Clinical Study Protocol

NCT Number: NCT05027308

Title: A Phase 3, Open-label Safety Study of Teduglutide in Japanese Pediatric Patients With Short Bowel Syndrome Who are Dependent on Parenteral Support, Aged 4 Months of Corrected Gestational Age or Older, and Requiring the Dosing of 1.25 mg Formulation

Study Number: TAK-633-3008

Document Version and Date: Amendment 2 / 19-May-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

Protocol:	TAK-633-3008
Title:	A Phase 3, Open-label Safety Study of Teduglutide in Japanese Pediatric Patients With Short Bowel Syndrome Who are Dependent on Parenteral Support, Aged 4 Months of Corrected Gestational Age or Older, and Requiring the Dosing of 1.25 mg Formulation
Short Title:	A Safety Study of Teduglutide in Japanese Patients with Short Bowel Syndrome Who are Dependent on Parenteral Support
Study Phase:	Phase 3
Drug:	TAK-633
IND Number:	Non-IND
EUDRACT Number:	Non-EUDRACT
Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan
Protocol History:	Original Protocol 1.0 02 Jun 2021 Amendment No. 1 02 Dec 2021 Amendment No. 2 19 May 2022

PROTOCOL SIGNATURE PAGE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.
- "Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (Ministry of Health, Labour and Welfare Ordinance No. 28, 27 March 1997; hereinafter referred to as "GCP Ordinance").
- "The Ministerial Ordinance that Partially Revises the Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (hereinafter referred to as "the revised GCP Ordinance").
- Pharmaceutical Affairs Law.
- Upon marketing approval of the teduglutide 1.25 mg formulation, the study will be continued as a post-marketing clinical study (phase 4 study), in accordance with GCP and Good Post-marketing Study Practice (GPSP), until each enrolled subject switches to the 1.25 mg commercial formulation. In the protocol, the term "clinical study" will be read as "post-marketing clinical study" after shifting to the post-marketing clinical study.

SIGNATURES

[redacted]

INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol for Study TAK-633-3008.

Title: A Phase 3, Open-label Safety Study of Teduglutide in Japanese Pediatric Patients With Short Bowel Syndrome Who are Dependent on Parenteral Support, Aged 4 Months of Corrected Gestational Age or Older, and Requiring the Dosing of 1.25 mg Formulation

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ *Date:* _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** **19 May 2022**	**Region** **All Sites**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that departing from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.		Section 1.1 Synopsis; Section 4.1 Overall Design
Made some changes to clarify the updated study procedures as follows: Subjects may proceed directly to the screening visit without entering to follow-up period if the efficacy is confirmed, or the investigator determines the appropriateness of the continuation of teduglutide treatment at Week 24.		Figure legend of Section 1.2 Schema; Footnotes of Section 1.3 Schedule of Activities; Section 6.2.5 Follow-up Period Escape Criteria
Added a study procedure "evaluation of escape criteria" at Week 24.		Visit 10 of Section 1.3 Schedule of Activities; Section 8.3.3.2 Weeks 4, 8, 12, 16, 20, and 24 (Window period ±7 days)
Added the maximum duration of treatment.		Section 4.3 Duration of Subject Participation and Study Completion Definition
Corrected a criterion of subjects' body weight, who develop renal impairment to continue the dosing during the study for consistency with the inclusion criterion 4; "above 10 kg" to "at least 10 kg".		Section 6.2.1 Dose, Regimen, and Administration by Parent or Guardian
Added a description to clarify that estimated glomerular filtration rates are calculated with the quintic equation.		Table 4 of Section 8.1.8 Procedures for Clinical Laboratory Samples
Corrected typographical errors.		Where applicable

CONTACTS

A separate contact information list will be provided to each site (refer to the **Protocol Annex**). Takeda-sponsored investigators will be provided with emergency medical contact information cards to be carried by each subject. General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is presented in Annexes and relevant guidelines provided to each site.

Contacts and Responsibilities for Study-Related Activities

Certain events and study-related activities will require the investigator and/or patient to have appropriate contact information. The sponsor or CRO will provide investigators with emergency medical contact information cards to be carried by each subject, per individual country requirements.

SAE Reporting

If a subject experiences a serious adverse event (SAE) or a non-serious AE requiring expedited reporting per the protocol, the investigator must report the event to the sponsor or CRO ***within 24 hours*** via the Electronic Data Capture (EDC) system, if possible. If the event cannot be reported via EDC during the required period, the SAE should be reported to the following:

[redacted]

Protocol and Safety-Related Questions or Concerns

For protocol- or safety-related questions or concerns, the investigator must contact:

[redacted]

Additional Information

See **Protocol Annex** for contact information related to the following:

- Medical monitor, for medical advice on the protocol and the study drug
- Sponsor's responsible medical officer
- Monitor assigned to the study site, for general advice on protocol procedures
- Serious adverse event (SAE) reporting
- Product complaints

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Takeda licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the "Clinical Trial Material Complaint Form" via the following email address:

[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
CI	confidence interval
CL/F	apparent clearance (clearance [CL] divided by bioavailability [F])
COVID-19	coronavirus disease 2019
(e)CRF	case report form (electronic)
CRO	contract research organization
EA	early antigen
EBNA	nuclear antigen
EEA	European Economic Area
EN	enteral nutrition
EOT	end of treatment
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
GPSP	Good Post-marketing Study Practice
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IRB	institutional review board
Ka	absorption rate constant
LKM	liver-kidney microsomal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NTT	no-teduglutide treatment
PK	pharmacokinetic
PN/IV	parenteral nutrition/intravenous fluid
PS	parenteral support
PT	prothrombin time
PTE	pretreatment event
SAE	serious adverse event

SAP	statistical analysis plan
SAS	safety analysis set
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VCA	viral capsid antigen
Vc/F	apparent central volume of distribution
WHO	World Health Organization

Study Definitions

Study completion	A subject would be considered as completing the study if the subject completed the end of treatment (EOT) visits, and does not withdraw from the study for any reason prior to the EOT visit, or the date when the study is discontinued, the subject's body weight is ≥15 kg, or the commercial teduglutide of 1.25 mg formulation is available.

Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

1. PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td colspan="2">Protocol number: TAK-633-3008</td><td>Drug: Teduglutide</td></tr>
<tr><td colspan="3">Title of the study: A Phase 3, Open-label Safety Study of Teduglutide in Japanese Pediatric Patients With Short Bowel Syndrome Who are Dependent on Parenteral Support, Aged 4 Months of Corrected Gestational Age or Older, and Requiring the Dosing of 1.25 mg Formulation</td></tr>
<tr><td colspan="3">Short title: A Safety Study of Teduglutide in Japanese Patients with Short Bowel Syndrome Who are Dependent on Parenteral Support</td></tr>
<tr><td colspan="3">Study phase: Phase 3</td></tr>
<tr><td colspan="3">Number of subjects (total and per treatment arm):
Approximately 5 subjects are planned to be enrolled into the study.</td></tr>
<tr><td colspan="3">Investigator(s):
Multicenter study.</td></tr>
<tr><td colspan="3">Site(s) and Region(s):
Approximately 6 sites in Japan</td></tr>
<tr><td colspan="2">Duration of Treatment:
Until subject with ≥15 kg of body weight (or ≥30 kg of body weight if a subject has moderate or greater renal impairment), transition to 1.25 mg formulation when commercially available or subject discontinuation, or study termination. The maximum duration of treatment is expected to be approximately 18 months.</td><td>Period of Evaluation:
Until subject with ≥15 kg of body weight (or ≥30 kg of body weight if a subject has moderate or greater renal impairment), transition to 1.25 mg formulation when commercially available or subject discontinuation, or study termination.</td></tr>
<tr><td colspan="3">Objectives:
Primary: To evaluate the safety of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with short bowel syndrome (SBS) who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation.
Secondary: To evaluate the efficacy of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation.</td></tr>
<tr><td colspan="3">Investigational product, dose, and mode of administration:
Teduglutide 0.05 mg/kg (0.025 mg/kg for patients with moderate or greater renal impairment) once daily via subcutaneous injection</td></tr>
</table>

Methodology:

This study is designed to allow access and administration of 1.25 mg formulation of teduglutide to pediatric patients with SBS of <10 kg body weight (or <20 kg of body weight if a subject has moderate or greater renal impairment) for whom the 5 mg formulation cannot be dosed.

This is a phase 3, open-label study to evaluate the safety of teduglutide in Japanese pediatric patients with SBS who are dependent on parenteral support (PS), aged 4 months (corrected gestational age) or older, and <10 kg of body weight (or <20 kg of body weight if a subject has moderate or greater renal impairment). A 2 to 4-week screening period will be used to verify eligibility. Subjects who fail screening may be re-screened with prior sponsor approval. After screening, subjects, who meet the inclusion criteria and meet none of the exclusion criteria, will start a 28-week treatment cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg (0.025 mg/kg for patients with moderate or greater renal impairment) subcutaneous once daily, followed by a 4-week follow-up (no treatment) period. Each subject will visit the site at baseline, weekly for the first 2 weeks (Week 1 and Week 2), and every 4 weeks after Week 4 (Weeks 4, 8, 12, 16, 20, 24, and 28). Telephone contacts will be made as needed during the treatment period. At all site visits and during all telephone contacts, safety will be evaluated and nutritional support will be reviewed and adjusted, as needed. A subject may "escape" the follow-up period between Week 24 and Week 28 and proceed immediately to another screening visit if the subject meets at least 1 of the follow-up period escape criteria. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to a no-teduglutide treatment (NTT) period. The subject in the NTT period may proceed to another screening visit at any time if at least 1 of the treatment eligibility criteria are met. The subjects will start a next cycle of teduglutide treatment if the eligibility is confirmed at another screening visit and baseline visit. A subject may participate in multiple treatment cycles and NTT periods depending on his or her clinical trajectory. The screening period for another treatment cycle following the NTT or follow-up period will be -28 to -1 days.

All attempts will be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and to be provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluid (PN/IV) (or PS) reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

The teduglutide treatment will continue until the teduglutide 1.25 mg formulation is commercially available and each subject is able to transition to the commercially available product, the subject's body weight increases to ≥15 kg (or ≥30 kg of body weight if a subject has moderate or greater renal impairment) requiring them to transition to the 5 mg formulation, the subject's participation in this study is discontinued, or the study is discontinued, whichever comes first. The 1.25 mg formulation can be used in subjects with <15 kg body weight (or <30 kg of body weight if a subject has moderate or greater renal impairment) in this study, depending on the subjects' condition, such as the status of the subjects' weight fluctuation. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the end of treatment (EOT) visit. The benefit of teduglutide treatment will be assessed at Week 24. If no benefit is observed at Week 24, as determined by the investigator, the treatment should be discontinued, and the subject should be discontinued from the study; otherwise, the subject may continue on the study at the discretion of the investigator and per the above guidance.

Inclusion and Exclusion Criteria

Inclusion Criteria:

Subject eligibility is determined according to the following criteria prior to entry into the study and the first dose:

1. In the opinion of the investigator, a parent/guardian is capable of understanding and complying with protocol requirements.
2. A parent or guardian signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Male or female pediatric patient of corrected gestational age 4 months or older.
4. Body weight at the time of screening and baseline visits of at least 5 kg and <10 kg for subjects with normal renal function or mild renal impairment (estimated glomerular filtration rate ≥50* mL/min/1.73 m^2), OR at least 10 kg and <20 kg for subjects with moderate or greater renal impairment (estimated glomerular filtration rate <50* mL/min/1.73 m^2).
5. Diagnosis of SBS with intestinal failure, defined as dependence on parenteral support (PS) to provide at least 30% of fluid or caloric needs.
6. Subjects to have stable PS for at least 1 month prior to screening as assessed by the investigator. Stable PS is defined as inability to significantly reduce parenteral nutrition/intravenous fluid (PN/IV) support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds), assessed by the investigator.

*This criterion is based on "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. Food and Drug Administration. May 1998."

Exclusion Criteria:

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. A parent/guardian who is not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements.
2. Clinically significant intestinal obstruction, active or recurrent pancreatic or biliary disease, or dysmotility that prevents the advancement of enteral intake.
3. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
4. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce PS, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
5. Major gastrointestinal (GI) surgical intervention including significant intestinal resection or bowel lengthening procedure within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm and endoscopic procedures are allowed).
6. Cardiac disease that makes the patient vulnerable to changes in fluid status.
7. History of cancer or known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of GI cancer (including hepatobiliary and pancreatic cancer).
8. Concurrent treatment with glucagon-like peptide-2 (GLP-2), human growth hormone, or analogs of these hormones (not including teduglutide) within 6 months prior to the screening visit, or concurrent treatment with octreotide or GLP-1 analogs within 30 days prior to the screening visit.
9. Concurrent treatment with biological therapy (eg, anti-tumor necrosis factor [anti-TNF]) for active Crohn's disease within 6 months prior to the screening visit.
10. Participation in a clinical study using an experimental drug (other than glutamine or intravenous lipid emulsions) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the screening visit and for the duration of the study.
11. Known or suspected intolerance or hypersensitivity to the study drug, closely related compounds, or any of the stated ingredients.
12. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period as meeting at least 2 of any of the following parameters:

a. International normalized ratio >1.5 not corrected with parenteral vitamin K
b. Platelet count $<100\times10^3/\mu L$ due to portal hypertension
c. Presence of clinically significant gastric or esophageal varices
d. Cirrhosis
e. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period during screening
f. Total bilirubin ≥2x upper limit of normal (ULN)
g. Aspartate aminotransferase (AST) ≥3x ULN
h. Alanine aminotransferase (ALT) ≥3x ULN

13. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Statistical Considerations

Safety Analysis

Adverse events will be summarized using the safety analysis set. Counts and percentages for subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) (any SAE, regardless of relationship to study drug) will be summarized descriptively by System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities terminology. Serious adverse events will also be summarized by severity and by relationship to study drug. For clinical laboratory tests, body weight, height (or length), and head circumferences, vital signs, urine, and fecal output, descriptive statistics will be used to summarize the absolute values and changes from baseline by visit.

Efficacy Analysis

For the continuous endpoints, the following statistics will be presented: non-missing values, mean, median, standard deviation, minimum, maximum, and 95% confidence interval (CI).

- Change from baseline in PS volume by each visit and EOT
- Percent change from baseline in PS volume by each visit and EOT
- Change from baseline in days per week of PS by each visit and EOT

For the binary endpoint, the following statistics will be presented: count, proportion, and 95% Clopper Pearson CI.

- Number and percent of subjects achieving at least 20% reduction in PS volume from baseline by each visit and EOT
- Number and percent of subjects achieving enteral autonomy, defined as complete weaning off PS by each visit and EOT

Analyses of PS will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

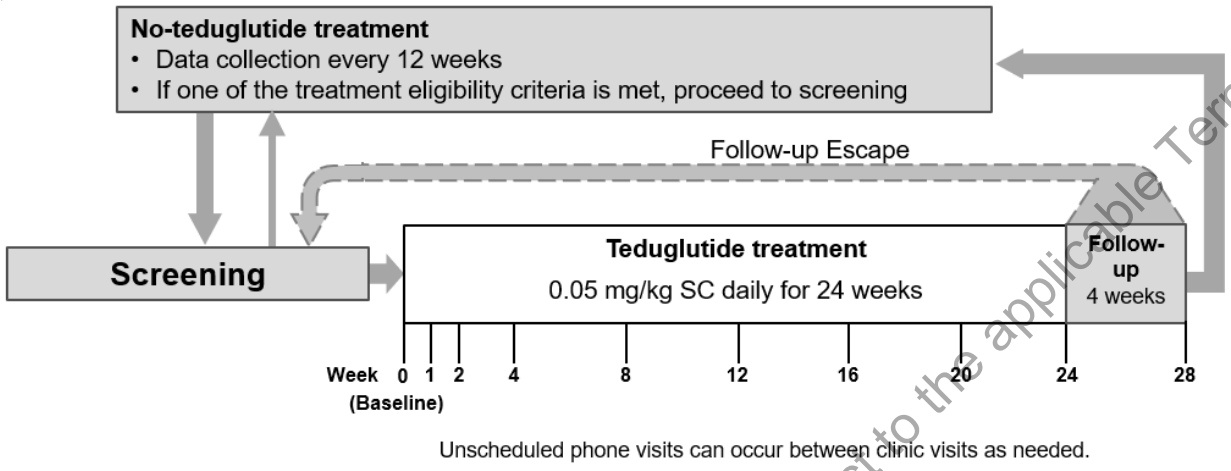
No formal statistical test will be performed due the limited sample size. Details of the analysis methods will be specified in the statistical analysis plan.

Sample Size Justification

The sample size is determined based on enrollment feasibility of this rare population in children in Japan, rather than statistical power calculation.

