# STATISTICAL ANALYSIS PLAN

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|---|---|
| **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 daily somatropin product in adults with growth hormone deficiency** |
| **Protocol:** | **TCH-306** |
| **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** |
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| **Date:** | **01 November 2023** |
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## ABBREVIATIONS

| | |
|---|---|
| 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 |
| 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] | |
| EQ VAS | visual analogue scale scores |
| 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 |
| MCMC | markov chain Monte Carlo |
| MCT | meaningful change threshold |
| MCV | mean corpuscular volume |
| mPEG | methoxypolyethylene glycol |
| [redacted] | |
| PK | pharmacokinetic |
| PD | pharmacodynamic |
| 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 efficacy and safety data as outlined and/or specified in the final TCH-306 study protocol (Version 4, 2022-Jun-04).

The final analysis of the study will be performed when all randomized subjects have either completed 38 weeks of study treatment with safety follow up visit or discontinued early. The primary, secondary, tertiary objectives of the trial will be evaluated.

This SAP was developed in accordance with the International Council on Harmonisation (ICH) E9 guidelines (US Federal Register 1998, ASA 2016). All decisions regarding statistical analysis of the trial, as defined in this SAP, will be made prior to unblinding of the trial data for the final analysis.

# 2. TRIAL DESIGN

Trial TCH-306 (foresiGHt) is a multicenter, randomized, parallel-arm, placebo-controlled (double-blind) and active-controlled (open-label), Phase 3 trial to assess the efficacy and safety of lonapegsomatropin in adults with growth hormone deficiency. The length of this trial will be 38 weeks. Approximately 240 subjects meeting the eligibility criteria will be randomized in a 1:1:1 ratio to the following 3 treatment groups:

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

Randomization will be stratified as follows:

- Dosing group
  - Group 1: Oral estrogen intake (any age) or < 30 years old
  - Group 2: ≥ 30 to ≤ 60 years old; no oral estrogen intake
  - Group 3: > 60 years old; no oral estrogen intake
- In the Dose group 2 ( ≥30 to ≤60 years old; no oral estrogen), randomization will be further stratified by sex.
- Diabetes mellitus status

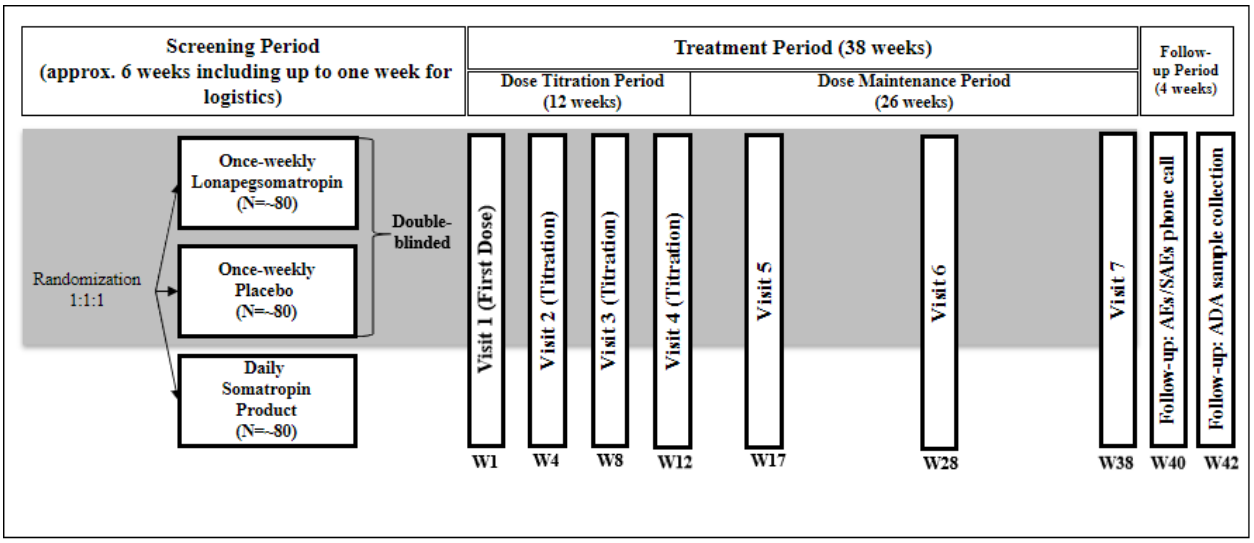
In Japan, randomization will be stratified by dosing group only.

After approximately 240 subjects have been enrolled under protocol amendment 2, enrollment in Asian countries will continue under amendment 4. To support applications across various countries, a total of approximately 282 subjects are expected to be enrolled in the trial.

This trial includes a screening period up to approximately 6 weeks, a treatment period of 38 weeks and a safety follow up period of 4 weeks.

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

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




W = Week; N = Number

**Table 1: TCH-306 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 AEsc | | × | × | × | × | × | × | × |
| Subject diary review | | | × | × o | × | × | × | × |
| Weight | × | × | × | × o | × | × | × | × |
| Height | × | | | | | | | |

| 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] |
|---|---|---|---|---|---|---|---|---|
| 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 | × | × | × | × |

| 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] |
|---|---|---|---|---|---|---|---|---|
| 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 (6:0010:00AM) 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.

# 3. BLINDING AND RANDOMIZATION METHODS

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 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.

Eligible subjects will be enrolled in the trial and sequentially assigned an identification number. A randomization schedule will be developed by an independent party to maintain blinding. Approximately 240 subjects will be randomized in a 1:1:1 ratio and assigned to a treatment sequence group via an Interactive Web Randomization System (IWRS).

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. In case of high IGF-1 values, a dose titration/reduction recommendation based on a predetermined algorithm will be provided by the unblinded team member. Refer to the trial blinding and dose adjustment plan for details.

Blinding of a weekly trial drug (lonapegsomatropin or placebo) versus daily comparator is not considered feasible. However, to protect the integrity of the trial, critical assessors (selected Sponsor team members, central vendors and other personnel as appropriate and feasible) will be blinded to all treatment assignment to minimize potential bias prior to database lock and trial unblinding. Refer to the trial data handling plan for details.

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

Staff working with the PK vendor, clinical trial supply and unblinded team members will be unblinded throughout the trial conduct. Refer to the blinding plan for details.

# 4. STUDY OBJECTIVES

## 4.1. PRIMARY OBJECTIVE

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

## 4.2. 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.

## 4.3. TERTIARY OBJECTIVE

[redacted]

# 5. SAMPLE SIZE CONSIDERATIONS

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. However, for local regulatory requirements, recruitment may be kept open in some countries after having this number reached for the global trial.

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%.

Sample size and power calculations were performed using the software SAS v 9.4.

# 6. PLANNED ANALYSIS

## 6.1. INTERIM ANALYSIS

No interim efficacy analysis for the main period is planned for this trial.

## 6.2. FINAL ANALYSIS

The final analysis of the trial will be conducted after the data base lock when all randomized subjects have completed 38 weeks of treatment or discontinued early.

# 7. DATA MONITORING COMMITTEE

Not applicable

# 8. ANALYSIS ENDPOINTS

## 8.1. EFFICACY ENDPOINTS

### 8.1.1. Primary Efficacy Endpoint

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

### 8.1.2. Key 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)

## 8.2. OTHER SECONDARY ENDPOINTS:

### 8.2.1. 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

### 8.2.2. Other Secondary Endpoint: Pharmacokinetic/Pharmacodynamic Endpoints

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

## 8.3. TERTIARY ENDPOINTS

[redacted]

## 8.4. EXPLORATORY ENDPOINTS

[redacted]

# 9. DEFINITIONS

## 9.1. DATE OF FIRST DOSE AND DATE OF LAST DOSE OF TRIAL DRUG

The date of the first dose of randomized trial drug is defined as the date when a subject receives the first dose of randomized trial drug. The date of the last dose of randomized trial drug during the 38 weeks of treatment is defined as the date a subject receives the last dose of randomized trial drug. If the complete date of last dose of trial drug is unknown, the last date the randomized trial drug was known to have been taken will be used.

The baseline value is defined as the last measurement on or before the first administration date (if time is not available) of the trial drug, unless otherwise specified.

## 9.2. STUDY DAY

Study day will be calculated with respect to the date of the first dose of trial drug (Study Day 1). For assessments conducted on or after the date of the first dose of trial drug, study day will be calculated as:

(Assessment date – date of first dose of trial drug) + 1

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

(Assessment date – date of first dose of trial drug)

For subjects who do not receive any amount of trial drug, study day will be calculated as above with respect to the date of randomization.

