced, and subsequent IGF-1 levels will be used for assessment of potential dose adjustment.

Subject who previously had a dose decrease due to weekly average IGF-1 SDS > 2.0 may be re-challenged (ie dose increased by 1 dose level) only once, in case of weekly average IGF-1 SDS < 0.0. In case average IGF-1 SDS would rise again >2.0 after the re-challenge, the dose will be decreased for 1 dose level (Table 3, Table 4) and will not be further increased.

The study drug dose at which weekly average IGF-1 SDS > 2.0 occurred will not be exceeded any time during the study, eg, if such case happens during Dose Titration Period further scheduled up-titrations will not be performed.

9.6.2. Dose Reductions and Possible Stopping

The investigator may stop or reduce the dose of study drug for an individual subject as per the dosing algorithms showed in Figure 3 and Figure 4, as well as at any time during the trial for the following reasons:

- HbA1c levels:
  - Subjects without diabetes diagnosis at trial start: In case the HbA1c level is >6.5 % and / or has an absolute increase of 0.8% from the prior visit HbA1c: Confirmation of HbA1c level is required. Once confirmed, the study drug dose (lonapegsomatropin/placebo or daily somatropin product) may be decreased to the next lower dose level (see Table 3 and Table 4) or a diet / nutritional counseling and / or diabetes medication may be added per investigator judgement. If appropriate follow-up monitoring shows progressively worsening glucose intolerance, additional lonapegsomatropin dose adjustments may be appropriate
  - Subjects with diabetes diagnosis at trial start: additional diabetes medication may be added as considered appropriate by the investigator
- Severe hGH-related AEs

Please notify the Medical Monitor as soon as possible in the presence of the following symptoms and laboratory abnormalities:

- Severe hGH-related AEs at any time during the trial
- Evidence of hypersensitivity to the study drug

For subjects who discontinue the study drug for reasons related to safety, unblinding of the treatment assignment for the subject may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the subject.

Refer to Section 7.3 for termination rules.

9.6.3. Required Stopping

The investigator **must** stop the study drug for an individual subject at any time during the trial in the presence of the following:

- Evidence of severe hypersensitivity to the study drug
- Confirmed neutralizing anti-hGH antibodies
- Evidence of tumor growth or new onset malignancy
- Evidence of progression or new onset retinopathy
- Pregnancy

9.7. DRUG ACCOUNTABILITY

Trial sites will be supplied with the study drug and ancillary supplies to distribute as required to subjects. In some countries, [redacted] 5 mg/1.5 mL comparator may be provided by prescription, with reimbursement by the Sponsor.

Investigator will be responsible for the study drug, ancillary supplies, and associated procedures, exercising accepted medical and pharmaceutical practices.

The study drug must be kept in a locked, temperature-controlled, and temperature-monitored area with access limited to designated trial staff and stored according to its labeling. Investigator or dedicated trial staff must evaluate the storage temperature and inform Ascendis Pharma immediately if the study drug has been stored outside the specified conditions on the label.

The trial will use an internet-based IRT as source to capture drug inventory and accountability data, including receipt of the study drug and supplies by the site, treatment assignment for each subject, distribution to subjects, return to the site from subjects, and return to the Sponsor (or destruction with the Sponsor's approval).

The IRT complies with all applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP]. Paper logs may be used as back-up solution in case there are access issues or other issues with the IRT.

The investigator or delegated site staff will be responsible for accountability and reconciliation of the study drug.

The site staff will provide the training on a proper storage and the study drug administration to each subject at Visit 1. This training will include a review of the IFU and on-site administration of the first dose of the study drug . A copy of the IFU will be provided to the subjects to take home.

NOTE: Under no circumstances will the investigator allow study drugs to be used other than as directed by this protocol.

See IMP Manual and IFU for further details.

9.8. TREATMENT COMPLIANCE

Treatment compliance will be assessed based on drug accountability and review of the Subject Diary. If a subject did not enter all doses in the diary, the investigator will include dose information in source data based on verbal information from the subject. These doses will be transcribed to the CRF. The investigator will reinforce the importance of updating the diary after each dose. Subjects will be instructed to return all used study drug at all trial visits after Visit 1. The completed Subject Diary should be reviewed at each site visit. All study drugs, used and unused, shall be returned if they are expired, or at the end of the subject's participation in the trial or at the visit following study drug discontinuation.

9.9. PRIOR AND CONCOMITANT THERAPIES

9.9.1. Prior Therapy

Prior therapy will be captured and recorded at least for the 12 months prior to providing informed consent. Any change in prior therapy must be recorded in the eCRF.

9.9.2. Permitted and Prohibited Therapies

Concomitant therapy is considered any medication other than the investigational products or comparators that is administered from the first dose of the study drug administration up until the

end of the trial. Any change in concomitant medication must be recorded in the eCRF, noting the type of medication, the dose, start, stop (if applicable), and indication. The use of prohibited medication does not necessarily lead to trial discontinuation, all efforts will be made to continue collecting follow-up data for that subject Section 7.3.1and Section 8.2.

9.9.2.1. Permitted Therapies

Therapies not listed as prohibited therapies are allowed when taking the precautions in this section into consideration.

Somatropin administration may increase the clearance of compounds known to be metabolized by cytochrome P450 isoenzymes.

Therefore, the clearance of compounds such as sex steroids, corticosteroids, anticonvulsants, and cyclosporine may be especially increased resulting in lower plasma levels of these compounds.

- Replacement therapy for other non-GH pituitary deficiencies. As hGH may enhance the transformation of hydrocortisone to cortisone, the investigator may increase the dose of hydrocortisone replacement therapy if needed (eg, for anticipated stress). As hGH may increase extrathyroidal conversion of T4 to T3, the investigator may increase the dose of thyroid replacement therapy if needed
- Stable doses of inhaled, intra-articular, or topical corticosteroids
- Estrogen (with maintenance of the same dose and route of estrogen administration throughout the trial in case of oral estrogen therapy. In case of non-oral estrogen therapy, the dose may be adjusted as required, but the route of administration must be maintained throughout the trial)
- Contraceptive methods (with maintenance of the same dose and route of estrogen-containing contraceptives throughout the trial)
- Testosterone
- Metformin and DPP-4 inhibitors. Any diabetes treatment other than nutritional counseling, metformin and DPP-4 inhibitors are prohibited at trial entry and discouraged throughout the trial. Dose-optimization of metformin and/or DPP-4 should be the first attempt in case of increasing glucose and/or HbA1c levels during the trial. In case optimized doses of metformin and/or DPP-4 are no longer expected to provide adequate glycemic control, the investigator is strongly encouraged to contact the Medical Monitor to discuss additional treatment options before adding additional medication which could influence the primary endpoint

9.9.2.2. Prohibited Therapies and Procedures

- Weight-reducing program, diets (unless indicated for diabetes treatment), drugs or appetite suppressants, including orlistat, zonisamide, lorcaserin, bupropion, topiramate, sibutramine, stimulants (eg, phentermine or ADHD medications such as methylphenidate or amphetamines), and GLP-1 receptor agonists (eg, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide) unless indicated for diabetes treatment (see Section 9.9.2.1)
- hGH therapies other than lonapegsomatropin and the daily somatropin product

- GH secretagogues (permitted if used in connection with stimulation tests for diagnosis of GHD [eg, macimorelin])
- Anabolic steroids other than the therapies described in Section 9.9.2.1
- Bariatric surgery
- Biotin > 0.03 mg/day from supplements. Higher doses of biotin may result in interference with commonly used biotinylated immunoassays and leading to false results
- Cabergoline above 0.5 mg weekly or bromocriptine above 20 mg weekly due to their effects on lowering IGF-1 and GH hormonal concentrations and their independent effects on weight (Abs, 1998; Korner, 2003; Thorner, 1975)

10. TRIAL PROCEDURES

Prior to any protocol-related activities or evaluations, informed consent will be obtained from each potential subject in accordance with ICH GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate Institutional Review Board/Human Research Ethics Committee/Independent Ethics Committee (IRB/HREC/IEC) prior to implementation. Release of medical information authorization should also be obtained at the time of informed consent.

10.1. TRIAL DURATION

The total duration of the trial for an individual subject is up to approximately 48 weeks up to 6 weeks of screening + 12 weeks dose titration + 26 weeks stable treatment + 4 weeks of follow-up treatment free period. Up to approx. 1 week is included in the pre-treatment period to allow for logistics and shipments). The treatment free follow-up period is not applicable for subjects continuing into the extension trial.

The subjects should be informed about the extension trial as early as possible. For subjects wishing to continue into extension, consent should be obtained at or prior to Visit 7.

10.2. TRIAL PERIODS AND VISITS

- Screening Period - up to approx. 6weeks to establish eligibility (approx. up to 1 week is included between randomization and the first dose to allow for logistics and shipments)
- Treatment Period – (38 weeks in total), consisting of:
  - Dose Titration Period - 12 weeks of dose titration, scheduled dose titration visits will occur at Week 4, Week 8, and Week 12
  - Dose Maintenance Period - 26 weeks of maintenance treatment, trial visits will occur at Week 17, Week 28, and Week 38
- Follow-up Period – (4 weeks in total), treatment free period, AEs/SAEs will be collected via phone 2 weeks after Week 38 (Week 40), an ADA sample will be taken 4 weeks after Week 38 (Week 42). Follow-up Period is not applicable for subjects participating in the extension trial.

All visits should be performed in the morning as the subject is asked to be fasted (except for Visit 3). Attempts should be made to adhere to the planned visit schedule. It is suggested that the site staff provide dosing, diary, and visit reminders (eg, phone calls) to subjects between visits. The investigator will ensure to follow the local regulations regarding diagnosis and monitoring of SARS-COV-2 infection when the subjects access the hospital facilities for a study visit. In case of a positive result whether symptomatic or asymptomatic, the investigator will ensure the needed medical care and will report as an AE in accordance with Section 12. The Sponsor will monitor the process is complied with. For subjects who are vaccinated, the vaccine details must be recorded as concomitant medication in accordance with Section 9.9.2.

The diagnostic test used will be a licensed test in the respective country (in France it will be on the list published by the Ministry of Solidarity and Health (https://covid-19.sante.gouv.fr/tests)).

The SARS-COV-2 test used should be documented together with the result in the medical records.

An overview of all visits is provided in the Scheduled of Events (Section 18.2).

For detailed descriptions of assessments refer to Section 11.

