CLINICAL TRIAL PROTOCOL

Protocol Title:	A Multicenter, Open-Label, Extension Trial to Investigate Long Term Efficacy and Safety of Lonapegsomatropin in Adults with Growth Hormone Deficiency
Trial ID/Protocol Number:	TCH-306EXT
EudraCT Number:	2021-004313-39
Protocol Version:	12.0
Version Date:	21 June 2023
Countries:	Selected countries where patients might exceed a time period of 8 weeks from trial TCH-306 Visit 7 until TCH-306EXT Visit 8
Compound:	Lonapegsomatropin
Trial Phase:	3
Sponsor:	Ascendis Pharma Endocrinology Division A/S, Tuborg Boulevard 12, DK-2900 Hellerup, Denmark

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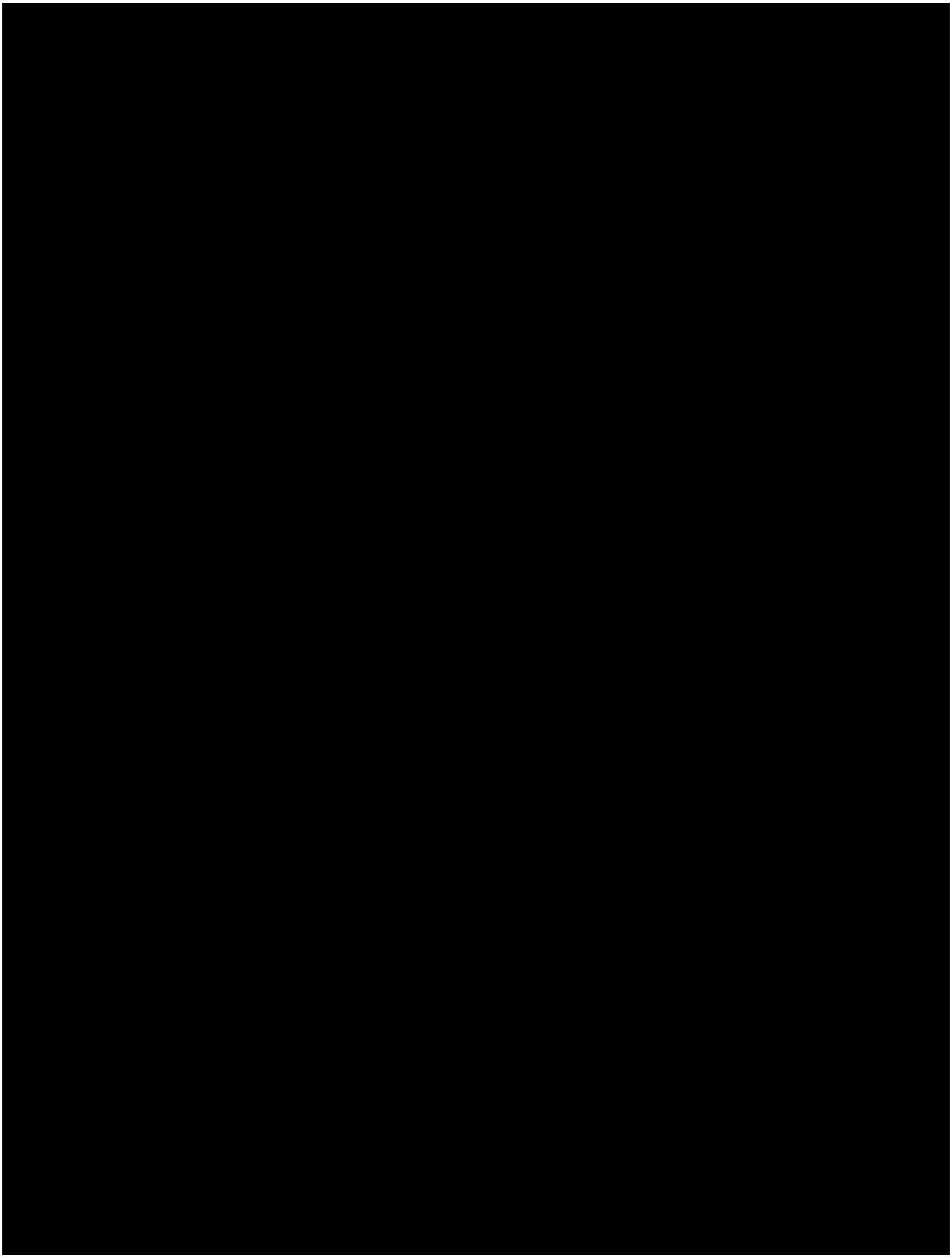
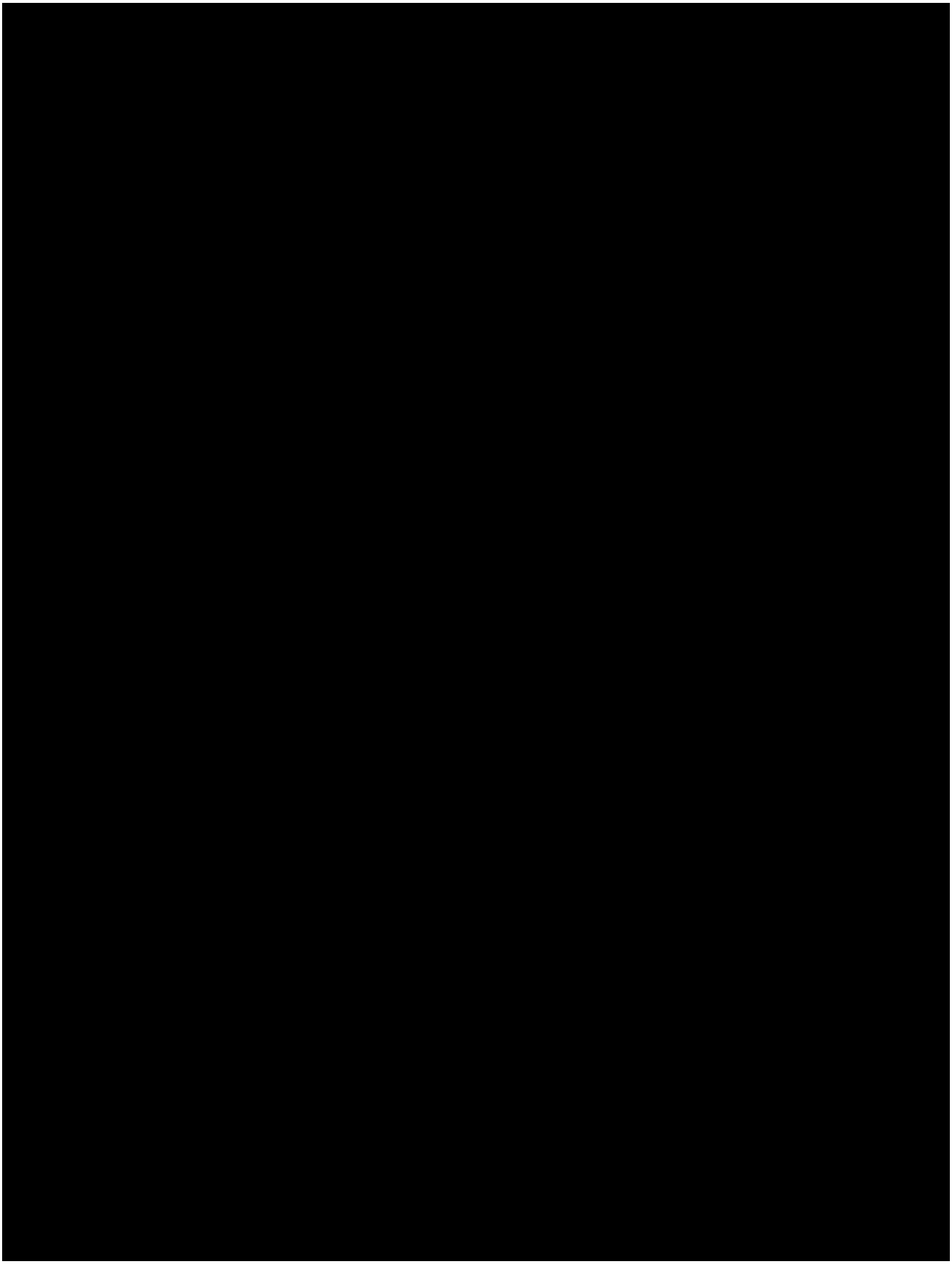
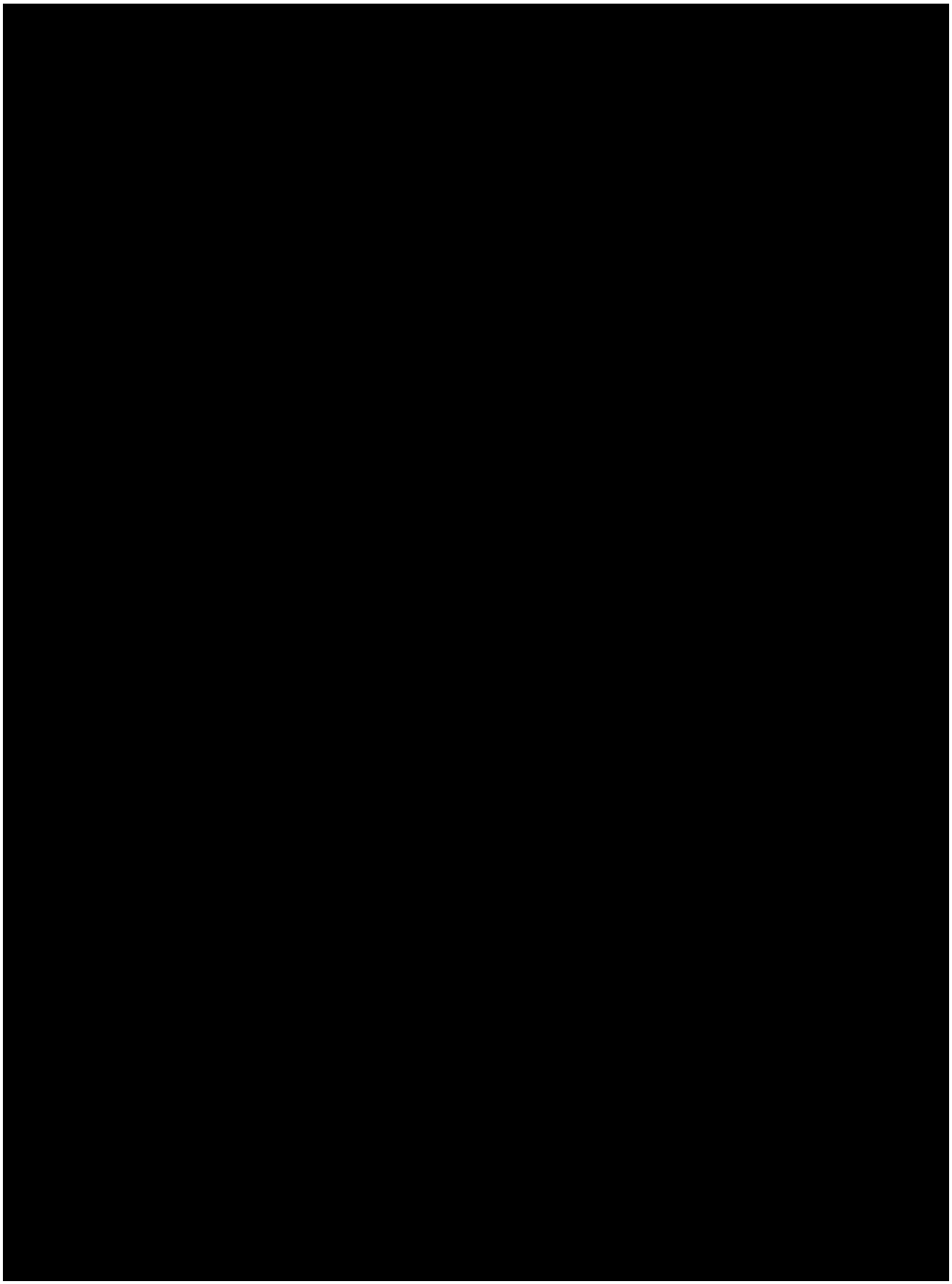
SAFETY REPORTING

