Clinical Study Protocol

NCT Number: NCT05150340

Title: A Phase 3, Open-label, Non-controlled Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of TAK-771 in Japanese Subjects with Primary Immunodeficiency Diseases (PID)

Study Number: TAK-771-3004

Document Version and Date: Amendment 1 / 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-771-3004**
Title:	A Phase 3, Open-label, Non-controlled Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of TAK-771 in Japanese Subjects with Primary Immunodeficiency Diseases (PID)
Short Title:	Pharmacokinetics, Safety and Tolerability, and Efficacy Evaluation of TAK-771 in Japanese Subjects with PID
Study Phase:	Phase 3
Drug:	TAK-771 Immune Globulin Infusion 10% (Human) [10% IGI] with Recombinant Human Hyaluronidase [rHuPH20]
IND Number:	Not Applicable
EUDRACT Number:	Not Applicable
Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan
Principal / Coordinating Investigator:	TBD
Protocol History:	**Protocol Amendment 1 (version date: 19 May 2022)** *replaces* Original Protocol (version date: 13 Jul 2021)

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

Signature: [redacted] Date: [redacted]

Investigator's Acknowledgement

I have read this protocol for Study TAK-771-3004.

Title: A Phase 3, Open-label, Non-controlled Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of TAK-771 in Japanese Subjects with Primary Immunodeficiency Diseases (PID)

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 Amendment Summary and Rationale:

The following is a summary of the changes made in the amendment 1.

Protocol Amendment			
Summary of Change(s) Since the Last Version of the Approved Protocol			
Amendment 1		**Amendment Date: 19 May 2022**	**Global/Region/Country/ Site Specific: Japan**
Description of Each Change and Rationale			**Section(s) Affected by Change**
1	Descriptions of 'Device used in clinical trial' were added.	Due to the modification of Japanese GCP, information required for the 'Device used in clinical trial' was added.	PRODUCT QUALITY COMPLAINTS Section 1.1 Mode of administration Section 6.3.3.2.2 Section 6.9 Section 10 Appendix 3.4
2	Infusion rate of 10%IGI was added	It was added to present enough information in the synopsis	Section 1.1 Mode of administration
3	Inclusion criteria 4 and relative description were modified.	It was modified due to the Japanese law which has been changed to recognize 18 years old as an adult	Section 1.1 Inclusion criteria Section 5.1 Section 8.1.1
4	Exclusion criteria 9 was modified.	It was modified since the assessment of anti-IgA antibodies is not commercially available in clinical practice in Japan.	Section 1.1 Exclusion criteria Section 5.2
5	Description in endpoints and analysis for Safety were modified.	For consistency between protocol and SAP	Section 1.1 Endpoints Section 3.2 Table 5 Section 3.2.2 Section 9.7
6	HRQoL index for Treatment satisfaction (Life Quality Index) was removed.	Due to a difficulty in use of Life Quality Index, it was not implemented in this study.	Section 1.1 Endpoints Section 3.2 Table 5 Section 3.2.2 Section 8.2.5.3.2 Section 9.8.1
7	Additional items to be summarized descriptively were included.	For consistency with tables to be produced.	Section 1.1 Statistical analysis Section 9.6 Section 9.7
8	Analysis for treatment preference was corrected	Error in summarization of treatment preference was corrected.	Section 1.1 Statistical analysis Section 9.8.1