10.2.1. Screening Period

The screening period will be used to collect clinical data to establish the subject's eligibility for the trial. Within the screening period, still missing assessments for inclusion / exclusion may be conducted. The following assessments will be performed, and appropriate data collected:

- Demography, including sex, age, childbearing potential, oral estrogen intake, ethnicity, and race
- Medical history, including a description of pituitary deficiencies
- Currently and previously taken relevant medications (for the 12 months prior to screening)
- Vital signs measurements
- Height and weight
- Physical examination
- Blood collection for the following laboratory assessments (fasting required; central analysis):
  - Routine chemistry and hematology (see Section 11.9)
  - Hormone status: TSH, fT4, fT3, and morning cortisol
  - Glycemic status: HbA1c, fasting insulin and fasting plasma glucose. In case of suspected glucose intolerance, a 2-hour oral glucose tolerance test should be performed
  - Fasting lipid panel
  - Females: Serum human chorionic gonadotropin (hCG)
  - Males: morning (6:00-10:00AM) serum total testosterone
  - IGF-1 and IGFBP-3

  - ADA:
    - The ADA analyses may only be conducted after enrollment and are not required for eligibility verification. These data will be used to support evaluation of post-dose antibody detection
    - Blood samples for immunogenicity assessment will be retained for up to 5 years following trial finalization for possible further characterization if requested by the authorities of a potential anti-drug antibody responses
- 12-lead ECG, local reading
- Fundoscopy
- DXA scan (central reading)
- MRI / CT scan: A pituitary MRI scan is required at screening if an MRI scan from within 6 months prior to screening is not available. A CT scan can be used if MRI scan is contraindicated.

Screening shall be stopped at any point in case any of the eligibility criteria not being met, such cases will be classified as screening failures.

All results will be reviewed by the Medical Monitor to verify eligibility of each subject prior to randomization. Eligible subjects will be centrally randomized to 1 of 3 arms. Following randomization, it is recommended to start the Dose Titration Period (Visit 1) within 2 weeks from the time of randomization.

Re-screening is permitted, and subjects will receive a new screening number. If the subject is re-screened, the ICF must be re-signed and obtained prior to initiating any new trial procedures. The Sponsor should be informed in case a subject is considered for re-screening.

10.2.2. Treatment Period

Randomized subjects will receive the study drug as assigned according to randomization and dosing group (Section 9). The trial procedures are indicated in the Schedule of Events (Section 18.2), Table 5, and detailed description in Section 11.

Visit 3 may be conducted via phone call per investigator's discretion, the following procedures are conducted at each visit (Visit 1 – Visit 7) if not otherwise indicated.

Table 5: Treatment Period Procedures

Assessment	Details and Comments
Concomitant medications and AEs	Visit 1 through Visit 7. If phone call (Visit 3): discussion only.
Subject Diary review	Visit 2 through Visit 7. If phone call (Visit 3): discussion only.
Weight	Visit 1 through Visit 7. Not required if Visit 3 is conducted via phone.
Physical examination and vital signs	Visit 1 through Visit 7. Not required if Visit 3 is conducted via phone.
12-lead ECG	Visit 1 and Visit 7 – all treatment arms; local reading. Weekly treatment arms will have an additional ECG assessment at 1-3 days post-dose at Visit 6, local reading.
Fundoscopy	Visit 7
Safety laboratory assessments	Visit 1 through Visit 7. Not required if Visit 3 is conducted via phone. Fasting status is required. Routine chemistry and hematology, hormone status, glycemic status, lipid panel (see Section 11.9).
Blood sampling for IGF-1 and IGFBP-3 assessments	Visit 1 trough Visit 7. Not required if Visit 3 is conducted via phone. Data will be reviewed, and dose titration guidance provided by unblinded team member, results will not routinely be distributed to the site staff.
Pregnancy test for females of childbearing potential	Visit 1 through Visit 7 and approximately at least 30 days after last study drug dose for subjects not participating in the extension trial. Not required if Visit 3 is conducted via phone. Blood test at central laboratory. Additionally, urine dipstick test at Visit 1 prior to the first dose and at any time during the trial if a menstrual period is missed. Pregnancy testing will not be required for women who have undergone a hysterectomy or bilateral tubal ligation, or for women above the age of 50 who have been without a menstrual period for at least 12 months.
Blood sampling for PK assessment	PK will be sampled on Visit 1 through Visit 7 in weekly treatment arms (lonapegsomatropin and placebo). PK will be sampled on Visits 1, 5 and 7 in daily somatropin treatment arm . PK analytes: hGH, lonapegsomatropin and mPEG will be analyzed at Visit 1 through Visit 7 in weekly lonapegsomatropin arm. PK analytes will not be analyzed in weekly placebo arm. PK analytes: hGH only, will be analyzed in daily somatropin arm. Data will not be distributed to the site staff.

Table 5: Treatment Period Procedures (Continued)

Assessment	Details and Comments
Samples for antibody assessment	At Visits 1, 2, 4, 6 and 7. Blood samples for immunogenicity assessment will be banked and may be used for additional characterization of ADA responses. Data will be reviewed by unblinded team member and results not routinely distributed to the site staff.
DXA scan	At Visits 1, 4 and 7; central reading. DXA scan at Visit 1 is not applicable for Germany. DXA assessments should be performed in a similar setting (+/- 2 hours compared to Visit 1 time, and similar hydration status) at each visit, using the same approved DXA machine throughout the trial. Body composition to be assessed at all DXA scans. Total body bone mineral content and bone mineral density to be assessed only at Visit 1. DXA assessment windows: Up to 1 week prior to Visit 1, pre-dose. Up to 1 week before or after Visit 4 (Weeks 11, 12, 13). Up to 1 week after Visit 7 (Week 38 or Week 39).
[redacted]	
Study drug administration training	Visit 1 and as needed. Includes the training on the IFU (also provided to the subject for reference throughout the trial). Includes instructions that administration of study drug should occur at approximately the same time of day (for daily arm) and on the same day of the week (for weekly treatment arms) throughout the trial. Details regarding adjustment of a subject's dose day or dosing time are provided in the IMP Manual. Includes study drug administration by the site staff at Visit 1 (weekly treatment arms), and as needed.
Dose titration	Visits 2, 3 and 4. Subjects may also be instructed about new dose via phone. Unscheduled dose titrations may be communicated via phone.
Injection site reaction assessment	Visit 1 through Visit 7. At Visit 1, the investigator shall review the injection site at least 15minutes post-dose; at other visits all prior injection sites shall be examined. For documentation and reporting see Section 11.13.

10.2.2.1. Visit Schedule of Weekly Treatment Arms (Lonapegsomatropin/Placebo)

1. Visit 1 will be performed on the day of the 1st dose (Week 1, Day 1) and all assessments will be done pre-dose, except for the injection site reaction assessment. The first dose will be given on site.
2. Visit 2 (Week 4) and Visit 3 (Week 8) will be conducted approx. 4 - 5 days post-dose (96-120 h post-dose +/- 3 hours) to be able to assess the average IGF-1 level (IGF-1 SDS) to support dose titration.
3. Visit 4 (Week 12) will be conducted approx. 4 - 5 days post-dose (96-120 h post-dose +/- 3 hours) to be able to assess the average IGF-1 level (IGF-1 SDS) to support dose titration. Subjects will be assigned their fixed dose for the next 26 weeks.
4. Visit 5 (Week 17, +/- 1 week) will be conducted on the day of the 17th dose (+/- 1 dose) to have a steady-state trough value and the upcoming dose given on site (144 – 168 h after the prior dose +/- 3 hours). All assessments (except for injection site reaction assessment) are suggested to be done pre-dose.
5. Visit 6 (Week 28, +/- 1 week) will be conducted 1-3 days post-dose (24-72 h post-dose +/- 3 hours) to have a maintenance phase sampling at approximate peak hGH and peak IGF-1 (IGF-1 SDS).
6. Visit 7 (Week 38, + 1 week, end of trial) will be conducted approx. 4 - 5 days post-dose (96-120 h post-dose +/- 3 hours) to be able to assess the average IGF-1 level (IGF-1 SDS) at the end of the trial. For subjects not participating in the extension trial: A phone call will be conducted up to 2 weeks after this visit to assess if ongoing AEs are closed. An ADA and a pregnancy test for females of childbearing potential sample will be collected approximately at least 30 days after the last study drug dose.

10.2.2.2. Visit Schedule of Daily Somatropin Treatment Arm

1. Visit 1 will be performed on the day of the 1st dose (Week 1, Day 1) and all assessments will be done pre-dose, except for the injection site reaction assessment. The first dose will be given on site.
2. Visit 2 (Week 4) and Visit 3 (Week 8) will be conducted at any day of the week.
3. Visit 4 (Week 12) will be conducted at any day of the week. Subjects will be assigned their fixed dose for the next 26 weeks. This dose may be given on site or at the subject's home.
4. Visit 5 (Week 17, +/- 1 week) and Visit 6 (Week 28, +/- 1 week) will be conducted at any day of the week.
5. Visit 7 (Week 38, + 1 week, end of trial) will be conducted the day after the 26th week (or 27th week) of fixed dosing is completed. For subjects not participating in the extension trial: A phone call will be conducted up to 2 weeks after this visit to assess if ongoing AEs are closed. An ADA and a pregnancy test for females of childbearing potential sample will be collected approximately at least 30 days after the last study drug dose.

10.2.3. Unscheduled Visits

Unscheduled visits are those visits that occur between regularly scheduled visits and are performed to assess a previously or currently noted AE, abnormal laboratory value(s), and/or clinical findings. In such cases, the subject will be contacted to arrange an unscheduled visit. Only focused assessments (guided by the reason for the visit) will occur at these visits. Unscheduled dose titrations may be communicated via phone and do not necessarily require an on-site visit.

10.2.4. Early Termination Visits

Early termination is when a subject's trial participation discontinues prior to completion of the trial. If trial participation is discontinued prematurely, an Early Termination Visit (procedures indicated for Visit 7 in the Schedule of Events table, as applicable) will be performed. The site staff should aim to collect AE / SAE and outcome data up to two weeks after the last study drug dose and an ADA sample approximately 30 days after the last study drug dose, either during the Early Termination Visit or a follow-up phone call (AE / SAE collection only).

For subjects who discontinue the study drug for reasons related to safety, unblinding of the treatment assignment for the subject may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the subject.

10.2.5. Follow-up

Follow-up Period is treatment free period when trial subjects will not be receiving any hGH treatment which is applicable only for the subjects who will not continue into the extension trial. Two weeks after Visit 7 (Week 40), the site will have a follow-up phone call with the subject to review AEs / SAEs (See Section 12.3.2). An ADA and for females of childbearing potential a pregnancy test sample will be collected approximately at least 30 days after the last study drug dose (Week 42).