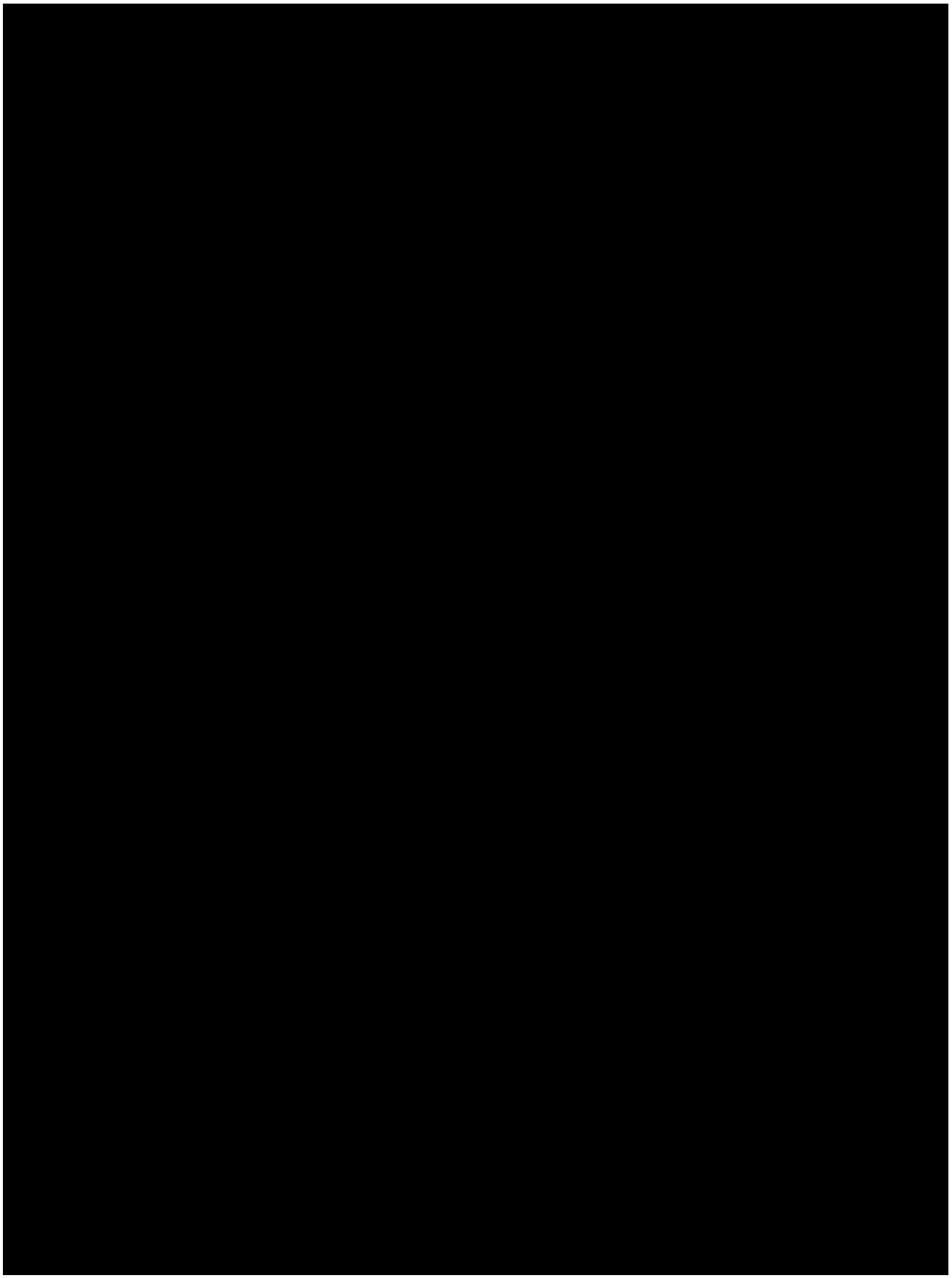
Contact details are found on the SAE Report form

