## *16.1.9 Documentation of Statistical Methods*

Final Statistical Analysis Plan, Version 1.0, dated 27-Nov-2024

# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Title** | **A Multicenter, Open-Label, Extension Trial to Investigate Long Term Efficacy and Safety of Lonapegsomatropin in Adults with Growth Hormone Deficiency** |
| **Protocol:** | **TCH-306EXT** |
| **IND/Eudra CT Number** | **IND:126053**<br>**EudraCT:2020-000929-42** |
| **Investigational Product:** | **Lonapegsomatropin** |
| **Phase:** | **3** |
| **Sponsor:** | **Ascendis Pharma Endocrinology Division A/S**<br>**Tuborg Boulevard 12, DK-2900**<br>**Hellerup, Denmark** |
| **Author:** | [redacted] |
| **Date:** | **27 November 2024** |
| **Version Number:** | **Version 1.0** |

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## ABBREVIATIONS

| | |
|---|---|
| ACTH | adrenocorticotrophic hormone |
| ADA | anti-drug antibodies |
| AE | adverse event |
| [redacted] | |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| CDF | cumulative distribution function |
| CMH | Cochran–Mantel–Haenszel |
| CRO | contract research organization |
| CT | computed tomography |
| d | day |
| DXA | dual-energy x-ray absorptiometry |
| eCRF | electronic case report form |
| eCDF | empirical cumulative density function |
| ECG | electrocardiographic |
| eGFR | estimated glomerular filtration rate |
| EOT | end of trial |
| [redacted] | |
| FDA | food and drug administration |
| fT3 | free triiodothyronine |
| fT4 | free thyroxine |
| GCP | good clinical practice |
| GGT | gamma-glutamyl transferase |
| GH | growth hormone |
| GHD | growth hormone deficiency |
| GLP | good laboratory practice |
| GLP-1 | glucagon-like peptide 1 |
| GMP | good manufacturing practice |
| HbA1c | hemoglobin A1c |
| HDL | high-density lipoprotein |
| hGH | human growth hormone |

| | |
|---|---|
| ICF | informed consent form |
| ICH | international council on harmonization |
| IGF-1 | insulin-like growth factor-1 |
| IGFBP-3 | insulin-like growth factor binding protein-3 |
| IM | investigator meeting |
| IND | investigational new drug |
| IP | investigational product |
| IWRS | interactive web randomization system |
| kg | kilogram |
| LDH | lactate dehydrogenase |
| LDL | low-density lipoprotein |
| LS mean | least square mean |
| MRI | magnetic resonance imaging |
| MAR | missing at random |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCT | meaningful change threshold |
| MCV | mean corpuscular volume |
| mPEG | methoxypolyethylene glycol |
| PGIS | patient global impression scale |
| [redacted] | |
| [redacted] | |
| PDF | probability density function |
| PRO | patient report outcomes |
| PT | preferred term |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDS | standard deviation score |
| SE | standard error |
| SOC | system organ class |
| TEAE | treatment emergent adverse event |
| [redacted] | |
| TSH | Thyroid stimulating hormone |
| VLDL | Very low density lipoprotein |
| WHO | World Health Organization |

## 1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide technical and detailed elaboration of the statistical analyses of long-term efficacy and safety data as outlined and/or specified in the final TCH-306 EXT study protocol (version 5.0 dated 16 June 2022).

The final analysis of the study will be performed when all subjects have either completed 52 weeks of study treatment with safety follow up visit or discontinued early in the extension period.

This SAP was developed in accordance with the International Council on Harmonization (ICH) E9 guidelines. All decisions regarding statistical analysis of the study, as defined in this SAP, will be made prior to unblinding of the study data for the final analysis.

## 2. STUDY DESIGN

This is a phase 3 open-label multicenter extension trial designed to evaluate the long-term safety and efficacy of lonapegsomatropin administered once-weekly. The trial participants are adults (males and females) with GHD having completed the treatment period in trial TCH-306 (foresiGHt) and therefore, are either previously treated with lonapegsomatropin, a daily somatropin product, or placebo in the main treatment period of TCH-306 or treatment experienced subjects who switched from commercially available daily somatropin treatment (Japan only).

The trial duration will up to 60 weeks in total and consist of:

- Screening Period – up to 3 weeks
- Treatment Period – (52 weeks), consisting of:
  - Dose Titration Period – 12 weeks, three visits
  - Dose Maintenance Period – 40 weeks, four visits
- Follow-up Treatment-free Period – (30-37 days/4-5 weeks), two visits, consisting of:
  - Two weeks after the last dose of trial drug: Collection of AEs, remotely
  - 30-37 days after the last dose of trial drug: Samples for ADA and pregnancy test (for females of childbearing potential)

A schematic of the study is presented in Figure 1 and a Schedule of Events in Table 1.