10.2.6. Home Visits / Virtual Visits

With Sponsor agreement, home visits and / or virtual visits may be conducted in place of in-person on-site visits for visits which do not require assessments to be performed on site. Home visits and / or virtual visits may also be permitted after Sponsor's approval in case of restrictions for subjects and / or physicians to access or enter the sites. Examples include, but are not limited to, shut-downs by the government, viral outbreak, natural disaster and / or significant safety risk.

11. ASSESSMENTS

11.1. SUBJECT DIARY

The Subject Diary will be provided / explained to the subject at the clinic visits and should be completed on the day of the study drug administration (weekly for lonapegsomatropin/placebo and daily for the daily somatropin arm. The data captured within the Subject Diary include:

- Date and time of the study drug administration
- Dose of the study drug
- Location of injection site

The subject will also have a chance to record an assessment of the injection site and changes to medications or subject's health.

The Subject Diary should be reviewed by trial staff at every trial visit as part of concomitant medication review, AE reporting and the study drug compliance confirmation.

11.2. WEIGHT MEASUREMENT

Weight should be measured at each on-site visit at approximately the same time of day using the same calibrated weight scale throughout the trial as possible (to minimize bias and reduce variability). Subjects should be wearing light clothing and no shoes for weight measurement at all visits.

11.3. HEIGHT MEASUREMENT

Height should be measured at screening on a stadiometer. Subjects should be wearing light clothing and no shoes.

11.4. PHYSICAL EXAMINATION

A physical examination of the following body systems should be performed:

- General appearance
- Integumentary (including injection site reaction assessment, see Section 11.13)
- Head, ears, eyes, nose, throat
- Neck / thyroid
- Lymphatic
- Cardiovascular
- Respiratory
- Abdomen
- Genitourinary
- Nervous system
- Musculoskeletal
- Extremities

11.5. VITAL SIGN MEASUREMENTS

Subject should rest for at least 5 minutes before assessment. The following vital signs should be measured:

- Heart Rate
- Blood Pressure
- Respiratory Rate
- Body Temperature

11.6. MRI / CT SCAN

An MRI scan is required at screening if a pituitary MRI scan from within 6 months prior to screening is not available. A CT scan can be used if MRI scan is contraindicated. An MRI scan is required at the end of trial for childhood cancer survivors.

11.7. 12-LEAD ECG

Local ECG readings and assessments will be conducted at screening, Visit 1, and Visit 7. For weekly treatment arms (lonapegsomatropin and placebo), an additional local ECG will be done at Visit 6.

11.8. FUNDOSCOPY

Fundoscopy is required for all subjects at screening and at Visit 7.

For subjects with a diagnosis of diabetes mellitus at screening, fundus photography is required at screening and Visit 7.

11.9. LABORATORY ASSESSMENTS

Blood will be collected at each on-site visit for assessments as listed in the Schedule of Events (Section 18.2). As described in Section 10.2, fasting is required. If not otherwise indicated, the routine chemistry and hematology assessments will include:

- Chemistry: sodium, potassium, calcium, chloride, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, total proteins, creatinine (also eGFR rate calculation per MDRD equation), urea-nitrogen, uric acid, ferritin and transferrin
- Hematology: hemoglobin, erythrocyte count, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocytes, differential blood count of leukocytes, platelet count
- Glucose metabolism: fasting insulin, fasting glucose, HbA1c
- Lipid metabolism (fasting): total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), Lp(a) lipoprotein, free fatty acids, very low-density lipoprotein (VLDL)

- Thyroid and adrenal status: TSH, fT4, and fT3 and morning (06:00-10:00AM) serum cortisol. Subjects who are not on glucocorticoid replacement therapy and are diagnosed with low morning cortisol may undergo an ACTH stimulation test including timepoint zero / baseline sample at any time during the trial
- Testosterone (males only): at Visits 1, 4, 6 and 7

The total blood volume collected in any 90-day-period during the trial will be up to approximately 100 mL. The total blood volume over 48 weeks of trial duration will not exceed 300 mL.

Blood samples will be analyzed at central and specialized laboratories in Germany, Sweden, and the US. The samples will be destroyed when analyses are final, except for samples collected for antibody measurements which may be stored up to five years after study end in order to allow additional antibody testing and characterization upon request from health authorities. This storage will be in Sweden and/or the US.

Detailed blood sampling, processing and assaying of samples will be provided in the Laboratory Manual.

11.9.1. Pregnancy Test

Testing for hCG should be performed at every on-site visit for female subjects of childbearing potential. A blood test will be run with every safety laboratory analysis run. Additionally, subjects will complete a urine dipstick test prior receiving the first dose of the study drug and at any time during the trial if a menstrual period is missed.

Pregnancy testing will not be required for women who are surgically sterile (for example have undergone a hysterectomy or bilateral tubal ligation), or for women above the age of 50 who have been without a menstrual period for at least 12 months.

Subjects who are sexually active must use an effective form of contraception.

See Section 9.6.3 and Section 12.4.1 for actions in case of pregnancy during the trial conduct.

11.10. PHARMACOKINETICS AND PHARMACODYNAMICS

Blood will be collected at each on-site visit for PK/PD assessments as listed in the Schedule of Events (Section 18.2), and described in Section 10.2. If not otherwise indicated, the PK and PD assessments will include:

PK will be sampled at Visit 1 trough Visit 7 in weekly treatment arms (lonapegsomatropin and placebo).

PK will be sampled at Visits 1, 5 and 7 in daily somatropin arm.

PK analytes: hGH, lonapegsomatropin, and mPEG serum levels will be assessed at Visit 1 through Visit 7 in weekly lonapegsomatropin arm.

PK analytes will not be analyzed in weekly placebo arm.

PK analytes: hGH , will be analyzed in daily somatropin arm.

PD will be sampled at screening and Visit 1 trough Visit 7: serum IGF-1 and serum IGFBP-3 serum levels and IGF-1 SDS and IGFBP-3 SDS.

PK and PD concentration data will be listed and summarized. PK and PD data from this trial may be combined with data from other trials in a population PK/PD analysis to characterize lonapegsomatropin PK and PD in the AGHD population and assess the effect of covariates on PK/PD of lonapegsomatropin.

11.11. ADA

An ADA sample will be collected at Visit 1, V2, V4, V6 and V7, and for subjects not continuing into the extension trial also approximately at least 30 days after the last study drug dose. For ADA samples, the planned analysis is that all collected samples except for the placebo treated and screen failures will be analyzed for anti-hGH antibodies. Pre-treatment samples from each cohort may be applied for cut point assessments. In addition, ADA samples from lonapegsomatropin treated subjects will be analyzed for anti-PEG and anti-lonapegsomatropin antibodies.

11.12. DXA SCAN

To ensure consistency, a central reader will evaluate the DXA scans on an ongoing basis.

It is recommended that DXA assessments are performed in a similar setting (time and hydration status) at each visit, using the same approved DXA machine throughout the trial. Sites should be following the DXA manufacturer's guideline for maintenance, calibration, and quality control, as well as the trial-specific guidelines as provided by the central reader in trial manuals. Cross-calibration phantoms will be distributed to all sites to ensure consistency.

DXA scans cannot be performed on subjects who are pregnant or suspected to be pregnant.

11.13. INJECTION SITE REACTION ASSESSMENT

Between visits, injection sites will be evaluated and documented by the subject preferably in writing and for example in the Subject Diary. At on-site visits, assessment of injection sites will be performed by the trial staff (documented as part of the physical exam, Section 11.4), in conjunction with the Subject Diary review. For injection site reaction reporting, please see Section 12.3.3.

12. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

12.1. ADVERSE EVENTS

12.1.1. Definition of Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can arise with any use (eg, in combination with another drug), route of administration, formulation, or dose, including an overdose. An AE 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 (investigational) product, whether or not related to that product.

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with GHD that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures, blood sampling).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run in, or other protocol-mandated interventions.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Based on the nonclinical and clinical program to date, the risks associated with the use of lonapegsomatropin are anticipated to be the same as those seen with daily somatropin products. Possible AEs associated with somatropin therapy are listed in the current Investigator Brochure which will serve as the reference for safety information for lonapegsomatropin

For complete information regarding clinical safety of the daily somatropin products, please refer to the Product Prescribing Information.

Clinically significant treatment-emergent abnormal findings from physical examination, laboratory abnormalities, and worsening of pre-treatment conditions may be recorded as AEs.

12.1.2. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence at any dose that meets any of the following criteria:

- It results in death (i.e., the AE cause or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form or was allowed to continue, might have caused death).
- It requires or prolongs inpatient hospitalization (see Section 12.3.3).
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug. (This applies if a subject exposed to an investigational product gives birth to a child with a congenital anomaly or birth defect.)
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject 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 AE (e.g., rated as mild, moderate, or severe, Section 12.2.2.1); 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 AE recorded on the eCRF.

SAEs 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 12.4.2 for reporting instructions).

12.1.3. Definition of Special Situation

Special situations are non-standard medical conditions that provide valuable information (e.g. clinical, safety) about a medicinal product, even when they do not occur in association with an adverse event or medical condition. Examples of special situations include and should all be captured in the study database:

- Pregnancy
- Breastfeeding
- Overdose
- Drug abuse
- Misuse
- Medication error

12.1.4. Important Identified Risk Associated with Lonapegsomatropin

There have been reports of hypersensitivity and/or anaphylaxis in clinical trials and the post-marketing setting with patients who have been exposed to lonapegsomatropin with/without previous exposure to growth hormone therapy. The reported events resolved after treatment with corticosteroids, antihistamine and /or epinephrine (see section Appendix 4, Anaphylaxis Precautions).

12.2. METHODS AND TIMING FOR ASSESSING AND RECORDING OF ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs including SAEs that are observed or reported during the study are collected and reported to the Sponsor, in accordance with FDA CFR 312.32 (IND Safety Reports) and ICH E6.

Confirmed SARs-CoV-2 infection and COVID-19 will be recorded as an AE.

12.2.1. Adverse Event Reporting Period

The Adverse Event Reporting Period is the period requiring reporting of AEs and SAEs for any subjects exposed to IMP product and/or any study related procedures.

The reporting period begins from the time when the informed consent is obtained and ends 2 weeks following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

If the EDC system is not available, the investigator should report these events directly to the sponsor as outlined in Section 12.4.2.

12.2.2. Severity, Causality, and Outcome Assessment

12.2.2.1. Severity Rating

The following guideline should be used by the investigator to grade the intensity of an AE: Table 6 provides guidance for assessing adverse event severity.

Table 6: Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity
Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 12.1.2).	

12.2.2.2. Causality Rating

All AEs, including SAEs, whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means must be reported appropriately.