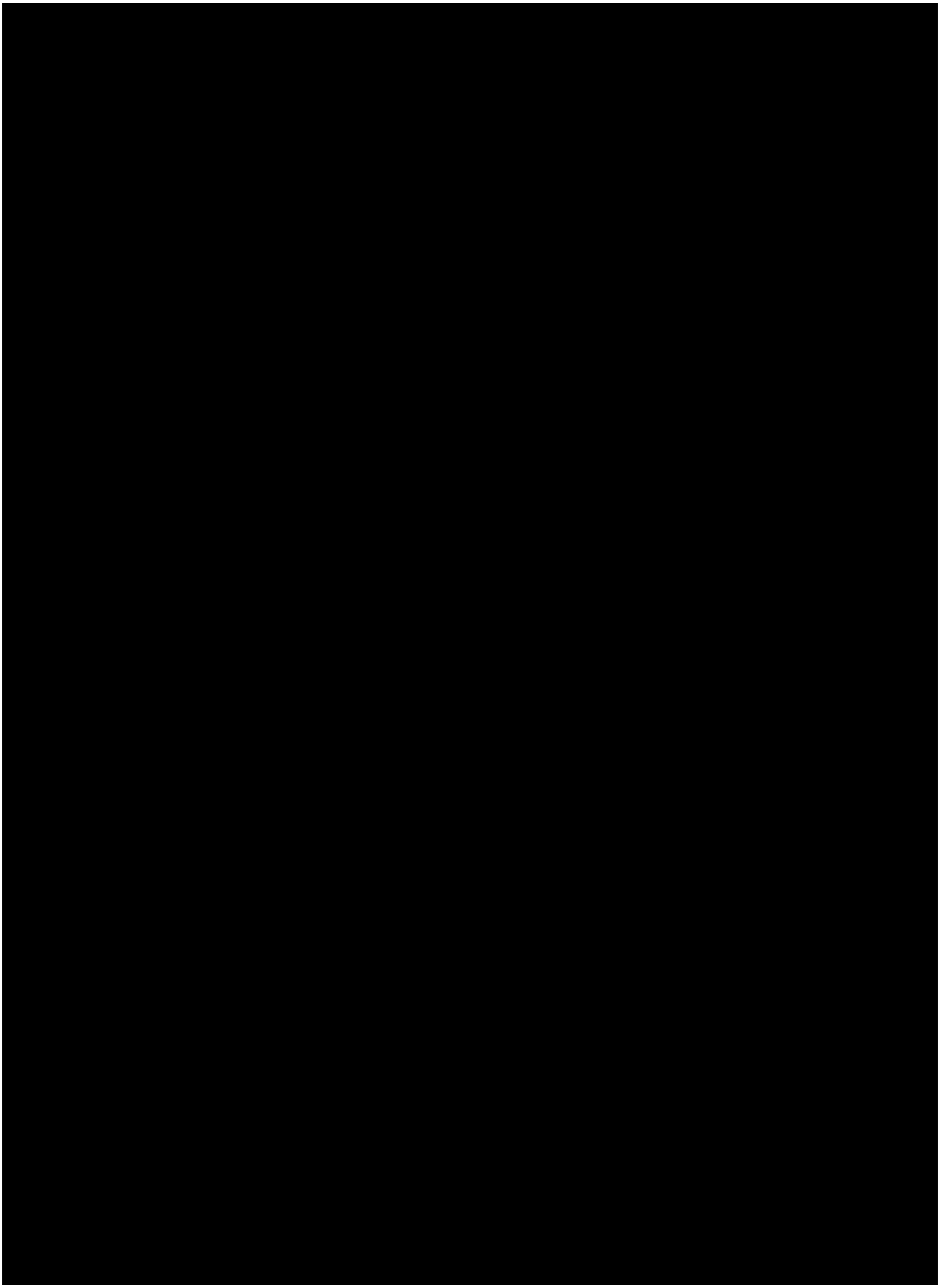
PROTOCOL VERSION SUMMARY OF CHANGES TABLE

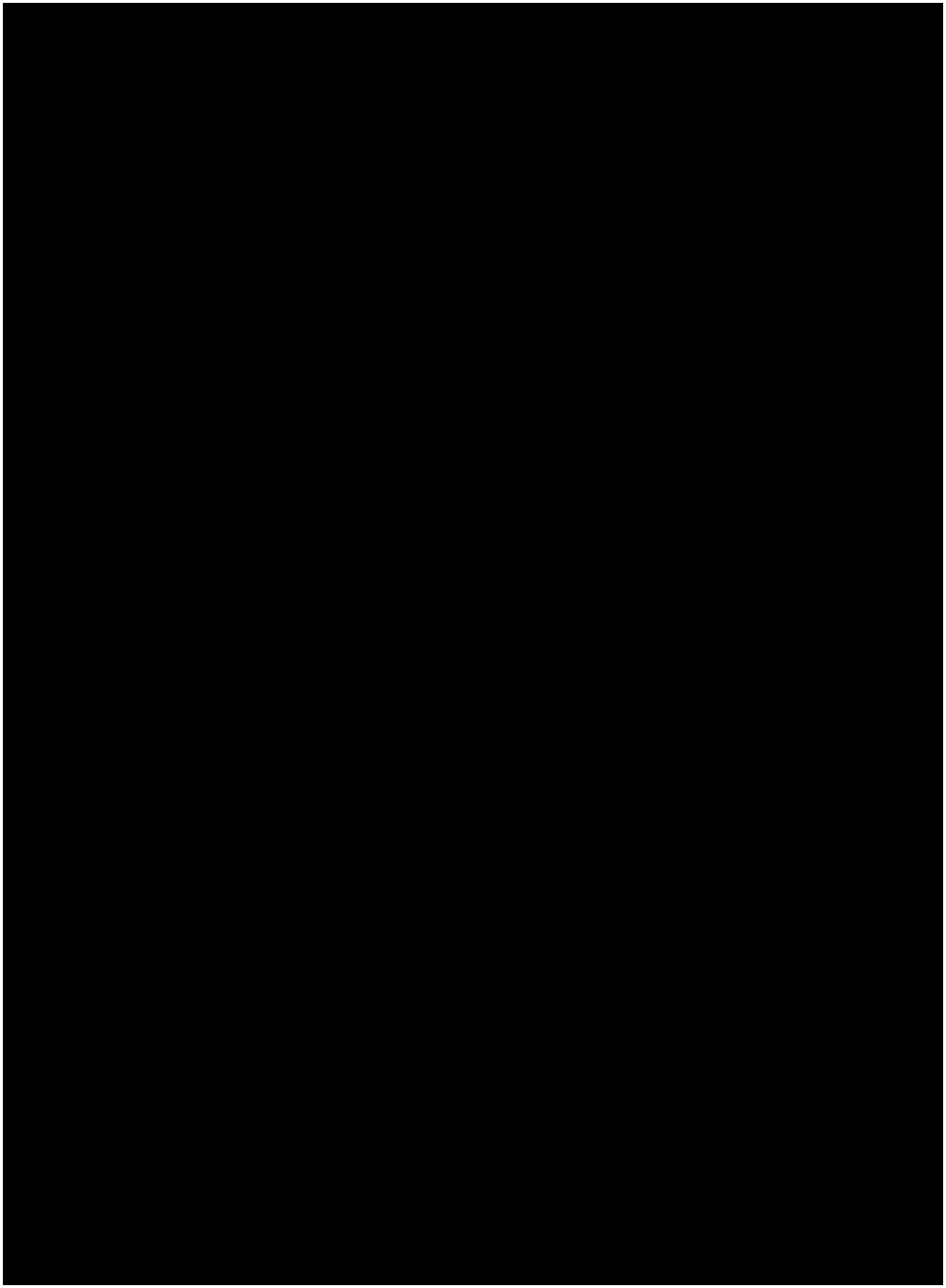


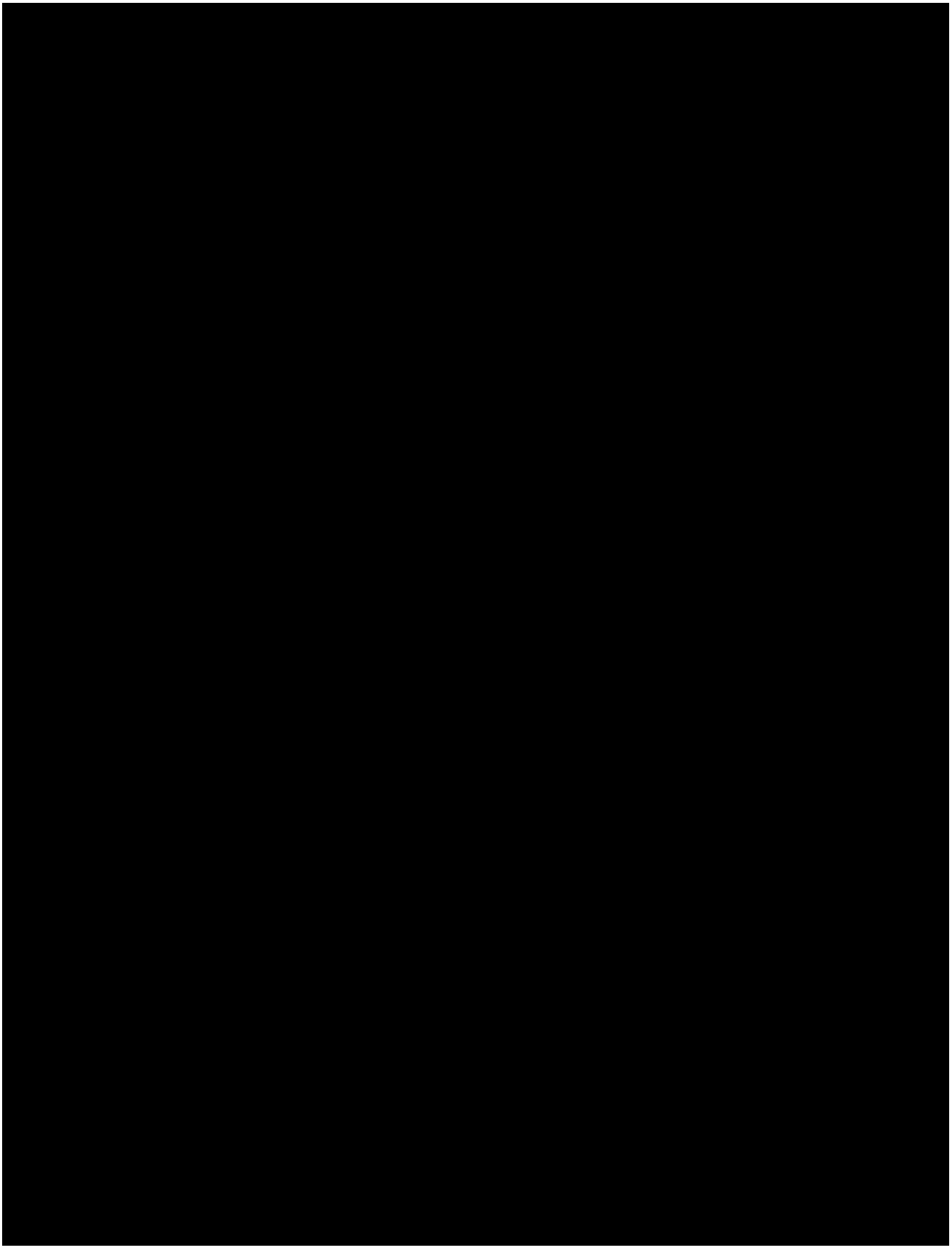


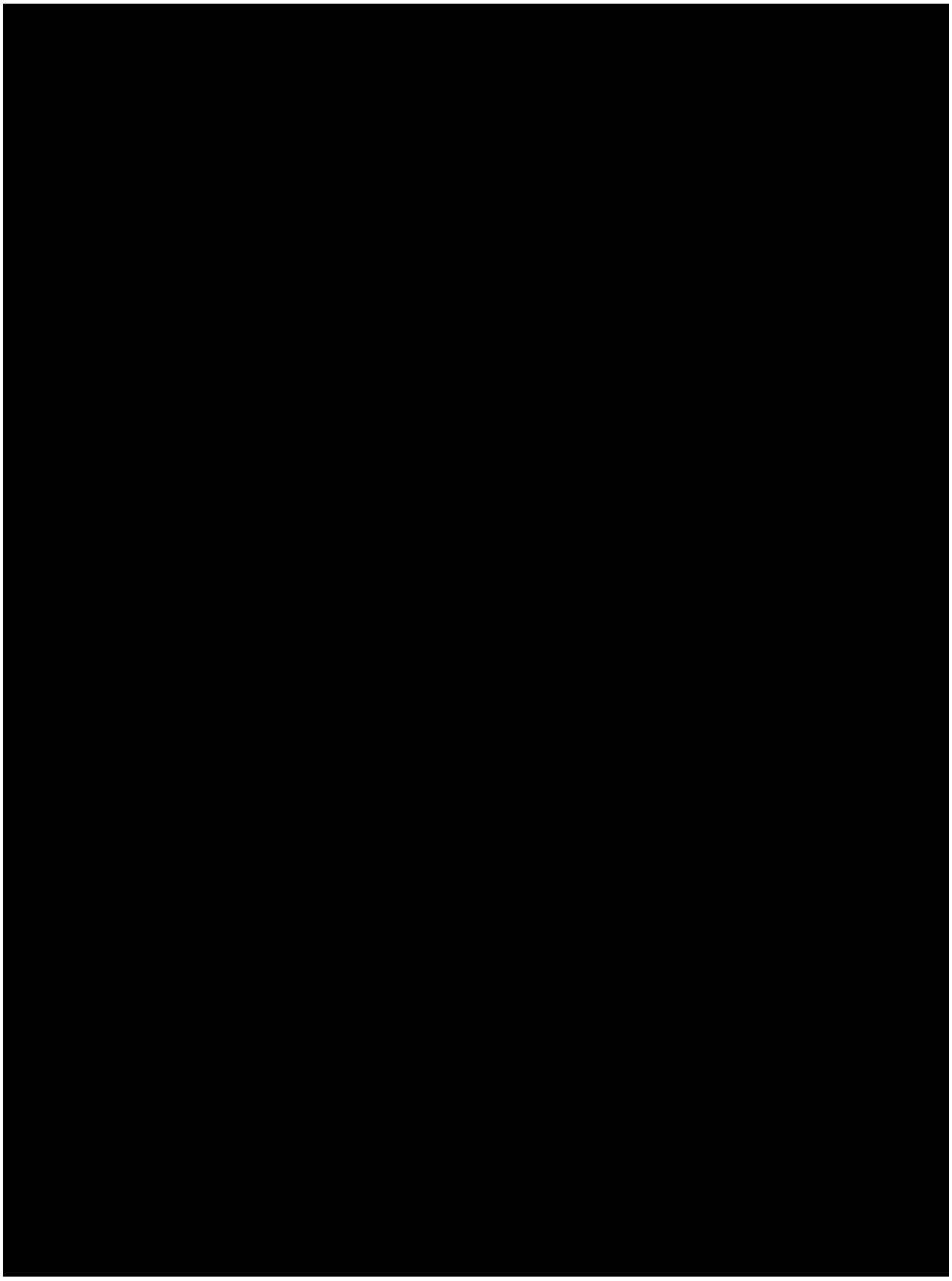


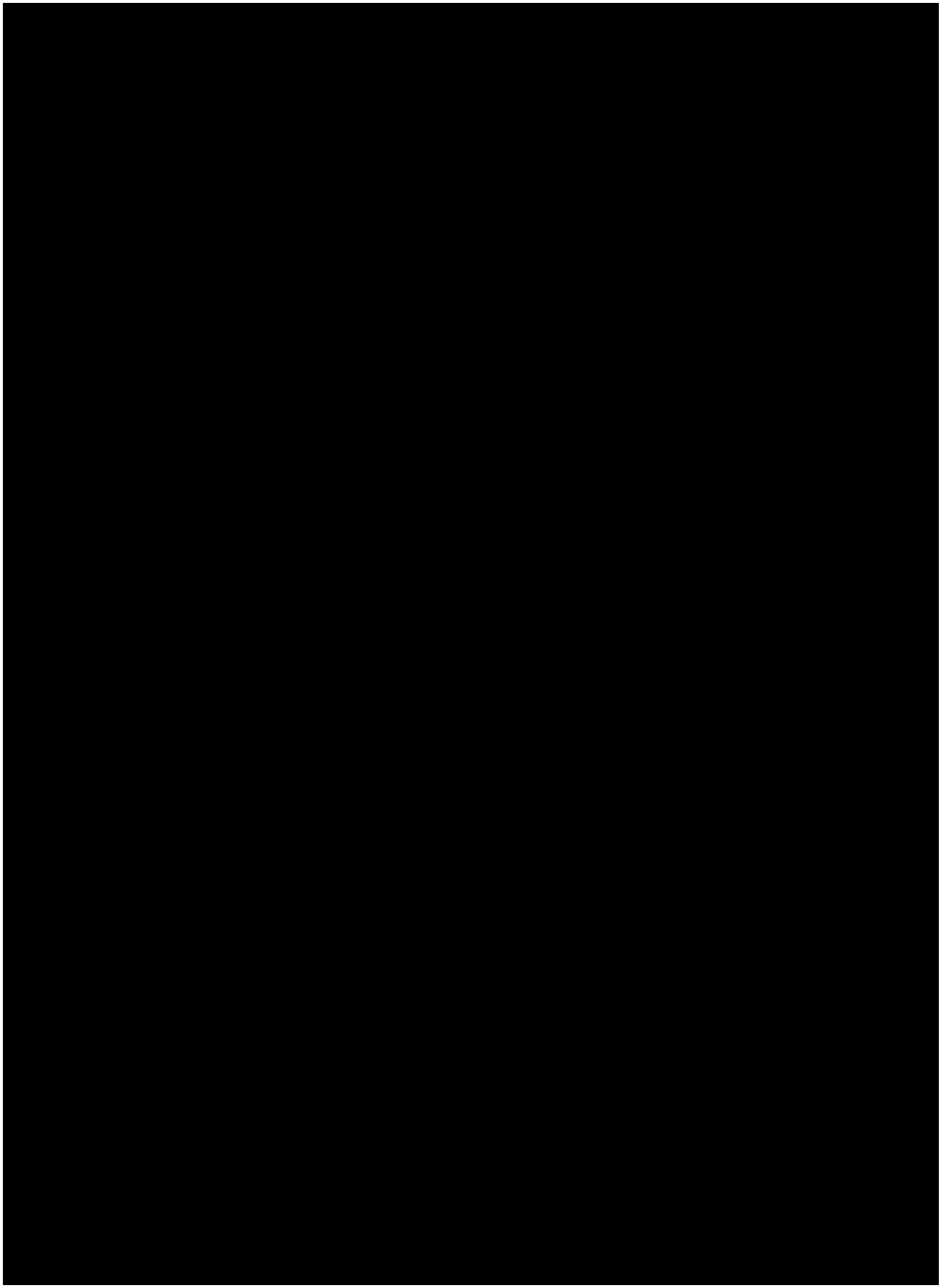


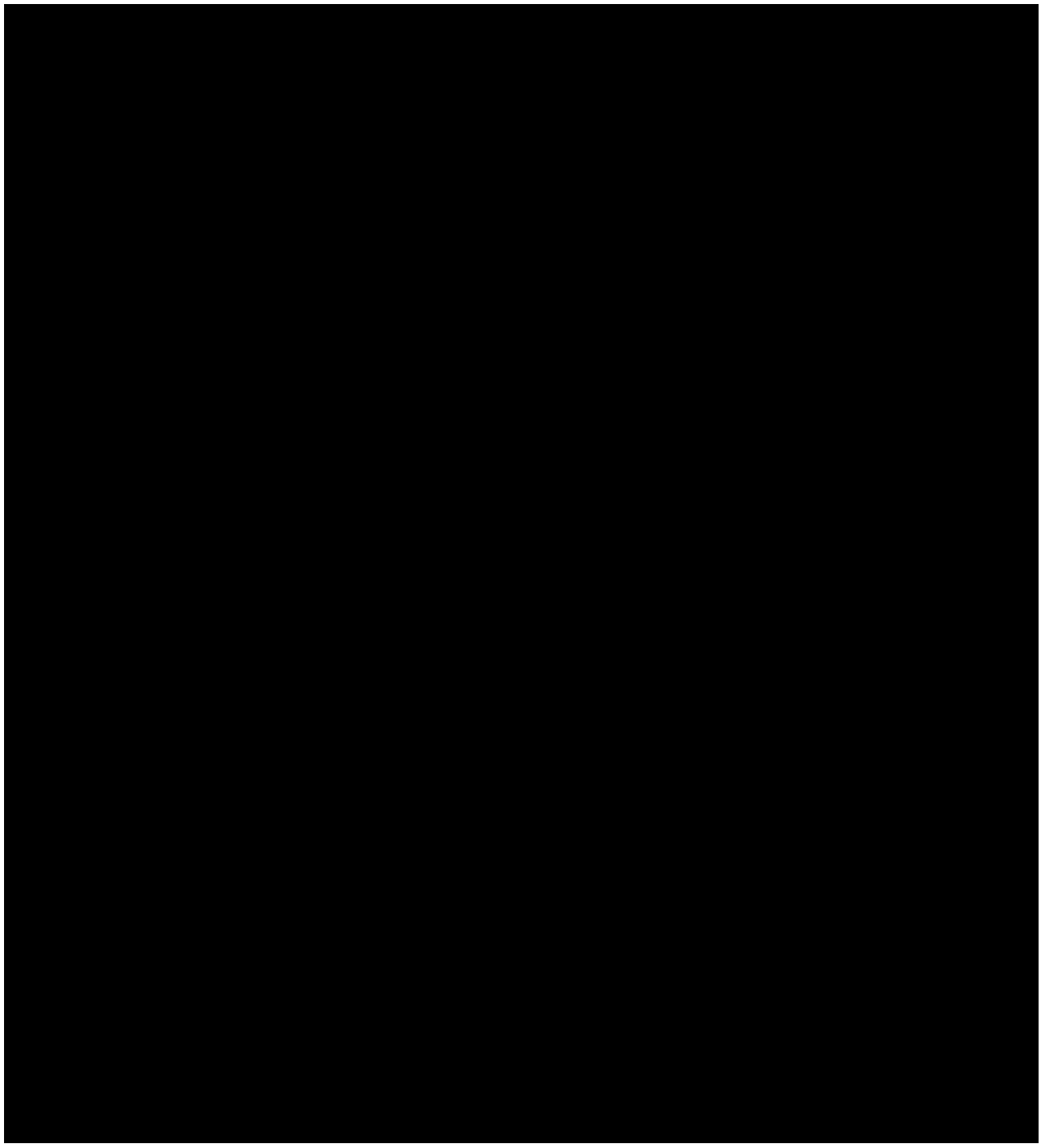












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1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Protocol Title:

A multicenter, open-label, extension trial to investigate long term efficacy and safety of lonapegsomatropin in adults with growth hormone deficiency

Trial Rationale:

To assess the long-term safety of once-weekly lonapegsomatropin in adults with growth hormone deficiency (GHD/AGHD) who participated in trial TCH-306.

Objectives and Key Endpoints:

Objectives	Key Endpoints
Primary	
• To evaluate the safety of once-weekly lonapegsomatropin in adults with GHD previously treated in trial TCH-306	Safety endpoints as measured throughout the treatment period: • Adverse events (AEs) • Laboratory values • Vital signs • Immunogenicity • 12-lead electrocardiogram (ECGs) • Fundoscopy
Secondary	
• To evaluate the efficacy of once-weekly lonapegsomatropin in adults with GHD [redacted]	At Week 52 (as assessed by dual-X-ray-absorptiometry (DXA): • Trunk percent fat • Trunk fat mass • Total body lean mass [redacted]

Overall 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 confirmed GHD having completed the treatment period in trial TCH-306 (foresiGHt).

Brief Summary:

The purpose of this trial is to assess long-term safety of lonapegsomatropin in participants who completed the treatment phase of trial TCH-306. Participants are adults with GHD previously treated with either lonapegsomatropin, a daily somatropin product, or placebo.

Trial details include:

- Trial duration will be up to 60 weeks
- Screening Period up to 3 weeks
- Treatment duration will be 52 weeks
  - Titration period 12 weeks
  - Maintenance period 40 weeks
- Follow-up period 30-37 days (approx. 4-5 weeks)
- Visit frequency will be every 4th week during titration, four visits during maintenance period, and two during follow-up. Two visits are remote (phone/web).

Number of Participants:

Participants who completed the treatment period of trial TCH-306 and meet eligibility criteria can be included in the trial. The sample size in trial TCH-306 is approximately 240.

Intervention Groups and Duration:

- Total duration of trial participation for each participant will be 60 weeks, up to 3 weeks for screening, 52 weeks on treatment and up to 37 days for follow up
- Route of administration is subcutaneous (sc) injections
- Dose regimen is once-weekly
- Starting dose depending on age and oral estrogen use, fixed titration period, with individual dose changes/adjustments if warranted due to AEs or IGF-1 values
- Participant safety and IGF-1 results will be continuously monitored by the medical monitors.