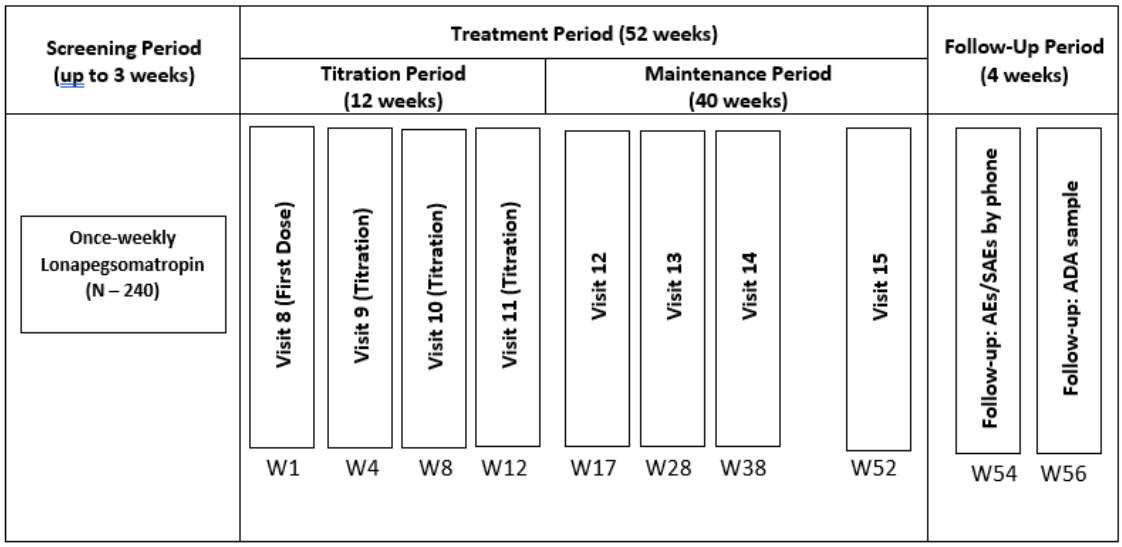
Subjects will be classified into one of the following treatment groups based on the treatment group the subject was randomized in the main treatment period of TCH-306 (foresiGHt):

- Lonapegsomatropin/Lonapegsomatropin: randomized to lonapegsomatropin in TCH-306
- Daily Somatropin/Lonapegsomatropin: randomized to daily somatropin in TCH-306
- Placebo/Lonapegsomatropin: randomized to placebo in TCH-306

Subjects that switched from commercially available daily somatropin treatment (Japan only) will be classified as:

- Commercial Switch

**Figure 1: TCH-306EXT Trial Design**




W = Week; N = Number

**Table 1: TCH-306EXT Schedule of Events**

| Timing | Screening | V8 | Titration Period | | | Maintenance Period | | | End of Treatment | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | V9 Week 4 | V10 Week 8 | V11 Week 12 | V12 Week 17 | V13 Week 28 | V14 Week 38 | V15 Week 52 | V16 Safety | V17/End of Trial |
| **Procedure** | **Subjects who Participated in TCH-306 Same Day or Later than V7 in TCH-306** | **Up to 3 Weeks after Screening** | **3 Weeks + 4-5 Days after V8** | **Remote Visit** | **4-5 Days Post Dose** | **4-5 Days Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **4-5 Days Post Dose** | **Remote Visit, 14-16 Days after Last Dose** | **30-37 Days after Last Dose** |
| | **Subjects who are Switching from Commercially Available Daily Somatropin Treatment (Japan Only)** | **Up to 6 Weeks after Screening** | | | | | | | | | |
| Informed consent[a] | Before or at screening | | | | | | | | | | |
| | X | | | | | | | | | | |
| Medical history, current and prior medications (≤ 12 months prior ICF), Demography | | | | | | | | | | | |
| | X | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | |
| | X | | | | | | | | | | |
| Physical examination | V7 TCH-306 | | | | X | | | | X | | |
| | X | | | | | | | | | | |
| Weight | V7 TCH-306 | | | | X | | | | X | | |
| | X | | | | | | | | | | |

| Timing | Screening | V8 | Titration Period | | | Maintenance Period | | | End of Treatment | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | V9 Week 4 | V10 Week 8 | V11 Week 12 | V12 Week 17 | V13 Week 28 | V14 Week 38 | V15 Week 52 | V16 Safety | V17/End of Trial |
| **Procedure** | **Subjects who Participated in TCH-306 Same Day or Later than V7 in TCH-306** | **Up to 3 Weeks after Screening** | **3 Weeks + 4-5 Days after V8** | **Remote Visit** | **4-5 Days Post Dose** | **4-5 Days Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **4-5 Days Post Dose** | **Remote Visit, 14-16 Days after Last Dose** | **30-37 Days after Last Dose** |
| | **Subjects who are Switching from Commercially Available Daily Somatropin Treatment (Japan Only)** | **Up to 6 Weeks after Screening** | | | | | | | | | |
| Height | | | | | | | | | | | |
| | X | | | | | | | | | | |
| Pregnancy test (females of childbearing potential only)[b] | V7 TCH-306 | X | X | | X | X | X | X | X | | X |
| | X | X | | | | | | | | | |
| Safety laboratory tests[c] | V7 TCH-306 | | X | | X | X | X | X | X | | |
| | X | | | | | | | | | | |
| IGF-1 and IGFBP-3 laboratory tests[c] | V7 TCH-306 | | X | | X | X | X | X | X | | |
| | X | | | | | | | | | | |
| [redacted] | | | | | | | | | | | |
| ADA/Antibody laboratory test | V7 TCH-306 | | X | | X | X | X | X | X | | X |
| | X | | | | | | | | | | |