1.2 Schema

Figure 1. Study Schematic Diagram



SC=subcutaneous

Figure legend: Subjects eligible for the study will enter a 28-week treatment cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at baseline (Week 0) and Weeks 1, 2, 4, 8, 12, 16, 20, 24, and 28. If at least 1 of the follow-up period escape criteria (Section 6.2.5) is met during the 4-week follow-up period, where teduglutide is not received, subjects may proceed directly to another screening visit. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to a no-teduglutide treatment period. Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to another screening visit at any time in order to assess eligibility (Section 6.2.4). Subject will start a next cycle of teduglutide treatment if at least 1 of the treatment eligibility criteria and none of the exclusion criteria are met. At Week 24, if the efficacy (eg, PS volume reduction from baseline) is confirmed, or the continuation of teduglutide treatment is appropriate as determined by the investigator, subjects may proceed directly to the screening visit without entering to follow-up period, otherwise subjects will enter the 4-week follow-up period.

The teduglutide treatment will continue until the following situations, whichever comes first:

- The teduglutide 1.25 mg formulation is commercially available, and each subject is able to transition to the commercially available product,
- The subject's body weight increases to ≥15 kg (or ≥30 kg of body weight if a subject has moderate or greater renal impairment) requiring them to transition to the 5 mg formulation,
- The subject's participation in this study is discontinued, or
- The study is discontinued.

1.3 Schedule of Activities

Table 1. Schedule of Study Procedures

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Follow-up (4 weeks)	NTT[p] (every 12 weeks)	After 52 weeks of treatment	EOT/ET[r]
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**-**		
Study day ±window (days)	**-28 to -14[g]**	**0**	**7 ±3**	**14 ±3**	**28 ±7**	**56 ±7**	**84 ±7**	**112 ±7**	**140 ±7**	**168 ±7**	**196 ±7**	**±7**		**±7**
Informed consent[a]	X[h]													
Eligibility	X[i]	X[k]												
Demographics, medical and surgical history, SBS history	X[h]													
Adverse events assessment	X	X[l]	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications/procedures	X	X[l]	X	X	X	X	X	X	X	X	X	X		X
Physical examination/vital signs/weight	X	X[l]	X	X	X	X	X	X	X	X	X	X		X
Height (or length) and head circumference[b]	X	X[l]			X	X	X	X	X	X		X		X
Safety laboratory tests[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X		X
Provide intake and output diaries	X	X[l]	X	X	X	X	X	X	X	X	X	X		
Review diaries[d]	X[j]	X[l]	X	X	X	X	X	X	X	X	X	X		X
Adjust nutritional support as needed[e]	X[j]	X[j]	X	X	X	X	X	X	X	X	X	X		X
Dispense investigational product[f]		X[l]	X	X	X	X	X	X	X					
Confirm administration proficiency		X[l, m]			X		X							
Evaluation of escape criteria										X[n]	X[o]			
Colonoscopy/sigmoidoscopy													X[q]	
Assessment of eligibility for additional treatment	X[j]	X								X	X	X		

Table 1. Schedule of Study Procedures

(e)CRF=case report form (electronic); EOT=end of treatment; ET=early termination; GI=gastrointestinal; NTT=no-teduglutide treatment; PS=parenteral support; SBS=short bowel syndrome; SC=subcutaneous

a. Informed consent and, if applicable, informed assent must be obtained prior to performing any study-related procedure.
b. Head circumference will be measured in subjects 36 months of age and younger.
c. Safety lab assessments (see Table 4) at site visits will consist of biochemistry, hematology (not required at Week 1 and Week 2), and urinalysis (not required at Week 1 and Week 2), with results processed by a central lab. At the discretion of the investigator, safety labs may be performed between study visits following adjustments to PS. Urine specimen collection should be attempted as part of the safety lab tests, but lack of urinalysis will not constitute a protocol deviation.
d. The volume of PS and oral/enteral intake will be recorded on the intake diary every day during the study by the subject or parent/guardian/study site staff (Section 8.1.13). Urine and stool output should be recorded in the output diary over the 48-hour period preceding every clinic visit. (Section 8.1.13 for more details).
e. Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data, and according to the guidelines for nutrition support management and weaning algorithms provided in Guidelines for Nutritional Support Management During the Study (Appendix 5) and Weaning Algorithms (Appendix 6), respectively.
f. The first SC injection will be administered under the supervision of the investigator/designee. The subject will be observed for possible hypersensitivity reactions for at least 4 hours after administration during their initial dosing visit. The site of administration (arm, thigh, abdomen) must be specified and recorded in the (e)CRF. The dose of study medication will be adjusted per body weight at Week 12 in each treatment cycle.
g. The screening period for another treatment cycle following the NTT or follow-up period will be -28 to -1 days.
h Not applicable for another treatment cycle.
i. Only exclusion criteria is needed for another treatment cycle.
j. Applicable only for another treatment cycle.
k. Subject eligibility will need to be re-confirmed before the first dose in the cycle.
l. The procedures will be performed before the administration of the study drug.
m. The first dose of teduglutide will be administered by a study physician. The study physician must observe the parent/guardian administer the study drug in compliance with the study drug administration checklist before the parent/guardian is allowed to administer the drug without direct observation by the physician. Refer to Section 6.2.1.1.
n. If the efficacy (eg, PS volume reduction from baseline) is confirmed, or the continuation of teduglutide treatment is appropriate as determined by the investigator, subjects may proceed directly to the screening visit without entering to follow-up period, otherwise subjects will enter the 4-week follow-up period. For the subjects who skip the follow-up period, the screening period will be -28 to -1 days. The Week 24 visit and the next round of screening visit may be combined.
o. If at least 1 escape criterion (Section 6.2.5) is met during the follow-up period, subjects may proceed directly to another screening visit.
p. Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the screening visit at any time in order to assess eligibility for the study, if at least 1 of the treatment eligibility criteria is met (Section 6.2.4).
q. Colonoscopy/sigmoidoscopy to identify colorectal polyps is recommended in each subject after 52 weeks of treatment while on continuous treatment with teduglutide, and/or if the subject has new or unexplained GI bleeding. Fecal blood test may be performed as needed.
r. If a subject terminates from the study prematurely, all EOT procedures should be done at the time of termination. In the case of ET, a phone contact should be done every week before the ET visit.

Note: Telephone contacts will be made as needed during the treatment period. A visit to the site may be undertaken, if necessary, instead of a phone contact and completed as an unscheduled visit.

2. INTRODUCTION

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal disease, which usually results in major surgical resections of the small intestine. In children, most cases of SBS begin in infancy. Common causes of SBS in children include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis (Duro et al. 2008; Squires et al. 2012). Similar to adults, new-onset SBS in older children usually stems from Crohn's disease, trauma, and cancer. The diminished absorptive capacity for fluids and nutrients often results in dependence on parenteral support (PS) to maintain energy and fluid and electrolyte homeostasis.

After resection or congenital loss, the small intestine is capable of remarkable adaptation. Mechanisms for adaptation include up-regulation of nutrient transporters, increased villus height and crypt depth, dilation, and delayed intestinal transit. The main principle of management of SBS is to provide the minimal necessary PS to maintain energy, fluid, and electrolyte homeostasis while maximizing enteral feeding to promote intestinal adaptation. In infants, rapid linear growth of the intestines during the first year of life dramatically complements the aforementioned adaptive responses. About 30% of infants who develop SBS during the neonatal period become independent of PS requirements by 12 months of age, and an additional 10% wean off PS by 24 months of age. After this time, linear intestinal growth slows. About 60% of children with SBS are able to become independent of PS within 5 years (Khan et al. 2015; Squires et al. 2012). Nevertheless, despite optimal medical management, many children remain dependent on PS.

It is highly unlikely that children with less than 10% of the expected length of small intestine reach enteral independence. These subjects reach a plateau in their ability to advance oral/enteral feeds or decrease PS (ie, are "stuck") and are not expected to achieve spontaneous adaptation. Subjects who have not progressed to full enteral adaptation by 12 months after their intestinal insults are very unlikely to demonstrate spontaneous improvement in their enteral function (Sigalet et al. 2011).

2.1 Indication and Current Treatment Options

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption. Chief among these is hormones glucagon-like peptide-2 (GLP-2), which is secreted from L-type enteroendocrine cells in the distal ileum and colon. Resection of these regions impairs the adaptive response by limiting endogenous production of GLP-2.

There are no approved pharmacological therapies that promote intestinal adaptation in children with SBS in Japan. In the United States (US) and European Union (EU), a GLP-2 analog called teduglutide is approved for the treatment of SBS in adult patients who are dependent on parenteral nutrition/intravenous fluid (PN/IV) support or PS.

2.2 Product Background and Clinical Information

Teduglutide (TAK-633, SHP633, ALX-0600) is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life ($t_{1/2}$) of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide is approved for the treatment of patient aged 1 year and above with SBS in the US and EU at a dose of 0.05 mg/kg subcutaneous (SC) once daily. In Japan, it was approved in June 2021 for the treatment of patients aged 4 months by corrected gestational age and above with SBS.

An overseas phase 3 study, Study SHP633-301, has been completed in infants 4 to 12 months of age with SBS who were dependent on PS, where the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment were evaluated. Subjects were randomized (1:1 ratio) to the teduglutide (0.05 mg/kg SC once daily) or standard of care treatment (standard medical therapy for SBS) arm. Based on subject diary data and prescribed data, overall data showed a reduction of PS volume and caloric intake, and of days per week of PS infusions over time, in infant subjects treated with teduglutide compared with the subjects receiving the standard of care. This reduction was similar to the results observed in previous pediatric studies. Teduglutide treatment was also demonstrated to be generally safe and well tolerated, and no new safety issues were identified. The safety profile was favorable and consistent with the safety profile seen in other pediatric studies.

A pediatric phase 3 study, Study SHP633-302, has been completed in Japanese pediatric patients with SBS. In that study, teduglutide 0.05 mg/kg was subcutaneously administered once daily for 24 weeks in 10 Japanese pediatric patients with SBS who were dependent on PS of 4 months (corrected gestational age) to 15 years (specifically, 8 children aged 1 to 15 years old and 2 infants aged 4 to <12 months [corrected gestational age]). Within the analyzed group of 8 subjects (6 children and 2 infants) who began treatment after Protocol Amendment 3 where the training process of self-injection has been changed, the ratios of subjects who achieved at least 20% reduction in weekly PS volume from baseline for the children group and the infant group were 66.7% (4/6 subjects) and 50.0% (1/2 subjects).

Change in PS volume (average±standard deviation [SD]) to end of treatment (EOT) from baseline and change rate were −14.5±8.03 mL/kg/day and −35.7±33.18% for children and −26.2±13.61 mL/kg/day and −26.7±15.14% for infants. The treatment responses observed in Japanese patients with SBS in this study were similar to those observed in previous non-Japanese-conducted studies in pediatric patients with SBS. Teduglutide was generally well-tolerated by Japanese pediatric subjects with SBS; the nature and frequency of the reported treatment-emergent adverse events (TEAEs) in Study SHP633-302 were generally consistent with the underlying disease and those reported in previous studies in pediatric patients with SBS.

Additional information is provided in the Investigator's Brochure.

2.3 Study Rationale

Teduglutide was designated as an orphan drug indicated for SBS in Japan on 20 Nov 2014. The total number of patients with SBS who are dependent on PS is estimated to be <1,000 patients in Japan. There is no established standard of care and there is a high unmet medical need.

The present TAK-633-3008 study in Japanese pediatric and infant subjects is designed [redacted] There are 2 options of the teduglutide drug product for injection: 5 mg and 1.25 mg formulations, which were used in the SHP633-301, the SHP633-302, and SHP633-305 studies based on the subjects' body weight (only 1.25 mg formulation was used in the SHP633-301 study). From the viewpoint of dose accuracy, however, the 5 mg formulation is not recommended for use in patients with a body weight of <10 kg who require a dose of <0.5 mg of teduglutide. The 1.25 mg formulation is for patients <10 kg to receive an accurate dose at such low body weight. In the clinical package, the lowest body weight in pediatric patients was 5.2 kg. The 1.25 mg formulation can also be used in patients who weight up to 15-20 kg. An application for this additional dosage form (1.25 mg formulation) is planned to be filed in Japan after the approval of the 5 mg formulation. If a subject has moderate or greater renal impairment, body weight should be considered as 2 times as a subject has normal renal function or mild renal impairment.

The teduglutide dose of 0.05 mg/kg daily is supported by results from a completed 12-week pediatric study. Teduglutide is approved for adult use in over 40 countries at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric study (TED-C13-003, A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year through 17 Years, with SBS who are Dependent on Parenteral Support) and the 28-week infant study (SHP633-301, A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population PK modeling and simulations were conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies including adult phases 1, 2, and 3 studies as well as the pediatric study (TED-C13-003); they suggested that the dose in pediatric subjects is likely to be the same as the dose in adults (O'Keefe et al. 2006).

Effect of renal impairment on PK have been investigated by a dedicated renal study (CL0600-018) and population PK analyses using data collected in subjects and SBS patients (adults and pediatrics) with and without various degrees of renal impairment. Results of these evaluations have recommended 50% dose reduction (from 0.05 mg/kg to 0.025 mg/kg) in patients with moderate or greater renal impairment, which were included in the approved drug labels of teduglutide across regions.

2.4 Benefit/Risk Assessment

The aim of teduglutide treatment is to increase absorptive capacity in order to yield decreases in PS. In addition, experts anticipate that there will be several direct benefits from decreased PS and advances in enteral feeds, including less exposure to PN/IV constituents, less central line manipulation with lower risk of infection, and more time to focus on oral rehabilitation strategies. Results of studies have confirmed these expectations (see Investigator's Brochure for study results).

The study is designed to allow access and administration of 1.25 mg formulation of teduglutide to pediatric patients with SBS of <10 kg body weight (or <20 kg body weight if a subject has moderate or greater renal impairment) for whom the 5 mg formulation cannot be dosed.

Always refer to the latest version of the teduglutide investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of teduglutide.

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; ICH E6 R2, 2016), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate the safety of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation.

3.1.2 Secondary Objectives

To evaluate the efficacy of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation.

3.2 Study Endpoints

3.2.1 Safety Endpoints

The following safety endpoints will be analyzed:

- Incidence of TEAEs, serious adverse events (SAEs), and adverse events of special interest (AESIs)
- Physical examinations
- Vital signs, including body temperature, respiratory rate, blood pressure, and pulse
- Body weight, height (or length), head circumference and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry, hematology, and urinalysis)
- Urine output
- Fecal output

3.2.2 Efficacy Endpoints

The following efficacy endpoints will be analyzed:

- Change from baseline in PS volume by each visit and EOT
- Percent change from baseline in PS volume by each visit and EOT
- Number and percent of subjects achieving at least 20% reduction in PS volume from baseline by each visit and EOT
- Number and percent of subjects achieving enteral autonomy, defined as complete weaning off PS by each visit and EOT
- Change from baseline in days per week of PS by each visit and EOT

4. STUDY DESIGN

4.1 Overall Design

This study is designed to allow access and administration of 1.25 mg formulation of teduglutide to pediatric patients with SBS of <10 kg body weight (or <20 kg of body weight if a subject has moderate or greater renal impairment) for whom the 5 mg formulation cannot be dosed.

This is a phase 3, open-label study to evaluate the safety of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and <10 kg of body weight (or <20 kg of body weight if a subject has moderate or greater renal impairment). A 2 to 4-week screening period will be used to verify eligibility. Subjects who fail screening may be re-screened with prior sponsor approval. After screening, subjects, who meet the inclusion criteria and meet none of the exclusion criteria, will start a 28-week treatment cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg (0.025 mg/kg for patients with moderate or greater renal impairment) SC once daily, followed by a 4-week follow-up (no treatment) period. Each subject will visit the site at baseline, weekly for the first 2 weeks (Week 1 and Week 2), and every 4 weeks after Week 4 (Weeks 4, 8, 12, 16, 20, 24, and 28). Telephone contacts will be made as needed during the treatment period. At all site visits and during all telephone contacts, safety will be evaluated, and nutritional support will be reviewed and adjusted, as needed. A subject may "escape" the follow-up period between Week 24 and Week 28 and proceed immediately to another screening visit if the subject meets at least 1 of the follow-up period escape criteria (Section 6.2.5). Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to a no-teduglutide treatment (NTT) period. The subject who escapes the follow-up period and immediately proceeds to another screening visit will start a next cycle of teduglutide treatment if at least 1 of the treatment eligibility criteria and none of the exclusion criteria are met. The subject in the NTT period may proceed to another screening visit at any time if at least 1 of the treatment eligibility criteria are met, and may start a next cycle of teduglutide treatment if at least 1 of the treatment eligibility criteria and none of the exclusion criteria are met. A subject may participate in multiple treatment cycles and NTT periods depending on his or her clinical trajectory. The screening period for another treatment cycle following the NTT or follow-up period will be -28 to -1 days.

All attempts will be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and to be provided in the protocol) for decisions regarding PN/IV (or PS) reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

The teduglutide treatment will continue until the teduglutide 1.25 mg formulation is commercially available and each subject is able to transition to the commercially available product, the subject's body weight increases to ≥15 kg (or ≥30 kg of body weight if a subject has moderate or greater renal impairment) requiring them to transition to the 5 mg formulation, the subject's participation in this study is discontinued, or the study is discontinued, whichever comes first. The 1.25 mg formulation can be used in subjects with <15 kg body weight (or <30 kg of body weight if a subject has moderate or greater renal impairment) in this study, depending on the subjects' condition, such as the status of the subjects' weight fluctuation. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the EOT visit. The benefit of teduglutide treatment will be assessed at Week 24. If no benefit is observed at Week 24, as determined by the investigator, the treatment should be discontinued, and the subject should be discontinued from the study; otherwise, the subject may continue on the study at the discretion of the investigator and per the above guidance.