1.2. SCHEDULE OF ACTIVITIES (SOA)

Timing	Screening Visit	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	Screening Visit and Screening Procedures should be performed unless the subject can be dosed at V8 ≤8 weeks after TCH-306 V7. Subjects may not be re-screened if they failed eligibility criteria at V7.	≤ 3 weeks after Screening Visit or TCH-306 V7[j]	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
Informed consent[a]	Before or at Screening Visit										
Inclusion and exclusion criteria[i]	X[i]	X[i]									
Physical examination	X				X				X		
Weight	X				X				X		
Pregnancy test (females of childbearing potential only)[b]	X	X	X		X	X	X	X	X		X
Safety laboratory tests[c]	X		X		X	X	X	X	X		
IGF-1 and IGFBP-3 laboratory tests[c]	X		X		X	X	X	X	X		
[redacted]											
ADA/Antibody laboratory test	X		X		X	X	X	X	X		X
DXA (dual-X-ray-absorptiometry) scan					X[d]				X[d]		
12-lead ECG	X		X						X		
Vital signs	X		X		X	X	X	X	X		
Fundoscopy[e]	X								X		
MRI/CT scan for childhood cancer survivors									X		
Trial drug dispensing		X	X		X	X	X	X			
Trial drug training and administration[f]		X[f]									
Dose titration instruction, if applicable			X	X	X						

Timing	Screening Visit	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	Screening Visit and Screening Procedures should be performed unless the subject can be dosed at V8 ≤8 weeks after TCH-306 V7. Subjects may not be re-screened if they failed eligibility criteria at V7.	≤ 3 weeks after Screening Visit or TCH-306 V7[j]	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
AE review, including injection site reactions			X	X	X	X	X	X	X	X	
Concomitant medication review			X	X	X	X	X	X	X		
Participant diary review			X	X	X	X	X	X	X		
[redacted]											
Drug accountability			X	X	X	X	X	X	X		

[a] Informed consent must be obtained before the start of any screening procedures unless performed as part of TCH-306 V7
[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 patient on the same weekday. Diary to be handed out to participant with instruction to enter every dose taken
[redacted]
Inclusion and exclusion criteria should be reviewed at TCH-306 V7, at Screening Visit if performed, and at V8. Eligibility review is documented under V7 of TCH-306 in the EDC system
[j] If a subject was consented for TCH-306EXT after TCH-306 V7 and no Screening Visit was done, V8 must occur ≤3 weeks after the date of consent AND ≤8 weeks after V7

2. INTRODUCTION

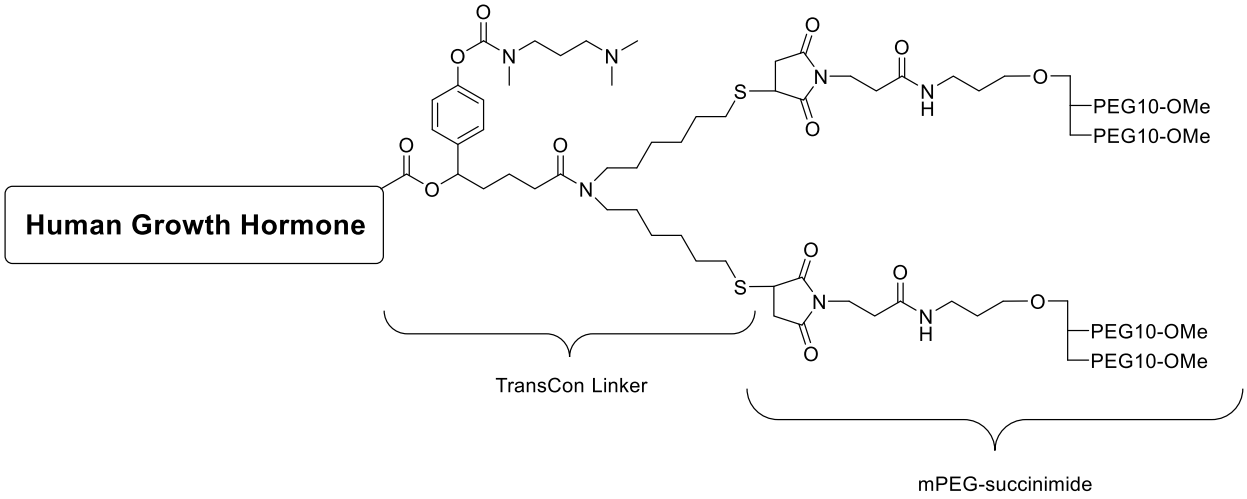
2.1. TRIAL RATIONALE

The primary objective of this open-label extension trial is to assess the long-term safety of once-weekly lonapegsomatropin in adults with GHD who participated in trial TCH-306. GHD in adults is associated with central adiposity, diminished lean muscle mass, decreased bone mass, and reduced quality of life (Melmed 2019). Growth hormone (GH) replacement therapy represents standard of care treatment that addresses multiple aspects of the condition (Ho 2007, Molitch 2011, Yuen 2019, Kim 2020). This trial evaluates the safety of once-weekly lonapegsomatropin in adults with GHD over 52 weeks. The proposed length of this extension is 52 weeks is considered adequate to assess safety and is supported by the extensive clinical experience for lonapegsomatropin approved by the Food and Drug Administration (FDA) for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH). The doses used in pediatric patients are higher (approximately 2-6-fold based on weight) than used in adults with GHD.

2.2. BACKGROUND

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

Figure 1: Structure of Lonapegsomatropin (ACP-011)



PEG10-OMe: 10 kDa methoxypolyethylene chain.

Please refer to the current version of the Investigator's Brochure for detailed information pertaining to lonapegsomatropin.

2.3. BENEFIT/RISK ASSESSMENT

In treatment of adults with GHD, lonapegsomatropin is an investigational long-acting prodrug of hGH with a proposed once-weekly dosing regimen designed to overcome the inconvenience and suboptimal compliance of daily hGH injections. The safety and efficacy profiles are anticipated to be comparable to currently approved hGH products for daily use, while maintaining similar exposure (C_{max} and weekly AUC). Moreover, the exposure to hGH over the weekly dosing interval is anticipated to enhance delivery of hGH into target tissues and optimize efficacy. Obviating the need for daily injections should increase compliance and therefore long-term efficacy, which would be of great benefit to adult patients with GHD. All participants will receive weekly lonapegsomatropin treatment during this trial. Lonapegsomatropin is approved by the FDA for treatment of pediatric GHD.

The safety of the participants will be monitored by the investigators as well as the medical monitors.

Stopping rules have been defined in the protocol. There are no high-risk procedures required and the measurement of the efficacy endpoint by dual-x-ray-absorptiometry (DXA) can be considered standard of care and is only associated with very low X-ray exposure.

In conclusion, the benefit-risk assessment for this trial is acceptable based on nonclinical, already gained clinical experience and safety data in the pediatric populations and the fact that no harming trial procedures are implemented.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lonapegsomatropin is found in the current version of the Investigator's Brochure, and in the prescribing information for Skytrofa®.

2.3.1. Risks Related to the COVID-19 Pandemic

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

2.3.2. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this trial, the potential risks identified in association with *trial intervention* are justified by the anticipated benefits that may be afforded to participants with GHD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety of once-weekly lonapegsomatropin in adults with GHD previously treated in trial TCH-306	Safety endpoints as measured throughout the treatment period: • AEs • Laboratory values • Vital signs • Immunogenicity • 12-lead ECGs • Fundoscopy
Secondary	
• To evaluate the efficacy of once-weekly lonapegsomatropin in adults with GHD [redacted]	At Week 52 (as assessed by DXA): • Trunk percent fat • Trunk fat mass • Total body lean mass [redacted]
[redacted]	

4. TRIAL DESIGN

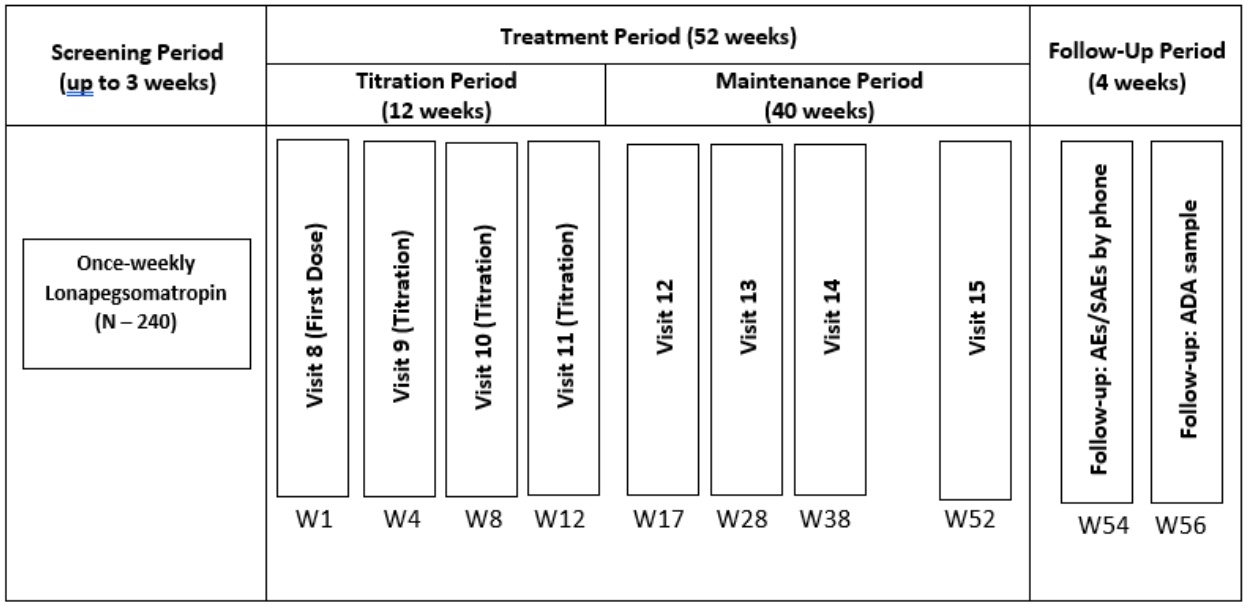
4.1. OVERALL DESIGN

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). Therefore, participants are either previously treated with lonapegsomatropin, a daily somatropin product, or placebo in trial TCH-306.

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

- Screening Period – up to 3 weeks starting at Screening Visit. A Screening Visit is not needed if all inclusion and no exclusion criteria were met at V7 and if V8 occurs ≤8 weeks after V7.
- 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), 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)

Figure 2: Trial Design



4.2. SCIENTIFIC RATIONALE FOR TRIAL DESIGN

This trial design allows characterization of long-term safety and efficacy for lonapegsomatropin in adults with GHD (38 weeks in TCH-306 followed by 52 weeks in TCH-306EXT). Long-term safety and efficacy data are important because GH treatment for adults with GHD is typically a lifelong therapy.

4.3. JUSTIFICATION FOR DOSE

Due to the different hGH dose requirements, this trial includes individual doses depending on age, concomitant oral estrogen use, and trial drug tolerability as assessed by the investigator. The trial includes three dosing groups.

Participants will be initiated on a low dose, and the dose will slowly be increased to avoid adverse reactions as much as possible (Dose Titration Period) until the target maintenance dose is reached (Dose Maintenance Period).

4.4. END OF TRIAL DEFINITION

The end of the trial is defined as the date of the last visit of the last participant.

A participant is considered to have completed the trial if he/she has completed the treatment period.

5. TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Inclusion and exclusion criteria should be reviewed at TCH-306 V7, at Screening Visit if performed, and at V8. Eligibility review is documented under V7 of TCH-306 in the EDC system.

5.1. INCLUSION CRITERIA

Participants are eligible to be included in the trial only if all the following criteria apply:

1. Signing of the trial specific informed consent
2. Completion of the treatment period and Visit 7 assessments of trial TCH-306, including collection and upload of Visit 7 DXA scan
3. Fundoscopy at Visit 7 in trial TCH-306 without signs/symptoms of intracranial hypertension or diabetic retinopathy stage 2 / moderate or above

5.2. EXCLUSION CRITERIA

Participants are excluded from the trial if any of the following criteria apply:

1. Diabetes mellitus if any of the following are met:
    a. Poorly controlled diabetes, defined as HbA_{1C} higher than 7.5% according to central laboratory at Visit 7 in trial TCH-306
    b. Use of diabetes mellitus drugs other than metformin and/or dipeptidyl peptidase-4 (DPP-4) inhibitors
2. Active malignant disease
3. Known history of hypersensitivity and/or idiosyncrasy to the investigational product (somatropin or excipients)
4. Female who is pregnant, plans to become pregnant, or is breastfeeding

5. Female participant of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) not willing throughout the trial to use contraceptives as required by local law or practice. Details included in Appendix 4/Section 10.4 of this protocol
6. Male participant not willing throughout the trial to use contraceptives as required by local law or practice. Details included in Appendix 4/ Section 10.4 of this protocol
7. Any disease or condition that, in the judgement of the investigator, may make the participant unlikely to comply with the requirements of the protocol or any condition that presents undue risk from the investigational product or trial procedures
8. eGFR <60 mL/min/1.73m² determined based on Modification of Diet in Renal Disease (MDRD) equation using serum creatinine from the central laboratory at screening
9. Hepatic transaminases (ie, AST or ALT) >3 times the upper limit of normal according to the central laboratory at screening

5.3. LIFESTYLE CONSIDERATIONS

The following should be avoided during the trial participation: weight-reducing program, and diets unless indicated for diabetes mellitus treatment.