## 9.3. DURATION OF TREATMENT AND COMPLIANCE

Treatment duration is defined as the duration of time from the date of the first dose of trial drug to the date of the last dose of trial drug as follows:

Lonapegsomatropin:

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

Treatment compliance = number of actual doses taken/total number of planned doses, where the total number of planned doses = Duration of lonapegsomatropin treatment/7

Placebo:

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

Treatment compliance = number of actual doses taken/total number of planned doses, where the total number of planned doses = Duration of Placebo/7

Daily somatropin:

Duration of treatment (day) = Last dose date of Daily somatropin – first dose date of Daily somatropin + 1

Treatment compliance = number of actual doses taken/total number of planned doses, where total number of planned doses = Duration of Daily somatropin treatment during the trial

### 9.4. 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, rounded down to the next integer. When the 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 11.2.1) 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.

### 9.5. BASELINE DXA MEASUREMENTS

The baseline value is defined as the last measurement on or before the first administration date (if time is not available) of the study drug, unless otherwise specified.

## 10. ANALYSIS POPULATIONS

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

### 10.1. SCREENED POPULATION

The Screened Population will consist of all subjects who underwent a Screening Visit and received a subject identification number.

### 10.2. RANDOMIZED POPULATION

The Randomized Population will consist of all enrolled subjects who were randomized to a treatment group in the trial.

### 10.3. INTENT TO TREAT ANALYSIS SET

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

### 10.4. PER-PROTOCOL ANALYSIS SET

The Per-Protocol Analysis Set will be a subset of Intent to Treatment population. This set will exclude subjects with the following protocol deviation during the trial:

- Treatment Non-Compliance (Missed or overdosed) at least +/- 20 % of lonapegsomatropin, placebo, or daily somatropin doses during the treatment period
- Failed to have a DXA measurement at Week 38 visit
- Violates major inclusion or exclusion criteria (inclusion 02,03,04 or exclusion 07,15,18)
- Early termination defined as subjects who withdraw from the trial prior to Week 38 visit

- Any Prohibited therapies and procedures:
  - anti-obesity drugs/appetite suppressants (unless prescribed for indication other than weight loss/obesity)
  - GLP-1 receptor agonists (even if indicated for diabetes mellitus)
  - hGH therapies other than trial drug, GH secretagogues
  - bariatric surgery
  - anabolic steroids other than testosterone
  - cabergoline >0.5 mg/week or bromocriptine >20 mg/week (due to their effects on lowering IGF-1 and GH hormonal concentrations and their independent effects on weight)

The Per-Protocol analysis set will be used for sensitivity analysis of the primary efficacy endpoint. The Per-Protocol analysis set and the criteria will be identified prior to unblinding the trial.

### 10.5. SAFETY ANALYSIS SET

The Safety analyses will be performed using the Safety analysis set. The Safety analysis set is defined as all randomized subjects who have received any amount of trial drug and will be analyzed by the actual treatment received (not the randomized treatment). If a subject received more than one type of treatment during the trial, such subject will be analyzed by the treatment group the subject received more of.

### 10.6. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) ANALYSIS SET

The PK/PD analyses will be performed using the PK/PD analysis set. This set will include all subjects in the Safety Analysis Set who have PK/PD assessments.

## 11. DATA SCREENING AND ACCEPTANCE

### 11.1. GENERAL PRINCIPLES

Data will be reviewed periodically. Any questionable 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.

### 11.2. 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 trial. Missing and incomplete data will be identified for investigation, and possible resolution by Data Management prior to the trial database lock or snapshot.

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

### 11.2.1. 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.

### 11.2.2. 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.

### 11.2.3. 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 definitely shown that the AE did not occur or worsen on or after the first dose in the trial (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 the month of first treatment or the start month is after the end month of end of study month or if the stop date/time is before the start of first treatment date.

If the start day and month 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.

### 11.2.4. 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 to be concomitant if it cannot be shown that it was not administered during the on-treatment period. Missing dates will not be replaced.

The on-treatment period is defined as the time from the first dose to 7 days after the last dose of lonapegsomatropin/placebo or from the first dose to 1 day after last dose of daily somatropin.

### 11.2.5. Missing Causal Relationship to the Trial Drug for Adverse Events

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

### 11.2.6. Missing Data for Trunk Percent Fat at Week 38

If there are sufficient number ($n \geq 5$) retrieved dropouts in the lonapegsomatropin group, where retrieved dropouts are subjects who discontinued treatment prior to Week 38 but still have their measurements at Week 38, a retrieved dropout imputation method will be used to impute the missing measurement of non-retrieved dropouts based on known measurements from retrieved dropouts in the lonapegsomatropin group.

In the case where there are not sufficient numbers ($n < 5$) of retrieved dropouts, missing data in the lonapegsomatropin group will be imputed by copy reference imputation method for the subjects without final assessment at the Week 38 window (See Table 2) for the primary endpoint analysis (Ayele 2014).

Subjects with missing primary endpoint will have trunk percent fat value imputed using a multiple imputation model stratified by the treatment [Schafer JL 1997, Schafer JL 1999]. Imputation of missing data will be conducted under assumption of missing not at random (MNAR). Missing not at random means that the data are missing is systematically related to the unobserved data, that is, the missingness is related to events or factors which are not measured.

In this analysis, intermittent missing values will be imputed to monotone missing pattern using the Markov Chain Monte Carlo (MCMC) methodology which assume that the joint distribution of the missing data and the model parameters are distributed multivariate normal. The variable list for imputations will include region (North America, Europe, Asia),dosing group and AGHD onset (adult vs. childhood), results from baseline and post baseline values for trunk percent fat.

Then all the monotone missing values will be multiply-imputed using the imputation model built from the placebo group, i.e., assuming the missing data in the treatment group will have a profile that equals the profile of the placebo group for all time points (i.e., a copy-reference imputation). The missing data imputation will be implemented using PROC MI in SAS 9.4 with the MNAR statement. Missing data in the daily somatropin group will be imputed following the same method as the lonapegsomatropin group. Missing data in the placebo group will be imputed using the imputation model built from the placebo group.

## 11.3. 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, PRO, PK/PD 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**

| Visit | Week | Target Study Day | Study Day Window |
|---|---|---|---|
| Visit 1 (Pre-dose)/Baseline | Week 1 | 1 | <=1 |
| Visit 2 | Week 4 | 29 | 2-43 |
| Visit 3 | Week 8 | 57 | 44-71 |
| Visit 4 | Week 12 | 85 | 72-102 |
| Visit 5 | Week 17 | 120 | 103-158 |
| Visit 6 | Week 28 | 197 | 159-232 |
| Visit 7 | Week 38 | 267 | 233 – ( 316 or <= first dose date in the TCH-306 EXT which ever is earlier ) |
| Safety Follow-Up[1] | | Date of last dose + 28 days | Date of last dose date + 7 days - Date of last dose + 49 days |

Study day is calculated with respect to the date of the first dose of trial drug (Study Day 1). Safety Follow Up visit will be included for ADA analysis collected at Safety follow up visit[1].

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

- Week 12, analysis will be performed based on the assessments performed at the scheduled visit.
- Week 38: Target Day of 267 and Study Day window from 240 - (295 or last assessment taken on or prior to the first dose date in the TCH-306 EXT, whichever is earlier)

After mapping, if there is more than one DXA assessment in the same window, 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.

For the analysis of PRO [redacted] and PK/PD parameters including IGF-1 and IGFBP-3, analysis will be performed based on the assessments performed at the scheduled visit. For listings, all data points (as observed) will be included.

## 11.4. TESTING/VALIDATION PLAN

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

## 11.5. SOFTWARE

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

# 12. STATISTICAL METHODS OF ANALYSES

## 12.1. GENERAL PRINCIPLES

In general, summaries will be performed descriptively by treatment group. Continuous, quantitative (absolute values at each timepoint 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 trial 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 treatment period (Week 1 to Week 38).

## 12.2. SCREEN FAILURE

Reasons for screen failure and number of screen failure subjects will be summarized.

## 12.3. DISPOSITION

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

- Intent-To-Treat population
- Subjects included in the Safety population
- Subjects who completed the 38-week randomized treatment period
- Subjects who discontinued early from the 38-week randomized treatment period and reasons for discontinuation
- Subjects rolling into the open-label extension trial (TCH-306 EXT)
- Subjects who entered the post-treatment safety follow-up period and did not enroll in the open label extension trial

## 12.4. PROTOCOL DEVIATIONS

Protocol deviations will be categorized as major and minor per the protocol deviation plan (v 3.0 dated 07 Novermber 2023).

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

## 12.5. INVESTIGATIONAL PRODUCT ADMINISTRATION

### 12.5.1. Extent of Exposure

The following parameters of the trial drug will be summarized and listed:

- Total duration of treatment (weeks)
- Total number of actual doses
- Actual total dosage (mg hGH)
- Actual average dosage received (mg/week)

Summary statistics per treatment group will be tabulated overall and by dosing group for the Safety Analysis Population.