Since the subjects will be exposed to teduglutide with the 1.25 mg formulation under development, safety will be evaluated during the study as the primary endpoint, including TEAEs, SAEs, AESIs, vital signs, urine/fecal outputs, and laboratory values. Efficacy will be also evaluated as secondary endpoints, including the reduction in PS volume from baseline to each visit, achievement of enteral autonomy by each visit and EOT, and reduction in days per week of PS from baseline to each visit.

Refer to Section 1.2 for a study design schematic and Section 1.3 for the study schedule of assessments.

4.2 Justification for Study Design, Dose, and Endpoints

The study population is defined as "Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation". The inclusion criterion defined 5 kg as the lower limit of body weight (or 10 kg for subjects with moderate or greater renal impairment) because no clinical trials in children with below 5 kg body weight have been performed.

The dosage and administration of teduglutide for adult patients and pediatric patients aged 1 years or older in all countries approved overseas is 0.05 mg/kg/day. The result of the Japanese clinical studies in adults appeared similar to the results observed in the overseas studies (see Investigator's Brochure), and a population PK analysis using modeling and simulation was performed using the Japanese and foreign adult and pediatric data (17 clinical studies), showing that race (Japanese vs Non-Japanese) does not affect the absorption rate constant (Ka), apparent clearance (CL/F), or apparent central volume of distribution (Vc/F).

However, the dose should be reduced by 50% (ie, 0.025 mg/kg/day) in patients with moderate or greater renal impairment based on the PK data from the clinical studies. These renal impaired patients with 10 to <20 kg of body weight are applicable for the teduglutide administration with the 1.25 mg formulation.

The teduglutide 0.05 mg/kg/day was administered for infant patients with SBS in the SHP633-301, the SHP633-302, and SHP633-305 studies. The treatment response was similar to the results observed in previous pediatric studies. Teduglutide treatment was also demonstrated to be generally safe and well tolerated, and the safety profile was favorable and consistent with the safety profile seen in other pediatric studies.

4.3 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be until the subject with ≥15 kg of body weight (or ≥30 kg of body weight if a subject has moderate or greater renal impairment), transitions to 1.25 mg formulation commercially available, subject discontinuation, or study termination. The maximum duration of treatment is expected to be approximately 18 months.

A subject will be considered as completing the study if the subject completed the EOT visits, and does not withdraw from the study for any reason prior to the EOT visit, or the date when the study is discontinued, the subject's body weight is ≥15 kg, or the commercial teduglutide of 1.25 mg formulation is available.

4.4 Sites and Regions

The study is planned for approximately 6 sites in Japan.

4.5 Premature Termination or Suspension of Study or Study Site

4.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination (ET) of the study. The study completion date is defined as the date when the final subject, across all sites, completes their final protocol-defined assessment.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for teduglutide, such that the risk /benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practices (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

4.5.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCPs, the study protocol, or the contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

4.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

Subject eligibility is determined according to the following criteria prior to entry into the study and the first dose:

1. In the opinion of the investigator, a parent/guardian is capable of understanding and complying with protocol requirements.
2. A parent or guardian signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Male or female pediatric patient of corrected gestational age 4 months or older.
4. Body weight at the time of screening and baseline visits of at least 5 kg and <10 kg for subjects with normal renal function or mild renal impairment (estimated glomerular filtration rate ≥50* mL/min/1.73 m^2), OR at least 10 kg and <20 kg for subjects with moderate or greater renal impairment (estimated glomerular filtration rate <50* mL/min/1.73 m^2).
5. Diagnosis of SBS with intestinal failure, defined as dependence on PS to provide at least 30% of fluid or caloric needs.
6. Subjects to have stable PS for at least 1 month prior to screening as assessed by the investigator. Stable PS is defined as inability to significantly reduce parenteral nutrition/intravenous fluid (PN/IV) support, usually associated with minimal or no advance in enteral feeds (ie, 10% or less change in PN or advance in feeds), assessed by the investigator.

* This criterion is based on "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. Food and Drug Administration. May 1998."

5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. A parent/guardian who is not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements.
2. Clinically significant intestinal obstruction, active or recurrent pancreatic or biliary disease, or dysmotility that prevents the advancement of enteral intake.

3. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
4. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce PS, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
5. Major GI surgical intervention including significant intestinal resection or bowel lengthening procedure within 3 months prior to screening (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm and endoscopic procedures are allowed).
6. Cardiac disease that makes the patient vulnerable to changes in fluid status.
7. History of cancer or known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of GI cancer (including hepatobiliary and pancreatic cancer).
8. Concurrent treatment with GLP-2, human growth hormone, or analogs of these hormones (not including teduglutide) within 6 months prior to the screening visit, or concurrent treatment with octreotide or GLP-1 analogs within 30 days prior to the screening visit.
9. Concurrent treatment with biological therapy (eg, anti-tumor necrosis factor [anti-TNF]) for active Crohn's disease within 6 months prior to the screening visit.
10. Participation in a clinical study using an experimental drug (other than glutamine or intravenous lipid emulsions) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the screening visit and for the duration of the study.
11. Known or suspected intolerance or hypersensitivity to the study drug, closely related compounds, or any of the stated ingredients.
12. Signs of active, severe, or unstable clinically significant hepatic impairment during the screening period as meeting at least 2 of any of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count $<100\times10^3/\mu L$ due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Cirrhosis
    e. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period during screening
    f. Total bilirubin ≥2x upper limit of normal (ULN)
    g. Aspartate aminotransferase (AST) ≥3x ULN

h. Alanine aminotransferase (ALT) ≥3x ULN

13. Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

5.3 Reproductive Potential

Not applicable to this study in infants.

6. STUDY INTERVENTION

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

6.1 Investigational Product

6.1.1 Identity of Investigational Product

In this protocol, the term study drug refers to teduglutide.

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be provided for this study. The study drug will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the study drug will also be provided and labeled in accordance with the applicable regulatory requirements.

All study drug used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practices. Further details are described separately in a "Pharmacy manual."

6.1.1.1 Study Drug

Teduglutide (TAK-633, SHP633, ALX-0600) for SC injection is provided in 3 mL vials containing 1.25 mg teduglutide as a lyophilized powder that must be reconstituted using 0.5 mL of sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the Investigator's Brochure.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

This is an open-label study; all subjects will receive teduglutide 0.05 mg/kg/day (0.025 mg/kg/day for patients with moderate or greater renal impairment) as described in Section 6.2.1.1. Subject numbers are assigned to all subjects as consent to take part in the study is provided. Within each site (numbered uniquely within a protocol), the subject numbers are assigned to subjects according to the sequence of presentation for study participation.

These numbers will be used to identify the subjects throughout the study period.
Once a number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a unique identifier is assigned incorrectly, the study monitor must be notified as soon as the error is discovered.

6.2.1 Dose, Regimen, and Administration by Parent or Guardian

A dose of 0.05 mg/kg/day of teduglutide will be administered once daily to subjects. However, the 0.025 mg/kg/day (a 50% reduced dosing) will be administered for patients with moderate or greater renal impairment. If a subject develops moderate or greater renal impairment during the study, the dose can be reduced to 0.025 mg/kg/day and continued after discussion with the sponsor's medical monitor. However, the subject's body weight must be at least 10 kg (see inclusion criteria 4). The dose calculation will be based on body weight measured at the baseline visit (Week 0) and will be adjusted per body weight at Week 12 in each treatment cycle. No other adjustments to dose will be made during the study period, unless discussed with Medical Monitor or designee.

Following reconstitution, teduglutide will be administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Each day, the injection site should be rotated. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the (e)CRF.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later. Detailed instructions for reconstitution and injection of the study drug can be found in the Instructions for Use.

The subject should be dosed at approximately the same time each day. If a dose is delayed, that day's dose should be administered as soon as possible, but consecutive doses should be separated by at least 12 hours. Do not administer more than 0.05 mg/kg (0.025 mg/kg for patients with moderate or greater renal impairment) in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM).

6.2.1.1 Administration by Parent/Guardian

The first dose of teduglutide will be administered by a study physician and the subject will be observed for possible hypersensitivity reactions for at least 4 hours after administration during their initial dosing visit.

The processes for training the parent/guardian to administer teduglutide and for providing oversight of study drug administration are described in the Site Training Guide. Before a parent/guardian is permitted to administer teduglutide, the study physician must observe the parent/guardian administering the study drug at least twice in compliance with the teduglutide administration checklist. The checklist is included as an Appendix to the Site Training Guide.

After the study physician certifies that the parent/guardian can safely administer the study drug, subsequent doses may be administered by the parent/guardian at home without direct supervision by the physician. However, at selected study visits (refer to Section 1.3), administration of the study drug must be performed under direct supervision by the study physician, and the teduglutide administration checklist must be completed again. This ensures that the parent/guardian continues to administer the study drug correctly and safely throughout the dosing period.

If at any time a study physician suspects that the parent/guardian is no longer capable of administering the study drug safely and accurately, the parent/guardian should be reassessed by a study physician using the teduglutide administration checklist. If the parent/guardian is deemed unable to administer the study drug, dosing must be performed by a study physician until the parent/guardian is retrained and proficiency is confirmed using the teduglutide administration checklist.

Eligibility for teduglutide to be administered by a parent/guardian will be judged by a study physician using the following criteria. Refer to the checklist included as an Appendix to the Site Training Guide.

Criteria to Initiate Teduglutide Administration by the Parent/Guardian:

- The subject's condition is stable.
- The parent/guardian has been sufficiently trained and is able to administer teduglutide in compliance with the checklist.

Criteria to Discontinue Teduglutide Administration by the Parent/Guardian:

- No benefit of teduglutide is observed at Week 24, as determined by the investigator.
- The parent/guardian is unable to administer teduglutide in compliance with the checklist.
- The subject's condition has deteriorated such that the study physician assesses it is inappropriate for the subject to have teduglutide administered by his/her parent/guardian. In addition to discontinuing administration of teduglutide by the parent/guardian, if a subject sustains an adverse drug reaction where the symptoms are considered intolerable, dose interruption or study drug discontinuation should be considered.

- The subject experiences an adverse event (AE) listed in Table 2 that is of severity ≥Grade 3 per the National Cancer Institute's Common Terminology Criteria for Adverse Events. All such AEs should be discussed with sponsor's medical monitor or designee as soon as possible.
- In the study physician's judgment, it is inappropriate for the parent/guardian to continue administration of the study drug for any other reason.

Table 2. Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal obstruction	Hospitalization indicated; invasive intervention indicated; limiting self-care activities of daily living	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>5.0 to 20.0x ULN if baseline was normal; >5.0 to 20.0 x baseline if baseline was abnormal	>20.0x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Blood bilirubin increased	>3.0 to 10.0x ULN if baseline was normal; >3.0 to 10.0 x baseline if baseline was abnormal	>10.0x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Bile duct stenosis	Severely altered gastrointestinal function; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated

Table 2. Adverse Events that May Lead to Dose Interruption

Adverse Event	Grade 3 Description	Grade 4 Description
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0x ULN and with signs or symptoms
Lipase increased[a]	>2.0 to 5.0x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0x ULN and with signs or symptoms
Cardiovascular Disease		
Heart failure	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

ULN=upper limit of normal
a. In the setting of clinically acute and symptomatic pancreatitis
Source: Common Terminology Criteria for Adverse Events, version 5.0, 27 November 2017

6.2.2 Unblinding the Treatment Assignment

Not applicable.

6.2.3 Dose Modification

For dose adjustment, see Section 6.2.1.

6.2.4 Treatment Eligibility Criteria for Initiation of a Next Teduglutide Treatment Cycle

Subjects are eligible for a next cycle of teduglutide treatment if at least 1 of the following criteria, and none of the exclusion criteria (Section 5.2), are met. In addition, the investigator and the parent/guardian must agree to proceed with treatment.

If subjects in the NTT meet at least 1 of the following criteria, they may proceed to another screening visit at any time. The screening period for another treatment cycle following the NTT or follow-up period will be -28 days to -1 days.

1. Increasing PS requirements following teduglutide discontinuation.
2. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
3. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.

4. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
5. Severe diarrhea related to teduglutide discontinuation.

6.2.5 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted or omitted, and the subject may proceed directly to another screening visit, if at least 1 of the following criteria is met. The screening period for another treatment cycle following the NTT or follow-up period will be -28 days to -1 days.

At Week 24, if the efficacy (eg, PS volume reduction from baseline) is confirmed, or the continuation of teduglutide treatment is appropriate as determined by the investigator, subjects may proceed directly to the screening visit without entering to follow-up period, otherwise subjects will enter the 4-week follow-up period. For the subjects who skip the follow-up period, the screening period will be also from -28 days to -1 days. The Week 24 visit and the next round of screening visit may be combined.

1. Increasing PS requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.
5. The subject escaped during the follow-up period of a previous teduglutide treatment cycle of the study.

6.2.6 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug at a dose above that which is assigned to that individual subject according to the study protocol. All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on AE CRF(s) according to Appendix 7.

Serious adverse events associated with overdose should be reported according to the procedure outlined in Appendix 7.

In the event of drug overdose, the subject should be treated by the investigator based on symptoms.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container. Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

Study drug must be kept in a locked area with access restricted to specific study personnel. Study drug will be stored refrigerated at a temperature between 2 and 8°C until dispensed to a subject. The pre-filled sterile water for injection syringes will be stored at a temperature between 2 and 25°C. Once dispensed/supplied to a subject, the study drug can be stored refrigerated up to a controlled room temperature (acceptable range of 2 to 25°C). Parent/guardian will be instructed to keep the subject's study drug and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the study drug may be refrigerated.

6.4 Drug Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The on-site pharmacist (site designee) will receive the pharmacy manual created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject's parent/guardian as well as return of them to the sponsor or destruction of them.

The on-site pharmacist (site designee) will immediately return unused study drugs to the sponsor after the study is closed at the study site.

6.5 Subject Compliance

Subjects must be instructed how to have unused investigational product and empty/used investigational product packaging assessed for drug accountability. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.6 Prior and Concomitant Therapy

All non-study treatment received within 30 days prior to the screening visit (Visit 1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded in the subject's source document.

6.6.1 Prior Treatment

Prior treatment includes all treatment received within 30 days of the date of first dose of investigational product. Prior treatment information must be recorded in the subject's source document.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the subject's source document.

6.6.3 Permitted Treatment

Treatments not listed in Section 6.6.4 are considered allowable.

6.6.4 Prohibited Treatment

The following medications in Table 3 are prohibited during teduglutide treatment and within the provided timeframe prior to the screening visit. Because the teduglutide 5 mg formulation is the same GLP-2 analog as study drug, and study drug is not known for interactions with various GI growth factors, the medications in Table 3 are excluded.

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, and digoxin), so consideration should be given to modifying concomitant enteral medication regimens.

Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index, are given.

Table 3. Common Excluded Treatments and Associated Washout Period

Prior Therapy	Time Restriction Prior to the Screening Visit
Teduglutide (5 mg formulation)	Any
GLP-2, human growth hormone, or analogs of these hormones (not including teduglutide)	6 months
Octreotide or GLP-1 analogs	30 days
Biological therapy (eg, anti-tumor necrosis factor [anti-TNF]) for active Crohn's disease	6 months

GLP=glucagon-like peptide

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If investigational product is discontinued, regardless of the reason, the evaluations listed for ET/EOT Visit will be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified evaluations at the ET/EOT Visit. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the investigational product, and the total amount of investigational product administered must be recorded in the source documents.

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.2. In addition, a subject may withdraw his or her participation without giving a reason at any time during the study, as described in Section 7.3.

7.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject is discontinued for more than 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 8.1.15.

1. Adverse event (AE).
   - Subjects who experience an AE may require ET because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the pretreatment event (PTE) or AE.
   - Subjects with abnormal liver test results should be evaluated to determine whether study drug should be continued, interrupted, or discontinued. See Appendix 3.
2. Significant protocol deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's parent/guardian) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Physician Decision. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
7. Lack of efficacy.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

Should a subject withdraw from the study, the primary criterion for termination must be recorded by the investigator, as described in Section 7.2. In addition, efforts should be made to perform all procedures scheduled for the EOT/ET visit.

7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (in person or by phone or video). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that the subject be assessed for final safety evaluations and return any unused investigational product.

8. STUDY ASSESSMENTS AND PROCEDURES

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Section 1.3.

8.1 Study Procedures

8.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 12.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time the signed informed consent is obtained; this subject number will be used throughout the study.

Subjects are pediatric patients in the study. The investigator is responsible for obtaining written informed consent from their parents or guardians.

8.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, and race as described by the subject, height (or length), head circumference (subjects 36 months of age and younger), and weight of the subject at screening.

Medical, surgical, and SBS histories to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 8.1.7). Any significant conditions or diseases relevant to the proposed indication include necrotizing enterocolitis, volvulus, Crohn's disease, cancer, intestinal atresia, gastric fistula, and central venous catheterization.

Medication history information to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within 28 days prior to signing of informed consent.