Each reported AE or SAE must be described by its duration (i.e., start and end dates), seriousness criteria if applicable, suspected relationship to the IMP (see following guidance), and actions taken. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Related (Yes) – There is a plausible temporal relationship between the onset of the AE and administration of the IMP. The AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. The AE follows a known pattern of response to the IMP or with similar treatments and/or the AE abates or resolves upon discontinuation of the IMP or dose reduction and, if applicable, reappears upon re-challenge.

Not Related (No) – Evidence exists that the AE has an etiology other than the IMP (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). The AE has no plausible temporal relationship to IMP administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the current Investigator's Brochure (IB).

Unexpected AEs are those not listed in the current IB. This includes AEs for which the specificity or severity is not consistent with the description in the IB. (For example, under this definition, hepatic necrosis would be unexpected if the IB only referred to elevated hepatic enzymes or hepatitis).

12.2.2.3. Outcome Assessment

One of five outcomes listed below must be recorded:

Recovered/Resolved – The event has stopped. The stop date of the event must be recorded.

Recovering/Resolving – The subject is clearly recovering from an event. The event is not yet completely resolved.

Not Recovered/Not Resolved – The event is still ongoing. (Could include stable and commensurate with ongoing disease processes).

Recovered/Resolved with sequelae – The event has reached a state where no further changes are expected, and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.

The stop date of the event must be recorded. In case of SAE, the sequelae should be specified.

Fatal – The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.

Unknown – Unknown to the investigator, e.g. subject lost to follow-up.

AE follow ups should be conducted in accordance with section Section 13.

12.3. PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS

12.3.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

12.3.2. Recording Procedures for All Adverse Events

All AEs will be documented in response to questions about the subject's well-being and whether any possible changes in well-being have occurred since the previous visit. Additionally, at each visit, site staff will review subject diary data with the subject, to determine if diary entries reflect any AEs.

AEs, including SAEs, will be documented through the end of the subject's participation in the trial or Early Termination visit. . All AEs must be recorded on the appropriate CRF. AEs either observed by the investigator or reported by the subject must be recorded regardless of causality. The following attributes must be documented for each reported AE:

- Subject ID
- AE Term
- Description (for SAEs)
- Onset date (if AE was present on Day 1, include whether onset was prior to or after the first dose of the study drug)
- Resolution date, if applicable
- Severity

- Causality (relationship to the study drug)
- Outcome
- Action taken
- Determination of "seriousness criteria" (whether serious or not serious)

Any medical history condition, signs, symptoms, and illnesses active during the Screening Period will be captured as baseline (pre-existing) events, if appropriate, to assure that any change(s) in these experiences during the trial also are recorded as an AE and a complete safety profile is obtained. An event that occurs after signing of ICF but prior to the first study drug administration will be documented as medical history unless the event is trial procedure–related, in which case it will be reported as a non–treatment-emergent AE. Any new or worsening pretreatment event that occurs from the time of the first study drug administration until the last visit will be recorded as an AE.

Routine titration of chronic, concomitant medications will not be considered to meet the criteria for AEs. In addition, increased IGF-1 levels requiring study drug dose decrease (ie, IGF-1 SDS > 2.0) will not be considered as AE. However, occurrence of clinically significant symptoms/conditions associated with increased IGF-1 levels will be considered as AE.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviation (e.g., hypertension for elevated blood pressure that persists and requires chronic treatment and follow-up, or increased blood pressure for elevated blood pressure that occurs for a limited time and does not persist or require ongoing treatment).

AEs will be documented at the maximum intensity experienced. If a previously recorded and closed AE or condition recorded as part of medical history increases in severity or frequency, it will be recorded as a new AE.

All AEs will be considered ongoing until they have completely resolved or are deemed stable or commensurate with ongoing disease processes by the investigator. At study completion or the Early Termination Visit, all AEs should have a statement regarding resolution, see also Section 10.2.4 and Section 10.2.5.

An accidental overdose is not an AE if there are no signs or symptoms. Any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate eCRF. Regardless of classification as an AE or not, *all* overdoses should be documented, and the subject(s) monitored. Since accidental overdoses with the study drug could have serious clinical consequences and/or represent a compliance issue, they should be reported to the Medical Monitor immediately and evaluated by the Sponsor. See Section 12.1.3.

12.3.3. Specific Instructions for Recording Adverse Events

Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification or titration, treatment interruption, or treatment discontinuation) *Note*: Increased IGF-1 levels (blinded to investigators in this study) requiring study drug dose decrease (ie, IGF-1 SDS > 2.0) will not be considered as AE. However, occurrence of clinically significant symptoms/conditions associated with increased IGF-1 levels will be considered as AE.
- 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 available laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 whether 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 AE.

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE 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 AE.

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.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available as separate AEs. If a diagnosis is subsequently established, it should be reported as follow-up information.

Injection Site Reaction (ISR)

Local signs or symptoms at the site of study drug administration are deemed to be adverse events. The reported AEs should include 'injection site'' in the reported term such as injection site erythema, injection site induration etc. The diagnosis is at the discretion of the investigator.

Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE.

For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and prior procedures. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., worsening type 2 diabetes mellitus).

Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 2 weeks after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug, a Pregnancy report form should be completed and expeditiously submitted to Sponsor. Follow-up to obtain the outcome of the pregnancy should also occur and the outcome reported to Sponsor. DXA scans cannot be performed on subjects who are pregnant or suspected to be pregnant.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be expeditiously reported as an SAE.

Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

The investigator should document as much information as possible including the product batch number and forward the information to the Sponsor immediately (refer to the pharmacy/IMP manual for further details). If the product complaint results in an adverse event to the study patient, the event must be reported on the AE eCRF and submitted. If the event is serious, the AE eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section Section 12.4.2.

12.4. SAFETY REPORTING REQUIREMENTS

12.4.1. Non-Serious Adverse Events Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities) and special situations (e.g.pregnancies) that may require permanent discontinuation of study drug should be discussed with the Medical Monitor prior to making any final decision.

12.4.2. Reporting

All initial and follow-up information regarding SAEs and Special Situations reporting must be reported by the investigator to the Sponsor or its representatives within 24 hours of discovery/awareness, including those related to protocol-mandated procedures and regardless of suspected causality.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 12.1.2 for seriousness criteria), severity (see Section 12.2.2.1), and causality (see Section 12.2.2.2).

Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE, AESIs, and Special Situations are the AE term (diagnosis), patient, study drug, reporter, and the investigator's initial causality assessment. Additional information must be reported to the Sponsor or its representatives as a follow-up report. All SAEs and Special Situation reports (including follow-up information) must be reported to

Ascendis Pharma using the Safety report form or the Pregnancy report form provided. A completed Safety report form / Pregnancy report form must be uploaded to the Safety Reporting Portal:

Safety.ascendispharma.com

Specific instructions regarding completion of the form and reporting details are provided on the Safety Report Form.

SAEs and Special Situations information is collected and reported via Safety Report Forms provided by the Sponsor or its representative. Pregnancy information is collected and reported via Pregnancy Forms provided by the Sponsor or its representative. The Sponsor (or its representatives) is responsible for reportingall SAEs qualifying as SUSARs within the time frame required by applicable regulations to:

- Investigators
- Central IRBs/HRECs/IECs (if applicable)
- National ethics committees (if applicable)
- Appropriate regulatory authorities

It is the investigators' responsibility to comply with the requirements of their local IRB/HREC/IEC for reporting SUSARs, other SAEs, and any new and/or relevant safety information provided by the Sponsor or its representatives. At minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

13. SAFETY MONITORING

Sponsor Follow-up: The Sponsor will conduct an ongoing review of all trial data, with particular attention given to laboratory findings (in particular related to glucose metabolism, thyroid function and liver function), AEs, and concomitant medications. Any important safety trends or other findings considered related to the study drug will be reported to the investigators and to regulatory authorities. In particular, the Sponsor will notify investigators and regulatory authorities of AEs that:

- Fulfill the criteria for SUSARs
- Occur at a meaningfully greater frequency than described in the current IB or Reference Safety Information.

Investigator Follow-up: Information should be elicited at all subject evaluation time points for all AEs at regular study visits. Any AE that occurs during the clinical trial should be monitored and followed up until:

- It has resolved or receded
- Pathology laboratory findings have returned to normal
- Subjects are deemed stable or commensurate with ongoing disease processes
- It has been shown to be unrelated to the study drug and/or trial related procedure

or

- Subject is lost to follow up or withdrawn consent or the subject has completed the study

Medical judgement should be used by the investigator to determine if attempts should be made to collect additional information for SAEs outside of regular study visits. Every effort should be made to follow all SAEs considered to be related to study drug or trial related procedure until a final outcome can be reported.

See Section 15.5.1 for more details about clinical data monitoring.

14. STATISTICS

The Statistical Analysis Plan (SAP) will provide a detailed description of the planned statistical analyses. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record.

14.1. TRIAL ENDPOINTS

14.1.1. Primary Efficacy Endpoint

Change from baseline in trunk percent fat (as assessed by DXA) at Week 38.

14.1.2. Secondary Efficacy Endpoints

- Change from baseline in trunk fat mass at Week 38 (as assessed by DXA)
- Change from baseline in total body lean mass at Week 38 (as assessed by DXA)

14.1.3. Exploratory Efficacy Endpoints:

14.1.4. Safety Endpoints

Safety endpoints as measured throughout the 38 weeks of treatment include:

- Incidence of AEs
- Laboratory values
- Vital signs
- Incidence of ADA and neutralizing antibodies against hGH
- ECGs
- Fundoscopy

14.1.5. Pharmacokinetic/Pharmacodynamic Endpoints

- hGH levels
- Lonapegsomatropin levels
- mPEG levels
- IGF-1 levels and IGF-1 SDS
- IGFBP-3 levels and IGFBP-3 SDS

14.2. SAMPLE SIZE DETERMINATION

This trial is powered for the efficacy comparison of lonapegsomatropin versus placebo. The daily somatropin product arm is included as a calibration arm and not powered for formal comparison.

Approximately 240 subjects will be randomized in a 1:1:1 ratio to once-weekly lonapegsomatropin, once-weekly placebo, or daily somatropin product. However, for local regulatory requirements recruitment may be kept open in some countries after having this number reached for the global study.

A sample size of 80 subjects per arm in the lonapegsomatropin and placebo once-weekly treatment arms will provide 90% power to detect a treatment difference of 1.9% between once-weekly lonapegsomatropin and placebo for the primary endpoint of change from baseline in trunk percent fat at Week 38 at the 2 sided 5% significance level, with the assumption of a common SD of 3.7%.

14.3. ANALYSIS POPULATIONS

Safety Analysis Set – The Safety Analysis Set will include all randomized subjects who have received at least one dose of the study drug. Subjects will be analyzed by the treatment arm as treated.