### 12.5.2. Measurement of Treatment Compliance

Descriptive statistics for trial drug compliance will be presented by treatment group for the Safety Analysis Population.

The number of injections and cumulative dose per subject administered and duration of exposure by treatment group 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.

### 12.5.3. Dose Adjustment

A descriptive summary including the frequency and percentages of subjects by each group will be presented for following dose adjustments categories for titration and maintenance period, separately:

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

## 12.6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Descriptive summaries will be provided for demographic and baseline characteristics on ITT and Per-protocol population, including but not limited to:

- 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/m2)
  - < 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
- Etiology of GHD:
  - Structural hypothalamic-pituitary defect
  - Pituitary tumor
  - Hypothalamic-pituitary surgery
  - Cranial irradiation
  - Traumatic brain injury
  - Genetic

- Other

- GHD Onset:
  - Childhood onset
  - Adulthood onset
- Pituitary Deficiencies:
  - GHD only
  - GHD and additional pituitary axis deficiencies
    a. Adrenal Deficiency
    b. Thyroid Deficiency
    c. Gonadal Deficiency
    d. Vasopressin Deficiency
- Time (yr) since diagnosis of GHD

## 12.7. 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. The most current March version of the dictionary will be used.

## 12.8. PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any medication started before the date of the trial drug administration (medication start date prior to the first dose date).

Concomitant medication is defined as any medication taken during the treatment period defined as medication end date on or after the date of the trial drug administration or ongoing.

Both prior and concomitant medications will be coded to ATC level 4 (Chemical Subgroup) and ATC level 3 (pharmacologic class) based on route and indication using World Health Organization (WHO) Drug Dictionary. The most current March version of the dictionary will be used. 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.

## 12.9. PRIOR AND CONCOMITANT PROCEDURES

Prior procedure is defined as any procedure started before the first date of the trial drug administration (procedure start date prior to the first dose date).

Concomitant procedure is defined as any procedures completed on or after the date of the trial drug administration (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. The most current March version of the dictionary will be used.

## 12.10. EFFICACY ANALYSIS

Efficacy analyses will be conducted on the ITT population according to the randomized treatment assignment.

### 12.10.1. Analysis of Primary Efficacy Endpoint

Population: The target trial population comprises adult subjects with GHD and who meet the inclusion and exclusion criteria as specified in the Protocol. The analysis population is the Intent-To-Treat population as defined in Section 10.3 who have baseline trunk percent fat assessed by DXA.

Variable: The variable is the primary efficacy endpoint, change from baseline in trunk percent fat as assessed by DXA at Week 38 (Study day 240 to 295).

Handling of intercurrent events (ICEs) and missing data: Treatment policy will be used to handle ICEs where all subjects should be followed to collect the efficacy outcome regardless of intercurrent events, including treatment discontinuation or taking rescue or prohibited mediations. Multiple imputation method will be used to impute the missing data if a subject is missing primary efficacy endpoint of change from baseline in trunk percent fat. See details in Section 11.2.6.

Population level summary: Treatment difference between lonapegsomatropin vs. Placebo in the change from baseline to Week 12 or Week 38.

Estimator: The difference in change from baseline at Week 38 in trunk percent fat will be estimated by the primary analysis of ANCOVA model adjusted for unequal variance, with multiple imputation for missing data as described in Section 11.2.6. The ANCOVA model will include treatment arm, region (North America, Europe, Asia-Pacific), baseline age group, gender, concomitant oral estrogen at screening in female subjects (yes vs. no), and AGHD onset (adult vs. childhood) and baseline trunk percent fat as a covariate.

For the primary efficacy analysis, a 2-sided 95% confidence interval will be calculated for the difference in least square means between the 2 treatment groups [lonapegsomatropin treatment minus placebo] at Week 38.

The absolute values and mean change from baseline of the primary endpoint variable by visit will be presented by treatment group with descriptive statistics.

### 12.10.2. Analyses of Key Secondary Efficacy Endpoint(s)

Secondary efficacy variables include the following 2 key secondary endpoints with alpha-protection. The treatment effect of lonapegsomatropin compared with placebo will be tested for the alpha-protected secondary endpoint using a fixed sequence testing procedure described in Section 12.10.3.

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

For the statistical method of analyzing the secondary endpoints, the ANCOVA model described in Section 12.10.1 will be repeated for the total body lean mass and trunk fat mass. The absolute values and mean change from baseline at each timepoint and at Week 38 for all secondary efficacy endpoints will be presented by treatment group.

In addition, correlation will be evaluated for the change from baseline in trunk fat mass and total body lean mass with the change in IGF-1 SDS level at Week 38.

Comparative statistics (p-values, 95% CI for differences) will be provided for the treatment comparison of lonapegsomatropin with placebo for all secondary efficacy endpoints. The 95% confidence intervals will be calculated for the mean treatment differences between lonapegsomatropin vs. placebo and lonapegsomatropin vs. daily somatropin.

### 12.10.3. Multiplicity Adjustment

A fixed-sequence testing procedure will be applied to control the family-wise error rate at a level of 0.05 (Guidance for Industry 2017). Under this testing procedure, the key secondary efficacy endpoints will be tested only if the superiority of primary efficacy endpoint of trunk percent fat for lonapegsomatropin over placebo is met at a two-sided 0.05 significance level. If the p-value for the primary endpoint is $< 0.05$, then the 2 key secondary endpoints listed below will be tested sequentially as below:

Test 1: Change from baseline in total body lean mass at Week 38

Test 2: Change from baseline in trunk fat mass at Week 38 (will be tested only if the result of Test 1 is significant $P < 0.05$)

### 12.10.4. Sensitivity Analyses

To assess the robustness of the primary analysis, the following sensitivity analyses of the primary endpoint will be performed.

**Sensitivity Analysis 1**

Analysis of the primary endpoint will be repeated in the per-protocol population.

**Sensitivity Analysis 2**

Analysis of the primary endpoint will be repeated for all subjects in the ITT Population who completed 38 weeks of trial treatment regardless of intercurrent event and have a DXA assessment within final assessment window between study day 240-295.

**Sensitivity Analysis 3**

To assess the impact of randomized subjects using different stratification factors across dosing groups and regions, analysis of the primary endpoint will be repeated for ANCOVA model which only includes treatment arm, region (Japan versus other countries), and dosing group and baseline trunk percent fat as covariates.

**Sensitivity Analysis 4**

The tipping point analysis will be conducted by iteratively assigning plausible outcomes to missing values for subjects in different treatment group independently until the conclusion is reversed (eg, analyses are no longer statistically significant). The same analysis method for the primary analysis as specified in Section 12.10.1 will be applied when analyzing adjusted data generated under each plausible shift parameter. The set of shift parameters, $K_1$ and $K_2$, will be selected to explore the space of possible missingness assumptions systematically and comprehensively. $K_1$ and $K_2$ are chosen such that the means are shifted to reduce the treatment effect and to identify the point where the p-value is tipped to be insignificant (P >=0.05) (Little 2002, Rubin 1987).

The steps for conducting tipping point analysis using PROC MI are described below:

Step 1: The pre-specified set of shift parameters are $K_1$ for lonapegsomatorpin group and $K_2$ for placebo group. $K_1$ is a set of shift parameters lying between 0 to 10 and $K_2$ is a set of shift parameters lying between $-10$ to 0. Let $k_1 \in K_1$ and $k_2 \in K_2$. Start the tipping point algorithm assuming $k_1$= 0 and $k_2$=0 (under the MAR assumption, an additional step will be performed to fill in the intermittent missing data to obtain a dataset with only monotone missing pattern before implementing PROC MI using the MONOTONE option)

Step 2: For each $k_1$ and $k_2$, impute missing data conditional on $k_1$and $k_2$ using PROC MI to form 100 complete datasets. The variable list for imputations will include region (North America, Europe, Asia),dosing group and AGHD onset (adult vs. childhood), results from baseline and post baseline values for trunk percent fat.

Step 3: Given the shift parameters ($k_1$, $k_2$), conduct pre-specified statistical analysis as described in Section 12.10.1 for each of the 100 complete datasets and integrate the results across 100 datasets by Rubin's rule using PROC MIANALYZE.

Step 4: In the event that the tipping point is not identified using the pre-specified set of shift parameters $K_1$ and $K_2$, extend $K_1$ to include additional shift parameters between 10 and 20 and extend $K_2$ to include additional shift parameters between $-20$ and $-10$. Repeat steps 2-3 utilizing the additional shift parameters until the tipping point is identified or all possible pairs have been analyzed.

Imputed P-values from the analysis described aboved will be graphically presented as a heat-map to demonstrate two dimensional tipping point between the 2 treatment groups (Lonapegsomatropin vs. Placebo).

### 12.10.5. Analyses of Subgroup

Subgroup analyses of the primary efficacy endpoint using the ANCOVA model will be repeated 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 subgroups outlined in Table 3.