5.4. SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical trial is not subsequently entered in the trial. A minimal set of screen failure information to be collected in the eCRF includes age, sex, reason for screen failure, and any serious adverse event (SAE) reported. No re-screening of patients who screen fail will be allowed in the study. Patients who were screened and screen failed using Visit 7 assessments in TCH-306 may not be re-screened in a separate Screening Visit.

5.5. CRITERIA FOR TEMPORARILY DELAYING

Not applicable.

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

Trial intervention is defined as any intervention(s), administered to a trial participant according to the trial protocol. All participants in this trial will receive the same investigational medicinal product (IMP).

6.1. TRIAL INTERVENTION ADMINISTERED

The trial drug will be labelled in accordance with regulatory requirements in each country and provided by the Sponsor. Once all data and results determining the participant eligibility are available and confirmed by the Investigator, the participant can be enrolled to receive lonapegsomatropin in accordance with Section 6.5. The trial intervention will either be provided in vials or in an electro-mechanical auto-injector using dual chamber cartridges (DCCs). The auto-injector will be introduced in this trial upon approval by regulatory authorities and IRB/IEC in selected countries. Participants will receive lonapegsomatropin via syringe and needles in countries and sites where the auto-injector is not yet available.

Table 1: Trial Intervention Administered/Investigational Medicinal Product

Intervention Name	Lonapegsomatropin
Intervention Description	Solution to be administered by sc injection via syringe and needle following reconstitution or via an electro-mechanical auto-injector using dual chamber cartridges
Type	Drug
Dose Formulation	A lyophilized powder in single-use glass vials requiring reconstitution with 1 mL sterile water for injection (sWFI). in DCCs to be used in the auto-injector that automatically reconstitutes the product through a series of steps
Unit Dose Strength(s)	[redacted]
Dosage Level(s)	Individual dose administered once-weekly
Route of Administration	Subcutaneous (sc) injection
Use	Active agent

All injections will be administered into the left or right buttock, left or right thigh, or left or right abdomen. To minimize local injection site effects, it is recommended to rotate the 6 injection sites in a subsequent manner (e.g., right thigh, right abdomen, right buttock, left thigh, left abdomen, left buttock).

For drug preparation and injection instructions, please refer to the Instruction for Use (IFU).

6.1.1. Medical Device

The auto-injector is considered a medical device. The auto-injector and DCC is considered a combination product with a device-constituent part (auto-injector) and drug-constituent part (DCC). Instructions for use for the medical device use are provided to the sites and participants by the sponsor. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical trial (see Section 8.3.6) and appropriately managed by the Sponsor. The auto-injector is able to record and store data pertaining to user handling. This data can be analyzed to improve usability of the auto-injector and includes number of injections, date and time of auto-injector use, dose size, and device performance characteristics.

6.2. PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

Lonapegsomatropin will be provided as a lyophilized powder in single-use glass vials requiring reconstitution with 1 mL sWFI or in DCCs, and administered by SC injection via syringe and needle or via the auto-injector.

The following materials for the trial drug reconstitution and administration will be provided to the investigational sites as needed and distributed by the investigator to the participant:

- IFU and Quick Reference Guide for the auto-injector, if applicable
- Auto- injector and DCCs or
- [redacted] hGH in single-use glass vials and sWFI and syringes for
- Needles for reconstitution
- Needles for administration
- Additional material as required (e.g., bags for transportation, alcohol swabs, etc.)

[redacted]

2. Lonapegsomatropin will be dispensed via an internet-based interactive response technology (IRT) in sufficient amounts to provide the participant with enough trial drug until the next dispensing visit. Details will be described in the Investigational Medicinal Product Manual.
3. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all trial products received, and any discrepancies are reported and resolved before use
4. Only participants enrolled in the trial may receive trial intervention, and only authorized site staff may supply the trial intervention. All trial intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
5. Lonapegsomatropin must be stored in refrigerator at 2°C – 8°C / 36°F – 46°F. Do not freeze. Store in the original carton to protect from light.
6. sWFI mut be stored in refrigerator or ambient at 2°C – 30°C / 36°F – 86°F
7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for trial product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records)
8. No unused or returned product may be disposed until reconciliation has been performed by the clinical research associate (CRA)

9. The CRA will ensure products are returned to the depot to be disposed, unless agreed otherwise. Further guidance and information for the final disposition of unused trial interventions are provided in the Investigational Medicinal Product Manual.

6.3. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4. TRIAL INTERVENTION COMPLIANCE

When participants are dosed at the site, they will receive trial intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

Participants self-administer trial drug at home, and compliance will be assessed at each visit. Compliance will be assessed by participant diary entries, direct questioning, and returned used and unused trial drugs during the site visits and documented in the source documents and relevant form.

A record of the quantity of the investigational product dispensed to each participant must be maintained and reconciled with trial intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

Deviations from the prescribed dosage regimen should be recorded.

6.5. DOSE MODIFICATION

Fixed, non-weight-based dosing will be used for this trial, hence not titration to a certain IGF-1 response.

Due to the different hGH dose requirements, depending on participants' age and receipt of concomitant oral estrogen, this trial will have three dosing groups. The starting doses, titration doses, and maintenance doses are shown as indicated in Table 2.

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

Table 2 shows the dosing groups, and the volume to be administered of lonapegsomatropin. It is imperative that investigators and patients follow the chart and administer the exact volume as indicated. The starting doses, titration doses, and target doses are also shown in Table 2. The dose adjustment parameters are described below this table.

Table 2: Dosing Table for Once-Weekly Administration of Lonapegsomatropin

Week		**Dose Group 1** Oral estrogen intake (any age) or below 30 years old	**Dose Group 2** 30 to 60 years old (both included) and no oral estrogen intake	**Dose Group 3** Over 60 years old and no oral estrogen intake
Weeks 1-4				
Weeks 5-8				
Weeks 9-12				
Weeks 13-52 (Dose Maintenance Period)				

CCI

[redacted]

sites.

Table 3: Dose Levels for Dose Titration for Once-Weekly Lonapegsomatropin

[redacted]

For each dosing group, the dose may not exceed the dose shown for Weeks 13-52 in Table 2 at any time during the trial. In addition, during the Dose Maintenance Period, the dose may not exceed the dose assigned at V11, which may differ from dosing table taking into consideration potential dose reductions during Titration Period due to tolerability or IGF-1 levels.

Participant who previously had a dose decrease in this TCH-306EXT trial due to weekly average IGF-1 SDS > 2.0 may be re-challenged (i.e., dose increased by 1 dose level) only once, in case of weekly average IGF-1 SDS < 0.0. In case average IGF-1 SDS would rise again >2.0 after the re-challenge, the dose will be decreased for 1 dose level (Table 3) and will not be further increased.

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

Table 4: Dosing Algorithm – Titration Period

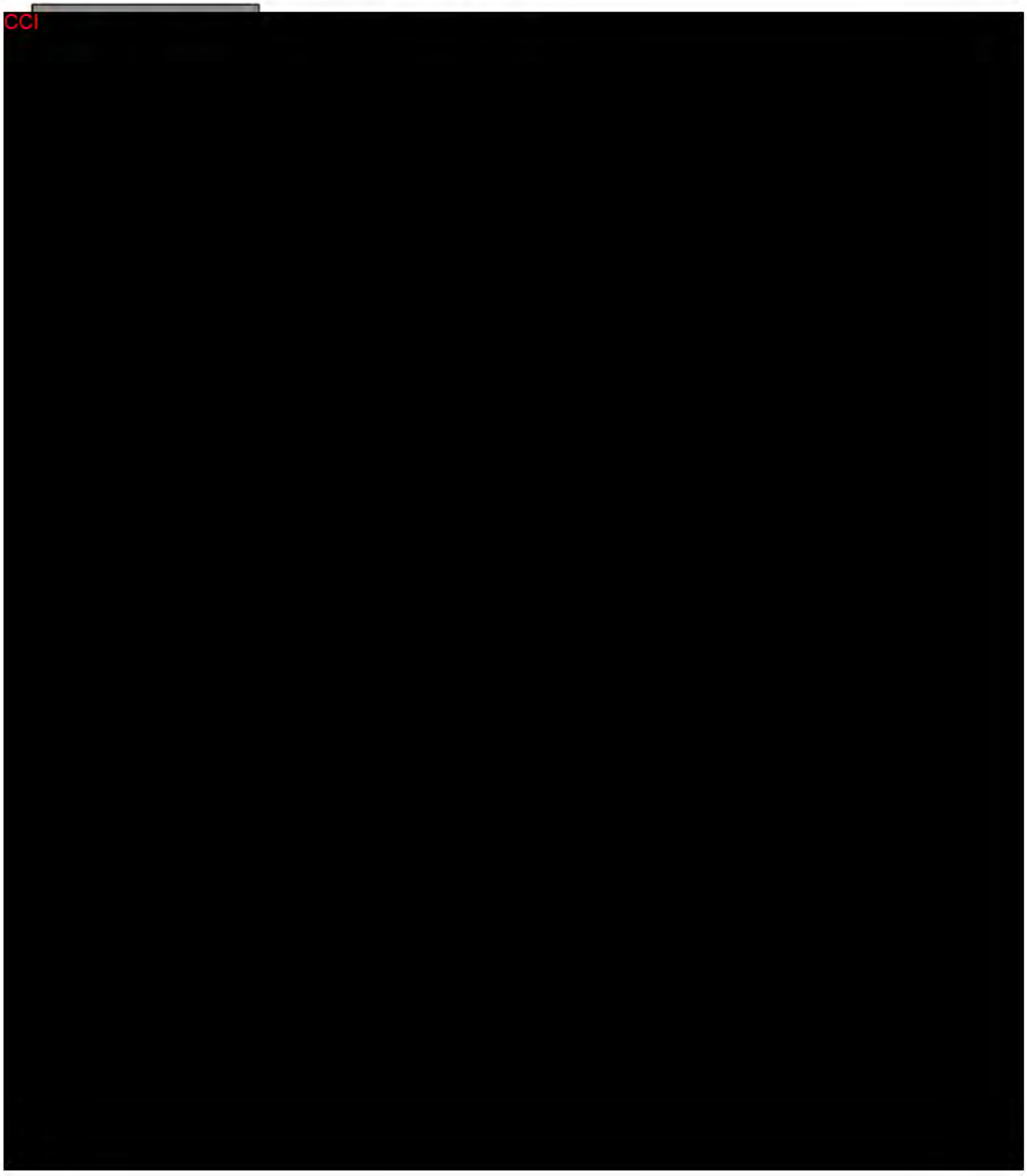
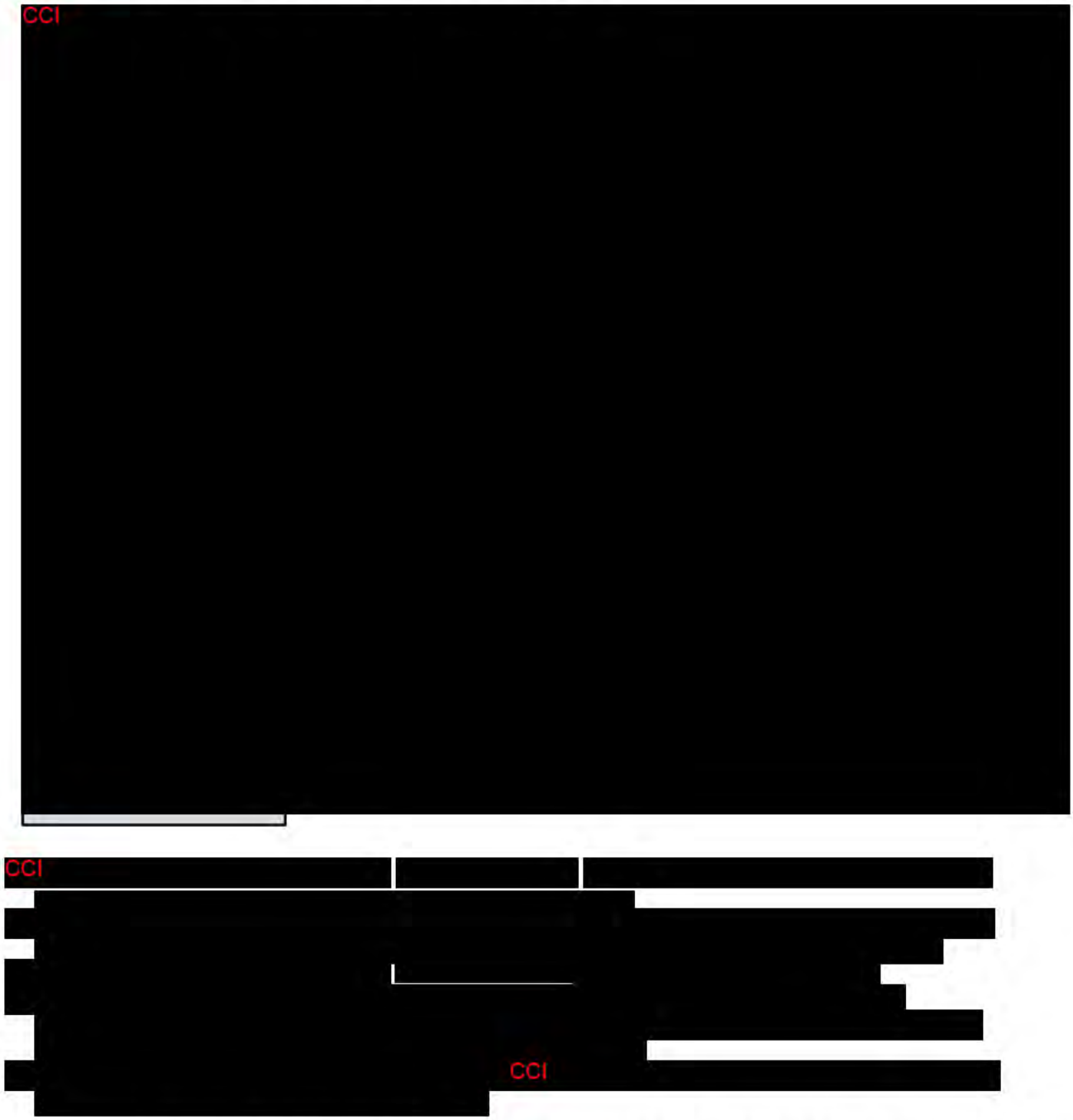


Table 5: Dosing Algorithm – Maintenance Period



6.6. CONTINUED ACCESS TO TRIAL INTERVENTION AFTER THE END OF THE TRIAL

Access to the trial drug after trial end will not be offered to any of the participants. Effective drugs for the indication are commercially available.