| Timing | Screening | V8 | Titration Period | | | Maintenance Period | | | End of Treatment | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | V9 Week 4 | V10 Week 8 | V11 Week 12 | V12 Week 17 | V13 Week 28 | V14 Week 38 | V15 Week 52 | V16 Safety | V17/End of Trial |
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| | **Subjects who are Switching from Commercially Available Daily Somatropin Treatment (Japan Only)** | **Up to 6 Weeks after Screening** | | | | | | | | | |
| DXA (dual-X-ray-absorptiometry) scan | V7 TCH-306 | | | | X[d] | | | | X[d] | | |
| | X | | | | | | | | | | |
| 12-lead ECG | V7 TCH-306 | | X | | | | | | X | | |
| | X | | | | | | | | | | |
| Vital signs | V7 TCH-306 | | X | | X | X | X | X | X | | |
| | X | | | | | | | | | | |
| Fundoscopy[e] | V7 TCH-306 | | | | | | | | X | | |
| | X | | | | | | | | | | |
| MRI/CT scan for childhood cancer survivors | V7 TCH-306 | | | | | | | | X | | |
| | X | | | | | | | | | | |
| Trial drug dispensing | | X | X | | X | X | X | X | | | |
| | | X | | | | | | | | | |

| Timing | Screening | V8 | Titration Period | | | Maintenance Period | | | End of Treatment | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | V9 Week 4 | V10 Week 8 | V11 Week 12 | V12 Week 17 | V13 Week 28 | V14 Week 38 | V15 Week 52 | V16 Safety | V17/End of Trial |
| **Procedure** | **Subjects who Participated in TCH-306 Same Day or Later than V7 in TCH-306** | **Up to 3 Weeks after Screening** | **3 Weeks + 4-5 Days after V8** | **Remote Visit** | **4-5 Days Post Dose** | **4-5 Days Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **4-5 Days Post Dose** | **Remote Visit, 14-16 Days after Last Dose** | **30-37 Days after Last Dose** |
| | **Subjects who are Switching from Commercially Available Daily Somatropin Treatment (Japan Only)** | **Up to 6 Weeks after Screening** | | | | | | | | | |
| Trial drug training and administration[f] | | X[f] | | | | | | | | | |
| | | X[f] | | | | | | | | | |
| Dose titration instruction, if applicable | | | X | X | X | | | | | | |
| AE review, including injection site reactions | | | X | X | X | X | X | X | X | X | |
| Concomitant medication review | | | X | X | X | X | X | X | X | | |
| | X | | | | | | | | | | |
| Participant diary review | | | X | X | X | X | X | X | X | | |
| [redacted] | | | | | | | | | | | |

| Timing | Screening | V8 | Titration Period | | | Maintenance Period | | | End of Treatment | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | V9 Week 4 | V10 Week 8 | V11 Week 12 | V12 Week 17 | V13 Week 28 | V14 Week 38 | V15 Week 52 | V16 Safety | V17/End of Trial |
| **Procedure** | **Subjects who Participated in TCH-306 Same Day or Later than V7 in TCH-306** | **Up to 3 Weeks after Screening** | **3 Weeks + 4-5 Days after V8** | **Remote Visit** | **4-5 Days Post Dose** | **4-5 Days Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **1-3 Days (8-75 hrs) Post Dose** | **4-5 Days Post Dose** | **Remote Visit, 14-16 Days after Last Dose** | **30-37 Days after Last Dose** |
| | **Subjects who are Switching from Commercially Available Daily Somatropin Treatment (Japan Only)** | **Up to 6 Weeks after Screening** | | | | | | | | | |
| [redacted] | | | | | | | | | | | |
| Drug accountability | | | X | X | X | X | X | X | X | | |

[a] Informed consent must be obtained no later than at screening
[b] At V8, pregnancy is checked by urine testing only, at all other visits this is determined by serum
[c] Fasting required (except at the follow-up visit). Lab samples to be processed as described in the Laboratory Manual and shipped to central lab on the day of sampling
[d] DXA scan window is up to 1 week before or after visit. To be uploaded to central reader. If DXA scan will be performed at the same visit, DXA scan should be conducted before MRI/CT scan that uses contrast.
[e] Fundus photography is required for participants with a diagnosis of diabetes mellitus
[f] First dose administered at site; subsequent doses administered by participant on the same weekday. Diary to be handed out to participant with instruction to enter every dose taken

[redacted]

## 3. STUDY OBJECTIVES

### 3.1. PRIMARY OBJECTIVE

To evaluate the safety of once-weekly lonapegsomatropin in adults with GHD previously treated in trial TCH-306 or with commercially available daily somatropin treatment (Japan only).

### 3.2. SECONDARY OBJECTIVES

To evaluate the efficacy of once-weekly lonapegsomatropin in adults with GHD or with commercially available daily somatropin treatment (Japan only).

## 4. SAMPLE SIZE CONSIDERATIONS

No formal sample size calculation is performed.

All participants (n=220) who have completed the treatment period of the TCH-306 trial and meet eligibility criteria can be assigned to trial intervention.