Protocol Amendment			
Summary of Change(s) Since the Last Version of the Approved Protocol			
Amendment 1		**Amendment Date: 19 May 2022**	**Global/Region/Country/ Site Specific: Japan**
Description of Each Change and Rationale			**Section(s) Affected by Change**
9	Screening visits column for subjects switching from IVIG/cSCIG treatment shown in schedule of activities and clinical laboratory tests were modified. The description in the body was also modified accordingly.	For administrative clarification	Section 1.3 Table 1, Table 3 Section 4.1 Appendix 2 Table 9, Table 11
10	Description of self-measurement of vital signs was added.	It was added to clarify the procedure of data collection when a subject chooses to have a self-infusion at home.	Section 1.3 Table 1, Table 2, Table 3, Table 4 Section 8.2.4.4 Section 8.2.8
11	An instruction for dose modification based on weight changes was added.	It was added to clarify the level of weight changes which require the dose modifications.	Section 6.3.4
12	The timing of specific antibody testing described in the body text was corrected, and it was added that the testing at PK troughs is not required for those who are not in the PK assessment.	It was added to clarify who don't need to have the test at PK troughs and correct the inconsistency between the text description in the body and appendix tables.	Section 8.2.2.3 Appendix 2 Table 9, Table 10, Table 11, Table 12
13	Information regarding analysis of antibody titer was added.	It was added to clarify how to analyze the antibody when there is more than one samples from a same subject.	Section 8.2.4.5.3
14	Information regarding QoL/treatment satisfaction data capturing was added.	For clarification	Section 8.2.5.3
15	Version number of SAS to be used in this study was added	For clarification	Section 9.1
16	Description of SAE reporting was modified.	It was modified to reflect the actual procedure accurately.	CONTACT Appendix 3.4
17	Description for reporting of abuse, misuse, overdose, or medication error was modified	It was modified to reflect the actual procedure accurately.	Appendix 3.9
18	The list of abbreviations was modified	For update	Appendix 8

Protocol Amendment			
Summary of Change(s) Since the Last Version of the Approved Protocol			
Amendment 1		**Amendment Date: 19 May 2022**	**Global/Region/Country/ Site Specific: Japan**
Description of Each Change and Rationale			**Section(s) Affected by Change**
19	Correction of error	Typos and errors were corrected.	Section 1.1 Endpoints Section 3.2 Table 5 Section 6.3.3.2.4 Section 8.2.4.5.2 Section 9.3 Section 9.4 Section 9.7.4 Section 9.8.1 Appendix 2 Table 14

See Appendix 9 for protocol history, including all previous amendments.

CONTACTS

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 contract research organization (CRO) will provide investigators with emergency medical contact information cards to be carried by each subject, per individual country requirements.

Serious Adverse Event Reporting

If a subject experiences a serious adverse event (SAE) or a non-serious adverse event (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, it should be reported to BELLSYSTEM 24 shown below via e-mail or fax using an SAE Form in the same time frame:

Serious Adverse Event Reporting Contact Information for Japan:

BELLSYSTEM24, Inc.

[redacted]

Protocol and Safety-Related Questions or Concerns

For protocol- or safety-related questions or concerns during normal business hours 9:00 AM through 5:00 PM Japan, the investigator must contact the CRO medical monitor:

[redacted]

For protocol- or safety-related questions or concerns outside of normal business hours, the investigator must contact the CRO local medical monitor:

[redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product/device-used-in-clinical-trial 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, as well as device-used-in-clinical-trial defined in this protocol, 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/device-used-in-clinical-trial 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 (including the device-used-in-clinical-trial quality issues) using "Clinical Trial Material Complaint Form" via the e-mail address:

[redacted]

For instructions on reporting AEs related to product complaints, see Appendix 3.4.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-771-3004	**Drug:** TAK-771 Immune Globulin Infusion 10% (Human) [10% IGI] with Recombinant Human Hyaluronidase [rHuPH20]
Title of the study: A Phase 3, Open-label, Non-controlled Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Efficacy of TAK-771 in Japanese Subjects with Primary Immunodeficiency Diseases (PID)	
Short title: Pharmacokinetics, Safety and Tolerability, and Efficacy Evaluation of TAK-771 in Japanese Subjects with PID	
Study phase: Phase 3	
Number of subjects (total and per treatment arm): 15 subjects will be enrolled.	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in 10 to 15 sites in Japan	
Study period (planned): Approximately 2 years	Clinical phase: 3

Objectives:

Primary:

To assess serum trough levels of total immunoglobulin G (IgG) when using TAK-771 as maintenance therapy in Japanese subjects with PID.

Secondary:

- To characterize the pharmacokinetic (PK) profiles of TAK-771 in Japanese subjects with PID following TAK-771 administration.
- To evaluate the safety and tolerability of TAK-771 in Japanese subjects with PID.
- To evaluate the efficacy of TAK-771 in Japanese subjects with PID.
- To assess disease activity and health-related quality of life (HRQoL) in Japanese subjects with PID following TAK-771 administration.