**Table 3: Planned Subgroup Analyses**

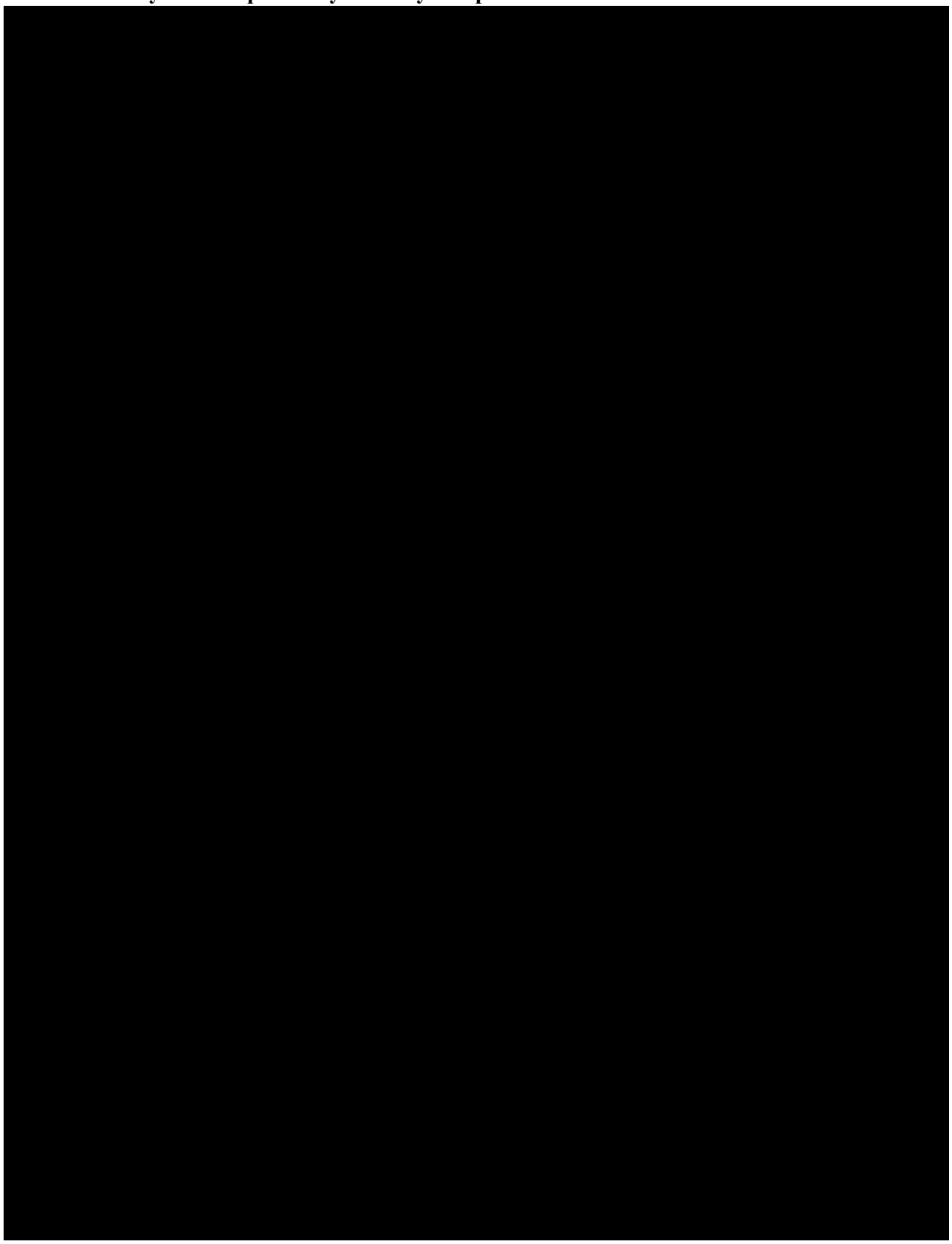
| Subgroup Name | Subgroup Levels |
|---|---|
| Region | North America, Europe, Asia-Pacific;<br>All regions except Japan vs. Japan; |
| Diabetes mellitus status (at baseline) | Yes, No |
| Age (years) | < 30, ≥ 30 - ≤ 60, > 60 |
| Sex | Male, Female |
| AGHD Onset | Adult, Childhood |
| BMI (kg/m^2) | < 30, >= 30 |
| Concomitant oral estrogen at screening for female | 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 |
| Race | American Indian or Alaska Native<br>Asian<br>Black or African American<br>Native Hawaiian or Other Pacific Islander<br>White<br>Other |
| Ethnicity | Hispanic or Latino<br>Noth Hispanic or Latino<br>Not Reported<br>Unknown |

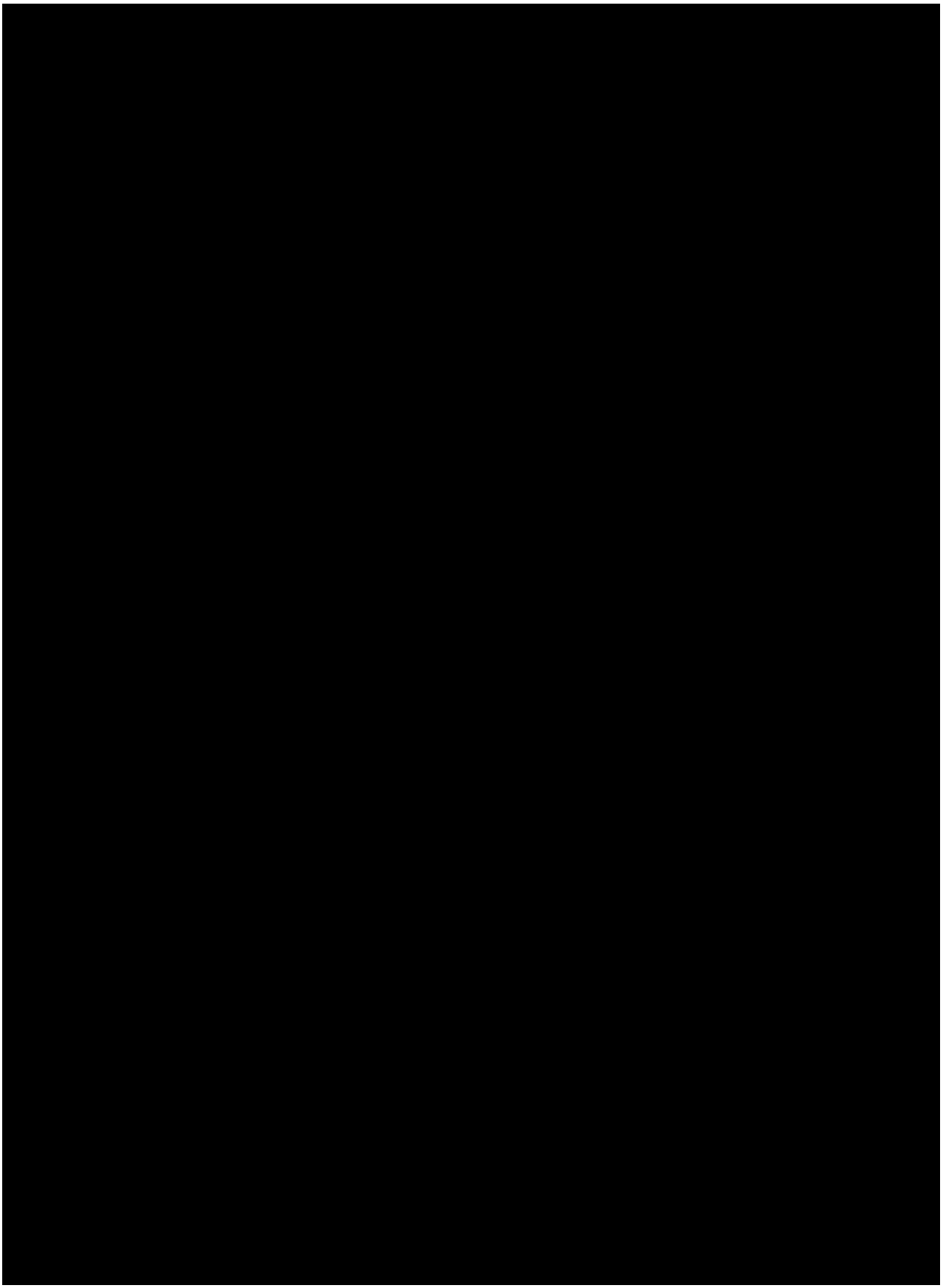
Some subgroups maybe collapsed when there is small number of subject in the category

### 12.10.6. Analyses of Tertiary Efficacy Endpoints

[redacted]

### 12.10.7. Analyses of Exploratory Efficacy Endpoints





## 12.11. PHARMACODYNAMICS AND PHARMACOKINETICS

### 12.11.1. Pharmacokinetics

The analysis of PK endpoints will be based on the PK/PD analysis set.