In addition, subjects switching from commercially available daily somatropin treatment (n=13) will be included in this trial.

## 5. PLANNED ANALYSIS

### 5.1. INTERIM ANALYSIS

Periodic analysis can be done at sponsor's discretion to support regulatory submission or product planning.

### 5.2. FINAL ANALYSIS

The final analysis of the study will be conducted after the data base lock when all subjects have completed extension period or discontinued early.

## 6. DATA MONITORING COMMITTEE

Not applicable

## 7. ANALYSIS ENDPOINTS

### 7.1. SAFETY ENDPOINTS

Safety endpoints as measured throughout the 52 weeks of treatment include:

- Incidence of AEs
- Laboratory values
- Vital signs

- Immunogenicity data
- ECGs
- Fundoscopy

### 7.2. EFFICACY ENDPOINTS

- Change from baseline in trunk percent fat at Week 52 (as assessed by DXA).
- Change from baseline in trunk fat mass at Week 52 (as assessed by DXA)
- Change from baseline in total body lean mass at Week 52 (as assessed by DXA)

## 8. DEFINITIONS

### 8.1. EXTENSION PERIOD

The extension period is up to 52 weeks of treatment period defined as the duration of the first dose date of the extension trial (TCH-306 EXT) to the last dose date of the study drug in the extension trial.

The date of the first dose of open label study drug in the extension period is defined as the date when a subject received the first dose of open label study drug. The date of the last dose of open label study drug during the extension period of 52 weeks of treatment is defined as the date a subject received the last dose of study drug. If the date of last dose of study drug is unknown, then the last date of the study drug was known to have been taken will be used.

## 8.2. STUDY DAY

Study day will be calculated with respect to the date of the first dose of open label study drug. For assessments conducted on or after the date of the first dose of open label study drug, study day will be calculated as:

(Assessment date – date of first dose of open label study drug) + 1

For assessments conducted before the date (and time) of the first dose of open label study drug, study day will be calculated as:

(Assessment date – date of first dose of study drug).

## 8.3. DURATION OF TREATMENT AND COMPLIANCE

Treatment duration is defined as the duration of time from the date of the first dose of study drug of open label lonapegsomatropin in the extension period to the date of the last dose of in the extension period as follows:

Duration of treatment (day) = Last dose date of treatment – first dose date of treatment + 7

Treatment compliance = 100 * (Number of actual doses taken/total number of planned doses), where the total number of planned doses= (Duration of treatment/7).

## 8.4. AGE

Unless otherwise specified, the age will be the integer value of the derived value which will be based on the informed consent date: Age = (Informed Consent Date – Birth Date)/365.25. When date of birth is missing, the age recorded on CRF at the screening visit will be used.

If birth date is missing and age recorded on CRF is also missing, the birth date will be imputed (see Section 10.3) before calculating the age.

For a specific measurement, Age (years) = (Date of measurement – Birth Date)/365.25 and Age (months) = (Date of measurement – Birth Date)/365.25*12.

## 8.5. BASELINE MEASUREMENTS

Unless otherwise specified, baseline used in this study will be the extension period baseline, defined as the TCH-306 Visit 7 assessments or the last assessment taken on or prior to the first dose of study drug in TCH-306EXT, whichever occurs later considering date and time.

For the subjects that switched from commercially available daily somatropin treatment (Japan only), baseline value is defined as the last measurement on or before the first administration date (if time is not available) of study drug in the extension period.

## 8.6. TREATMENT GROUP

Subjects in the extension period will be classified into one of the following treatment groups based on the treatment group the subject was randomized in the main treatment period of TCH-306 (foresiGHt):

- Lonapegsomatropin/Lonapegsomatropin
- Daily Somatropin/Lonapegsomatropin
- Placebo/Lonapegsomatropin

Subjects that switched from commercially available daily somatropin treatment (Japan only) will be classified as:

- Commercial Switch

## 9. ANALYSIS POPULATIONS

Number and percent of patient meeting the definition of each analysis population will be summarized by treatment group.

### 9.1. SAFETY ANALYSIS POPULATION

All subjects who are exposed to any amount of the lonapegsomatropin in TCH-306EXT. All efficacy analysis will be conducted using this population

[redacted]

## 10. DATA SCREENING AND ACCEPTANCE

### 10.1. GENERAL PRINCIPLES

Data will be reviewed periodically. Any discrepant data will be reported to the clinical data manager promptly for query and resolution. The observed data will be reported as is in listings. Imputed data will be used for summary analysis.

### 10.2. HANDLING OF MISSING AND INCOMPLETE DATA

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

### 10.3. MISSING BIRTH DATES

To impute missing birth date, the following rules will be applied:

- If day is missing, impute 15.
- If month is missing, impute June.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is later than any study visit date/observed adverse event start date/ observed concomitant medication start date or any event start date, then earliest available visit date/adverse event start date/ concomitant medication start date or any event start date will be used without changing observed information.

## 10.4. MISSING MEDICAL HISTORY RELATED DATES

- If only day is missing, impute 1.
- If month is missing, impute January 1st.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is earlier than the birth date, then the birth date will be used.

## 10.5. MISSING DATES IN ADVERSE EVENTS

For determination of treatment-emergent adverse event (TEAE), if the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen on or after the first dose in the study (worst case approach).