Rationale:

Approximately 2,900 to 3,500 people are diagnosed with PID in Japan, and the number of diagnosed patients is increasing (Ishimura et al., 2011). Immunoglobulin (IG) replacement therapy has been widely used for patients with PID and the administration route is commonly either monthly intravenous (IV) or weekly subcutaneous (SC) injection. TAK-771 has been developed to address the major limitation of conventional subcutaneous immunoglobulin (cSCIG) therapy and it significantly enhances SC administration in PID by offering improved bioavailability (as compared to cSCIG therapy) without requiring greater doses than those administered intravenously. TAK-771 allows the SC administration of standard PID monthly dosing volumes, and the utilization of infusion rates equal to IV administration while preserving the advantages of SC administration.

This proposed study is designed to evaluate serum trough IgG levels, safety and tolerability, and efficacy of TAK-771 which will be administered subcutaneously at 3- or 4-week intervals, and assesses disease activity and HRQoL in subjects with PID in Japan. It aims to demonstrate maintenance of total IgG trough levels in PID patients after being on stable doses of TAK-771. The results from this study will extend/support the data obtained in the global pivotal study (Study 160603) and the extension study (Study 160902), in which switching from intravenous immunoglobulin (IVIG) to TAK-771 in patients with PID was evaluated. Data from these global studies will be used for the regulatory submission for the approval of TAK-771 in Japan.

Investigational product, dose, and mode of administration:

Investigational product: TAK-771 (10% IGI with rHuPH20)

Dosage form: injectable SC solution

Dose: [rHuPH20] 80 U/g IgG (rHuPH20 drug product: 160 U/mL)

[10% IGI] equivalent IgG amount to previous treatment of each patient (after the initial ramp-up) (In the case of switching from subcutaneous immunoglobulin (SCIG), to be calculated on the basis of weekly equivalents from SCIG treatment, that is to say the TAK-771 doses at 3- or 4-week intervals are calculated by multiplying SCIG weekly dose by 3 or 4.)

Dosage frequency: starting with a ramp-up: dosing interval of 1 week, then 2 weeks, then 3 weeks; then once every 3 or 4 weeks (as tolerated and as scheduled during pre-study period)

Subjects with 4-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/4 of full dose
Week 2	2nd. infusion	1/2 of full dose
Week 4	3rd. infusion	3/4 of full dose
Week 7 and the following 4-week intervals	4th. infusion and the following infusions	full dose

Subjects with 3-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/3 of full dose
Week 2	2nd. infusion	2/3 of full dose
Week 4 and the following 3-week intervals	3rd. infusion and the following infusions	full dose

Mode of Administration: SC infusion of rHuPH20 solution at a dose of 80 U/g IgG will be administered first, to be followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution. For the initial 2 administrations of rHuPH20 in the study, it will be infused at 60 to 120 mL/h/site as tolerated and the rate may be increased as tolerated by the subject and at the discretion of the investigator, but not to exceed 300 mL/h/site. SC infusion of 10% IGI will be administered via an infusion pump (Sapphire™ Multi-Therapy) at 1, 2, or 3 infusion sites per infusion day. For the initial 2 infusions in the study, the maximum infusion rate should be 80 mL/h and 240 mL/h per site, for subjects <40 kg and ≥40 kg body weight, respectively.

Step-wise increases are suggested in subsequent infusions with rate increases of up to 160 mL/h and 300 mL/h per site, for subjects <40 kg and ≥40 kg body weight, respectively.

Methodology:

This is a phase 3, open-label, non-controlled, multi-dose, multicenter study to evaluate PK, efficacy, safety and tolerability of TAK-771 in Japanese subjects with PID, as well as to assess disease activity and HRQoL. The patients who have been treated with IVIG, cSCIG, or TAK-664 can be enrolled in this study. After confirmation of eligibility, subjects will receive SCIG of TAK-771 in the treatment period. The TAK-771 administration is started with ramp-up infusion and subsequently in 3- or 4-weeks dosing frequency continued for 24 weeks.
A schematic of the study design is included as Figure 1.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