8.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

8.1.4 Weight, Height (or length), and Head Circumference

A subject should have weight and height (or length) measured while wearing indoor clothing and with shoes off. Height (or length) is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place.

Head circumference will be measured in subjects 36 months of age and younger.

Z-scores for weight, height (or length), and head circumference will be calculated by the sponsor.

8.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure (systolic and diastolic), and pulse (bpm). Measurements should be in the same method, on the same extremity, and in the same position throughout the study.

8.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects' parents or guardians will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

8.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, or physical examination abnormalities noted at screening/baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

8.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 6.8 mL, and the approximate total volume of blood for the study is 47.8 mL until Week 24 and 112.8 mL until the longest study period (18 months). Details of these procedures and required safety monitoring will be given in the laboratory manual. Appendix 4 describes total blood volume to be collected.

Table 4 lists the tests that will be obtained for each laboratory specimen.

Table 4. Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hematocrit	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Platelet count	Alanine aminotransferase	Leucocytes
White blood cell count with differential	Amylase	Microscopic analysis
	Aspartate aminotransferase	pH
	Bicarbonate	Protein
	Bilirubin (total, direct, and indirect)	Specific gravity
	Blood urea nitrogen	
	Calcium (total)	
	Chloride	
	Cholesterol	
	C-reactive protein	
	Creatinine	
	Estimated glomerular filtration rate (calculated with the quintic equation[a])	
	Gamma-glutamyl transferase	
	Glucose	
	Lipase	
	Magnesium	
	Phosphorus	
	Potassium	
	Sodium	
	Triglycerides	
	Uric acid	
Other:		
Coagulation		

Prothrombin time/International normalized ratio will be measured in all subjects at screening and subsequently if drug-induced liver injury is suspected.

a. eGFR=110.2 × (reference serum Cr/patient's serum Cr) + 2.93
Reference serum Cr levels (y) are shown by the following two equations of body length (x):
Males: y = −1.259x5 + 7.815x4 − 18.57x3 + 21.39x2 − 11.71x + 2.628
Females: y =−4.536x5 + 27.16x4 −63.47x3 + 72.43x2 −40.06x + 8.778 (Uemura et al. 2014)

The central laboratory will perform laboratory tests for hematology, biochemistries, urinalysis, and coagulation. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Urine specimen collection should be attempted as part of the safety lab tests, but lack of urinalysis will not constitute a protocol deviation.

Safety laboratory tests to be performed at site visits and processed by a central lab. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Additional evaluations may be performed at the discretion of the investigator in consultation with the Medical Monitor or designee.

For subjects with treatment-emergent ALT elevations ≥3x ULN, see Appendix 3 for additional monitoring, evaluation, and follow-up recommendations.

The collected samples for this study will be stored at LSI Medience Corporation for up to 15 years from when the study results are reported or if less, the maximum period permitted under applicable law or until consent is withdrawn.

8.1.9 Telephone Contacts

Telephone contacts will be made as needed during the treatment period. At all site visits and during telephone contacts, safety will be evaluated, and nutritional support will be reviewed and adjusted, as needed.

8.1.10 Adjustment of Nutritional Support

Nutritional support includes PS, EN, and other food and fluids. Nutritional support adjustments should be made after review of the intake and output diaries and safety lab data according to the guidelines for nutrition support management and weaning algorithms provided in Guidelines for Nutritional Support Management During the Study (Appendix 5) and Weaning Algorithms (Appendix 6), respectively.

8.1.11 Dispense Study Drug

The first SC injection will be administered under the supervision of the investigator/designee. The subject will be observed for possible hypersensitivity reactions for at least 4 hours after administration during their initial dosing visit. The site of administration (arm, thigh, abdomen) must be specified and recorded in the (e)CRF. The dose of study medication will be adjusted per body weight at Week 12 in each treatment cycle. No other adjustments to dose will be made during the study period, unless discussed with Medical Monitor or designee.

8.1.12 Adverse Events Assessment

Safety will be evaluated based on the occurrence of all AEs, SAEs, AESIs, physical examination findings, vital signs (heart rate, blood pressure), clinical laboratory parameters (biochemistry, hematology, and urinalysis), and urine/fecal outputs (obtained from an output diary). See Appendix 7.1 for definitions of AEs, SAEs, and AESIs.

8.1.13 Diaries

The subject's parent/guardian or study site staff will complete the appropriate fields of the PS and EN (formula) sections of the intake diary.

Intake diary: The following information should be provided in the intake diaries, which will be completed every day of the study from screening through EOT/ET visit:

- Parenteral support volume and infusion duration.
- Enteral nutrition (formula) volume.

Site personnel will determine the actual PS and EN daily calories based on diary entries.

Output diary: Urine and stool output should be recorded in the output diary over a 48-hour period of PS and EN stability before every site visit and within 1 week of implementing a change in the PS prescription.

- Urine data.
  - Toilet-trained subjects (who do not wear diapers).

    Measure and record all urine output in mL or cc. The subject or parent will perform dipstick specific gravity tests on the first urine produced after the daily infusions of PS.
  - Nontoilet-trained subjects (who wear diapers).

    Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc.

    At the discretion of the investigator, the parent may be asked to collect the first void after the daily PS infusion to measure specific gravity.
- Stool data (includes diapers with mixed urine and stool).
  - Toilet-trained subjects (who do not wear diapers).

    Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see output diary).
  - Nontoilet-trained subjects (who wear diapers).

    Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (see output diary). Stool volume will be calculated using the formula: 1 g (scale weight) = 1 mL or 1 cc.

All ostomy output volume should be recorded. Ostomy output will not be scored using the Bristol Stool Form Scale.

All diaries will be reviewed by the investigator or their designee at each clinic and telephone contact to assess clinical status and opportunity for PS reduction and advance in feeds.

8.1.14 Colonoscopy/Sigmoidoscopy

Colonoscopy/sigmoidoscopy to identify colorectal polyps is recommended in each subject after 52 weeks of treatment while on continuous treatment with teduglutide, and/or if the subject has new or unexplained GI bleeding. Fecal blood test may be performed as needed.

8.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the (e)CRF.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other study-specific.
- Other.

Subject identification numbers assigned to subjects who fail screening should not be reused.

8.1.16 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable (e)CRF.

8.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused study drugs to each dispensing site visit. All supplies used to administer study drug to the subject will be recorded on the (e)CRFs.

8.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Section 1.3. Assessments should be completed at the designated visit/time point(s).

8.3.1 Screening

Subjects will be screened between 28 and 14 days prior to baseline (Week 0). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 5. Another round of screening after Week 24 will occur for subjects who skip the follow-up period. The Week 24 visit and the next round of screening visit may be combined. See Section 8.1.15 for procedures for documenting screening failures.

The following procedures will be performed and documented at the screening visit:

- Informed consent (not applicable for another round of screening).
- Inclusion/exclusion criteria (only exclusion criteria for another round of screening).
- Treatment eligibility criteria (applicable only for another round of screening).
- Demographics, medical, medication, surgical, and SBS histories (not applicable for another round of screening).
- Adverse event assessment.
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Height (or length) and head circumference (head circumference will be measured in subjects 36 months of age and younger).
- Safety laboratory tests.
- Providing intake and output diaries.
- Diary review (applicable only for another round of screening).
- Adjustment of nutritional support (as needed. applicable only for another round of screening).

8.3.2 Study Entrance

Study entrance will take place at Week 0. The following procedures will be performed and documented at study entrance visit:

- Inclusion/exclusion criteria (only exclusion criteria for another round of treatment).
- Treatment eligibility criteria (applicable only for another round of treatment).
- Adverse event assessment.
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Height (or length) and head circumference (head circumference will be measured in subjects 36 months of age and younger).
- Safety laboratory tests.
- Providing intake and output diaries.
- Diary review.
- Adjustment of nutritional support (as needed. applicable only for another round of treatment).
- Dispensing study drug.
- Confirmation of administration proficiency.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for study entrance, the subject should be enrolled. Subjects' parents or guardians will be instructed on when to take the first dose of study drug as described in Section 4.1. The procedure for documenting screening failures is provided in Section 8.1.15.

8.3.3 Treatment, Follow-up, and No-teduglutide treatment period

The subjects will visit the site weekly for the first 2 weeks (Week 1 and Week 2), and then every 4 weeks after Week 4 (Weeks 4, 8, 12, 16, 20, and 24).

8.3.3.1 Week 1 and Week 2 (Window period ±3 days)

The following procedures will be performed and documented at Week 1 and Week 2 visits:

- Adverse event assessment.
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Safety laboratory tests (only biochemistry).

- Providing intake and output diaries.
- Diary review.
- Adjustment of nutritional support (as needed).
- Dispensing study drug.

8.3.3.2 Weeks 4, 8, 12, 16, 20, and 24 (Window period ±7 days)

The following procedures will be performed and documented at Weeks 4, 8, 12, 16, 20, and 24:

- Adverse event assessment (including telephone contacts as needed).
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Height (or length) and head circumference (head circumference will be measured in subjects 36 months of age and younger).
- Safety laboratory tests.
- Providing intake and output diaries.
- Diary review.
- Adjustment of nutritional support (as needed).
- Dispensing study drug (not applicable for Week 24).
- Confirmation of administration proficiency (only at Week 4 and Week 12).
- Evaluation of escape criteria (only at Week 24).
- Assessment of eligibility for additional treatment (only at Week 24).

8.3.3.3 Follow-up period (4 weeks) (Window period ±7 days)

The following procedures will be performed and documented during 4 weeks of the follow-up period:

- Adverse event assessment (including telephone contacts as needed).
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Safety laboratory tests.
- Providing intake and output diaries.
- Diary review.

- Adjustment of nutritional support (as needed).
- Assessment of eligibility for additional treatment.
- Evaluation of escape criteria.

8.3.3.4 No-teduglutide treatment period (every 12 weeks)

The following procedures will be performed and documented every 12 weeks during the NTT period:

- Adverse event assessment (including telephone contacts as needed).
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Height (or length) and head circumference (head circumference will be measured in subjects 36 months of age and younger).
- Safety laboratory tests.
- Providing intake and output diaries.
- Diary review.
- Adjustment of nutritional support (as needed).
- Assessment of eligibility for additional treatment.

8.3.4 End of Treatment or Early Termination (Window period ±7 days)

The final visit will be performed on at EOT/ET visit. The following procedures will be performed and documented at the EOT/ET visit:

- Adverse event assessment.
- Concomitant medications/procedures.
- Physical examination, vital signs, and weight.
- Height (or length) and head circumference (head circumference will be measured in subjects 36 months of age and younger).
- Safety laboratory tests.
- Diary review.
- Adjustment of nutritional support (as needed).

For all subjects receiving study drug, the investigator must complete the End of Study (e)CRF page.

8.3.5 Alternative Approaches to Study Procedures and Data Collection Due to Coronavirus Disease 2019

In unavoidable circumstances that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Section 1.3), in particular during the coronavirus disease 2019 (COVID-19) pandemic, contingency measures may be implemented. The following information provides guidance regarding changes to the study procedures that could be implemented for study subjects or study sites that are affected by the COVID-19 public health emergency. This guidance is aligned with the current guidance from global health authorities on the conduct of clinical studies during the COVID-19 pandemic.

As the COVID-19 pandemic may peak in different regions at different times, and as restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the sponsor or designee, while maintaining subject safety and confidentiality as the priority.

The principal investigator should also notify the local IRB, as appropriate, of any deviation for temporary use of alternative methods for conducting subject visits (eg, video conferencing, telephone visits) in the event of restrictive measures due to the COVID-19 pandemic, per local requirements.

Procedural changes due to COVID-19 may include the following:

- No routine COVID-19 testing is required during the study unless the subject has signs or symptoms of COVID-19-related disease or COVID-19 pneumonia in the opinion of the investigator or the subject has been identified by national or local public health authority as a close contact of a probable or confirmed case of COVID-19. The decision to have the subject tested for COVID-19 is left to the subject and the investigator unless required by the health authority.
- Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the study may be re-screened if the sponsor or designee agrees.
- All attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:

  - Sites impacted by the COVID-19 pandemic must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection.
  - Sites may seek approval from the Medical Monitor to continue subjects in the study despite departure from the Schedule of Study Procedures. Principal investigators are expected to evaluate the impact to the safety of the study subjects and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.

- Informed Consent Procedure: If necessary, informed consent from a potential or current study participant's parent or guardian may be obtained via verbal consent when these individuals are unable to travel to the site. Informed consent forms will be signed once the subject and his/her parent or guardian can return in-person to the study site.
- Visits: All visits must be done with the subject present at the study site.
  - Protocol Deviations: Any deviations from the protocol-specified procedures due to COVID-19 will be recorded as related to COVID-19.
  - Visit Window Extension: Sites may seek approval from the sponsor or designee to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to COVID-19.
  - Local laboratory test may be appliable for assessing clinical chemistry and hematology
- EOT/ET visit: The EOT/ET visit should be performed with the subject present at the study site. Sites may seek approval from the sponsor or designee to extend a visit window in order to conduct an on-site visit. If the visit cannot be conducted on-site within the visit window granted by the sponsor or designee, sites may conduct EOT/ET visit procedures remotely as is feasible, including using local laboratories for assessment of biochemistry, hematology, and urinalysis (as specified in Table 4). Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to COVID-19.

- When a physical examination or other in-person procedure is needed in response to an AE, the subject should be evaluated in-person at the site per protocol if possible. If the subject cannot visit the site due to COVID-19, the site should contact the Medical Monitor.
- Discontinuation or Withdrawal from the Study or Study Medication: If a subject chooses to withdraw from the study or study medication due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this must be specified as the reason for subject withdrawal in the (e)CRF.
- Allow transfer of study subjects to study sites away from risk zones or closer to their home to sites already participating in the study or new ones.
- For subjects who are impacted by certain factors, any alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Study Procedures) due to the COVID-19 pandemic must be documented in the study records as related to COVID-19. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

9. DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. Adverse events, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

9.1 CRFs (Electronic)

Completed (e)CRFs are required for each subject whose parent or guardian signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor or its designee will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the sponsor's personnel (or designees) and will be answered by the site.

The principal investigator must review the (e)CRFs for completeness and accuracy and must e-sign the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

The following data will not be recorded into the (e)CRFs; laboratory test values.

After the lock of the study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator with use of change and modification records of the (e)CRFs/(e)CRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

9.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 9.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1), 2), or 3) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued).
2. The day 3 years after the date of ET or completion of the study.
3. Upon market approval of the teduglutide 1.25 mg formulation and once the clinical study is shifted to the post-marketing clinical study, until the end of re-review or re-evaluation, whichever comes later.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

10. STATISTICAL METHODS

10.1 Statistical and Analytical Plans

A SAP will be prepared and finalized prior to database lock. There is no hypothesis testing planned for this study. Descriptive statistics will be provided for all analysis. Following is an overview of the planned analyses; the SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objective.

10.1.1 Analysis Sets

The full analysis set (FAS) and safety analysis set (SAS) are defined for this trial.

FAS: The FAS will include all enrolled patients, who are not screen failures. Subjects will be in FAS regardless of whether they took any dose of teduglutide in the study. The FAS will be used for all the efficacy analyses.

SAS: The SAS will include all subjects who received at least 1 dose of study teduglutide. Safety analyses will be conducted using the SAS.

The details of the definitions for the analysis sets will be documented in the SAP.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, with consulting a medical expert as needed. If necessary, the SAP will be supplemented with new handling rules that were not discussed at the planning stage.

10.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be analyzed by using the SAS.

10.1.3 Safety Analysis

Adverse events will be summarized using the SAS. Counts and percentages for subjects with treatment-emergent AEs and SAEs (any SAE, regardless of relationship to study drug) will be summarized descriptively by System Organ Class and Preferred Term using MedDRA terminology. Serious adverse events will also be summarized by severity and by relationship to study drug. For clinical laboratory tests, body weight, height (or length), and head circumferences, vital signs, urine, and fecal output, descriptive statistics will be used to summarize the absolute values and changes from baseline by visit.

Details of the analysis methods will be specified in the SAP.

10.1.4 Efficacy Analysis

For the continuous endpoints, the following statistics will be presented: non-missing values, mean, median, SD, minimum, maximum, and 95% confidence interval (CI).

- Change from baseline in PS volume by each visit and EOT.
- Percent change from baseline in PS volume by each visit and EOT.
- Change from baseline in days per week of PS by each visit and EOT.

For the binary endpoint, the following statistics will be presented: count, proportion, and 95% Clopper Pearson CI.

- Number and percent of subjects achieving at least 20% reduction in PS volume from baseline by each visit and EOT.
- Number and percent of subjects achieving enteral autonomy, defined as complete weaning off PS by each visit and EOT.

Analyses of PS will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

No formal statistical test will be performed due the limited sample size. Details of the analysis methods will be specified in the SAP.

10.1.5 Missing Data Analysis

No imputations for missing data (eg, last observation carried forward) will be applied, except for partial dates for AEs and prior/concomitant medications.

Missing daily PS volumes from subject diaries will not be imputed and a maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals will be allowed; otherwise, the interval will be classified as missing, with 2 following exceptions. One exception to this rule is the baseline interval, which is filtered back within the stabilization period beyond 14 days until 9 data points were obtained. The other exception is the PS adjustments due to an AE that is excluded, in which case the last 14 days during the interval which are not considered to be impacted by the AE will be used.