The following rules will be used for TEAE determination where the AE has a missing start date.

If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from treatment-emergent AEs if the start day is before day of first treatment or the start day is after end of study day.

If the start time and day are missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if the start month is before month of first treatment or the start month is after end month of end of study month or if the stop date/time is before the start of first treatment.

If the start day and months are missing but the start year is complete, an AE will only be excluded from treatment-emergent AEs if the start year is before year of first treatment or if the start year is after end of study year or if the stop date/time is before the start of first treatment.

If the start date is completely missing, an AE will not be excluded from treatment emergent AEs unless the stop date/time is before the start of first treatment.

## 10.6. MISSING DATES IN PRIOR AND CONCOMITANT MEDICATION

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed the medication was administered concurrently during the treatment period, unless there is evidence to show otherwise.

The on-treatment period is defined as the time from the first dose to 7 days after the last dose of lonapegsomatropin.

## 10.7. MISSING CAUSAL RELATIONSHIP TO THE STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study drug is missing for an AE that started on or after the date of the study drug administration, a causality of “related” will be assigned. The imputed values for causal relationship to study drug will be used for the incidence summary; the values will be shown as missing in the data listings.

## 10.8. VISIT TIME WINDOWS

All post-baseline visits will be mapped to the post-baseline scheduled visit with the closest target study day for each scheduled assessment with exception of DXA data, [redacted] parameters.

If the unscheduled visit is in the middle of two scheduled visits, it will be mapped to the later one. After mapping, if there is more than one visit in the same window, the visit closer to the target assessment day will be used. If more than one visit has an equal distance to the target day, then the later one will be used; if more than one visit occurs on the same day, the time or the sequence number will be used to select the later record. For listings, all data points (as observed) will be included.

**Table 2: Analysis Window (All Parameters Except DXA, [redacted] Parameters)**

| PERIOD | VISIT | Week | Target Study Day | Study Day Window |
|---|---|---|---|---|
| Extension | Visit 8 | Date of first open label study drug | X1 | <=1 |
| | Visit 9 | (EXTENSION) Week 4 | X1+ 28 | ($X_1$+1) - ($X_1$+42) |
| | Visit 10 | (EXTENSION) Week 8 | X1+ 56 | ($X_1$+43) - ($X_1$+70) |
| | Visit 11 | (EXTENSION) Week 12 | X1+ 84 | ($X_1$+71) - ($X_1$+101) |
| | Visit 12 | (EXTENSION) Week 17 | X1+ 119 | ($X_1$+102) - ($X_1$+157) |
| | Visit 13 | (EXTENSION) Week 28 | X1 +196 | ($X_1$+158) - ($X_1$+231) |
| | Visit 14 | (EXTENSION) Week 38 | X1 +266 | ($X_1$+232) - ($X_1$+315) |
| | Visit 15 | (EXTENSION) Week 52 | X1 + 364 | ($X_1$+316) - ($X_1$+413) |
| Safety follow-up/End of Study | | Safety follow-up | Date of last dose + 28 days | (Date of last dose date + 14 days)-(Date of last dose + 49 days) |

Study day in the extension period is calculated with respect to the date of the first dose of study drug. $X_1$= First dose date of Open Label extension in study day in reference to the first dose day from the main period.

For the analysis of efficacy endpoints and [redacted] assessed by DXA, following study day window will be used:

- (EXTENSION) Week 12: analysis will be performed based on the assessments performed at the scheduled visit.
- (EXTENSION) Week 52: analysis will be performed based on the assessments performed at the scheduled visit.

If there are more than one DXA assessment in the same visit, the visit closer to the target assessment day will be used. If more than one DXA assessment with an equal distance to the target day, then the later one will be used in the analysis.

[redacted]

## 10.9. TESTING/VALIDATION PLAN

Data will be periodically reviewed by the cross functional team and issues will be addressed by Clinical Data Management.

## 10.10. SOFTWARE

SAS® software version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

# 11. STATISTICAL METHODS OF ANALYSES

## 11.1. GENERAL PRINCIPLES

In general, summaries will be performed descriptively by treatment group. Continuous, quantitative (absolute values at each time point and change from baseline if applicable) variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum values.

Categorical, qualitative variable summaries will include the frequency and percentage of subjects in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the cohorts.

All statistical tests will be two-sided and tested at statistical significant level of 0.05. P-values will be rounded and displayed in three decimals. If a p-value is less than 0.0001, it will be shown in tables as <0.0001. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

Unless otherwise specified, all summaries including by-visit summaries will be analyzed for the extension period (52 weeks of treatment) and for the commercial switch population, all analyses will be repeated and analyzed separately.

## 11.2. DISPOSITION

The number and percentage of subjects for each of the following categories will be summarized by treatment group:

- Subjects who enrolled in the open-label extension period
- Subjects who discontinued early from the 52-week open-label extension period and reasons for discontinuation
- Subjects who entered the post-treatment safety follow-up period

For Commercial Switch population following categories will be summarized:

- Subjects included in the extension period

The summaries will be presented in a table and subject disposition data will be presented in a listing.