6.7. TREATMENT OF OVERDOSE

There is no antidote for somatropin overdose. Treatment is symptomatic and supportive. It is recommended to monitor thyroid function following an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether trial intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until trial intervention can no longer be detected systemically or for at least 7 days.
- Obtain a plasma sample for PK analysis as soon as possible if requested by the medical monitor (determined on a case-by-case basis).
- Report as an AE in accordance with Section 8.3 and document the quantity of the excess dose as well as the duration of the overdose.

6.8. CONCOMITANT THERAPY

For participants receiving oral estrogen or estrogen-containing therapy, participants must intend to maintain the same dose and route of estrogen administration throughout the trial.

The following should be avoided during trial participation: weight-loss drugs or appetite suppressants, including orlistat, zonisamide, lorcaserin, bupropion, topiramate, sibutramine, stimulants (e.g., phentermine or ADHD medications such as amphetamines or methylphenidate), and GLP-1 receptor agonists (e.g., dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide) unless indicated for diabetes mellitus treatment.

In addition to the medication recorded in trial TCH-306, medications (including over-the-counter or prescription medicines) or vaccines (including COVID-19 vaccines) that the participant is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Dates of administration including start and end dates
- Dosage information including dose and frequency

The following concomitant therapies are prohibited:

- hGH therapies other than lonapegsomatropin
- GH secretagogues
- Anabolic steroids other than when used as replacement therapies
- Biotin in doses higher than 0.03 mg/day from supplements. Higher doses of biotin may result in interference with commonly used biotinylated immunoassays, leading to false results.
- Cabergoline above 0.5 mg weekly or bromocriptine above 20 mg weekly due to their effects on lowering IGF-1 and GH hormonal concentrations and its independent effects on weight (Abs 1998, Korner 2003, Thorner 1975)

The medical monitor should be contacted if there are questions regarding concomitant therapy.

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. DISCONTINUATION OF TRIAL INTERVENTION

The investigator may discontinue treatment of a participant due to safety reasons e.g., AEs. If the participant agrees, the investigator may decide that the participant should continue the trial off treatment.

The investigator must stop the treatment for an individual participant in case of:

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

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE TRIAL

- A participant may withdraw from the trial at any time at the participant's own request or trial intervention may be withdrawn at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted similar to the end-of-treatment visit, as shown in the SoA (Section 1.2).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent
- If a participant withdraws from the trial, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records

7.3. LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. TRIAL ASSESSMENTS AND PROCEDURES

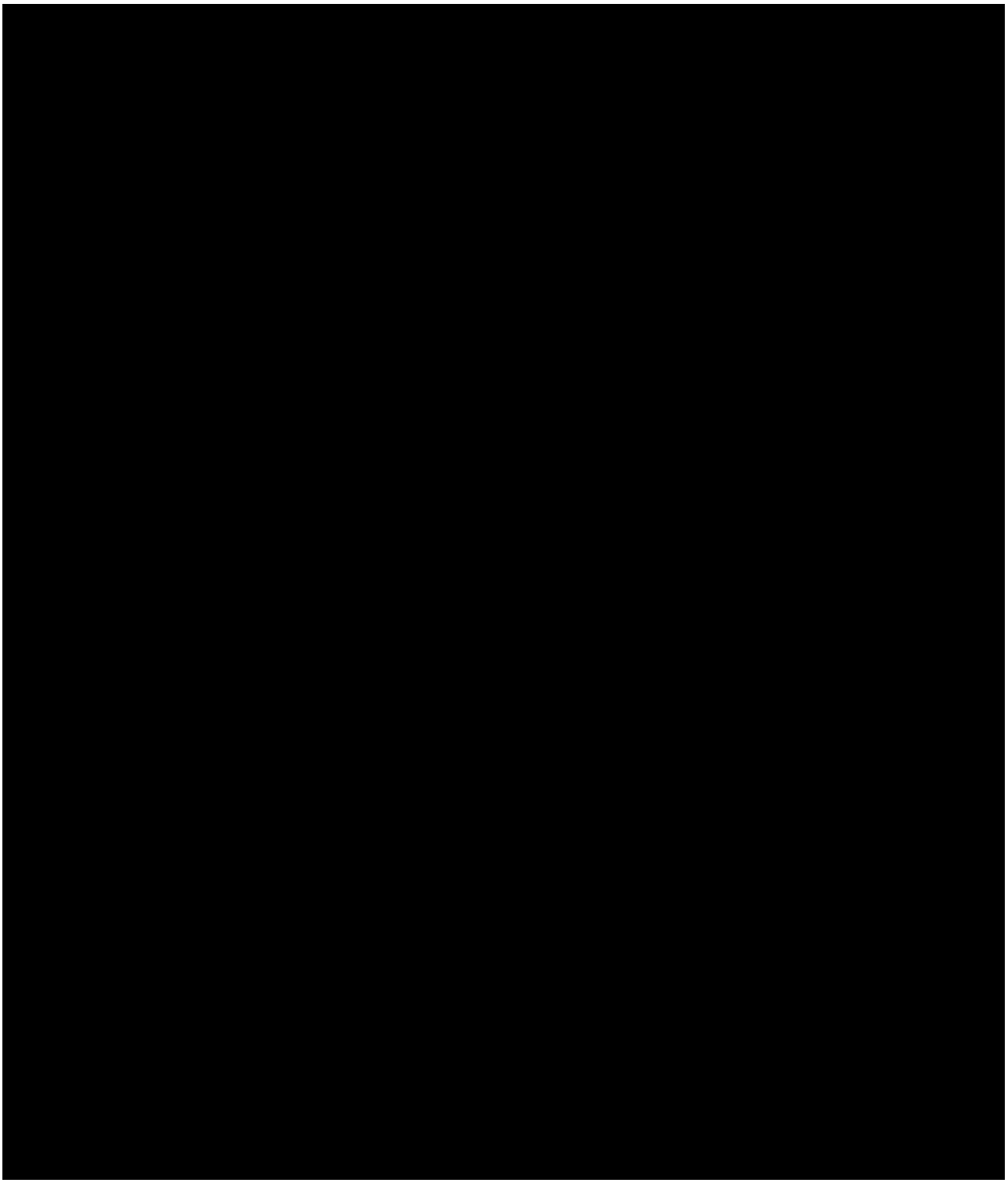
- Participants will continue to be identified with the same 8-digit participant number as in trial TCH-306. Likewise, the site numbers will remain the same.
- Trial assessments, procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- All lab sampling should be drawn in the morning (6:00-10:00 AM) as participants are required to attend in a fasting status having consumed only water for the last 8 hours
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue trial intervention.
- Adherence to the trial requirements, including those specified in the SoA Section 1.2, is essential and required for trial conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet the eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted, results obtained and recorded in the case report form (CRF) as part of the participation in trial TCH-306 obtained before signing of the informed consent form (ICF) will be utilized for screening or baseline purposes in this trial.
- CCI [redacted] CI
- The maximum amount of blood collected from each participant over the duration of the trial, will not exceed 300 mL.
- A diary will be handed out to the participants at each site visit. The participants will be instructed to enter every injection with the dose, date, and time together with the injection site i.e., right thigh, right abdomen, right buttock, left thigh, left abdomen, left buttock.

8.1. EFFICACY ASSESSMENTS

Planned timepoints for all assessments are provided in the SoA, Section 1.2.

8.1.1. DXA Scan

To ensure consistency, a central reader will evaluate the DXA scans on an ongoing basis. It is recommended that DXA assessments are performed in a similar setting (time and hydration status) at each visit, using the same approved DXA machine throughout the trial. Sites should be following the DXA manufacturer's guideline for maintenance, calibration, and quality control, as well as the trial-specific guidelines as provided by the central reader in trial manuals. Cross-calibration phantoms will be distributed to all sites using a scanner that was not cross-calibrated during TCH-306 to ensure consistency. DXA scans cannot be performed on participants who are pregnant or suspected to be pregnant.



8.1.3. Clinical Efficacy Laboratory Tests

- Detailed blood sampling, processing, and assaying of samples will be provided in the Laboratory Manual.
- See Appendix 2/Section 10.2 for the list of clinical laboratory tests to be analyzed at the central laboratory.

8.2. SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

8.2.1. Physical Examinations

- Weight [with light clothes] will be measured and recorded as outlined in the SoA (see Section 1.2).
- A physical examination will include assessments of the skin (including injection site reaction assessment), head, ears, eyes, nose, throat, neck / thyroid, lymphatic, cardiovascular, respiratory, abdomen, genitourinary, nervous system, musculoskeletal, extremities as outlined in the SoA see Section 1.2. Clinically significant abnormalities must be reported as an AE in accordance with this protocol.

8.2.2. Vital Signs

- Vital signs will be obtained as outlined in the SoA, see Section 1.2. Systolic and diastolic blood pressure (BP) and pulse rate should be preceded by at least 5 minutes of rest and assessed with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (Section 1.2). Clinically significant abnormalities must be reported as an AE in accordance with this protocol.

8.2.4. Clinical Safety Laboratory Tests

- See the SoA (Section 1.2) for the timing and frequency of blood sampling.
- All lab sampling should be performed in the morning as participants are required to attend in a fasting status.
- Detailed blood sampling, processing, and assaying of samples will be provided in the Laboratory Manual.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants 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
- See Appendix 2/Section 10.2 for the list of clinical laboratory tests to be analyzed at the central laboratory.

8.2.5. Pregnancy Testing

- Pregnancy test (hCG) should be performed for females of childbearing potential as outlined in the SoA (Section 1.2).
- Additional testing is required if menstrual period is missed, or pregnancy is suspected.
- Pregnancy test will not be required for women who are surgically sterile, with permanent hypogonadism with proven cause (for example have undergone a hysterectomy or bilateral tubal ligation) or above the age of 50 who have been without a menstrual period for at least 12 months.

8.3. ADVERSE EVENTS SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3/Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver).

The investigator is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remains responsible for following up on all AEs including AEs that are serious, considered related to the trial treatment or trial procedures, or that caused the participant to discontinue the trial treatment (see Section 7 and Section 8.3.3).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3/Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected until the first follow-up visit (i.e., 2 weeks after the last administration of trial drug or trial discontinuation/ termination, whichever is earlier). After this period, investigators should only report SAEs that are attributed to prior study treatment.

All SAEs will be reported to the Sponsor or designee immediately and within 24 hours of awareness, as indicated in Appendix 3/Section 10.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs after the first follow-up visit. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the trial intervention or trial participation, the investigator must notify the Sponsor within 24 hours of awareness.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs, including SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Nonserious AEs will be followed up until recovered/resolved, recovering/resolving, recovered/resolved with sequelae or until last scheduled contact with the investigator, whichever comes first. If the AE has not resolved by this timepoint, the final outcome of these ongoing AEs will be captured as 'not recovered/ not resolved' or 'recovering/resolving', whichever is applicable. Further information on follow-up procedures is provided in Appendix 3/Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a trial intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it in the Investigator Site File and will notify the IRB/IEC, if appropriate according to local requirements.

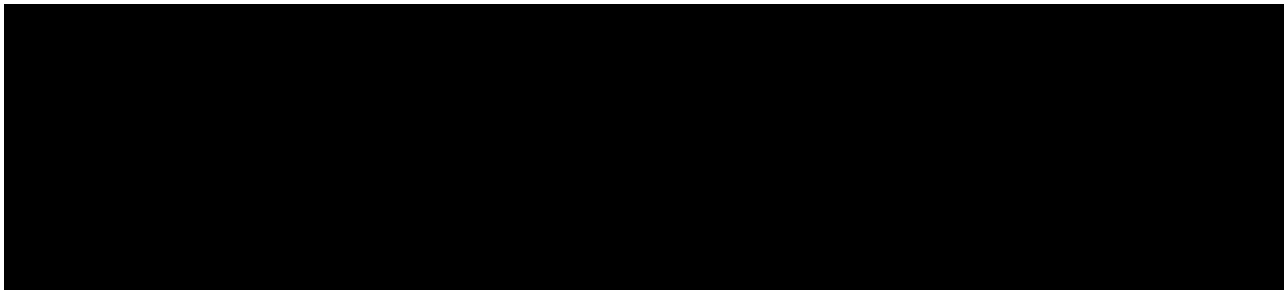
8.3.5. Pregnancy

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy while the participant was receiving the trial drug or within 2 weeks after the last dose of trial drug.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-trial pregnancy-related SAE considered reasonably related to the trial intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former trial participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Trial intervention must be discontinued immediately if a female participant pregnancy is reported.

8.3.6. Medical Device Deficiencies

The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible including the product batch number and forward the information to the Sponsor (refer to the Investigational Medical Product Manual for further details). If the medical device results in an AE to the trial participant, the AE must be reported on the AE eCRF and if the event is serious, the SAE must also report via the SAE Form within 24 hours after learning of the event, as outlined in Section 10.3.4.2.