1. Be a Japanese person.
2. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving antibody formation and requiring gammaglobulin replacement, as defined according to the International Union of Immunological Societies (IUIS) Committee 2017. The diagnosis must be confirmed by the Medical Director prior to TAK-771 treatment.
3. Subject is 2 years or older at the time of screening/enrollment.
4. Written and/or electronic informed consent is obtained from either the subject or the subject's legally authorized representative prior to any study-related procedures and study product administration. If a subject is <18 years of age, written and/or electronic informed consent should also be obtained from the subject's legally authorized representative in addition to written informed assent by a subject if appropriate.
5. Subject has been receiving a stable clinical dose of IVIG or cSCIG, which is equivalent to approximately 200 to 600 mg/kg body weight per 3 to 4 week period for IVIG and approximately 50 to 200 mg/kg body weight per week for cSCIG based on the description in the package insert, consistently over a period of at least 3 months prior to screening, or

   Subject has been receiving of TAK-664 with fixed dose and dosing frequency at least 3 months prior to enrollment. That is, subject is about to complete Study TAK-664-3001 or participating in Study TAK-664-3002.
6. Subject who has been receiving IVIG or cSCIG had all serum trough levels of IgG ≥5 g/L within 1 month prior to the screening/enrollment.
7. Serum trough levels at screening/enrollment meet one of the following:
   a. IVIG-treated, cSCIG-treated subjects
      Subject who had serum trough levels of IgG ≥5 g/L at the last 2 points in screening procedure before the first administration of TAK-771.
   b. TAK-664-treated subjects
      Subject who had serum trough levels of IgG ≥5 g/L at the last 2 points in Study TAK-664-3001 or Study TAK-664-3002 (TAK-664 studies, hereafter) before the first administration of TAK-771
8. Subject is willing and able to comply with the requirements of the protocol.
9. Subject is willing and able to comply with use of digital tools and applications

Exclusion Criteria:

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

1. Subject has a known history of or is positive at screening/enrollment for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
   For subjects who are switching from TAK-664 studies, the eligibility will be reconfirmed after the result of the specialty test conducted at Week 1 become available.
2. Abnormal laboratory values at screening/enrollment meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
   a. Persistent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN) for the testing laboratory*
   b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] $\leq 500/mm^3$)*
3. Subject has presence of renal function impairment defined by eGFR <60 mL/min/1.73m^2.*
4. Subject has been diagnosed with, or had a malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) unless the disease-free period prior to screening exceeds 5 years.
5. Subject is receiving anti-coagulation therapy or has a history of thrombotic episodes (including deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening/enrollment or a history of thrombophilia.
6. Subject has abnormal protein loss (protein losing enteropathy, nephrotic syndrome).
7. Subject has anemia that would preclude phlebotomy for laboratory studies according to standard practice at the site.
8. Subject has an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IVIG, SCIG, and/or Immune Serum Globulin infusions
9. Subject has immunoglobulin A (IgA) deficiency (serum IgA less than 0.07 g/L) and history of hypersensitivity, or history of confirmed anti-IgA antibodies, or both.
10. Subject is on preventative (prophylactic) systemic antibacterial antibiotics at doses sufficient to treat or prevent bacterial infections, and cannot stop these antibiotics at the time of screening/enrollment**.
11. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening/enrollment** or had a serious bacterial infection within the 3 months prior to screening/enrollment.
12. Subject has a bleeding disorder, or a platelet count less than 20,000/μL*, or in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of SC therapy.
13. Subject has total protein >9 g/dL* or myeloma, or macroglobulinemia (IgM) or paraproteinemia.
14. Subject has a known allergy to hyaluronidase.
15. Women of childbearing potential who meet any one of the following criteria:
    a. Subject presents with a positive pregnancy test.
    b. Subject is breast-feeding.
    c. Subject intends to begin nursing during the course of the study.

d. Subject does not agree to employ adequate birth-control measures (e.g. intrauterine device, diaphragm or condom [for male partner] with spermicidal jelly or foam, or birth-control pills/patches) throughout the course of the study.

16. Subject has participated in another clinical study and has been exposed to an investigational product or device within 30 days prior to study enrollment, (exception: TAK-664 studies).
17. Subject is scheduled to participate in another non-observational (interventional) clinical study involving an investigational product or device during the course of the study.
18. Subjects who experiences clinically significant adverse events (AEs) in TAK-664 studies and it may worsen by participating in this study.
19. Subject has severe dermatitis that would preclude adequate sites for safe product administration. *: For subjects who are switching from TAK-664 studies, the latest laboratory data obtained in the TAK-664 studies will be used to determine the eligibility.