## 11.3. PROTOCOL DEVIATIONS

Protocol deviations will be categorized as major and minor per the protocol deviation plan (v 1.0 dated 02 December 2022). Protocol deviations include following categories:

- Deviation from inclusion/exclusion criteria (Eligibility and Randomization)
- Deviation in proper subject's consenting (Informed Consent)
- Deviation in the process assessing the study endpoints (Primary and secondary efficacy endpoint analysis)
- Deviations in study procedures (Study procedures for safety and efficacy (other than primary or secondary efficacy study endpoints)
- Deviations from visit schedule (Missing study visit or visit out of window)
- Deviations in Adverse Events reporting and follow-up (Adverse events)
- Deviation in study drug dosing and handling (IP)
- The intake of prohibited medication(s) (Prohibited / restricted medication and procedures)
- ICH/GCP deviations (Other)
- ICH/GCP deviations (Investigational Site staff related)

Major protocol deviations will be summarized by deviation category for all subjects in the full analysis population. A by-subject listing of major protocol deviations will be provided.

## 11.4. INVESTIGATIONAL PRODUCT ADMINISTRATION

### 11.4.1. Extent of Exposure

The following parameters of the study drug will be summarized and listed for the extension period:

- Total number of injections received
- Total amount of dose received (mg)
- Cumulative amount of dose received by weeks (mg/week)
- Total duration of treatment (weeks)

Summary statistics per treatment group will be tabulated by dosing group and total for the Safety Analysis Population. For Commercial Switch Population (Japan only), descriptive summary of first dose date of open label extension since the last dose date of commercially available daily somatropin will be included.

### 11.4.2. Measurement of Treatment Compliance

Descriptive statistics for study drug compliance will be presented by treatment groups for the Safety Analysis Population.

The number of injections and cumulative dose per subject administered and duration of exposure by treatment groups will be summarized. Treatment compliance will be calculated as total number of actual dose received divided by total number of planned dose expected over specified period will also be displayed.

### 11.4.3. Dose Adjustment

A descriptive table including the frequency and percentages of subjects by each group will be presented for following dose adjustments categories for Titration period and Maintenance period:

- Titration
- AE
- IGF-1
- Rechallenge
- Other

## 11.5. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Descriptive summaries of the extension period baseline will be summarized:

- Age (years)
- Age category (< 30, ≥30 - ≤60 and > 60 years)
- Sex (male, female)
  - Females (on oral estrogen, not on oral estrogen)
- Race
- Ethnicity
- Region
  - North America
  - Europe
  - Asia-Pacific
- Weight (kg)
- Body mass index (BMI) ($kg/m^2$)
  - < 25 kg/m2
  - 25≤ - <30 kg/m2
  - 30≤ - <35 kg/m2

  - 35≤ - <40 kg/m2
  - ≥ 40 kg/m2
- Body mass index (BMI) SDS
- IGF-1, IGF-1 SDS:
  - IGF-1 SDS < -2.0
  - IGF-1 SDS -2.0≤ - < -1.0
  - IGF-1 SDS -1.0≤ - < 2.0
  - IGF-1 SDS 2.0≤ - < 2.5
  - IGF-1 SDS 2.5≤ - < 3.0
  - IGF-1 SDS ≥ 3.0
- IGFBP-3, IGFBP-3 SDS

## 11.6. MEDICAL HISTORY

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term for Commercial Switch Population (Japan only). In addition, Medical History in the extension period is inclusive of medical history collected from the main period and interval history collected since the last visit of the main period (Visit 7/Week 38) and will be providing in the listing.

## 11.7. PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any medication started before the date of the study drug administration (medication start date prior to the first dose date) for Commercial Switch Population in the extension period.

Concomitant medication is defined as medication taken on or after the date of the first dose of lonapegsomatropin in the extension period, where the medication end date is on or after first lonapegsomatropin dose date (or ongoing).

Both prior and concomitant medications will be coded by ATC level 4 (Chemical Subgroup) and ATC level 3 (pharmacologic class) using World Health Organization Drug Dictionary (WHO Drug). If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class in summary tables. Prior and concomitant medications will be summarized overall and by treatment groups in tables for the Safety Analysis Population and will also be presented in a listing.

## 11.8. PRIOR AND CONCOMITANT PROCEDURES

Prior procedure is defined as any procedure started before the date of the study drug administration (procedure start date prior to the first dose date) for Commercial Switch Population in the extension period.

Concomitant procedure is defined as any procedures taken on or after the date of the study drug administration of lonapegsomatropin in the extension period (procedure end date on or after the dose date [or ongoing]).

Prior and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by overall and by treatment groups in tables for the Safety Analysis Population and will also be presented in a listing.

## 11.9. EFFICACY ANALYSIS

Efficacy analyses will be conducted on the ITT population.