Serum concentration values below the limit of quantification (BLQ) will be set to zero when calculating summary statistics; hGH baseline-corrected values which are negative will be set to zero. Baseline-corrected concentrations will be derived by subtracting individual's baseline (i.e. pre-dose at V1) from each trial visit:

[baseline-corrected serum concentration data] = [Visit X] – [baseline (i.e. V1 pre-dose)

hGH (absolute and baseline-corrected), lonapegsomatropin and mPEG serum levels (ng/mL) will be summarized by dosing group and visit using descriptive statistics (number of subjects, arithmetic mean, arithmetic SD, arithmetic CV, median, minimum, and maximum, if applicable) and box plot will be presented.

### 12.11.2. Pharmacodynamics

The analysis of PD endpoints will be based on the PK/PD analysis set.

All serum concentration values BLQ will be set to lower limit of quantification when calculating summary statistics; baseline-corrected values which are negative will be reported as negative values. Baseline-corrected concentrations will be derived by subtracting individual's baseline (i.e. pre-dose at V1) from each trial visit: [baseline-corrected serum concentration data] = [Visit X] – [baseline (i.e. V1 pre-dose)].

Absolute and baseline-corrected serum concentration data will be listed and summarized by time point for using descriptive statistics (number of subjects, arithmetic mean, arithmetic SD, arithmetic CV, median, minimum, and maximum, if applicable). The absolute values and changes from baseline in IGF-1 (ng/mL), IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS will also be analyzed by visit using an ANCOVA models and descriptive summary by dosing groups will be provided.

Box plot of IGF-1, IGFBP-3, IGF-1SDS and IGFBP-3 SDS serum concentration data (absolute and baseline-corrected).