Intent-To-Treat Population – The Intent-To-Treat population will consist of all randomized subjects who have received any amount of the study drug. Subjects will be analyzed by the treatment arm as randomized.

PK/PD Analysis Set – The PK/PD analysis set will include all randomized subjects who have received at least one dose of the study drug and have post-randomization PK/PD data. Subjects will be analyzed as treated.

14.4. STATISTICAL ANALYSES

In general, data from clinical assessments will be summarized using descriptive statistics.

Categorical data will be presented using counts and percentages of subjects. Continuous variables will be presented using number of subjects, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum.

14.4.1. Definition of the Estimand and Estimator for Primary Analysis

Population: the treatment effect is to be estimated for the Intent-To-Treat population of adult subjects with GHD as defined by the protocol inclusion/exclusion criteria.

Primary endpoint: efficacy is to be measured using the primary endpoint of change from baseline in trunk percent fat (as assessed by DXA) at Week 38.

Handling missing data/Intercurrent events (ICEs) missing reasons will be taken into considerations into multiple imputation. The Markov Chain Monte Carlo (MCMC) method will be used to impute the missing data, under the multivariate normality assumption to impute the missing data by treatment arm and dose group. Details will be provided in the SAP.

The difference in change from baseline at Week 38 in trunk percent fat will be estimated by the primary analysis of ANCOVA model, with multiple imputation for missing data. The ANCOVA model will include treatment arm, dose group, diabetes mellitus, and region (Japan vs. all regions except Japan) as factors, and baseline trunk percent fat as a covariate. Additional factors may include, baseline age group, sex, concomitant oral estrogen at screening (yes vs. no), and AGHD onset (adult vs. childhood). The daily somatropin product arm will be included in the ANCOVA model, but no formal statistical testing will be performed on this arm.

Subgroup analyses of the primary efficacy endpoint will be performed to determine whether treatment effects are consistent across clinically meaningful subgroups. The difference in change from baseline at Week 38 in trunk percent fat and their 95% confidence intervals will be displayed in a forest plot. Subgroups will include but not limited to the following: region, age group, gender and diabetes mellitus status.

Details on the analyses including derivation, handling of missing data, statistical method, sensitivity analyses including per-protocol analysis and subgroups will be provided in the SAP.

14.4.2. Secondary Efficacy Endpoint Analyses

For the endpoints evaluating the change from baseline in trunk fat mass and total body lean mass at Week 38, the analysis method used for the primary endpoint will be applied. And similar by-visit ANCOVA models with multiple imputation will also be applied with corresponding baseline value as a covariate.

To control familywise error rate at level of 0.05, the secondary endpoints will be adjusted by Hochberg procedure only if the test for the primary endpoint (lonapegsomatropin vs. placebo) is statistically significant. The positive correlation between secondary endpoints will also be evaluated.

Details of statistical methods will be provided in the SAP.

14.4.3. Pharmacokinetic / Pharmacodynamic Analyses

PK (hGH, lonapegsomatropin and mPEG) serum levels (ng/mL), IGF-1 serum levels (ng/mL), IGF-1 SDS, IGFBP-3 serum levels (ng/mL) and IGFBP-3 SDS will be summarized descriptively. The absolute values and changes from baseline in IGF-1 (ng/mL) and IGF-1 SDS will also be analyzed by by-visit ANCOVA models. Proportion of subjects with average IGF-1 SDS between -1.0 to +2.0 will be summarized by visit and treatment arm.

14.4.4. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set and summarized by treatment arm as treated. Reporting of the safety data will be descriptive and all data will be listed and summarized by visit. The safety parameters include AEs, clinical laboratory, immunogenicity data, vital signs, ECG parameters, fundoscopy, and other safety parameters. All AEs will be coded to preferred term and system organ class using MedDRA. The incidence of AEs will be presented by MedDRA system organ class and preferred term, by causality and severity. A subject reporting the same AEs more than once is counted once and at the maximum severity or strongest relationship to the study treatment when calculating incidence.

Details of statistical methods will be provided in the SAP.

14.4.5. Planned Interim Analyses

There are no planned interim efficacy analyses.

15. TRIAL CONDUCT

15.1. SITE INITIATION

Prior to participation, the investigational sites and investigators will be evaluated for appropriate qualifications and ability to execute the trial. Each investigational site must undergo appropriate training on the trial protocol and ancillary trial procedures and documents through participation in a Site Initiation Visit (SIV) or Investigator Meeting (IM). Training must take place before any subjects are enrolled at a site, including documentation of GCP training. SIVs and IMs will include but may not be limited to the study drug preparation and administration procedures, data collection requirements, and subject eligibility requirements.

15.2. SCREEN FAILURES

Screening shall be stopped at any point in case any of the eligibility criteria not being met. Such cases will be classified as screening failures.

Re-screening is permitted, and subjects will receive a new screening number. Re-screening of subjects who had to adjust their hormonal replacement therapy may be considered ≥ 6 weeks after dose adjustment.

15.3. MAINTENANCE OF ENROLLMENT LOGS

Procedures for maintenance of enrollment logs are discussed in the trial documentation.

15.4. DATA HANDLING AND RECORD KEEPING

15.4.1. Collection of Data

Data will be collected in the eCRF and other computerized systems.

The eCRF is an integral part of the trial and subsequent reports. It must be used to capture trial-specific data collected and must be kept current to reflect subject status during the course of the trial. Only a subject identification number will be used to identify the subject. The investigator must keep a separate subject identification code list with subject names and medical record numbers (or other personal identifiers).

The trial will use an internet-based remote data entry system to collect clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 GCP (R2). The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system is configured based on the requirements from the Sponsor. Source documents are to be retained to enable a reconstruction and evaluation of the trial. Source documents include the hospital files and trial worksheets provided by the Sponsor. Data will be recorded in the trial worksheets as appropriate to complete and/or clarify the source data.

The design of the computerized system complies with all the applicable regulatory requirements for record keeping and record retention in clinical trials, ie 21 CFR Part 11 and ICH E6 GCP (R2) to the same degree of confidence as is provided with paper systems. Clinical investigators must retain either the original or a certified copy of all source documents sent to the Sponsor or its representatives, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

15.4.2. Coding Dictionaries

Prior and concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A complete description of data to be collected is provided in the trial documentation.

15.4.3. Data Handling

The eCRFs should be completed in a timely manner which usually is within 48 hours but not later than 5 days from the date of the visit/of obtaining the information to enable the Sponsor or designee to evaluate eligibility and to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock, the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or Sponsor, who routinely review the data for completeness, correctness, and consistency. The site is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and by providing the reason for the update (eg, data entry error). At the conclusion of the trial, Sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 15.4.5.

15.4.4. Direct Access to Source Data/Documents

The investigator/trial site is to provide direct access to source data/documents for trial-related monitoring, audits, IRB/HREC/IEC review, and regulatory inspection; this includes access to electronic health records.

15.4.5. Record Keeping

The investigator is responsible for maintaining adequate records to fully document the conduct of the trial consistent with that noted in ICH E6 GCP (R2), including but not limited to the following:

- All applicable versions of the IB
- Signed Protocol and Amendments in effect during the conduct of the trial
- Signed ICFs
- Source documents, including adequate case histories, questionnaires, and subject diaries
- Signed, dated, and completed eCRFs and documentation of data corrections
- Notification of SAEs and related reports
- Dated and documented IRB/HREC/IEC approvals and approval by regulatory authorities, as required
- Normal laboratory reference ranges
- Laboratory certifications
- Curricula Vitae of all clinical investigators
- Completed Forms FDA 1572, if applicable

- SIV documentation
- Delegation of Authority Log
- Subject Screening & Enrollment Log(s), Subject Identification Code List
- Study drug accountability documentation
- Signed agreements between involved parties
- Relevant communication, including that related to monitor site visits (eg, letters, meeting notes, telephone calls notes)
- Documentation of deviations, including explanations
- Interim, annual, or final reports to IRBs/HREC/IEC and regulatory authorities, as required
- Audit certificate(s), if applicable

15.5. DATA QUALITY CONTROL

15.5.1. Monitoring Procedures

The Sponsor and/or its representative will periodically review the trial data to ensure that data are being appropriately collected and reported. Queries and corrections will be made as needed.

Risk-based monitoring including reduced source data verification, triggered monitoring, centralized monitoring, and targeted monitoring will be conducted (EMA Reflection Paper 2013, FDA Guidance for Industry 2013, EMA Guidance 2020, FDA Guidance 2020). All critical data will require source verification by the monitor and critical data will be identified in advance, to ensure subject's safety and the reliability of trial results. The extent and details of monitoring including source data verification will be described in the Clinical and Central Monitoring Plans.

The trial site must not enroll any subject before the initiation was performed and a final eligibility of the site is confirmed by the CRO and Sponsor. Depending on the COVID-19 pandemic situation at the trial site, a site qualification and SIVs may be performed remotely. During the trial, regular monitoring visits will be performed according to ICH GCP, the Sponsor's designee's or local CRO's standard operating procedures (SOP), and local regulations. The frequency and type of monitoring visits will depend amongst other factors on the trial site's recruitment rate and current pandemic situation in each country and trial site.

Physical monitoring visits at the trial sites may not be feasible or may be restricted for some time due to COVID-19 pandemic situation, and either a combined remote and on-site monitoring or full remote monitoring visit will be conducted during these periods. The Sponsor authorizes the designated local CROs to include remote monitoring visits according to the applicable guidelines and regulations into the monitoring activities. In line with local laws and regulations, remote source data verification might be part of the remote monitoring visits and if so, it has to be agreed between the Sponsor designee, the investigator and additional investigational staff at each trial site. The relevant trial documents (eg, monitoring plan) will be adjusted to reflect these activities that will be held during the period when standard monitoring visits are not feasible.

Prior to site activation, the CRA will ensure a procedure is agreed with each investigational site to ensure remote source data verification in case of SARS-COV-2 crisis.

In EU: All remote monitoring will be conducted in accordance with European Medicines Agency Guidance on the Management of Clinical Trials During COVID-19 (Coronavirus) Pandemic (EMA, 2021). Options for remote monitoring - in compliance with the local, country specific regulations, requirements and relevant guidelines - might include phone calls, audio/videoconferencing, and sharing of medical records (eg, direct access to electronic health records (EMA Reflection Paper 2010, FDA Guidance for Industry 2018) sharing redacted/blinded medical records in a secured way, etc.), depending on the trial site's capabilities.

For remote monitoring purposes, no medical records may be sent, even if pseudonymized.

The ICH GCP requirements and applicable data protection and privacy regulations must be met in any case and for any selected monitoring approach. As part of the ICF, the subjects need to agree to a remote monitoring of data.