10.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

10.3 Determination of Sample Size

Approximately 5 subjects are planned to be enrolled into the study. The sample size is determined based on enrollment feasibility of this rare population in children in Japan, rather than statistical power calculation.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the study site guarantee access to source documents by the sponsor or its designee contract research organization (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

11.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

11.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan).

If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 11.1.

12. ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix 1. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

12.1 IRB

Institutional review boards must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity/signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug/notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

12.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject's parent or guardian. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject's parent or guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject, or the subject's parent or guardian, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's parent or guardian, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's parent or guardian, at the time of consent and prior to the subject entering into the study. The subject or the subject's parent or guardian should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

12.2.1 Dissemination of New Information

When new information important to the proper conduct of the clinical study becomes available, such as on diseases, impairment, and deaths suspected to be due to the effect of the study drug, onset of infections suspected to be due to the use of the study drug, and other information related to study drug quality, efficacy, and safety, the sponsors will inform the investigators and heads of medical institutions in writing in a timely manner.

When the investigator receives information which the investigator judges may affect the intention of subjects to continue participation in the clinical study, the investigator will make available this information immediately to subjects and their parent or guardian, to be recorded in writing, and confirm whether the subject will continue to participate in the study.

12.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventative actions in response. These actions will be documented and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 12.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

12.4 Publication, Disclosure, and Clinical Trial Registration Policy

12.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

12.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

12.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

12.6 Payment

The financial aspects of the study should be documented in a clinical trial agreement or memorandum between the sponsor, the medical institution, and the CRO.

13. STUDY-SPECIFIC COMMITTEES

Because the efficacy and safety of teduglutide have been already examined and confirmed in previous studies (see Investigator's Brochure), and this study is designed specifically [redacted], no steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

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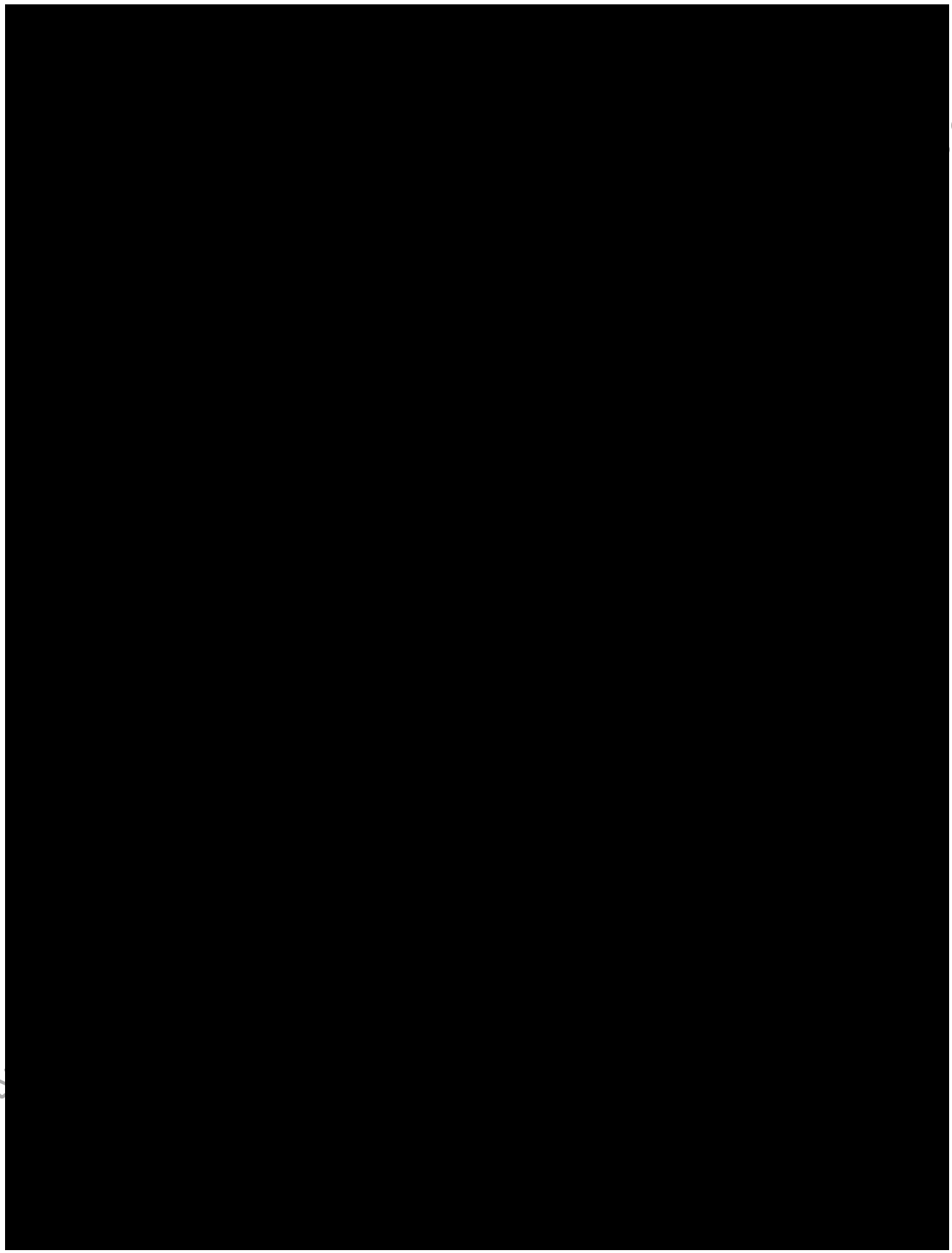