In addition, the proportion of subjects with IGF-1 SDS level categories will be summarized at each timepoint.

## 12.12. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Set. 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.

### 12.12.1. Adverse Events

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 (the most current March version of the dictionary).

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose of investigational product and was not present prior to the first dose, or it was present at the first dose but increased in severity during the trial through 14 days after the last dose of treatment on the main period or the date of first dose on the extension period whichever occurs first.

- 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 trial 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 trial, TEAEs leading to the discontinuation of treatment, AEs leading to death and special situation will also be generated.

### 12.12.2. Injection Site Reactions

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

### 12.12.3. Other Adverse Events to Monitor

#### 12.12.3.1. 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.

#### 12.12.3.2. 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.

#### 12.12.3.3. 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 trial will be presented by treatment group and by treatment period.

#### 12.12.3.4. Electrocardiogram

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

#### 12.12.3.5. MRI and Fundoscopy

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

## 13. REFERENCES

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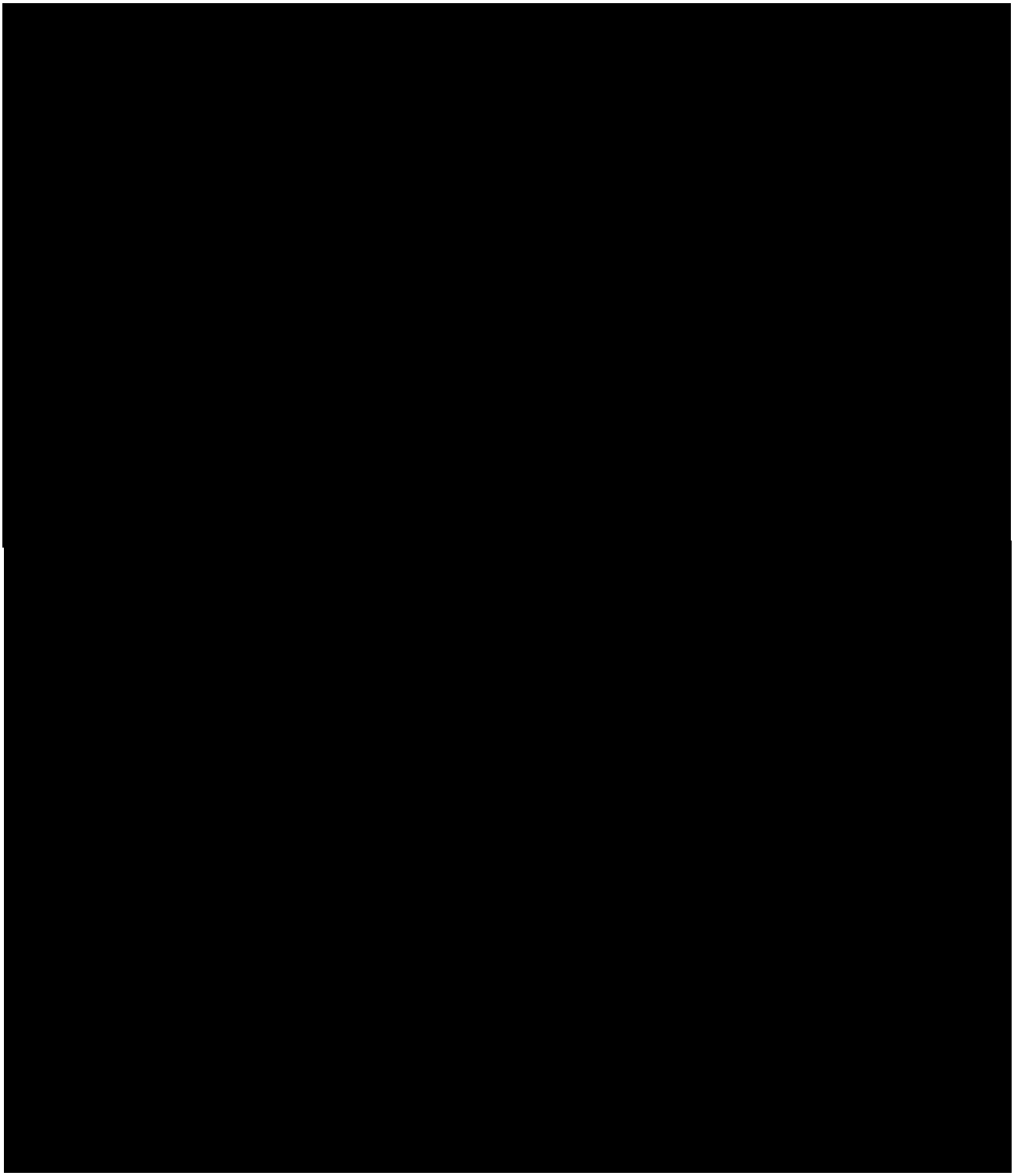
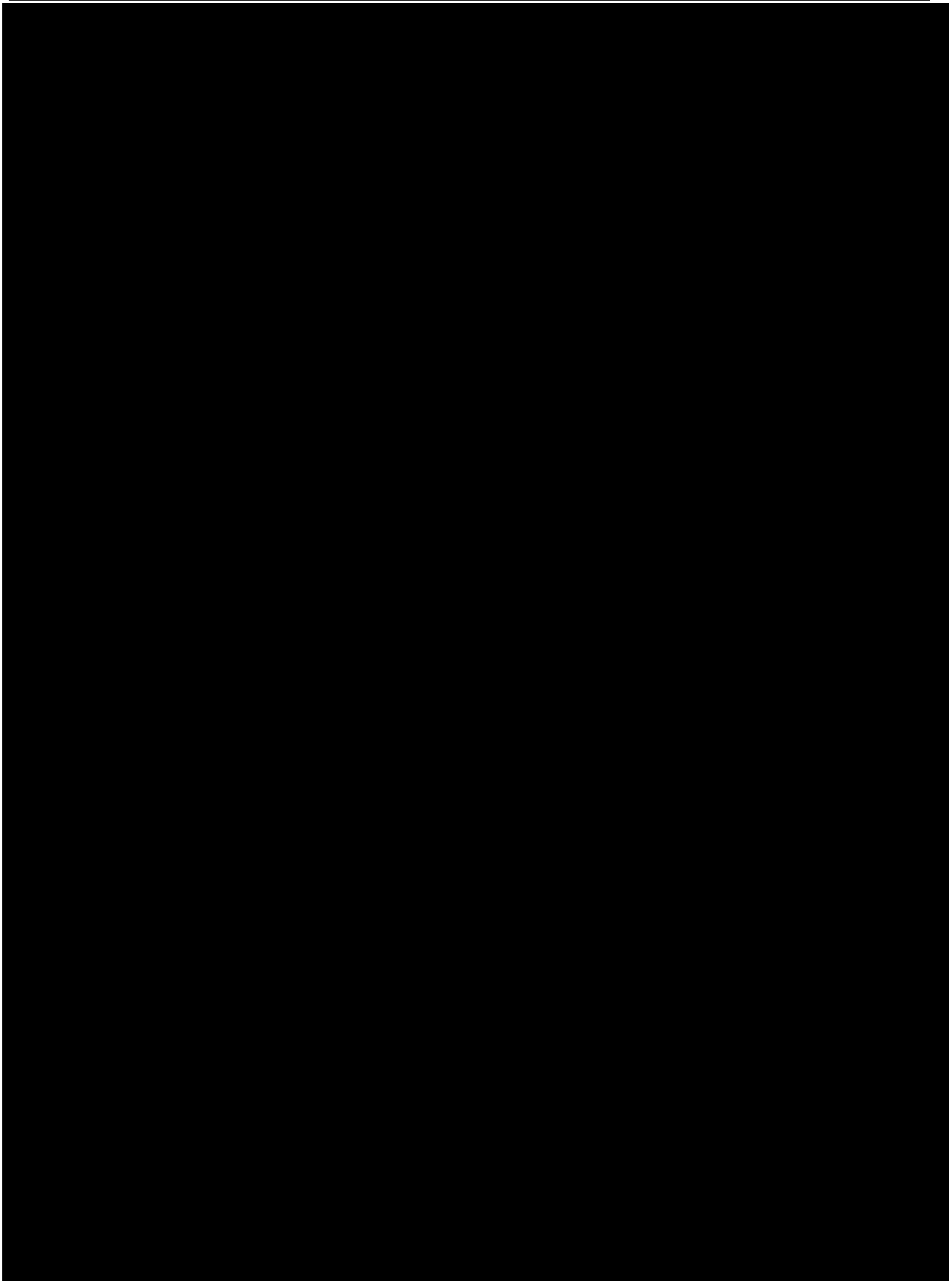
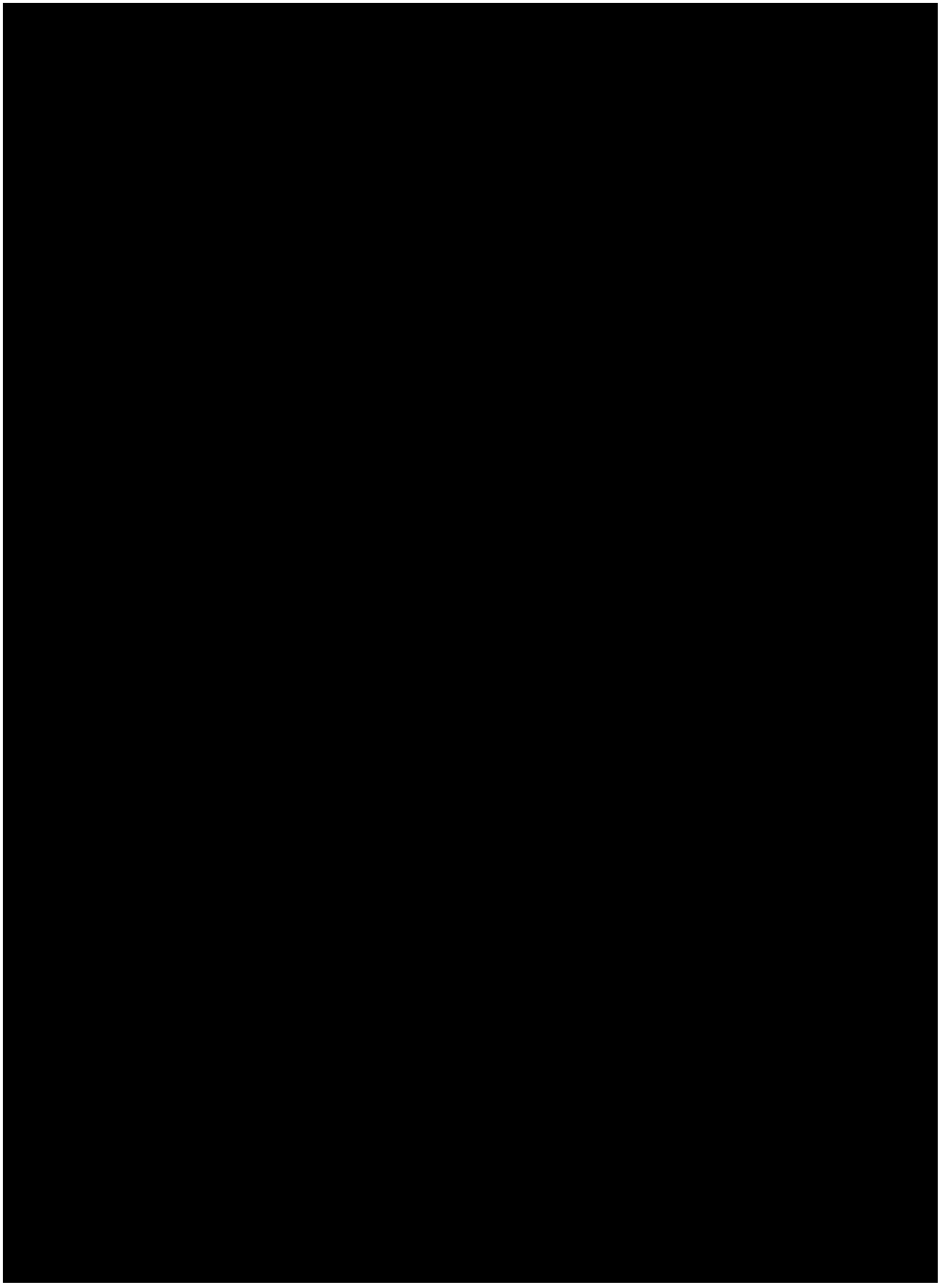
# 14. APPENDICES