8.5. GENETICS

Genetics are not evaluated in this trial.

8.6. BIOMARKERS

Biomarkers evaluated in this trial include IGF-1 and IGFBP-3.

8.7. IMMUNOGENICITY ASSESSMENTS

Antibodies to trial drug will be evaluated in serum samples collected from all participants according to the SoA, Section 1.2. Additionally, serum samples should also be collected at the final visit from participants who discontinued trial intervention or were withdrawn from the trial.

Samples will be tested at special laboratories as specified in Appendix 2/Section 10.2.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of GH treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the trial at a facility selected by the Sponsor to enable further analysis of immune responses if requested by the authorities.

8.8. HEALTH ECONOMICS

Not applicable.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database lock and it will include a more detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. STATISTICAL HYPOTHESES

No formal statistical hypotheses testing will be performed.

9.2. ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	All participants entering this extension trial
Safety analysis set	All participants who are exposed to any amount of the trial drug

The full analysis set is used to analyze endpoints related to the efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety.

9.3. STATISTICAL ANALYSES

9.3.1. General Considerations

Last assessment taken prior to the first dose of the treatment in TCH-306EXT will be used as baseline data; these include: weight, vital signs, central laboratory results, and result of DXA scan and fundoscopy.

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

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

Details of statistical methods will be provided in the Statistical Analysis Plan.

9.3.2. Safety Endpoints

Safety endpoints as measured throughout the treatment period:

- AEs
- Laboratory values
- Vital signs
- Immunogenicity
- 12-lead ECGs
- Fundoscopy

9.3.3. Efficacy Endpoints

- Trunk percent fat
- Trunk fat mass
- Total body lean mass

Analyses will be performed on observed value and change from baseline (from both TCH-306 baseline and TCH-306EXT baseline) by treatment received during TCH-306.

9.3.5. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set. Reporting of the safety data will be descriptive and all data will be listed and summarized by visit as applicable. The safety parameters include AEs, clinical laboratory, immunogenicity data, vital signs, ECG parameters, fundoscopy, and other safety parameters. All AEs will be coded to preferred term and system organ class using medical dictionary for regulatory activities (MedDRA). The incidence of AEs will be presented by MedDRA system organ class and preferred term, by causality and severity. A participant reporting the same adverse event(s) more than once is counted once and at the maximum severity or strongest relationship to the trial treatment when calculating incidence.

Details of statistical methods will be provided in the statistical analysis plan (SAP).

9.4. INTERIM ANALYSIS

Not applicable.

9.5. SAMPLE SIZE DETERMINATION

No formal sample size calculation is performed. All participants who have completed the treatment period of the TCH-306 trial and meet eligibility criteria can be assigned to trial intervention. The sample size in trial TCH-306 is approximately 240.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT CONSIDERATIONS

10.1.1. Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable International Council for Harmonization Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to trial participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical trials (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

- The investigator or his/her designee will explain the nature of the trial, including the risks and benefits, to the participant and answer all questions regarding the trial.
- Participants must be informed that their participation is voluntary. Participants will be required to date and sign an ICF.
- The authorized person obtaining the informed consent must also sign the ICF.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.
- Participants must be reconsented to the most current approved version of the ICF during their participation in the trial.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Data Protection

- Participants will continue with the unique identifier assigned in trial TCH-306. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

- Participant safety and IGF-1 results will be continuously monitored by the medical monitors. All trial required blood samples are analyzed at central laboratories. Contract research organizations are contracted by the Sponsor to perform translations, local trial submissions and on-site trial monitoring. No data monitoring committee or data safety monitoring board is used for this trial.

10.1.6. Dissemination of Clinical Study Data

Provision of study results, including disclosure of the clinical trial report, periodic safety reports, and clinical study summary reports after review by regulatory authorities, will be in accordance with regulatory requirements. This includes access to the clinical trial report also in the case of negative outcomes and in case of premature termination of the trial. This also includes posting of company-sponsored trial information and tabular trial results on the US National Institutes of Health's website www.clinicaltrials.gov, EudraCT and other publicly accessible sites.

10.1.7. Data Quality Assurance

- All participant data relating to the trial will be recorded on electronic CRFs, Safety Report Form and Pregnancy Report Form, if applicable or transmitted to the Sponsor electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided.
- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of trial critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plans.
- The Sponsor is responsible for the data management of this trial, including monitoring and quality checking of the data.
- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the electronic case report form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- CRAs will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents.

10.1.9. Trial and Site Start and Closure

Trial/Site Termination

The Sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the Sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the Sponsor or investigator may include but are not limited to:

For trial termination:

- Discontinuation of further trial intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data.
- Authorship will be determined by Sponsor and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. APPENDIX 2: CLINICAL LABORATORY TESTS

The analytes listed below are protocol-required laboratory tests that will be analyzed at the central laboratories.

- 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 estimated glomerular filtration rate [eGFR] rate calculation per MDRD equation), urea-nitrogen, uric acid, ferritin, and transferrin
- Hematology: hemoglobin, erythrocyte count, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocytes, differential blood count of leukocytes, platelet count
- Glucose metabolism: fasting insulin, fasting glucose, HbA_{1c}
- Lipid metabolism (fasting): total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), Lp(a) lipoprotein, free fatty acids, very low-density lipoprotein (VLDL).
- Thyroid and adrenal status: TSH, fT4, and fT3 and morning serum cortisol.
- Testosterone (males only)
- Pregnancy: human chorionic gonadotropin (hCG) test (women of childbearing potential only)
- Biomarkers: IGF-1 and IGF-1 SDS, IGFBP-3 and IGFBP-3 SDS
- [redacted]
- Anti-drug antibodies: anti-hGH antibodies, anti-PEG antibodies, anti-lonapegsomatropin antibodies, and neutralizing antibodies against hGH.

Instructions for the collection and handling of the blood samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample must be recorded.

Investigators must document their review of each laboratory report.

10.3. APPENDIX 3: AES AND SAES – DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1. Definitions

10.3.1.1. Adverse Events Definition

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can arise with any use (e.g., in combination with another drug), route of administration, formulation, or dose, including an overdose. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution.
- AEs not previously observed in the participant that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with GHD that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures, blood sampling).
- If applicable, AEs that occur prior to assignment of trial treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Based on the nonclinical and clinical program to date, the risks associated with the use of lonapegsomatropin are anticipated to be the same as those seen with daily somatropin products.

Possible AEs associated with somatropin therapy are listed in the current Investigator's Brochure (IB).

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

10.3.1.2. Serious Adverse Events Definition

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

- It results in death (i.e., the AE cause or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form or was allowed to continue, might have caused death).
- It requires or prolongs inpatient hospitalization (see Section 10.3.3.3).

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the trial drug.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe see Section 10.3.2.2.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 10.3.4.2 for reporting instructions).

10.3.1.3. Special Situation Definition

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

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

The medical monitor will review all safety information on an ongoing basis.

10.3.1.4. Important Identified Risk Associated with Lonapegsomatropin

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

10.3.1.5. Anaphylaxis Precautions

Definition of Anaphylaxis

For this study, anaphylaxis is defined according to [redacted] (See Table 6 below).

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

Anaphylaxis is highly likely when any ONE of the following three criteria are fulfilled.

FOR REFERENCE ONLY:

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

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

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

Management of severe hypersensitivity including anaphylaxis

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

1. *Maintain adequate airway*
2. *Administer subcutaneous epinephrine, and/or other medications as required by patient's status and as directed by physician in charge.*

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

10.3.2. Methods and Timing for Assessing and Recording Safety Variables

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

10.3.2.1. Adverse Event Reporting Period

The AE reporting period continues without interruption after completion of trial TCH-306 and ends 2 weeks following the last injection of trial drug in trial TCH-306EXT or trial discontinuation/ termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to trial treatment.

If the electronic data capture (EDC) system is not available, the investigator should report these events directly to the Sponsor outlined in Section Section 10.3.4.2.

10.3.2.2. Severity, Causality, and Outcome Assessment

10.3.2.2.1. Severity Rating

The following guideline should be used by the investigator to grade the intensity of an AE:

Table 7: Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a SAE in Section 10.3.1.2.

10.3.2.2.2. Causality Rating

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

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

- **Related (Yes)** – There is a plausible temporal relationship between the onset of the AE and administration of the IMP. The AE cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies. The AE follows a known pattern of response to the IMP or with similar treatments and/or the AE abates or resolves upon discontinuation of the IMP or dose reduction and, if applicable, reappears upon re-challenge.
- **Not Related (No)** – Evidence exists that the AE has an etiology other than the IMP (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). The AE has no plausible temporal relationship to IMP administration (e.g., cancer diagnosed 2 days after first dose of trial drug).

The Sponsor will assess the expectedness of the AEs through use of the Reference Safety Information in the Lonapegsomatropin IB. Expected AEs are those listed or characterized in the current IB.

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

10.3.2.2.3. Outcome Assessment

One of five outcomes listed below must be recorded:

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

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

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

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

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

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

Unknown – Unknown to investigator (e.g., participant lost to follow up).

AE follow-up should be conducted in accordance with Section 10.3.5, Appendix 3

10.3.3. Procedures for Eliciting, Recording and Reporting Adverse Events

10.3.3.1. Eliciting Adverse Events

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

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

10.3.3.2. Recording Procedures for All Adverse Events

AEs will be documented in response to questions about the participant's well-being and whether any changes in well-being have occurred since the previous visit. Additionally, at each visit, site staff will review participant diary data with the participant, to determine if diary entries reflect any AEs. AEs, including SAEs, will be documented from start of trial participation until 2 weeks after the last dose of trial drug was taken. All AEs must be recorded on the appropriate eCRF. AEs either observed by the investigator or reported by the participant must be recorded regardless of causality. The following attributes must be documented for each AE:

Trial ID

Subject number

AE Term

For SAEs: Description

Onset date

Resolution date, if applicable

Severity

Causality (relationship to the trial drug)

Outcome

Action taken with trial drug

Determination of "seriousness criteria" (whether serious or not serious)

Medical history conditions, signs, symptoms, and illnesses active during the TCH-306 Screening Period represent the medical history for participants continuing from TCH-306 into TCH 306EXT. Thus, information collected during the Screening period of TCH-306 serves as baseline for assessing AEs in TCH-306 and TCH-306EXT.

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

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

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

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

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

10.3.3.3. Specific Instructions for Recording Adverse Events

10.3.3.3.1. Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin above 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

10.3.3.3.2. Abnormal Vital Sign Values

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

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

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF. Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available as separate AEs. If a diagnosis is subsequently established, it should be reported as follow-up information.

Injection Site Reaction

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

Deaths

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

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a participant is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:

Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions;

Hospitalization or prolonged hospitalization required to allow efficacy measurement for the trial; or

Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the trial.

Preexisting Medical Conditions

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

Pregnancy

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

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

Product Complaints

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

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

10.3.4. Safety Reporting Requirements

10.3.4.1. Non-Serious Adverse Events Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities and pregnancies) that may require permanent discontinuation of trial drug should be discussed with the medical monitor prior to making any final decision.

10.3.4.2. Reporting

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

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 10.3.1.2 or seriousness criteria), severity (see Section 10.3.2.2.1), and causality (see Section 10.3.2.2.2).

Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE, and Special Situations are the AE term (diagnosis), participant number, trial drug, reporter, and the investigator's initial causality assessment. Additional information must be reported to the Sponsor or its representatives as a follow-up report. All SAEs and Special Situation reports (including follow-up information) must be reported to Ascendis Pharma using the Safety Report Form or the Pregnancy Report Form provided. A completed Safety Report Form / Pregnancy Report form must be uploaded to the Safety Reporting Portal at

[redacted]

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

SAEs and Special Situations information is collected and reported via the Safety Report Form provided by the Sponsor or its representative. Pregnancy information is collected and reported via Pregnancy Forms provided by the Sponsor or its representative.

The Sponsor (or its representatives) is responsible for reporting within the time frame required by applicable regulations all SAEs qualifying as suspected unexpected serious adverse reactions (SUSARs) to:

Investigators

Central IRBs/IECs (if applicable)

National ethics committees (if applicable)

Appropriate regulatory authorities

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

10.3.5. Safety Monitoring

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

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

Investigator Follow-up: Any AE that occurs during the clinical trial must be monitored and followed up until:

- It has resolved or receded
- Pathology laboratory findings have returned to normal
- Steady-state has been achieved
- It has been shown to be unrelated to the study drug and/or trial related procedure

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

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

or

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

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

10.4. APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1. Contraception Guidance

Throughout the trial, i.e., from the first until the last trial visit:

- Females of childbearing potential must use adequate contraceptive methods:
  a. Acceptable highly effective methods of contraception include intrauterine device (IUD); intrauterine system (IUS); bilateral tubal occlusion (must be documented); combined or progestogen-only hormonal contraception associated with inhibition of ovulation; vasectomized partner (must be documented); or sexual abstinence (only when it is the usual and preferred lifestyle of the participant).
  b. Clinically acceptable methods of birth control include male or female condom with or without spermicide; progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; or cap, diaphragm, or sponge with spermicide.

     Note: Permanent sterilization includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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

     Note: For participants using oral combined hormonal contraception (i.e., containing estrogen), the dose and route must be stable throughout the trial.
- Male participants must:
  a. use a condom, or
  b. his female partner of childbearing potential must use adequate contraceptive methods as described above.