### 11.9.1. Analysis of Efficacy Endpoints

- Change from baseline of extension period in trunk percent fat (as assessed by DXA) at Week 52.
- Change from baseline of extension period in trunk fat mass at Week 52 (as assessed by DXA)
- Change from baseline of extension period in total body lean mass at Week 52 (as assessed by DXA)

The ANCOVA model used in the TCH-306 main period will be implemented for the analysis of the efficacy endpoints outlined above. [redacted]

### 11.9.2. Analyses of Subgroup

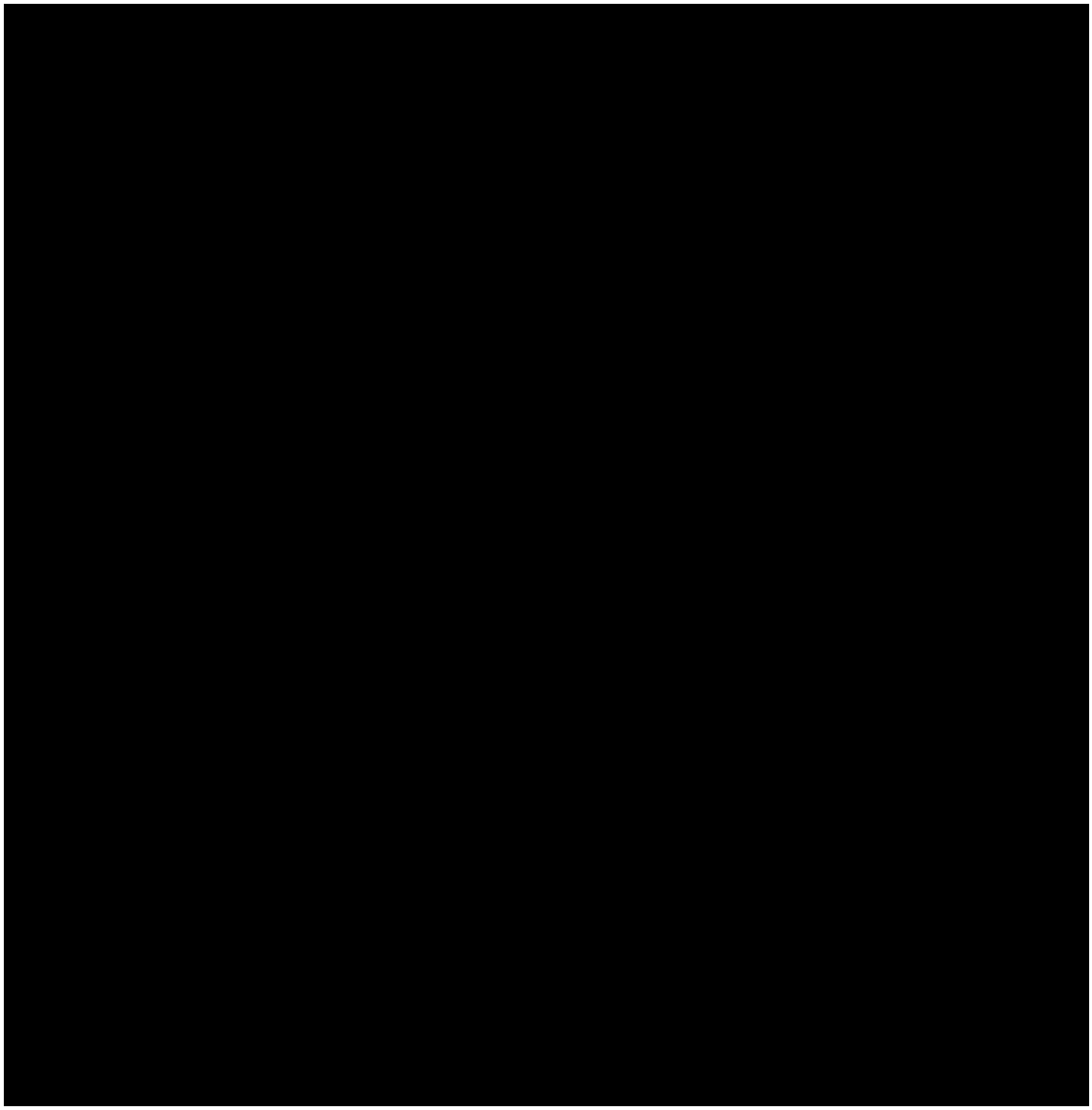
Subgroup analyses of the primary efficacy endpoint using the ANCOVA model will be performed. Subgroups will include but not limited to, the subgroups outlined in Table 3.

**Table 3: Planned Subgroup Analyses**

| Subgroup Name | Subgroup Levels |
|---|---|
| Region | North America, Europe, Asia-Pacific;<br>All regions except Japan vs. Japan |
| Diabetes mellitus Status (at baseline) | Yes, No |
| Age (years) | < 30, ≥30 - ≤60, > 60 |
| Sex | Male, Female |
| [redacted] | |
| BMI (kg/m$^2$) | < 30, ≥ 30 |
| Concomitant oral estrogen at screening | Yes, No |
| Dosing Group | Group 1: Oral estrogen intake (any age) or < 30 years old<br>Group 2: ≥ 30 to ≤ 60 years old; no oral estrogen intake<br>Group 3: > 60 years old; no oral estrogen intake |

The absolute values and mean change from baseline by visit will be presented with descriptive statistics for all treatment groups using the baseline extension period baseline. For subjects switched from syringe to auto-injector during the extension period, the following analysis will be repeated for the subjects who switched from syringe to auto-injector:

- Exposure/compliance
- TEAEs
- Injection site reaction
- Antibody (only positive vs negative)
- Device related PRO



## 11.11. SAFETY ANALYSIS

Unless otherwise specified, safety analyses will be performed using the Safety Analysis population for the extension period. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG) parameters, MRI, fundoscopy, immunogenicity, and other safety parameters if collected. For safety endpoints, all analyses will be based on the observed data (i.e., with no imputation of missing data), unless otherwise stated. These summaries will be presented by treatment group in the extension period.