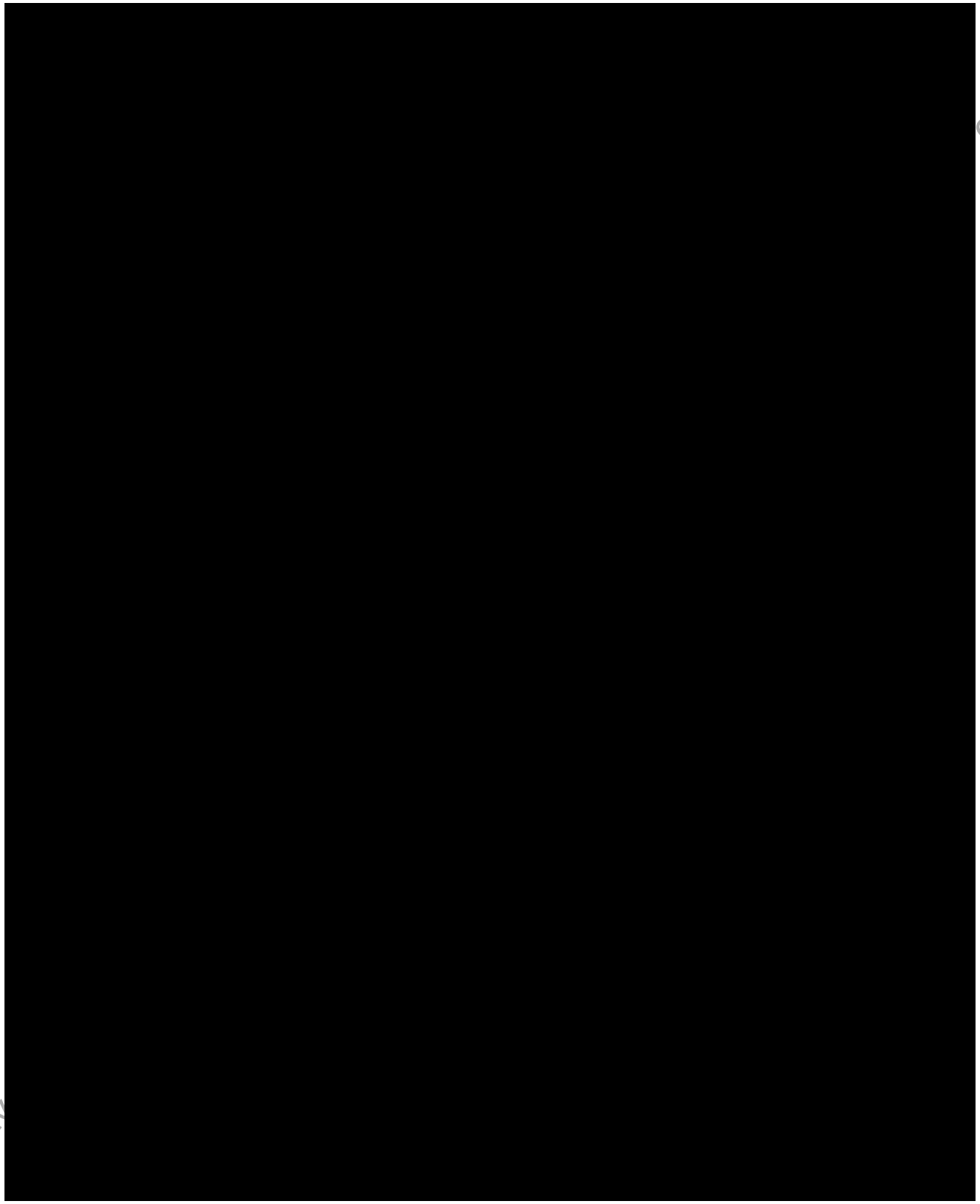

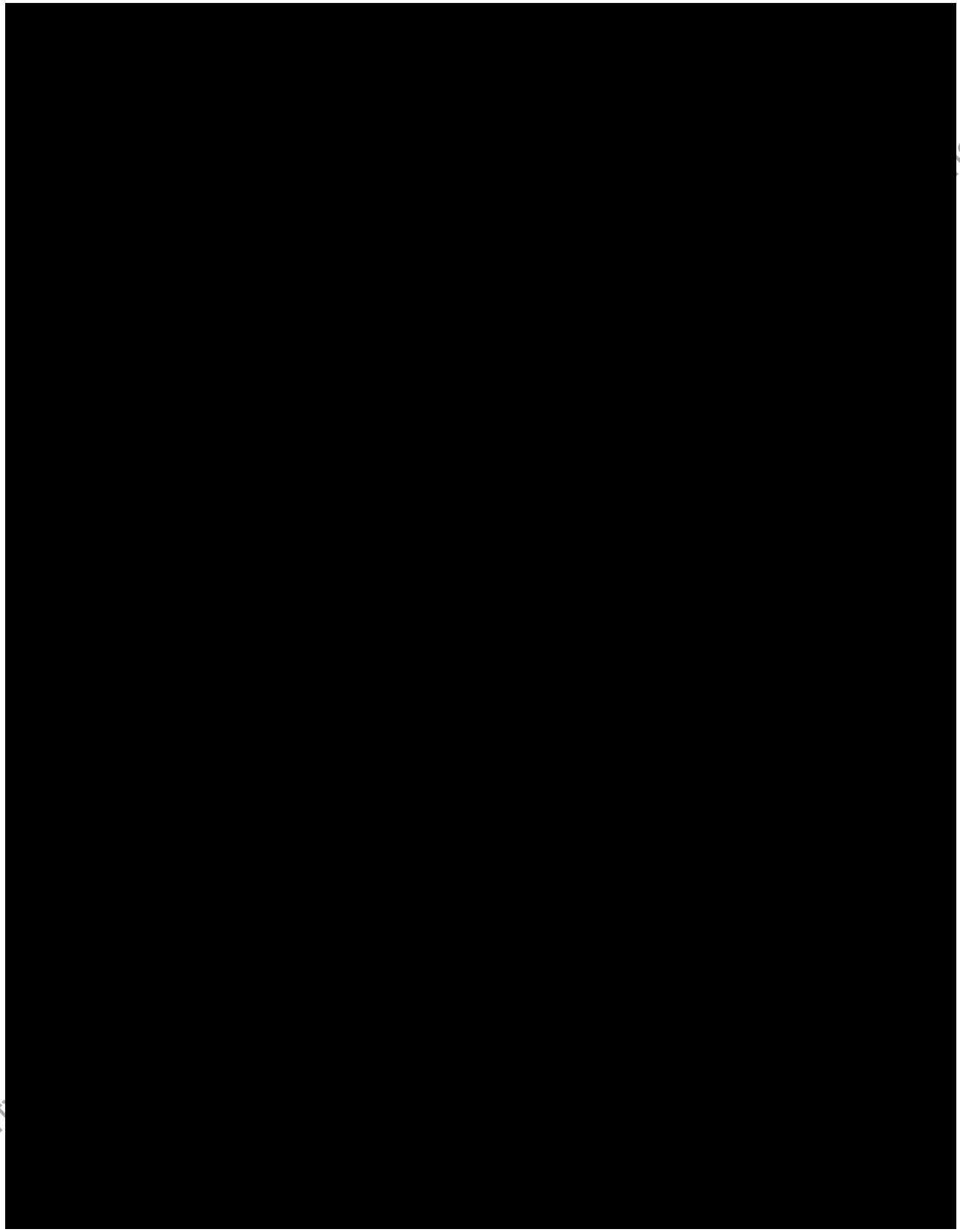

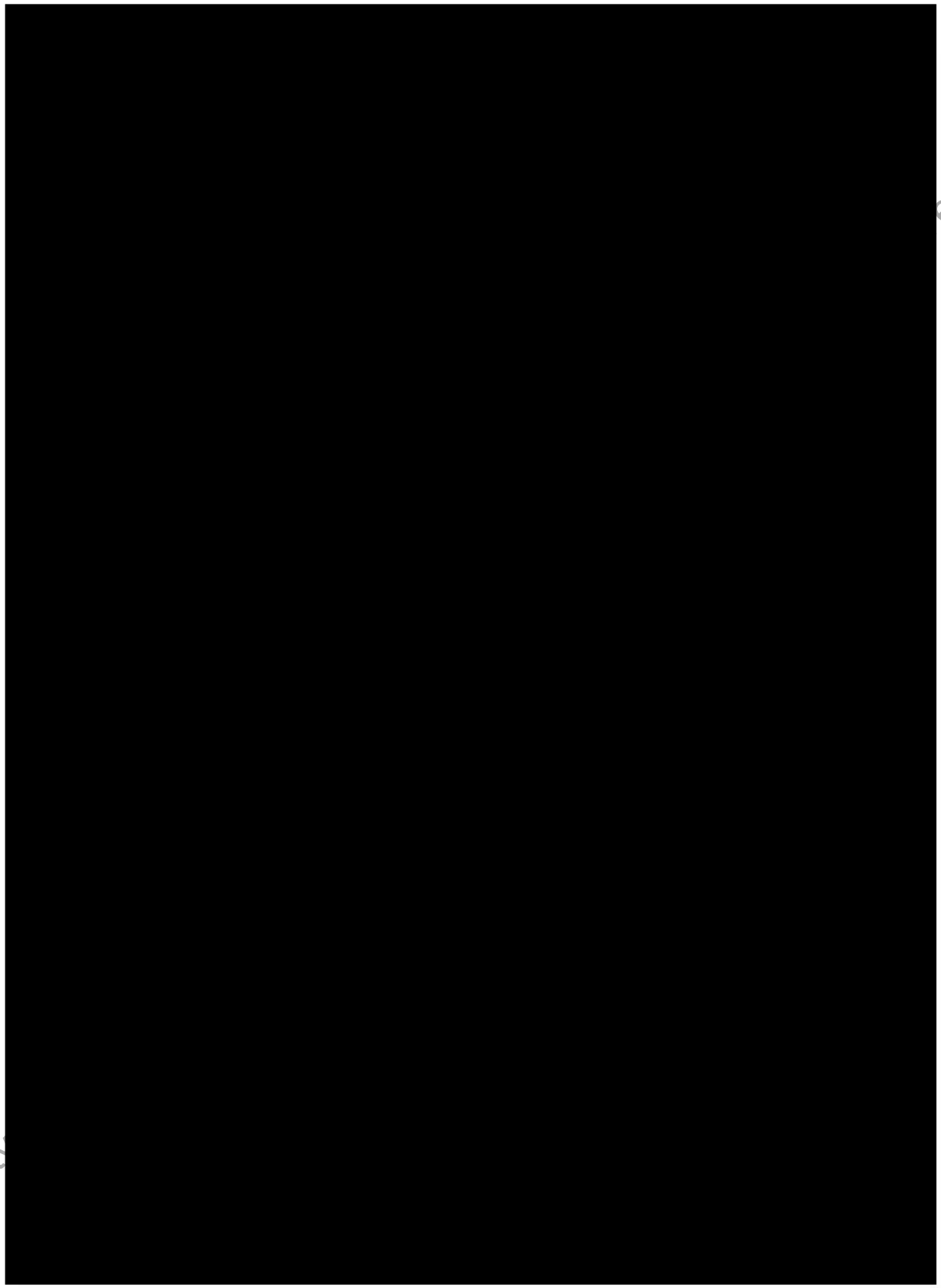

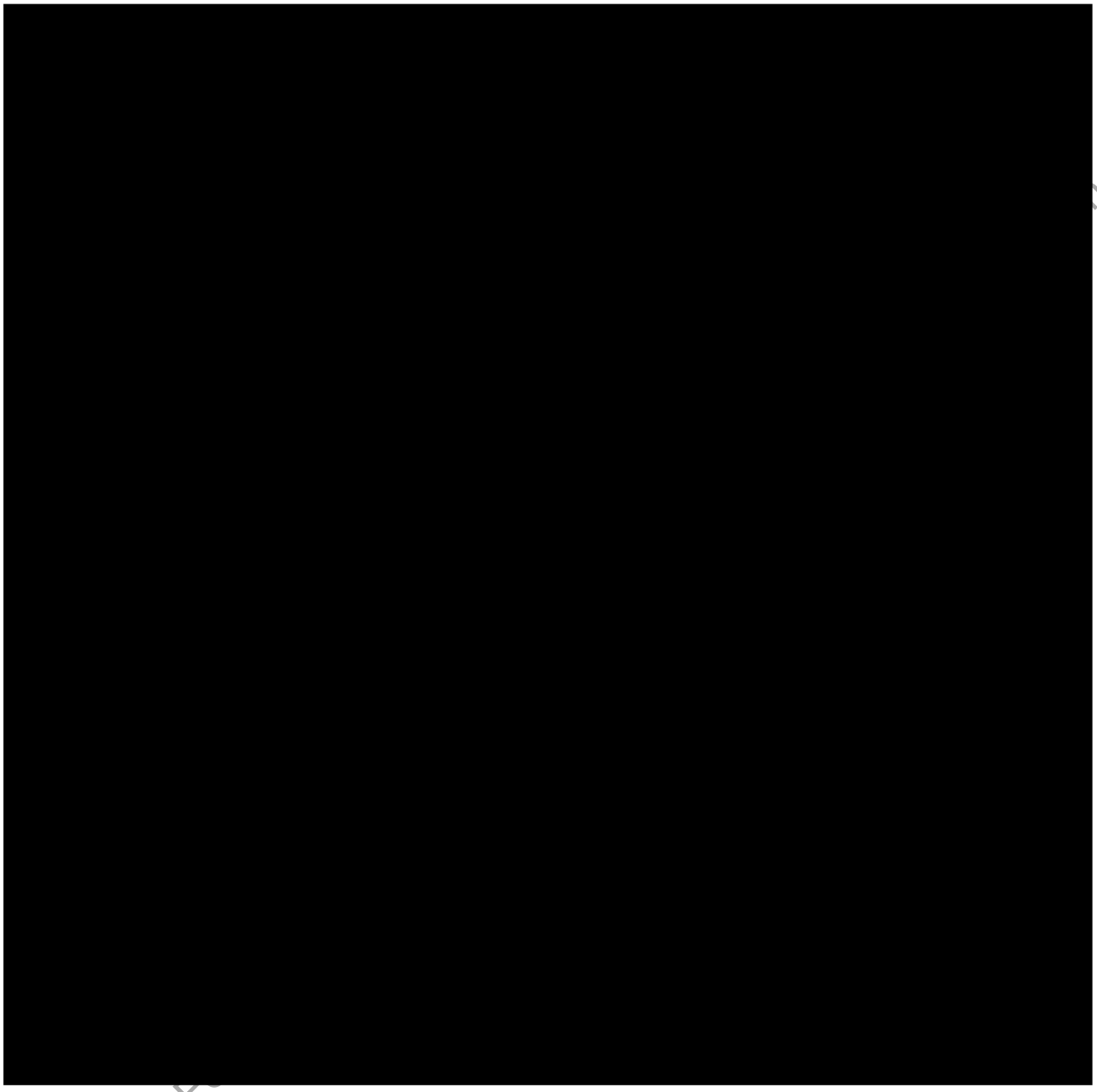

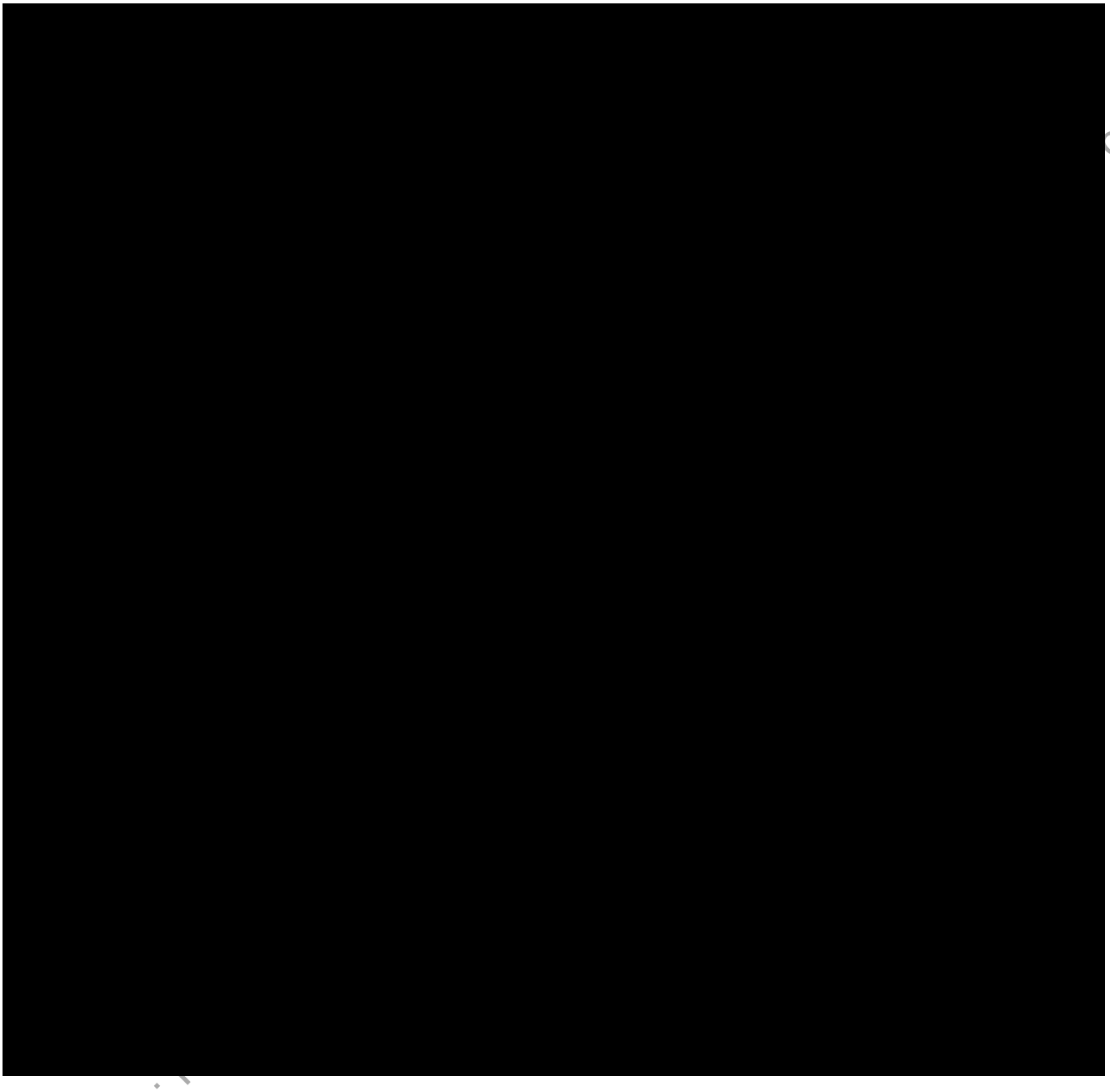

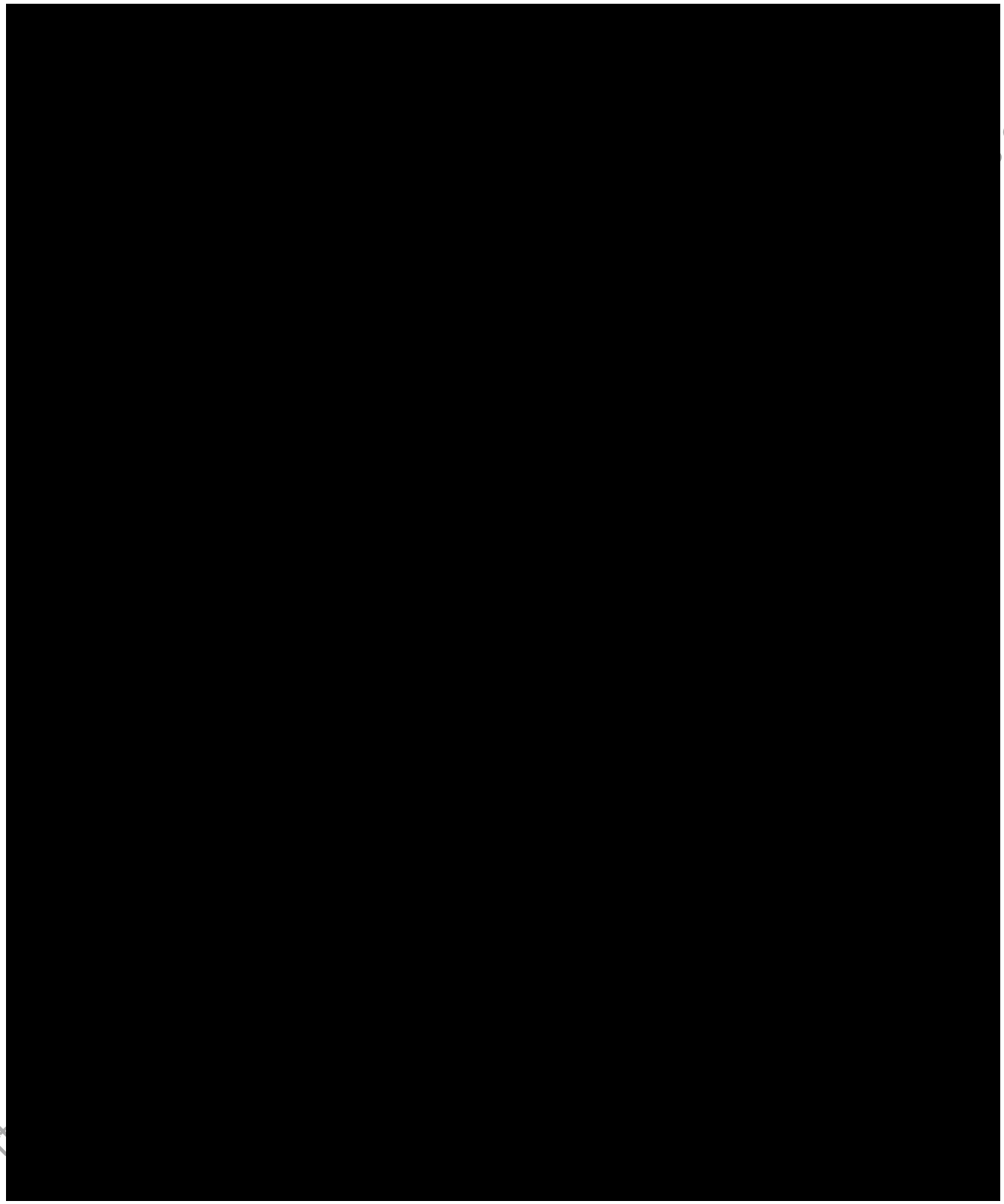

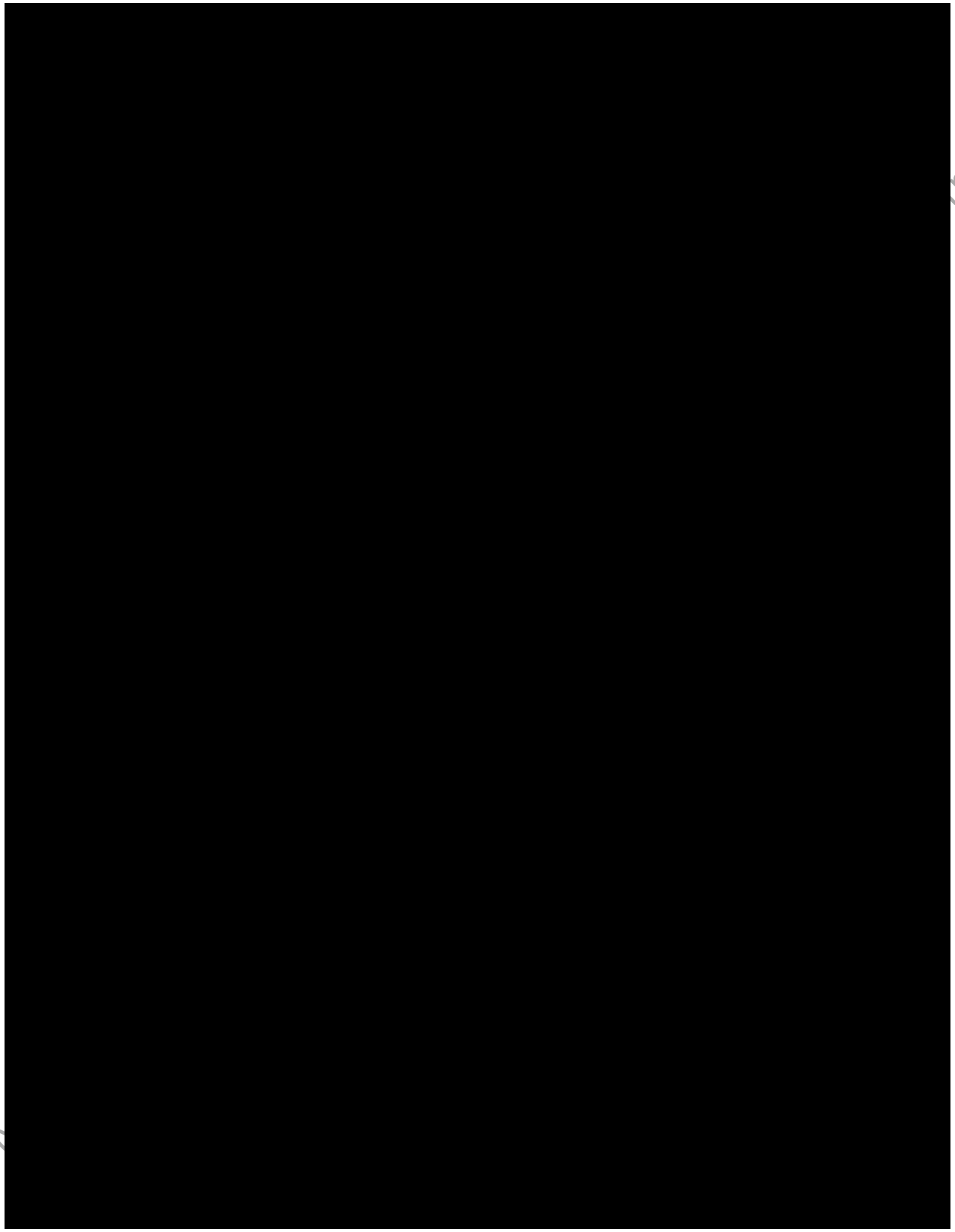

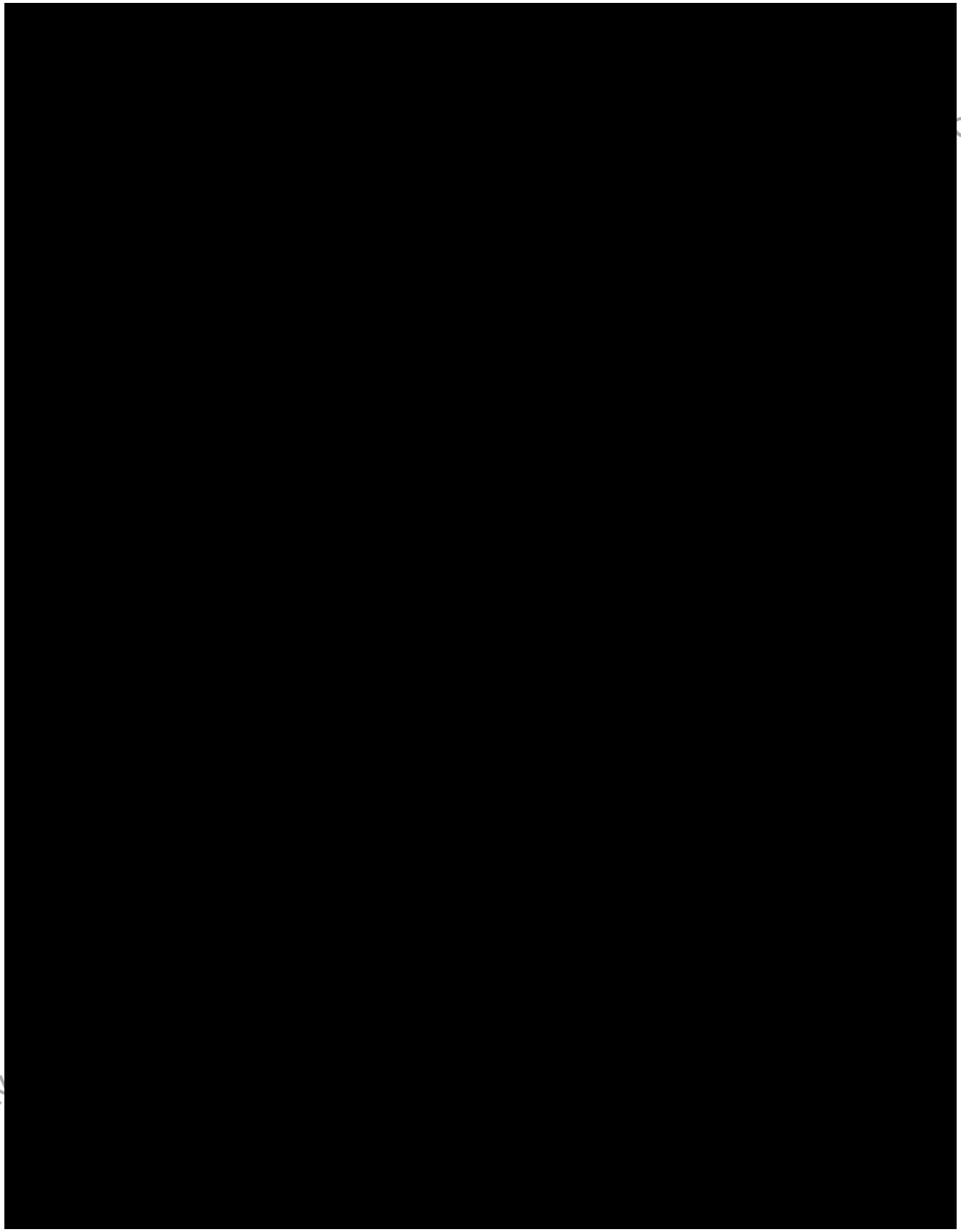

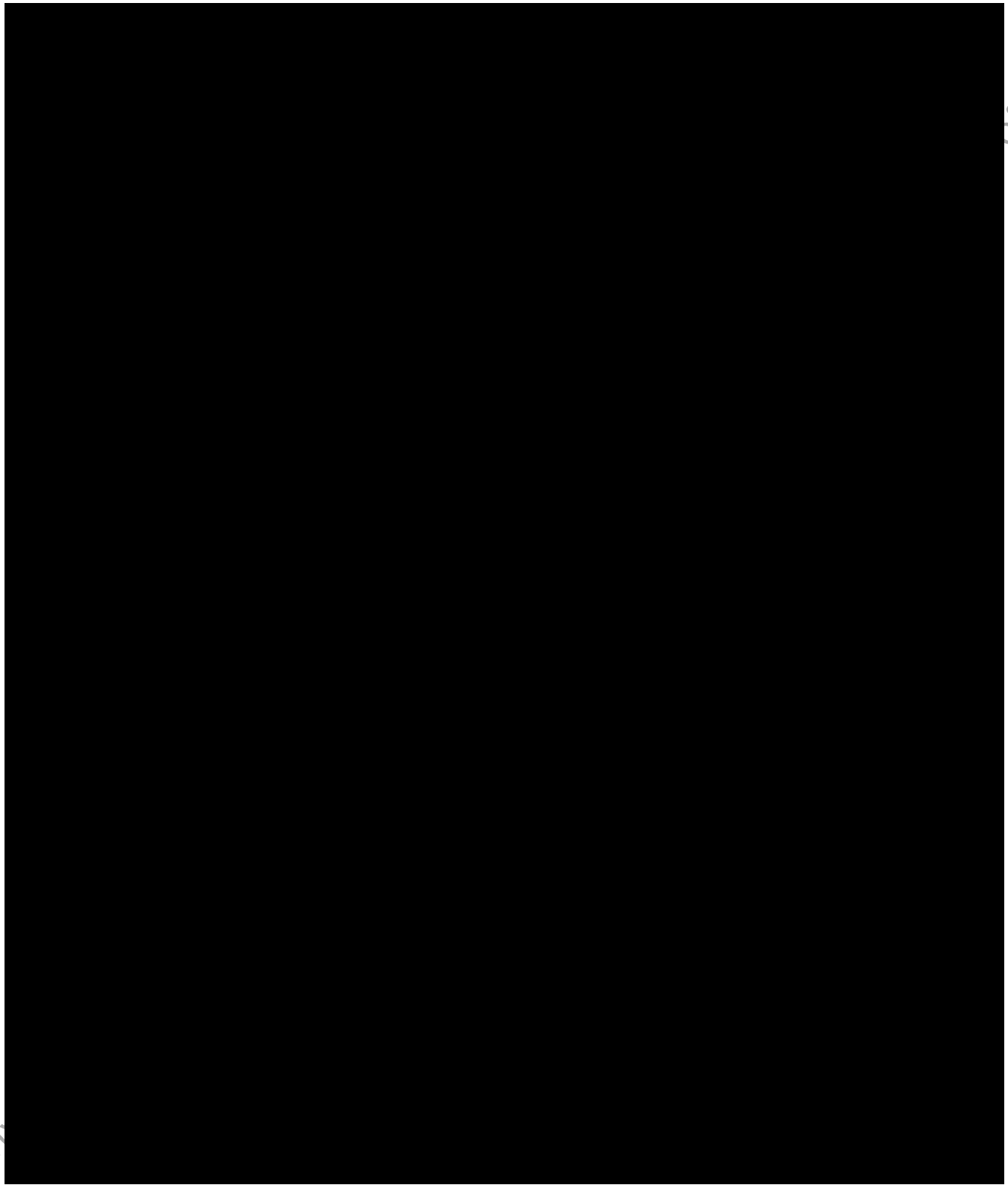

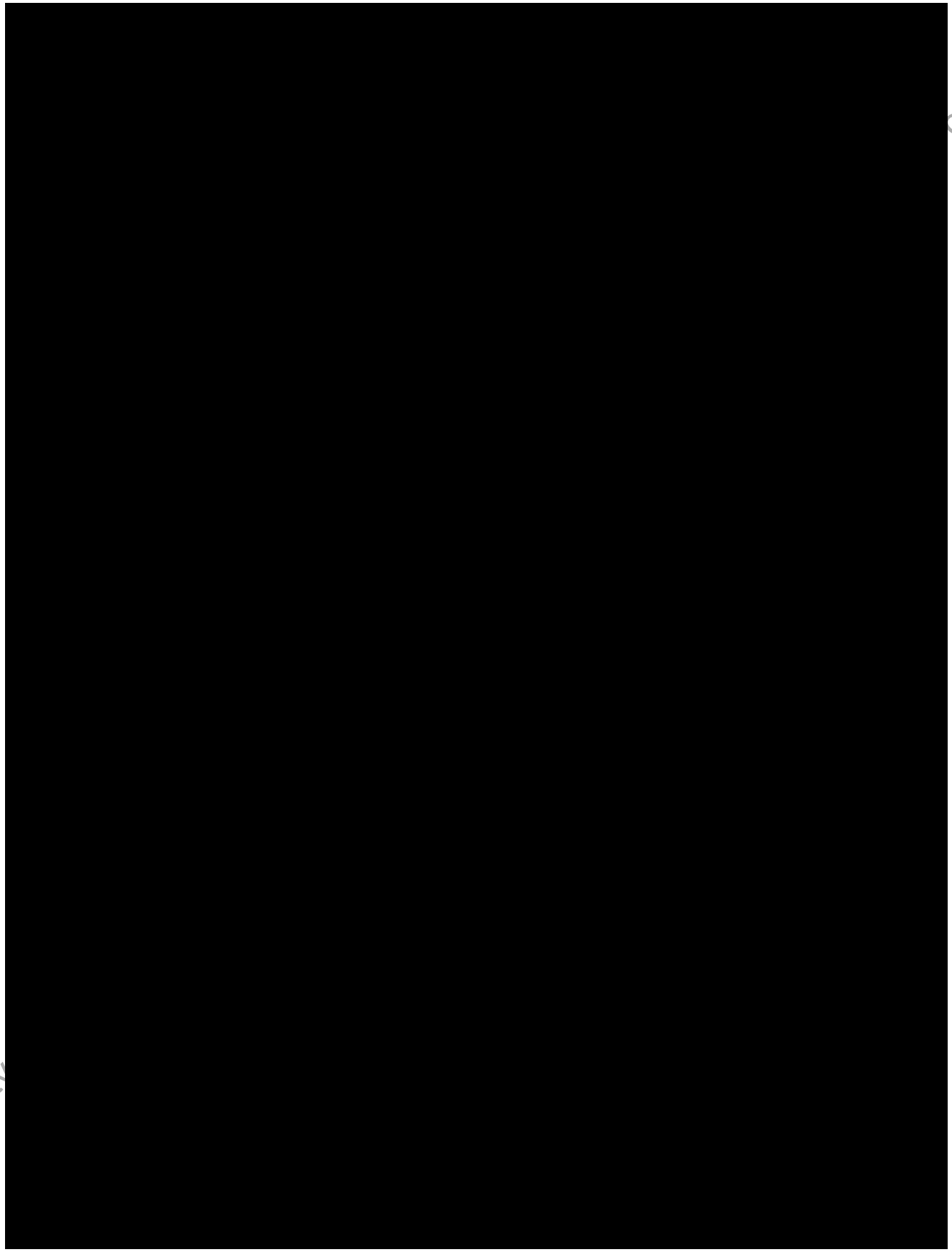

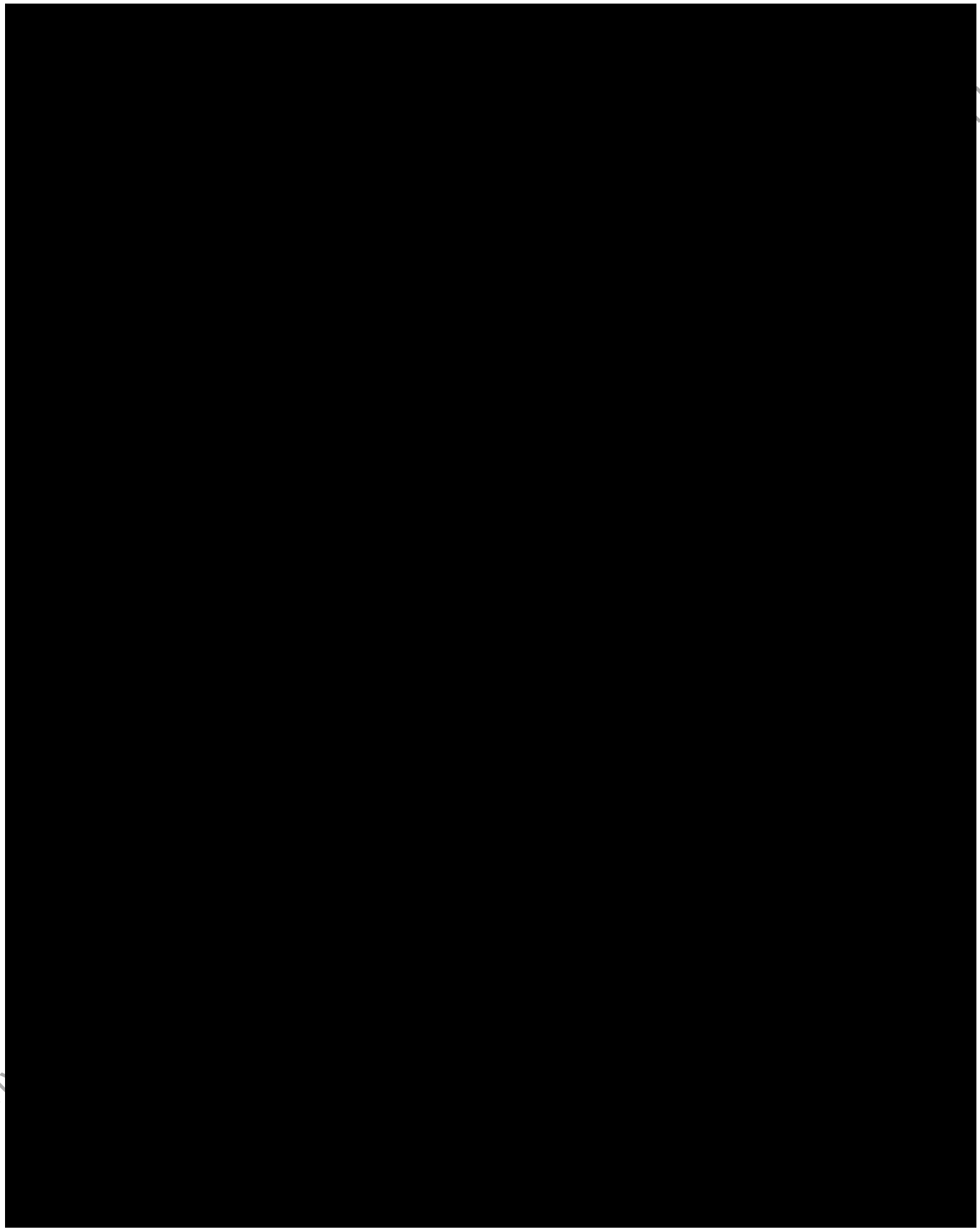

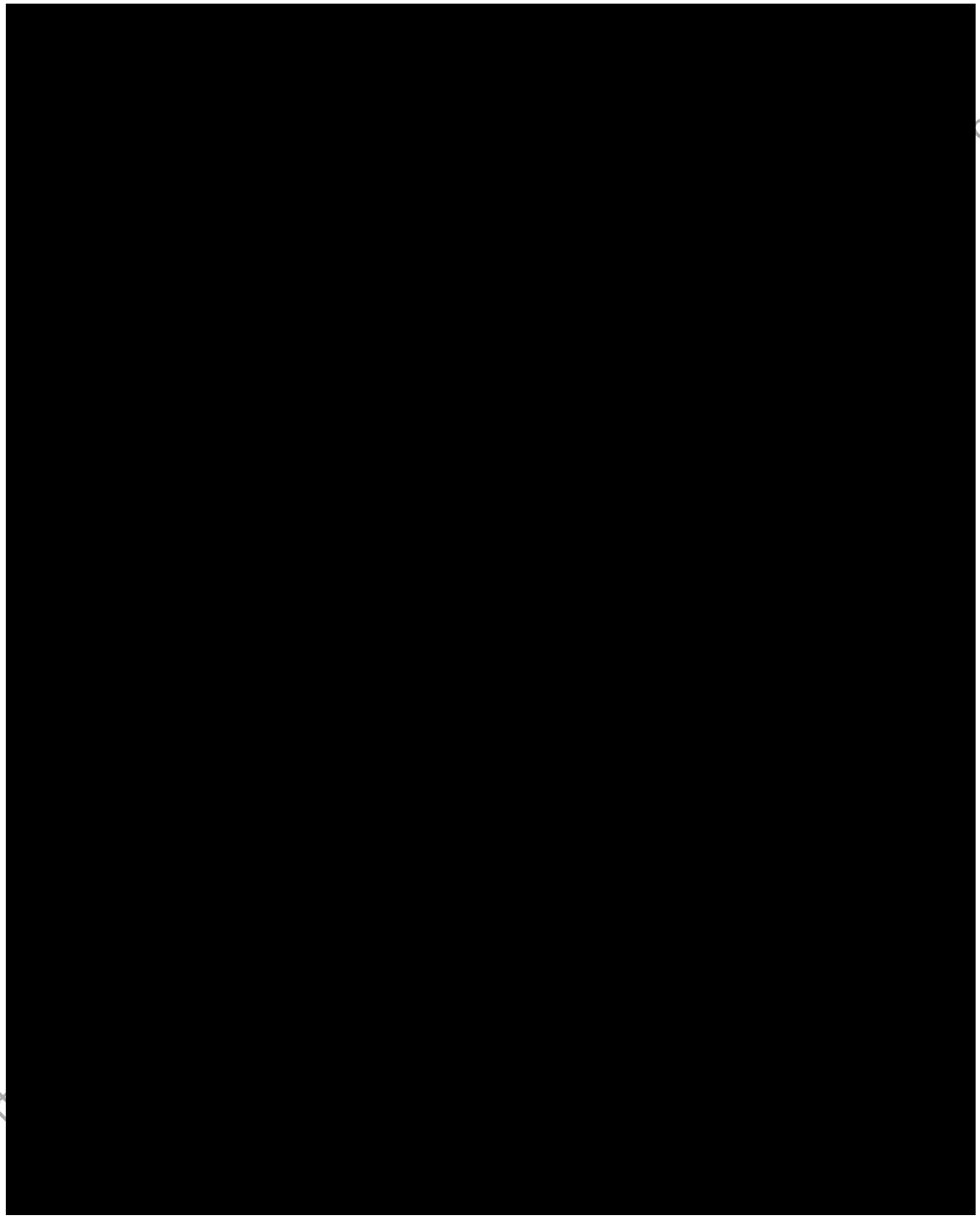

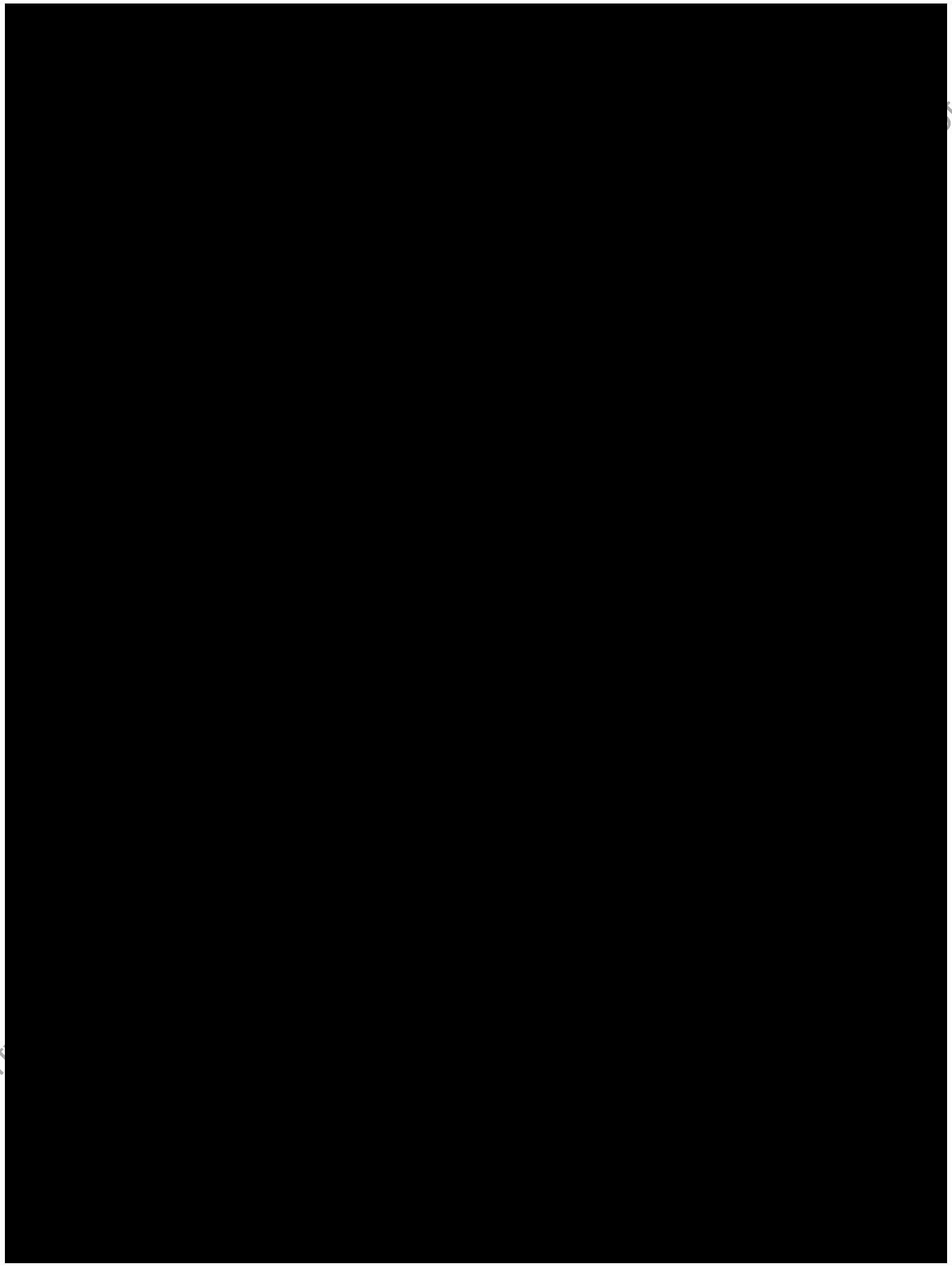

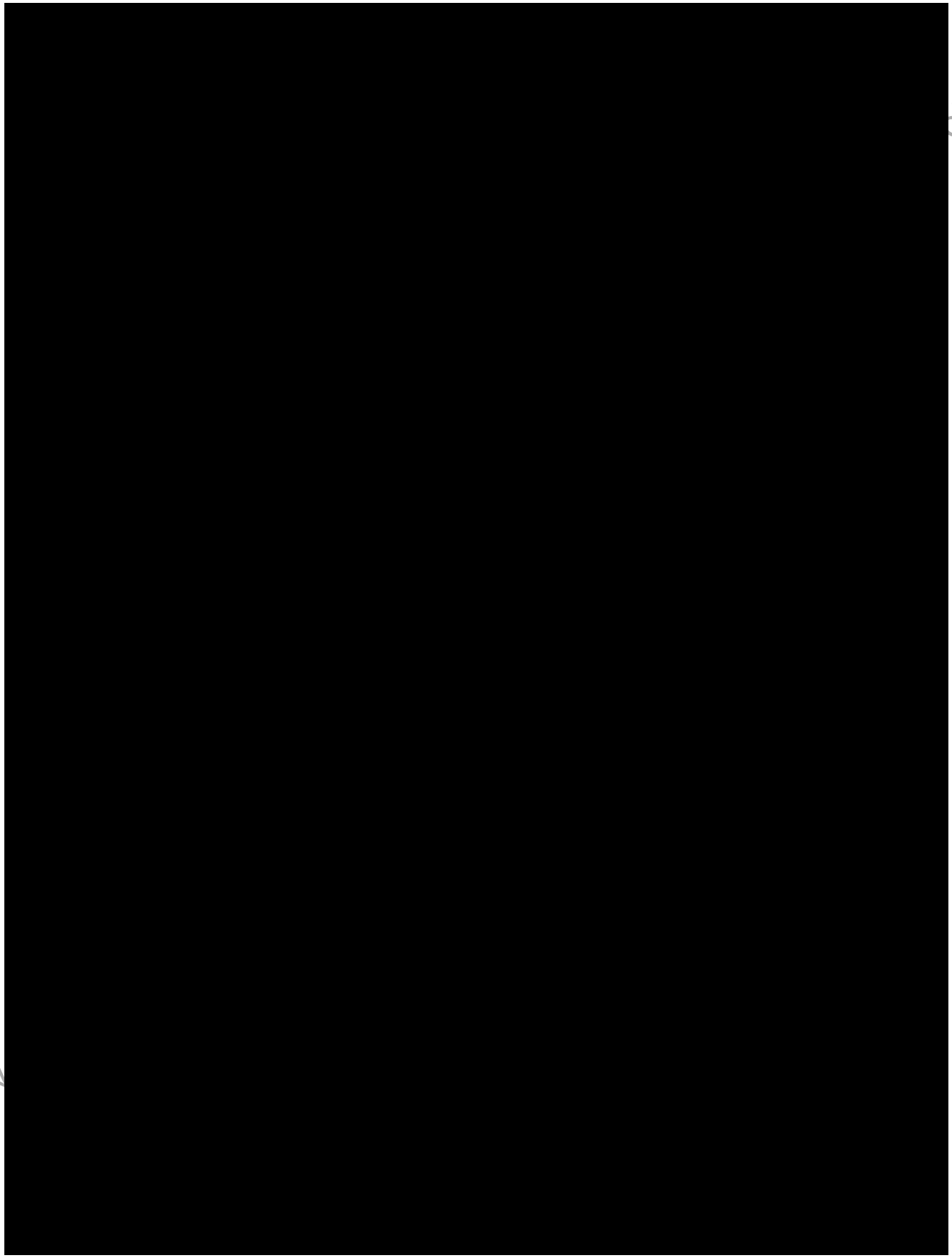

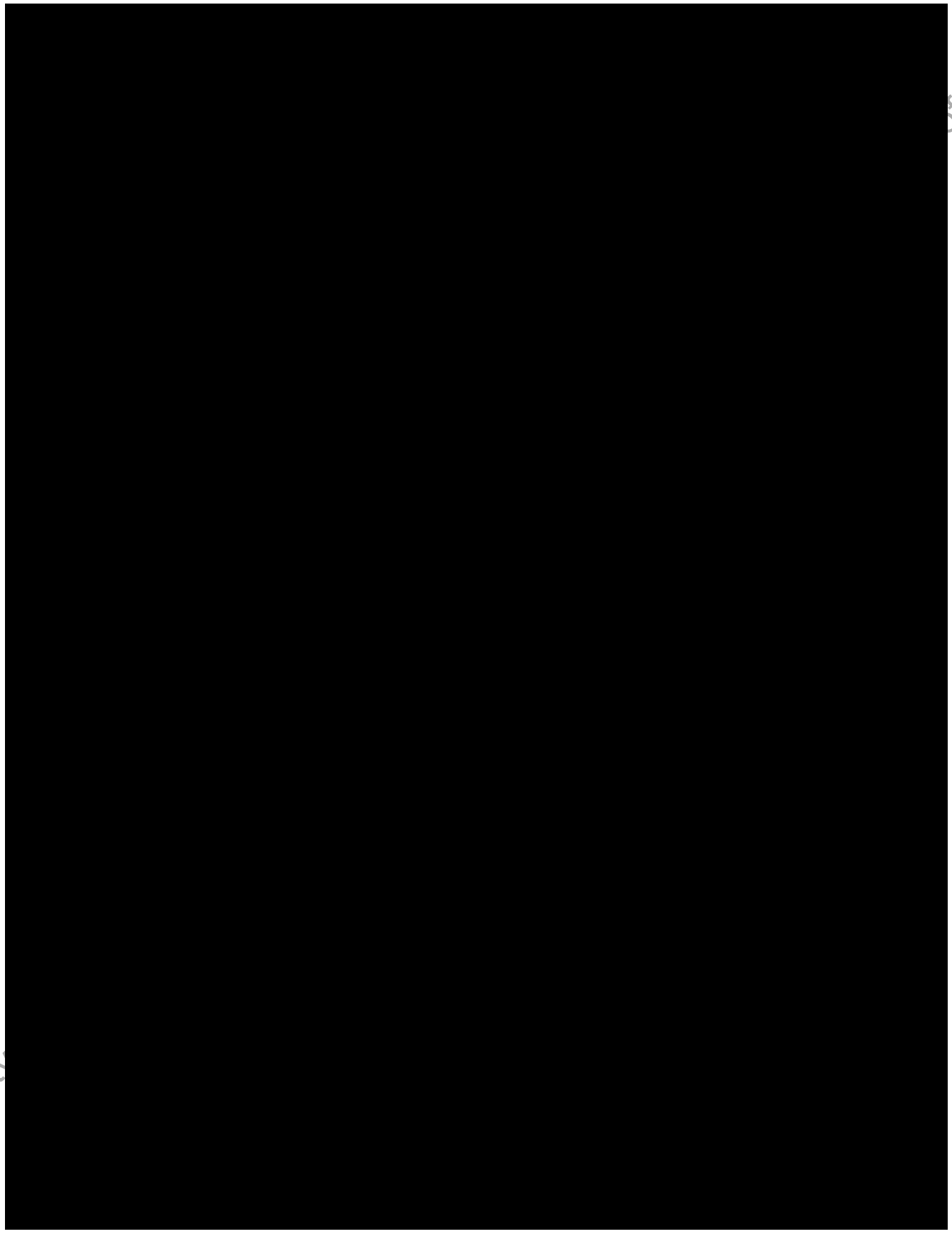

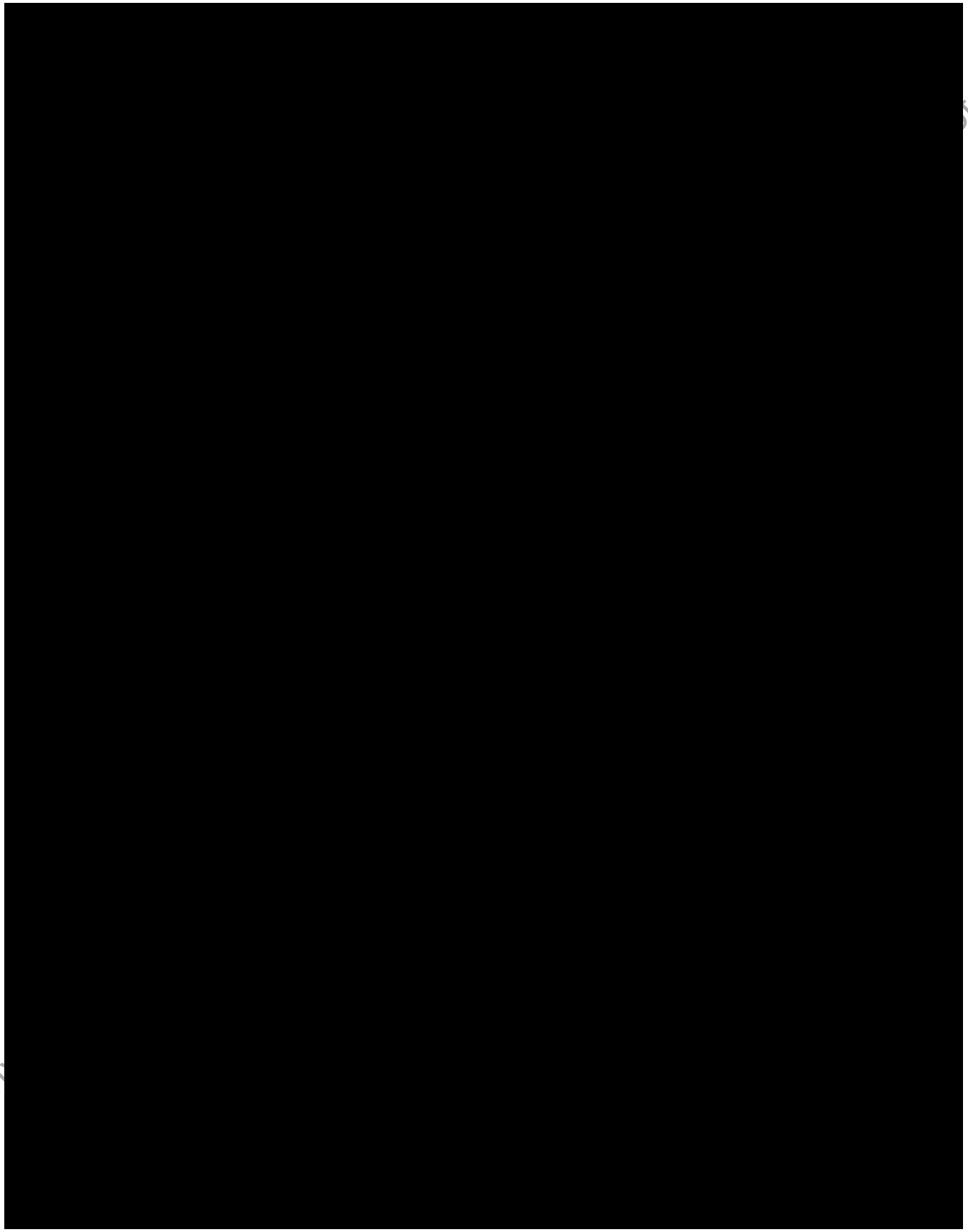

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Appendix 8 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	02 Jun 2021	All sites
Amendment No.1	02 Dec 2021	All sites
Amendment No.2	19 May 2022	All sites

Protocol Amendments		
Summary of Change(s) in Amendment 1		
Amendment Number 1	**Amendment Date** **02 Dec 2021**	**Region** **All Sites**
Description of Change and Rationale		**Section(s) Affected by Change**
Changed name of sponsor protocol signatory to Andre Gabriel, MD, MS.		Signature page
Updated the form name and email address for product quality complaints.		Product Quality Complaints