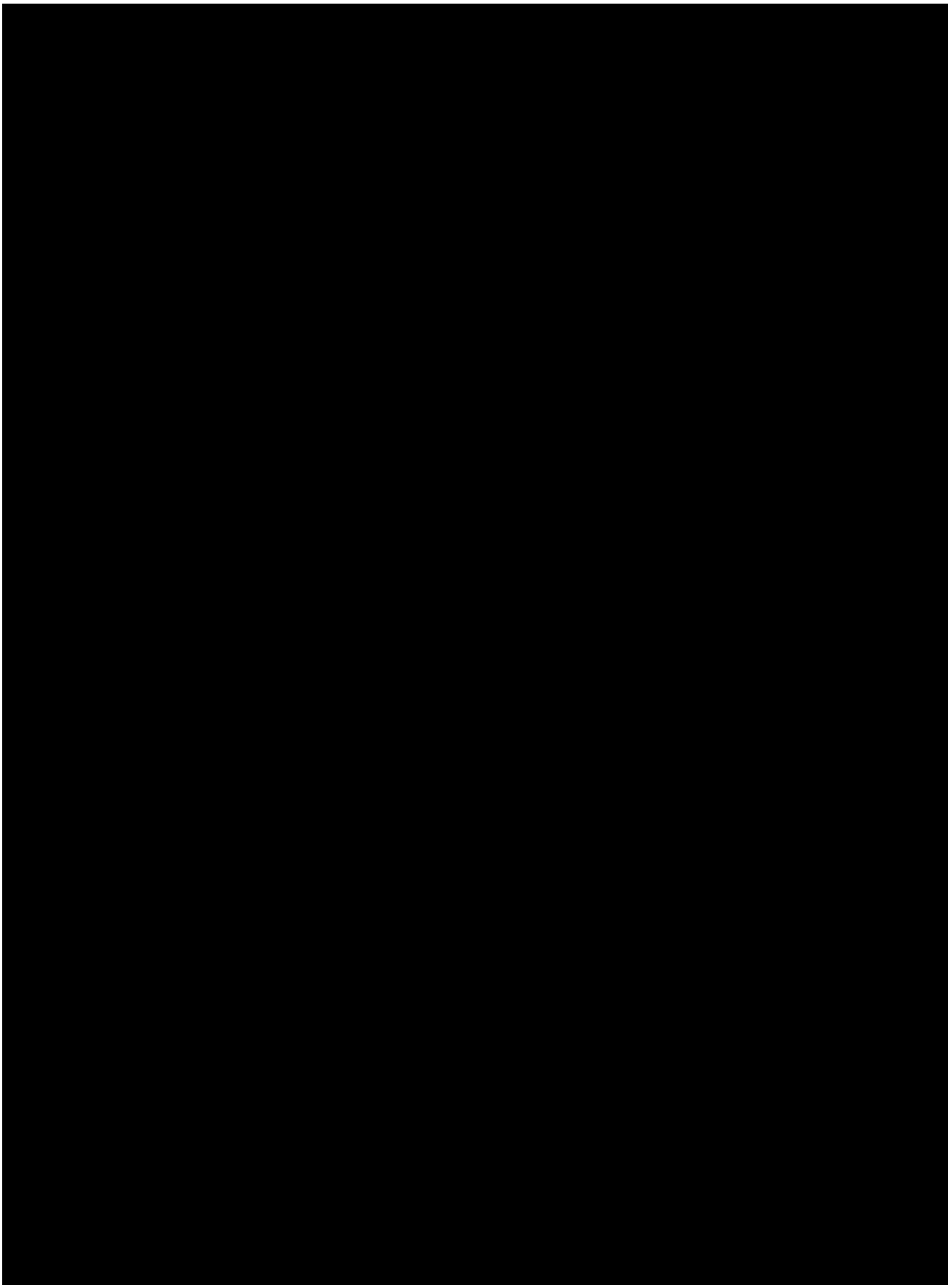
10.5. APPENDIX 5: COUNTRY-SPECIFIC REQUIREMENTS

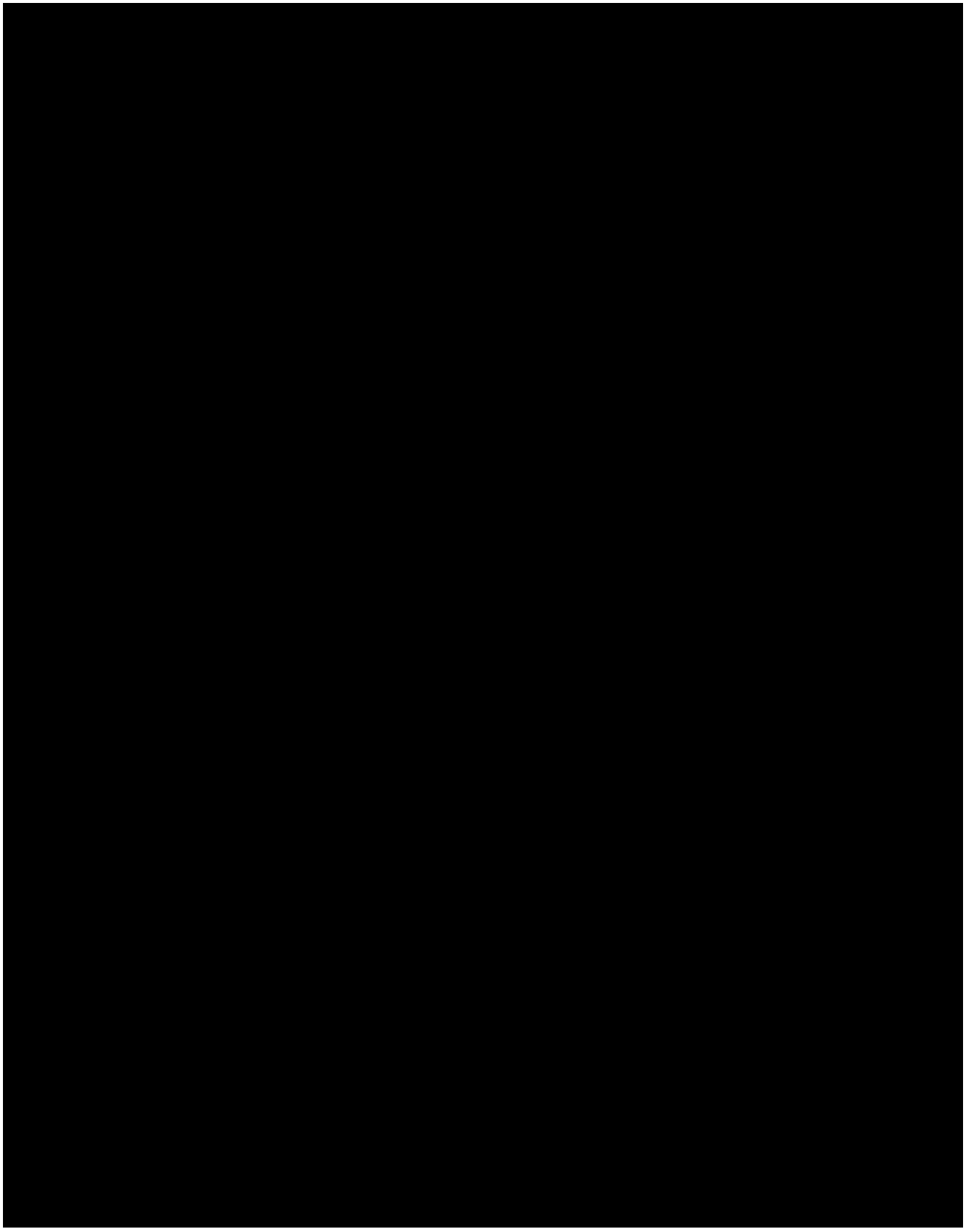
The trial will be conducted in North America, Europe, Asia including Japan, and Oceania.

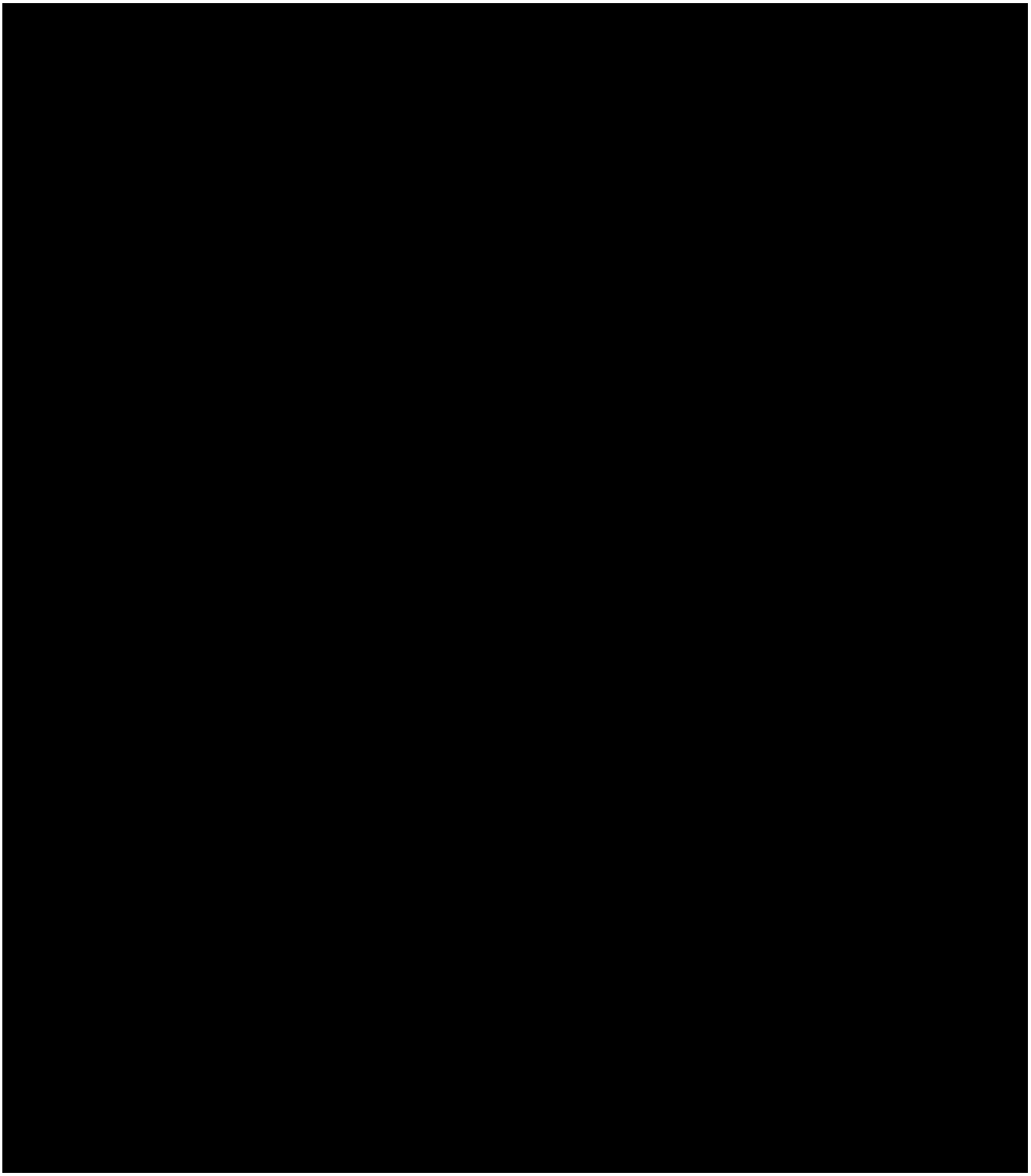
The countries selected for CCI [redacted].

10.6. APPENDIX 6: ABBREVIATIONS

Abbreviation	Definition
AE	adverse events
AGHD	adult growth hormone deficiency
BP	blood pressure
CRF	Case Report Form
CRA	Clinical research associate
DXA	dual-energy X-ray absorptiometry
DCC	dual chamber cartridge
ECG	electrocardiogram
[redacted]	
eCRF	electronic case report form
IEC	Independent ethics committee
FDA	Food and Drug Administration
GCP	good clinical practice
GH	growth hormone
GHD	growth hormone deficiency
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization Technical Requirements for Pharmaceuticals for Human Use
IFU	instructions for use
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
MedDRA	medical dictionary for regulatory activities
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
[redacted]	







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12. INVESTIGATOR SIGNATURE OF AGREEMENT

In signing this protocol, the investigator agrees to:

- Conduct the trial in accordance with the relevant, current protocol and will not make any changes in the research without IRB/EC approval and only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human participants
- Comply with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline on Good Clinical Practice (GCP) plus appropriate regional regulatory laws and requirements and all other requirements regarding the obligations of clinical investigators and all other pertinent requirements
- Ensure requirements relating to obtaining informed consent and regional ethical or institutional review board approval have been met
- Ensure all associates, colleagues, and employees assisting in the conduct of the trial are informed of their obligations in meeting their commitments
- Maintain all information in this document and regarding the trial as confidential, to use it only for the purpose of conducting the trial, and make these available for inspection by the Sponsor and/or its representative or any regulatory agency authorized by law
- Report to the Sponsor or its representative any adverse events (AEs) that occur in the course of the investigations, as specified in Section 10.3 of the clinical protocol
- Promptly report to the regional ethical or institutional review board all changes in research activity and all unanticipated problems involving risks to human subjects or others
- Sign a Form 1572, as applicable

I have read and understand the information in this clinical trial protocol, including the potential risks and side effects of the trial drug, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will not deviate from the protocol, except when necessary to protect the safety, rights, or welfare of subjects. I agree to inform all participants that the trial drug is being used for experimental purposes, and I will ensure that the requirements related to obtaining informed consent are met. I agree to report to the Sponsor any AEs that occur in the course of the investigation(s).

Investigator:

Printed Name and Title: _____

Signature: _____

Date: _____

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Approval	[redacted] Management 05-Jul-2023 12:42:28 GMT+0000

Approval	[redacted] Reviewer 05-Jul-2023 15:45:58 GMT+0000

Approval	[redacted] Clinical 11-Jul-2023 15:07:03 GMT+0000

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