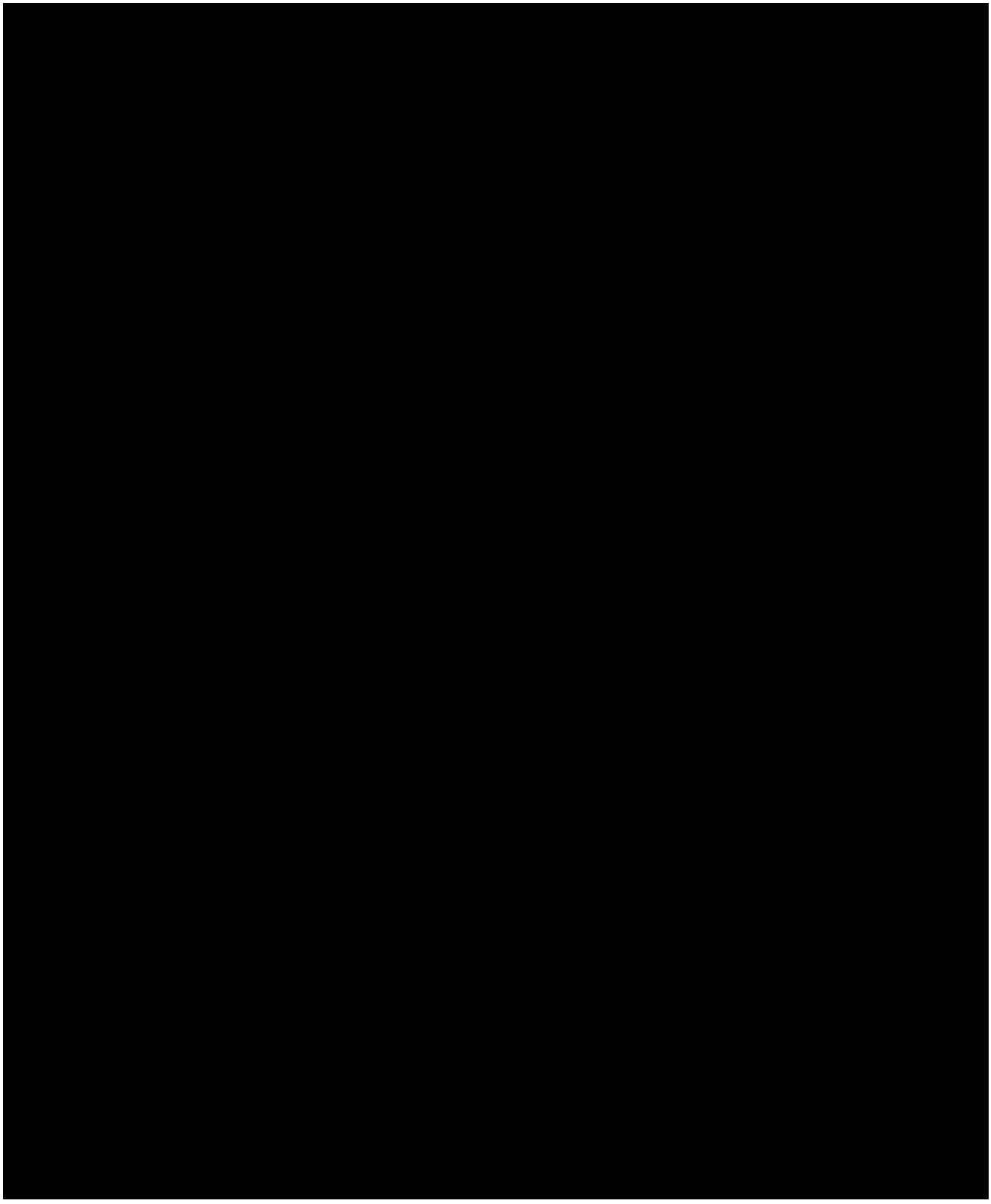


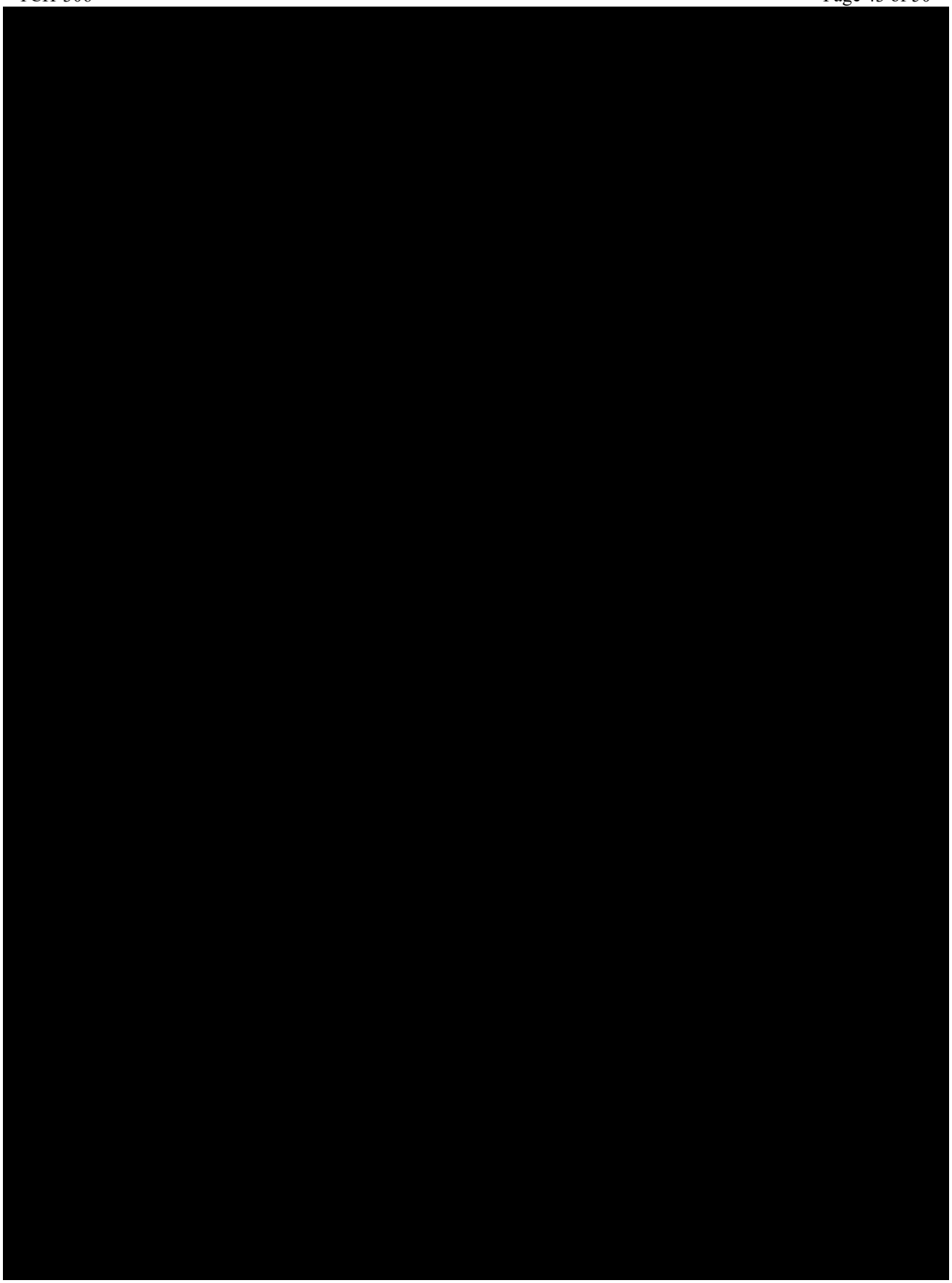
### 14.1.1.2. Target Anchor Category

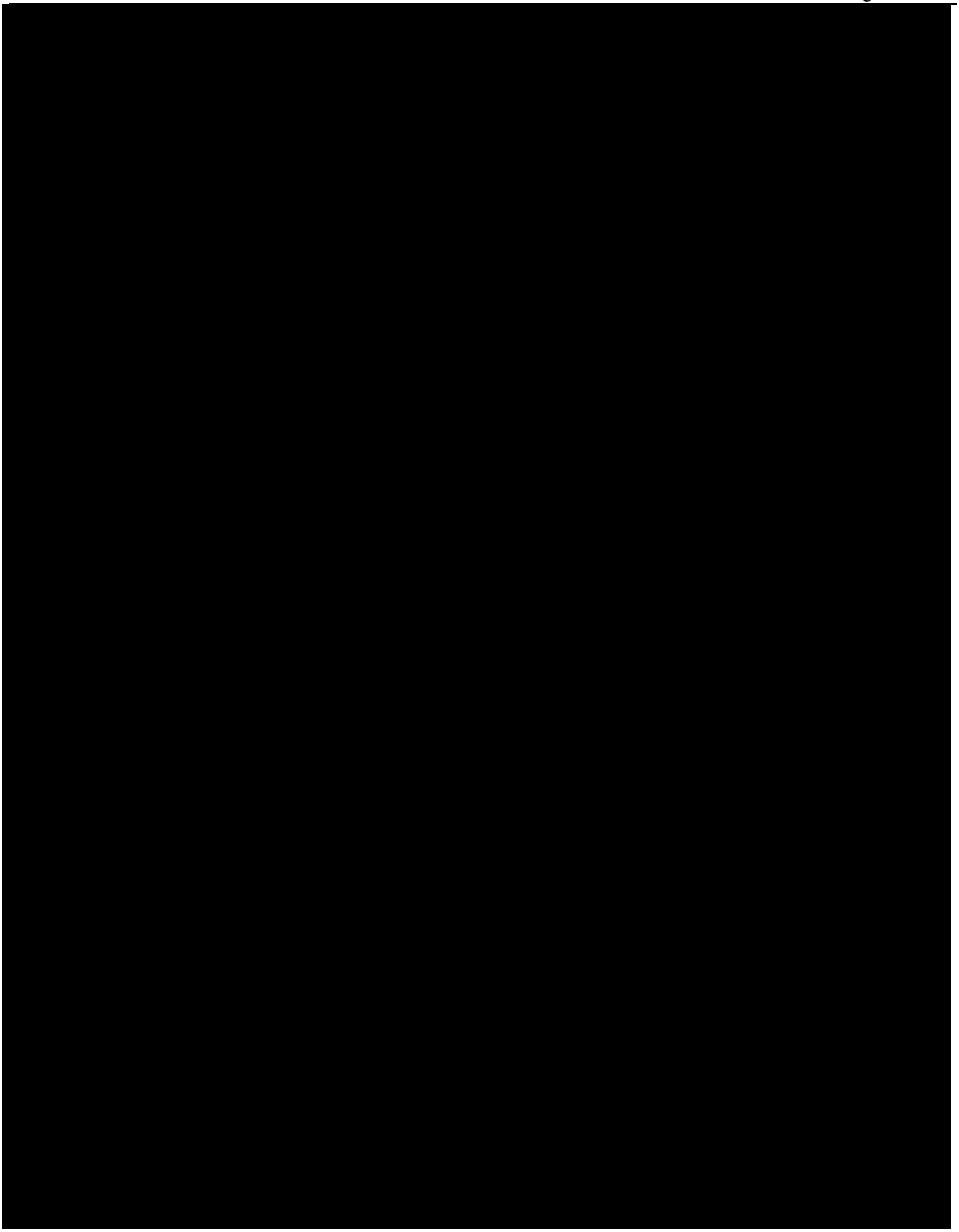
The target anchor category is the anchor category that represents the minimum meaningful change and is used as the starting point to identify potential candidates for a meaningful change threshold.