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

An extension period AE (classified by preferred term) will be considered as treatment emergent adverse event (TEAE) if it occurred on or after the first dose of open-label lonapegsomatropin and was not present prior to the first dose of open-label lonapegsomatropin, or it was present at the first dose of open-label lonapegsomatropin but increased in severity during the study through 14 days after the last dose of treatment on the extension period.

A TEAE that started on or after the first dose date of open-label lonapegsomatropin will be counted as extension period TEAE.

- Summary of TEAEs by treatment
- TEAEs by treatment, SOC and PT (sorted by descending frequency by SOC and PT)
- TEAEs by treatment, SOC and PT Reported by > 5% of subjects in any treatment group
- Related TEAE by treatment, SOC and PT
- Serious TEAEs by treatment, SOC and PT (sorted by descending frequency by SOC and PT)
- Serious Related TEAEs by treatment, SOC and PT (sorted by descending frequency by SOC and PT)
- AEs leading to death by treatment, SOC and PT (sorted by descending frequency by SOC and PT)
- TEAEs leading to discontinuation of study by treatment, SOC and PT (sorted by descending frequency by SOC and PT)
- TEAEs leading to discontinuation of treatment by treatment, SOC and PT (sorted by descending frequency by SOC and PT)
- TEAEs by treatment and PT (sorted by descending frequency of PT)
- Related TEAEs by treatment and PT (sorted by descending frequency of PT)
- Serious TEAEs by treatment and PT (sorted by descending frequency of PT)
- Deaths by treatment

Detailed listings for all AEs, serious TEAEs, AEs leading to the discontinuation of study, TEAEs leading to the discontinuation of treatment, AEs leading to death, deaths and special situation will also be generated.

### 11.11.1. Injection Site Reactions

The number and percentage of subjects will be presented for injection site reactions and injection site reactions resulting in discontinuation of the treatment.

### 11.11.2. Other Adverse Events to Monitor

#### 11.11.2.1. Clinical Laboratory Parameters

Descriptive summaries of actual (absolute) values and changes from baseline values if applicable will be presented for the following by treatment and visit:

- 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 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, HDL, LDL, Lp(a) lipoprotein, free fatty acids, VLDL
- Thyroid and adrenal status: TSH, fT4, fT3, morning (06:00-10:00AM) cortisol
- Testosterone (males only)

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges

Data listings of laboratory will also be provided, displaying details of each laboratory test for central and local laboratories separately.

#### 11.11.2.2. Antibodies

The appropriateness of the approach taken to analyze and report anti-drug antibody data should be evaluated on a case-by-case basis (FDA Guidance for Industry 2016), following recent regulatory guidance and a white paper (Shankar G 2014). Statistical analysis of antibodies against drug (ADA) will include (but not be limited to) the following tabulated summaries of antibody frequencies and percentages:

1. Incidence of pre-existing anti-hGH binding antibodies (positive Baseline)
2. Incidence of treatment induced anti-hGH binding antibodies by positive types (treatment emergent positive and treatment boosted positive) and overall
3. Incidence of treatment induced, transient anti-hGH binding antibodies by positive types (treatment emergent positive and treatment boosted positive) and overall
4. Incidence of treatment induced anti-hGH neutralizing antibodies by positive types and overall

In addition, treatment induced anti-TransCon hGH and anti-PEG binding antibodies will also be summarized by visit and positive types and overall.

Treatment induced ADA will include two positive types:

- Treatment emergent positive: if baseline (pre-treatment sample) is negative for ADA and post-treatment sample is positive for ADA
- Treatment boosted positive: if baseline (pre-treatment sample) is positive and post-treatment sample has a titer which is at least 4-fold higher than the pre-treatment sample.

The baseline antibody status is the status before the first dose of lonapegsomatropin.

#### 11.11.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, BMI and weight) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

#### 11.11.2.4. Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTc), QTcF interval aggregate and changes from baseline values at each assessment time point to the end of study will be presented by treatment group.

#### 11.11.2.5. MRI and Fundoscopy

Data listings of Fundoscopy and MRI results will be provided separately.

## 12. REFERENCES

FDA Guidance for Industry (Draft). Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. April 2016. [Online]. Available from: https://www.fda.gov/media/77796/download.

Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J. 2014;16(4):658-673.

## 13. APPENDICES

### 13.1. SAP APPROVAL FORM

# STATISTICAL ANALYSIS PLAN AND AMENDMENT APPROVAL SIGNATURE FORM

**Title** A Multicenter, Open-Label, Extension Trial to Investigate Long Term Efficacy and Safety of Lonapegsomatropin in Adults with Growth Hormone Deficiency

**Protocol:** TCH-306EXT

**Original Statistical Analysis Plan: Amendment Version #:**

**Author:**

[redacted] _____ _____
Date

**Approved by:**

[redacted] _____
Date

[redacted] _____
Date

[redacted] _____
Date