The investigators must permit the monitor access to the subject's medical records and all other applicable source documents. The data will be pseudonymized correspondingly in all data analyses.

It is the investigators' obligation to assure documentation of all relevant data in the subject's file, such as medical history and concomitant diseases, date of trial enrolment, visit dates, results of examinations, administrations of the IP, any concomitant medication, and AEs.

The Sponsor and/or its representative may make periodic visits to the investigational site to assess compliance with trial procedures and regulatory requirements to ensure that the safety, welfare, and privacy of subjects are being protected and to verify the accuracy and integrity of the trial data. In addition, independent Quality Assurance site audits may be conducted as verification of the quality and compliance of trial conduct.

15.5.2. Data Management

Sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and SOPs of the Sponsor and / or delegates, details will be described in the trial documentation. A comprehensive Data Management Plan (DMP) will be developed including a data management overview, database development, validation and maintenance, data entry and processing, external data transfer, data validation and archive, and medical coding processes.

Trial site personnel will be responsible for providing resolutions to data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the trial documentation.

15.6. AUDITING PROCEDURES

In addition to the routine monitoring procedures, a GCP Quality Assurance audit may be initiated by the Sponsor. The investigator has to ensure that subjects are aware of and consent to personal information being reviewed during the data verification process as a part of monitoring/auditing/inspection by the Sponsor, properly authorized agents of the Sponsor, or competent authorities. In addition, participation and personal information is treated as strictly confidential to the extent that applicable law permits and to which it is not publicly available.

The purpose of audits and inspections is to evaluate compliance with the principles of GCP, international and local regulatory requirements, and the trial protocol. The audit or inspection may include, for instance, a review of all source documents, drug records, original clinic medical notes, and some or all of the facilities used in the trial.

The audits may be conducted by the Sponsor or Sponsor's selected agent in accordance with Sponsor's SOP or SOPs of the selected and properly authorized agent. Investigators will facilitate audits within a reasonable timeframe and on dates agreed upon with the auditor. A competent authority may also wish to conduct an inspection during the trial or after its completion. If an inspection is requested by a competent authority, the investigator must inform the Sponsor immediately that this request has been made. The investigator and his/her institution will permit all monitoring, audits, and regulatory inspections, providing direct access to source data (including access to electronic health record systems).

Depending on the COVID-19 pandemic situation of the trial sites with regards to their accessibility, remote audits or regulatory inspections might be considered in line with the local laws and regulations and without adding additional burden to the trial staff.

15.7. LABORATORY QUALITY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local and central laboratories. Some blood samples may be used for laboratory test validation.

The laboratories will provide qualification documentation and a list of reference ranges for applicable analyses before trial start. These will be held in the investigator site file and the trial master file. The methods employed for each assay should be available on request. Any change in the laboratory procedures, reference values, etc., during the trial must promptly be communicated to the Sponsor. The laboratories may also be audited by the Sponsor or by competent authorities.

15.8. TRIAL TERMINATION OR COMPLETION

The investigator should notify the IRB/HREC/IEC in writing of the completion or early termination of the trial. Upon trial completion or termination, applicable regulatory reporting requirements will be followed. The Sponsor reserves the right to terminate the trial at any time for any reason.

15.9. CHANGES TO THE PROTOCOL

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and must be approved by the investigational site's IRB/HREC/IEC and regulatory authorities, as required, before the amendment is implemented. However, in the event of apparent immediate hazard to a subject, a deviation from the protocol may be implemented to eliminate the hazard. In this case, the deviation, and the reason for it must be submitted as soon as possible for approval or acknowledgement as required by regional regulations to the Sponsor, applicable IRB/HREC/IEC, and regulatory authorities, along with a proposed protocol amendment if appropriate.

Protocol amendments may only be made with prior written approval of the Sponsor and/or its representative and documented approval or favorable opinion from applicable regulatory authorities or regional IRB/HREC/IEC, as required. The investigator must send a copy of the documented approval to the Sponsor and/or its representative.

15.10. OTHER CHANGES IN TRIAL CONDUCT

Changes in trial conduct are not permitted. Any unforeseen changes in trial conduct will be recorded in the clinical study report.

15.11. USE OF INFORMATION AND PUBLICATION

The data and information generated in this trial are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this trial. Publication of the results will be based on appropriate analyses and review of the complete data. Authorship will be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the trial. Publication of any data of this trial without prior Sponsor approval is not permitted.

Ascendis Pharma, the Sponsor of this trial, will conduct this clinical trial in an ethical and rigorously scientific manner, in collaboration with clinical experts in AGHD. The Sponsor will facilitate publication of the clinical data from this study in a timely, objective, accurate, and balanced manner. The Sponsor will follow publication guidelines that are consistent with requirements of the International Committee of Medical Journal Editors, the Consolidated Standards of Reporting Trials group, and the individual journal. The Sponsor will work with investigators on this clinical trial to produce any manuscripts for peer-reviewed publication. Publication by the site of any data from this trial must be carried out in accordance with the clinical trial agreement.

This clinical trial will be listed on websites as required by relevant regulatory authorities. Synopses of the clinical results will be provided on those same sites per timeframes established by those regulatory authorities.

The Sponsor will provide all investigators with the clinical trial results. Publication by the site of any data from this clinical trial must be carried out in accordance with the clinical trial agreement. The Sponsor maintains the right to be informed of any plans for publication and to review any resulting abstracts, presentations or manuscripts before they are submitted.

The clinical trial database will be available to the Sponsor and relevant regulatory agencies as required.

16. ETHICAL AND LEGAL CONSIDERATIONS

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- GCPs as outlined in ICH E6 (R2) and regional regulations
- Regional required subject data protection laws and regulations
- Other applicable regional and local regulations

16.1. INFORMED CONSENT

The draft ICF must be reviewed by the Sponsor and/or its representative prior to submission to a regional IRB/HREC/IEC for approval. A copy of the ICF approved by the IRB/HREC/IEC must be forwarded to the Sponsor and/or its representative.

The ICF (and subject information sheet) documents the trial-specific information the investigator provides to the subject and the subject's agreement to participate. The investigator or designee will fully explain in layman's terms the nature of the trial along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and ICH guidelines. Furthermore, the subject should be informed his/her personal data will be pseudonymized, all information collected about him/her during the clinical trial will be kept strictly confidential to the extent permitted by the applicable laws and/or regulations and will not be made publicly available. The ICF and subject information sheet must be appropriately signed and dated before the subject undergoes any trial-related procedure. One original of the signed and dated ICFs and subject information sheets must be retained at the trial site in the investigator site file. The second signed and dated ICFs and subject information sheets must be provided to the subject.

The ICF will be revised whenever important new information becomes available that may be relevant to the subject's consent, or when there is an amendment to the protocol that necessitates a change in the content of the ICF. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised/amended ICF. The revised/ amended ICF must receive the IEC approval/favorable opinion in advance of use.

16.2. IRB/HREC/IEC APPROVALS

The Principal Investigator at each site is responsible for obtaining approval from the appropriate IRB/HREC/IEC for the final protocol, Sponsor-approved ICF and subject information sheet, and any advertisements to recruit subjects. Written approval of these documents must be obtained from the committee before any subject is enrolled at a trial site.

The Principal Investigator is also responsible for the following interactions with the IRB/HREC/IEC:

- Obtaining IRB/HREC/IEC approval for any protocol amendments and ICF revisions before implementing the changes
- Providing the IRB/HREC/IEC with any required information before or during the trial
- Submitting progress reports to the IRB/HREC/IEC as required during the conduct of the trial, requesting re-review and approval of the trial as needed, and providing copies of all IRB/HREC/IEC re-approvals and relevant communication to the Sponsor and/or its representative
- Notifying the IRB/HREC/IEC of all serious and unexpected AEs related to the study drug reported by the Sponsor and/or its representative, as required
- Notifying the IRB/HREC/IEC of the end of trial participation, in accordance with regional guidelines and regulations

16.3. SUBJECT COMPENSATION FOR ADVERSE EFFECTS ON HEALTH

The Sponsor and/or its representative will adhere to regional regulations regarding clinical trial compensation of subjects whose health is adversely affected by taking part in the trial.

16.4. FINANCE AND INSURANCE

Will be described in trial documents.

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18. ATTACHMENTS

18.1. SIGNATURE OF AGREEMENT

In signing this protocol, the investigator agrees to:

1. Conduct the trial in accordance with the current protocol and make changes only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human subjects.
2. Comply with the International Conference on Harmonization Tripartite Guideline on GCP plus applicable local and regional regulatory laws and requirements.
3. Personally conduct or supervise the described investigation.
4. Inform any subjects or persons used as controls that the study drugs are being used for investigational purposes.
5. Ensure requirements relating to obtaining informed consent and ethical or Institutional Review Board approval have been met.
6. Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Section 12.
7. Read and understand the IB, including potential risks and side effects of the study drug.
8. Ensure all associates, colleagues, and employees assisting in the conduct of the trial are appropriately qualified, trained, and informed of their obligations in meeting their commitments.
9. Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative or any regulatory agency authorized by law.
10. Promptly report to the ethical or Institutional Review Board all changes in research activity and all unanticipated problems involving risks to human subjects or others.
11. Comply with all other requirements regarding the obligations of clinical investigators and all other relevant requirements.
12. Administer the study drug only to subjects who meet trial entry criteria and are enrolled in the trial and only according to the guidelines set forth in this protocol.

SIGNATURE OF AGREEMENT

I have read and understand the information in this Clinical Trial Protocol, including the potential risks and side effects of the study drug, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will deviate from the protocol only after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to inform all subjects that the study drug is being used for experimental purposes, and I will ensure that the requirements related to obtaining informed consent are met. I agree to report to the Sponsor any AEs that occur in the course of the investigation(s).

1. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments.
2. I will not make any changes in the research without Sponsor and IRB/HREC/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
3. I agree to maintain all information in this document and regarding the study as confidential and to use it only for the purpose of conducting the study. I agree not to forward this document to any other party without the prior written authorization of the Sponsor.