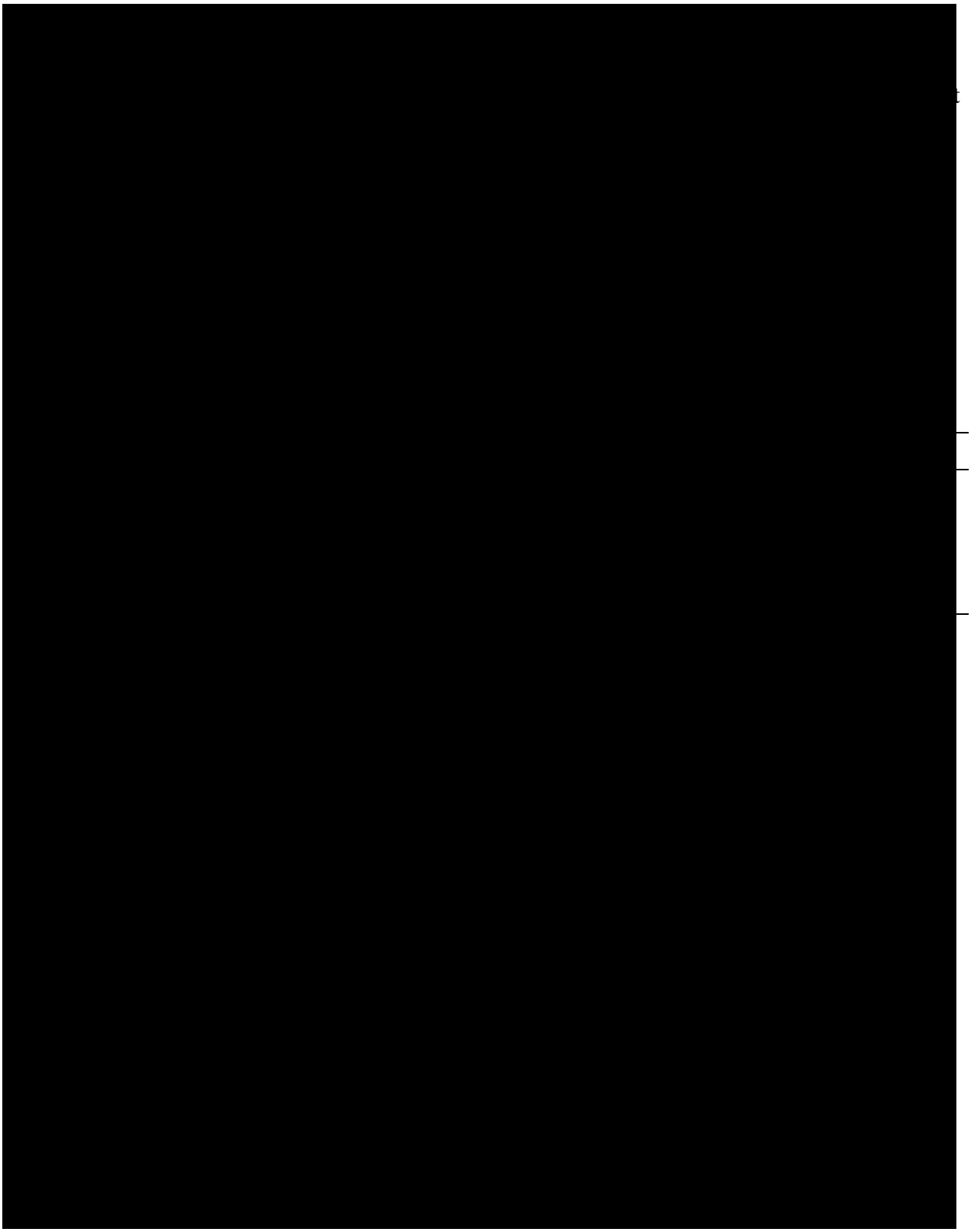


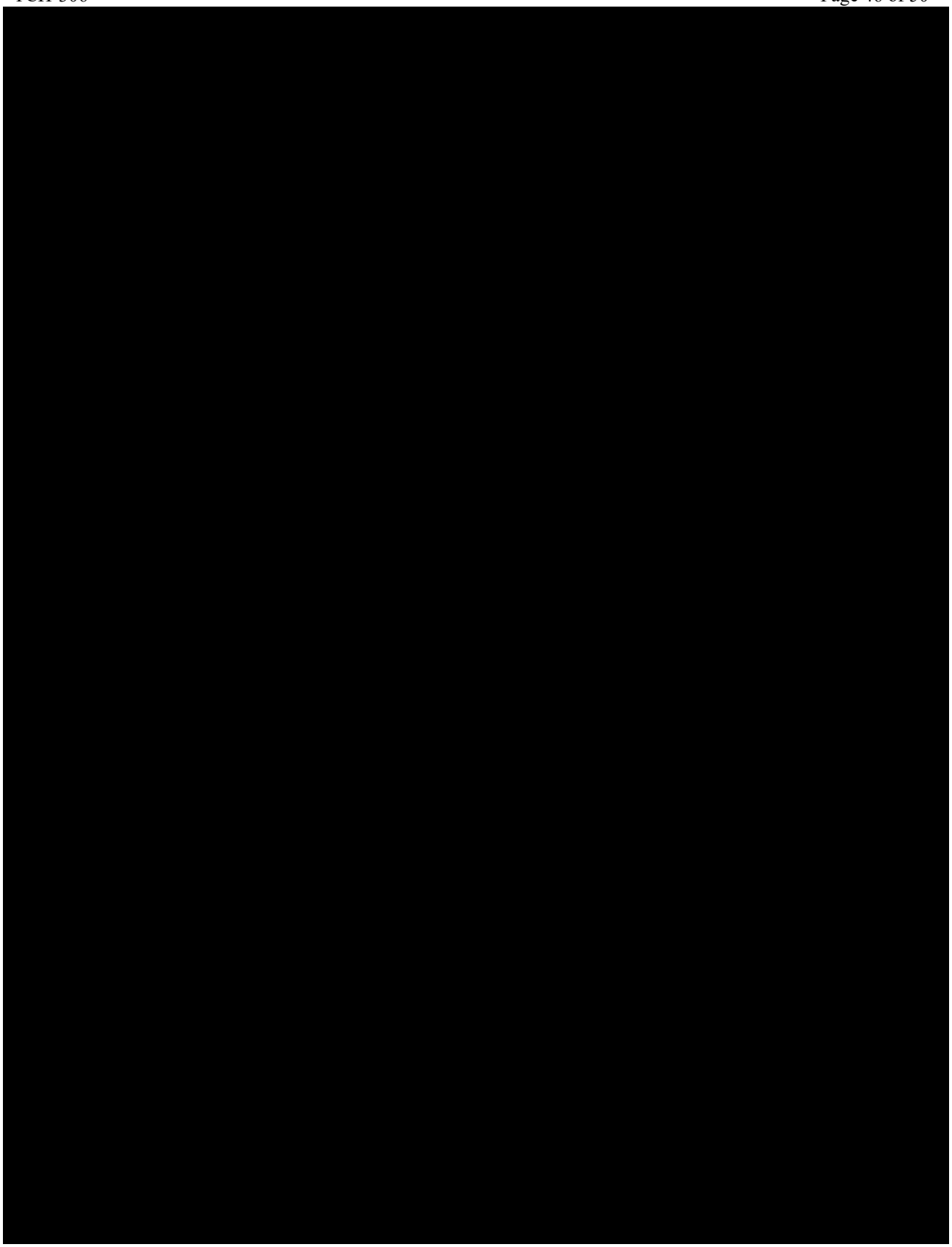












## 14.2. SAP APPROVAL FORM

# Statistical Analysis Plan And Amendment Approval Signature Form

| | |
|---|---|
| **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:** | **TCH-306** |

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

**Author:**

_____ _____

Name, Title [redacted] Date

**Approved by:**

_____ _____

Name, Title [redacted] Date

_____ _____

Name, Title [redacted] Date

_____ _____

Name, Title [redacted]

Date

## 14.3. VERSION HISTORY

| SAP Version | Change | Rationale |
|---|---|---|
| V 3.0 | The key changes includes:<br>Updated section 11.3 to add details and clarify analysis window of DXA assessment<br>Updated section 14.2 to update names of the approvers | To clarify definition<br><br>Updated to final approvers name and titles |
| V 2.0 | The key changes includes:<br>Updated section 11.2.6 to implement copy reference method<br>Updated Visit window definition for Visit 7assessment<br>Updated section 12.10.1 to clarify estimand<br>Updated section 12.10.3 to fixed testing procedure<br>Updated section 12.10.4 to add sensitivity analysis #3 and #4<br>Updated section 12.10.5 to add race and ethnicity subgroup | To addresss comments from FDA's review on the SAP |
| V 1.0 | Not Applicable | Original Version |

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|---|---|
| Approval | [redacted]<br>Management<br>04-Dec-2023 18:27:22 GMT+0000 |

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| Approval | [redacted]<br>Medical<br>04-Dec-2023 18:43:09 GMT+0000 |

| | |
|---|---|
| Approval | [redacted]<br>Reviewer<br>04-Dec-2023 23:04:23 GMT+0000 |

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