Changed the screening period for another treatment cycle following the NTT or follow-up period to "-28 to -1 days" to allow subjects who need to resume teduglutide treatment immediately in another treatment cycle to enter the treatment period.		Section 1.1 Synopsis; Table 1 Schedule of Study Procedures; Section 4.1 Overall Design; Section 6.2.4 Treatment Eligibility Criteria for Initiation of a Next Teduglutide Treatment Cycle; Section 6.2.5 Follow-up Period Escape Criteria
Added the expected maximum duration of treatment (approximately 18 months).		Section 1.1 Synopsis
Added the following description below to the estimated glomerular filtration rate criteria (50 mL/min/1.73 m^2) in inclusion criteria 4 to clarify the reference. "*This criterion is based on "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. Food and Drug Administration. May 1998."		Section 1.1 Synopsis; Section 5.1 Inclusion criteria
Amended the errors related to the change of screening period for another treatment cycle.		Table 1 Schedule of Study Procedures; Section 8.3 Schedule of Observations and Procedures
Removed "enteral glutamine" from exclusion criteria with considering the clinical settings in Japan.		Section 1.1 Synopsis; Section 5.2 Exclusion Criteria; Table 3 Common Excluded Treatments and Associated Washout Period
Updated the approval status in Japan.		Section 2.2 Product Background and Clinical Information

Protocol Amendments		
Summary of Change(s) in Amendment 1		
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Description of Change and Rationale		**Section(s) Affected by Change**
Added the following description below to allow the subjects who develop renal impairment during the study to continue the dosing. "If a subject develops moderate or greater renal impairment during the study, the dose can be reduced to 0.025 mg/kg/day and continued after discussion with the sponsor's medical monitor. However, the subject's body weight must be above 10 kg (see inclusion criterion 4)."		Section 6.2.1 Dose, Regimen, and Administration by Parent or Guardian
Added the following description to avoid the situation that teduglutide is administered twice a day with more than 12 hours separation. "Do not administer more than 0.05 mg/kg (0.025 mg/kg for patients with moderate or greater renal impairment) in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM)".		Section 6.2.1 Dose, Regimen, and Administration by Parent or Guardian
Clarified the needed blood volume for clinical laboratory test.		Section 8.1.8 Procedures for Clinical Laboratory Samples; Appendix 4 Blood Volume Table
Error modifications and description adjustments		Where applicable