Investigator:

Printed Name and Title: _____

Signature: _____

Date: _____

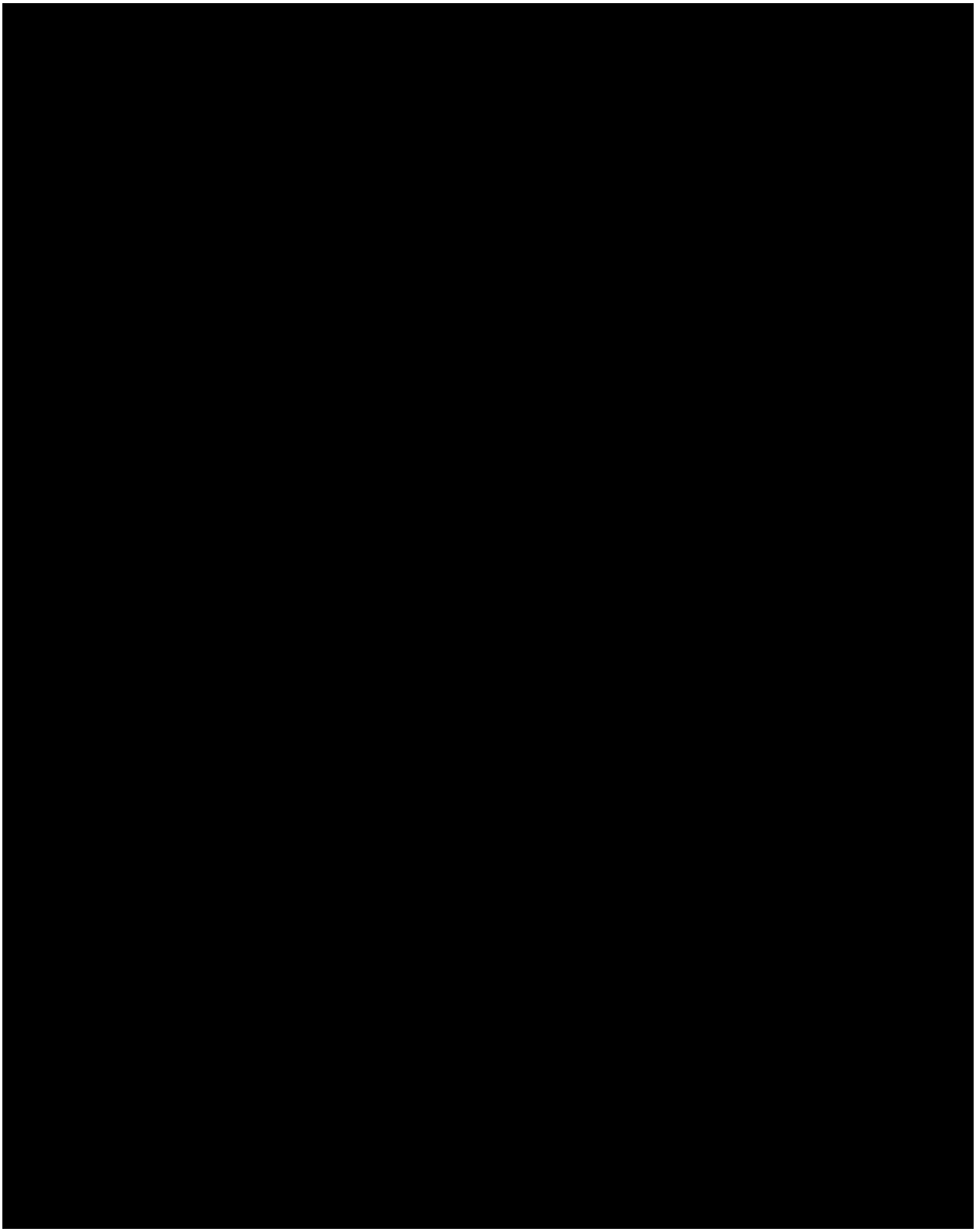
18.2. SCHEDULE OF EVENTS

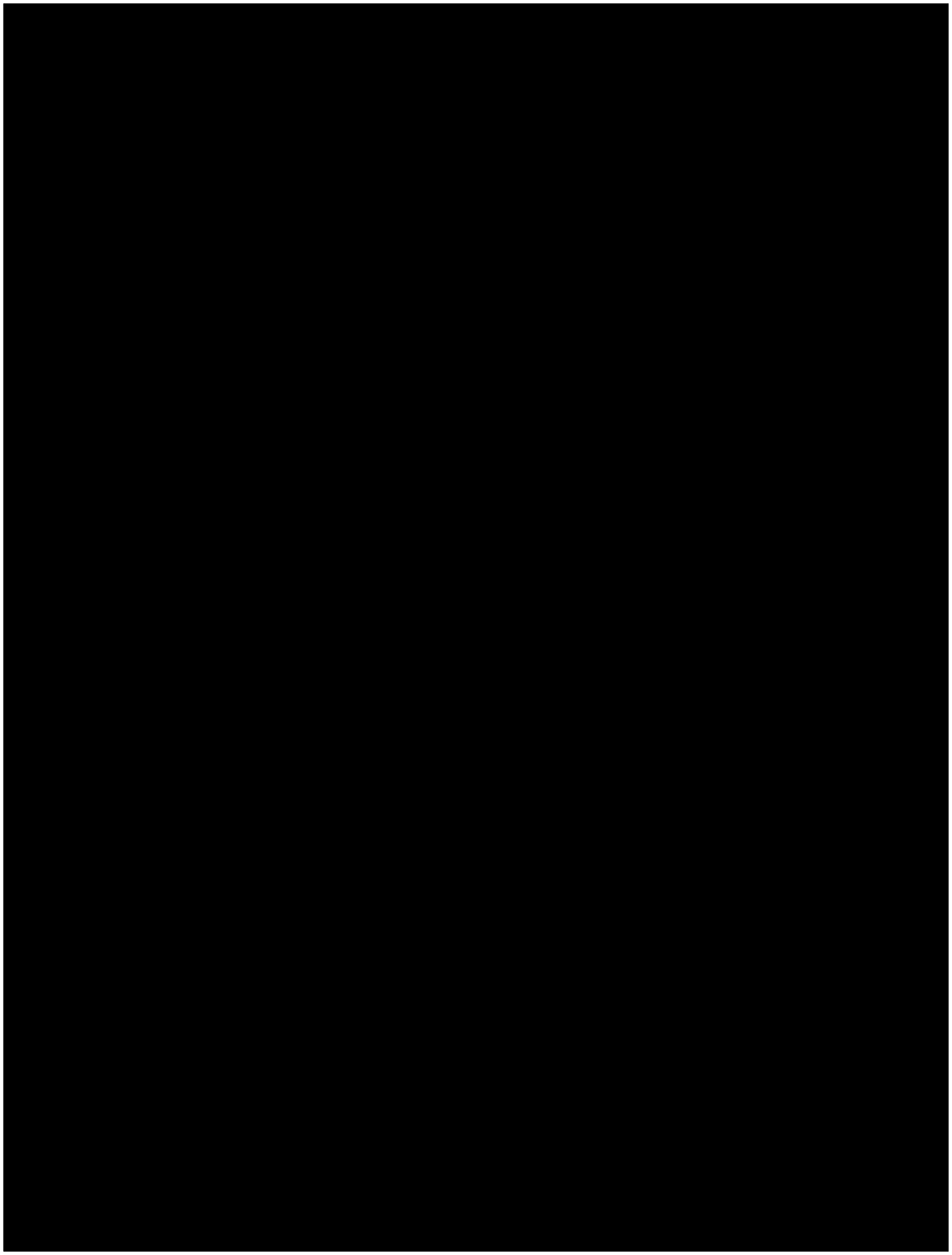
Visit	Screening (-6 to Week 1) [a]	Visit 1 (First dose) (Week 1) [a]	Visit 2 (Titration) (Week 4)	Visit 3 (Titration) (Week 8) [b]	Visit 4 (Titration; Start of maintenance dose) (Week 12)	Visit 5 (Week 17)	Visit 6 (Week 28)	Visit 7 (Week 38 + 4 weeks) Early Term., EoT[c]
Weekly Visit Window	– 2 weeks	NA	-	-	-	+/-1 week	+/- 1 week	+ 1 week
Once-weekly lonapegsomatropin or placebo visit days:	NA	Pre-dose	4-5 days post-dose (96 – 120 h post-dose +/-3 h)	4-5 days post-dose (96 – 120 h post-dose +/-3 h)	4-5 days post-dose (96 – 120 h post-dose +/-3 h)	pre-dose (144 – 168 h post-dose +/-3 h)	1-3 days post-dose (24 – 72 h post-dose +/-3 h)	4-5 days post-dose (96 – 120 h post-dose +/-3 h)
Daily somatropin product visit days:	NA	Pre-dose	Any day	Any day	Any day	Any day	Any day	End of 26 weeks at target maintenance
Informed consent	×							
Medical history, current and prior medications (≤ 12 months prior ICF), Demography	×							
Concomitant medications and AEs[c]		×	×	×	×	×	×	×
Subject Diary review			×	× [o]	×	×	×	×
Weight	×	×	×	× [o]	×	×	×	×
Height	×							
Physical examination and vital signs	×	×	×	× [o]	×	×	×	×
GH stimulation test(s)[d]	×							
ACTH stimulation test[e]	×							
MRI / CT scan [f]	×							**x**[f]
12-lead ECG	×	×					× (weekly treatment arms)	×
Fundoscopy [g]	×							×
Fasting required	×	×	×		×	×	×	×
Safety laboratory assessments [h]	×	×	×		×	×	×	×
IGF-1 and IGFBP-3 assessments [i]	×	×	×	× [o]	×	×	×	×
Pregnancy test for females of childbearing potential	×	×	×	× [o]	×	×	×	×
Samples for PK assessment [j]		×	×	× [o]	×	×	×	×
Samples for antibody assessment [k]	×	×	×		×		×	×
DXA scan [l]	×	×[l]			×			×
Study drug administration training		×	× (as needed)	× [o] (as needed)	× (as needed)	× (as needed)	× (as needed)	
Scheduled dose titration [m]			×	×	×			
Injection site reaction assessment		×	×	× [o]	×	×	×	×
PRO completion [n]		×			×		×	×

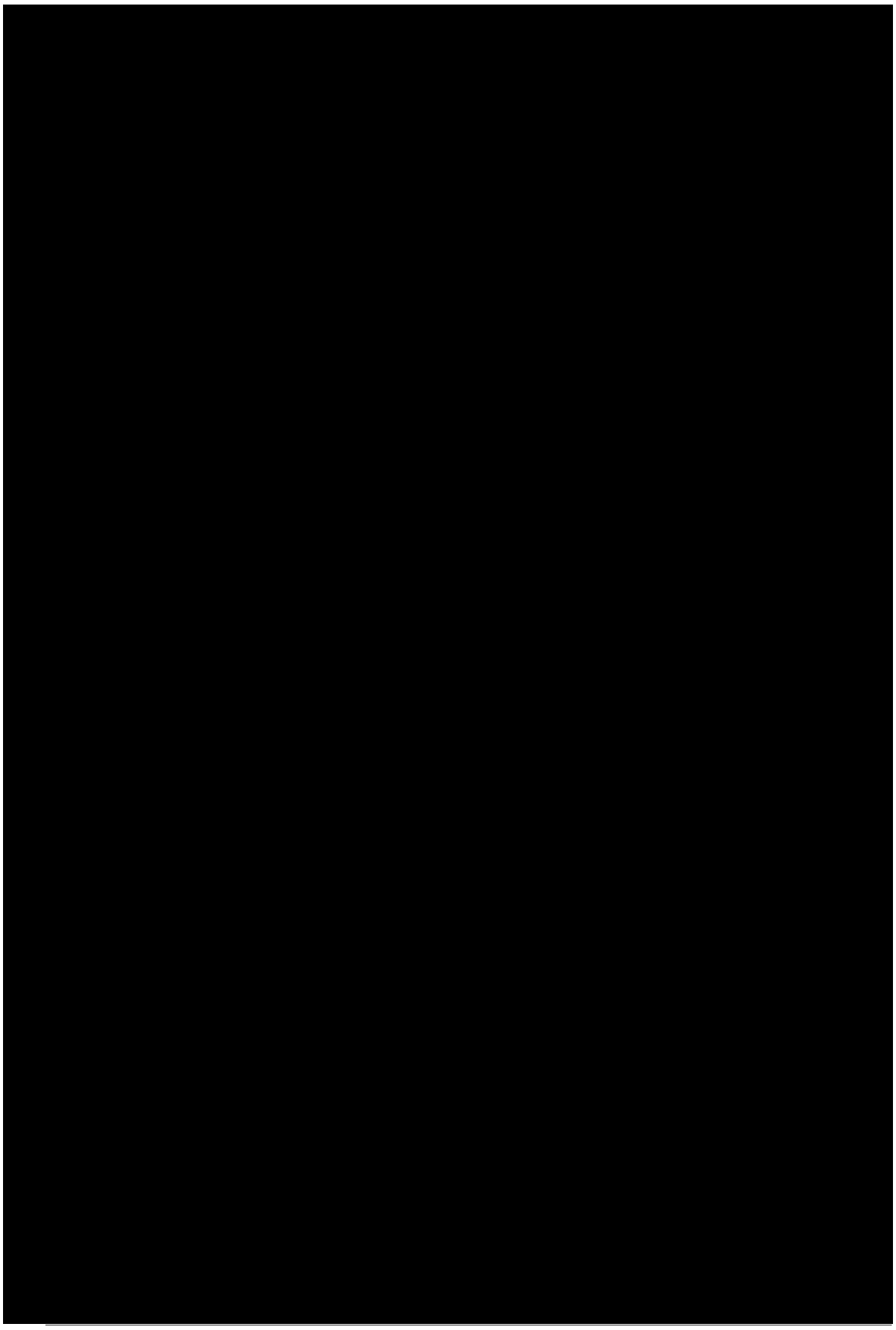
[a] Randomization happens after screening is complete and subject is confirmed to be eligible, up to approx. 1 week is included between randomization and the first dose to allow for logistics and shipments.
[b] Visit 3 may be conducted over the phone.
[c] The AE collection period begins with signing of ICF and ends at Visit 7 if the subject continues into extension or 2 weeks after the last dose of the study drug.
[d] May be conducted according to local protocols. Historic tests may be accepted. Stimulation test protocols and results are subject to review and approval by the Medical Monitor.
[e] May be conducted according to local protocols. ACTH test at screening is required if subject is not on glucocorticoid replacement therapy; morning (6:00-10:00AM) serum cortisol is < 15.0 µg/dL (measured at central laboratory), and if ACTH stimulation test or ITT (with serum cortisol measurements) performed within 90 days of screening is not available. Subjects who are not on glucocorticoid replacement therapy and are diagnosed with low morning cortisol may undergo an ACTH stimulation test at any time during the trial.
[f] Only if MRI/CT scan within 6 months prior to screening is not available. MRI scan is required at Visit 7 for childhood cancer survivors. If DXA scan will be performed at the same visit, DXA scan should be conducted before MRI/CT scan that uses contrast.
[g] Fundus photography is required for subjects with a diagnosis of diabetes mellitus at screening.
[h] Blood draw should be between 6:00 and 10:00AM.
[i] Data reviewed by unblinded CRO team member; results not distributed to the trial site.
[j] Results not distributed to the site.
[k] An ADA sample will be collected at V7. An ADA sample and a pregnancy sample for females of childbearing potential will be collected approximately atleast 30 days after the last study drug dose for subjects not continuing into the extension trial.
[l] DXA assessment windows: Up to 1 week prior to Visit 1, pre-dose; Up to 1 week before or after Visit 4 (Weeks 11, 12, 13); Up to 1 week after Visit 7 (Week 38 or Week 39). Body composition to be assessed at all DXA scans. Total body bone mineral content and bone mineral density to be assessed only at Visit 1. For subjects in Germany Visit 1 DXA will not be performed
[m] As V2, V3 and V4 will be performed 4-5 days after injection for the once-weekly treatment arms, at these visits it will be assessed if scheduled up-titration can be performed and subjects will be instructed about the dose for further administration, starting with next injection 2-3 days after the visit.
[n] PRO completion on site by subject The order of PRO completion is [redacted]
[o] Not required if visit is conducted over the phone. The Subject Diary content cannot be reviewed but should be discussed.

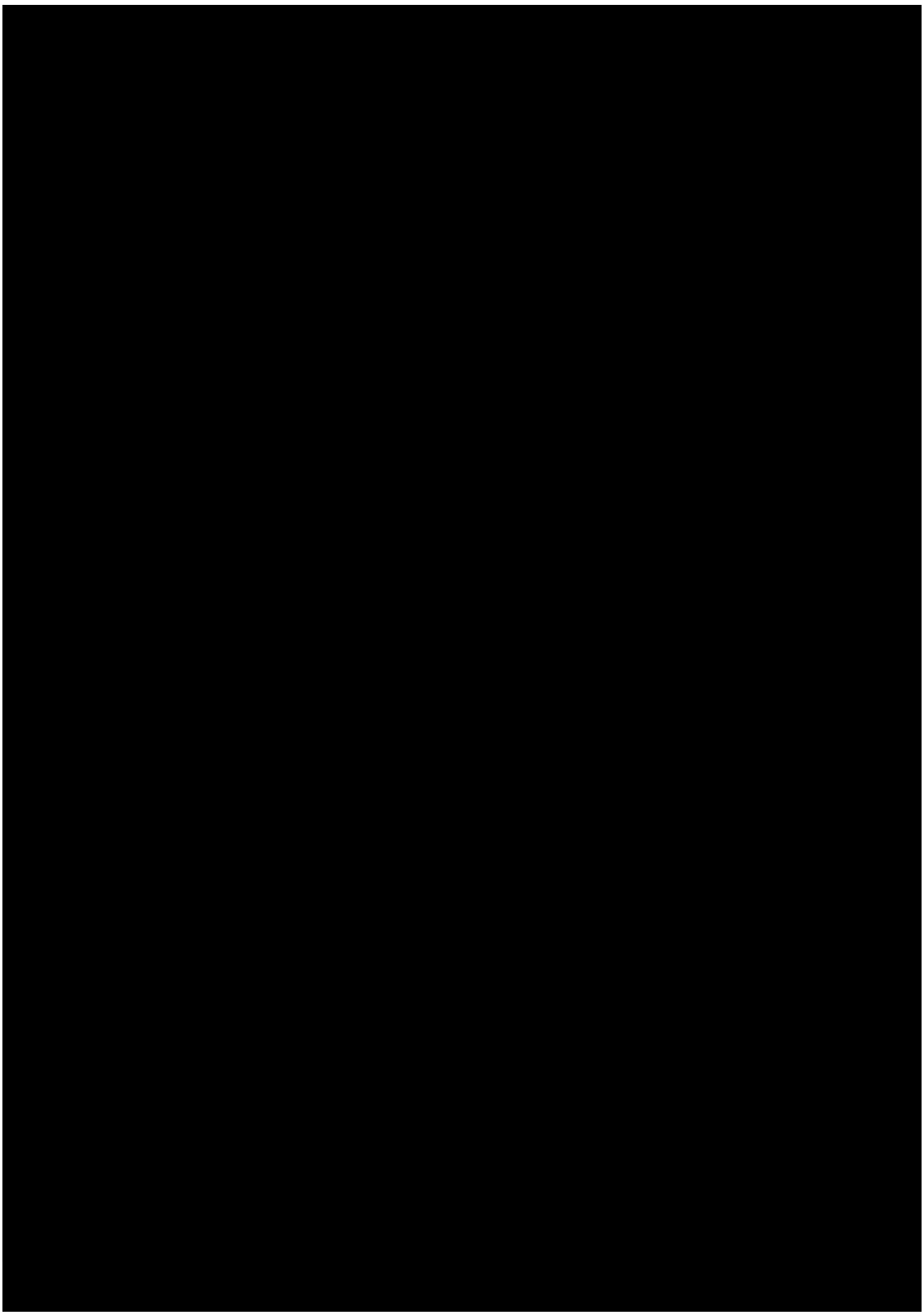
19. APPENDICES

Appendix 4 –ANAPHYLAXIS PRECAUTIONS









APPENDIX 4. ANAPHYLAXIS PRECAUTIONS

Definition of Anaphylaxis

For this study, anaphylaxis is defined according to [redacted] Criteria (See Table 1 below)

Following institutional standards, the subject and/or caregiver should be able to recognize the signs and symptoms of hypersensitivity, including anaphylaxis, prior to consideration of self-administration of study drug. If appropriate, based on investigator medical judgement, the availability of epinephrine for emergency use may be considered. In the event of hypersensitivity reaction, the subject should seek medical care immediately and should be provided supportive care per institutional standards.

[redacted]

FOR REFERENCE ONLY:

The following is intended for reference only and should not supersede any local standard operating procedures and clinical judgment.

Precautions for severe hypersensitivity reaction including anaphylaxis: consider the availability of the following:

- *Injectable epinephrine for subcutaneous use*
- *Antihistamine*
- *Corticosteroids*
- *Monitoring devices: Blood pressure monitor, Oxygen saturation monitor*
- *Take into consideration whether prompt transfer to an Emergency room would be feasible, considering the availability of*
  - *Oxygen*
  - *Nebulizer, bronchodilator agent*
  - *IV infusion solution, tubing, catheter, tape*

Management of severe hypersensitivity including anaphylaxis

In the event of suspected ***severe hypersensitivity reaction including anaphylaxis****, consider the following procedures:*

1. Maintain adequate airway

Administer subcutaneous epinephrine, and/or other medications as required by patient's status and as directed by physician in charge.

Continue to observe the patient and document observations, and consider prompt transfer to Emergency room if indicated.

Approval Signatures

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Document Number: VV-SUB-066638

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