**: The exceptional use of antibiotics is allowed. See Section 6.8.4 for the details.

Maximum duration of subject participation in the study:

- Screening period: up to 13 weeks
- Treatment period [TAK-771 SCIG treatment period]:
  - Epoch 1: 3 weeks (3-week interval infusion) or 6 weeks (4-week interval infusion) of ramp-up dosing period
  - Epoch 2: 12 weeks of dose adjustment period and 12 weeks of trough evaluation period

Endpoints

Analysis Populations /Analysis Sets:

- Enrolled Set: All enrolled subjects who have signed informed (e)Consent and are assigned to subject identification codes. Background summaries (e.g., subject disposition) will be based on the Enrolled Set.
- Full Analysis Set (FAS): All enrolled subjects who received investigational drug at least once. Analysis of efficacy, disease activity and HRQoL will be based on the FAS.
- Safety Analysis Set (SAS): All enrolled subjects who received investigational drug at least once. Analysis of safety, tolerability and product administration will be based on the SAS.
- Pharmacokinetic Analysis Set (PKAS): All enrolled subjects who received investigational drug at least once, have had at least 1 evaluable serum IgG concentration, and no major protocol deviations or events that would affect the serum IgG concentration analysis results. Analysis of serum IgG trough concentrations will be based on the PKAS and analysis of PK profiles will be based on the subset of 5 to 7 subjects aged 12 years and older in the PKAS.

Primary Endpoint:

Serum trough levels of total IgG (total serum trough IgG antibodies) measured during the trough evaluation period of Epoch 2 (administration of TAK-771).

Secondary Endpoints:

Endpoints cover PK, safety and tolerability, efficacy, and disease activity and HRQoL.

Pharmacokinetic endpoints and parameters:

- PK parameters for total serum levels of IgG and for IgG subclasses in the PK assessment period of Epoch 2 (in a subset of 5 to 7 subjects aged 12 years and older), which may include but not limited to the following: maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), half-life, apparent total clearance (CL/F), apparent volume of distribution (V_z/F), minimum concentration (C_{min})
- Serum trough levels of IgG subclasses in the trough evaluation period of Epoch 2
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae [HIB], Hepatitis B virus [HBV]) in Epoch 1 and 2

Safety and Tolerability Endpoints:

- Occurrence of treatment-emergent adverse events (TEAEs) in Epoch 1 and 2, including but not limited to: TAK-771-related and non-related, serious, non-serious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs
- Changes in clinical laboratory parameters in Epoch 1 and 2
- Changes in vital signs and body weight in Epoch 1 and 2
  Change from baseline in vital signs and body weight, and change from pre-infusion to post-infusion in vital signs
- Development of positive titer (≥ 1:160) binding antibodies, and development of neutralizing antibodies, to rHuPH20 in Epoch 2
  Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160
  Number and percentage of subjects who develop neutralizing antibodies to rHuPH20
- Occurrence of tolerability events related to the infusion of TAK-771 in Epoch 1 and 2
  A tolerability event is considered to have occurred if an infusion was not tolerable, which is defined as any changes in dosing of TAK-771 such as reduction of infusion rate, interruption or discontinuation of TAK-771 due to TEAEs related to TAK-771. Number and percentage of subjects who experienced tolerability events will be measured.
- Number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1
- Percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2
- Percentage of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2

Efficacy endpoints:

- Annual rate of validated acute serious bacterial infections (ASBIs) per subject in Epoch 1 and 2
- Annual rate of all infections per subject in Epoch 1 and 2
- Healthcare Resource Utilization in Epoch 1 and 2
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)
  - Number of acute (urgent or unscheduled) physician visits due to illness/infection

- Infusion parameters in Epoch 2 including but not limited to: number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site

Disease activity and health-related quality of life endpoints:

- QoL: PEDS-QL (Varni et al., 1999), SF-36 v2 (Ware and Sherbourne, 1992), EQ-5D-3L Health Questionnaire (Shaw et al., 2005) in Epoch 1 and 2
- Treatment Satisfaction (TSQM-9) (Daly et al., 1991) in Epoch 1 and 2
- Treatment Preference at end-of-study (EOS)/Early termination

[redacted]

Statistical analysis

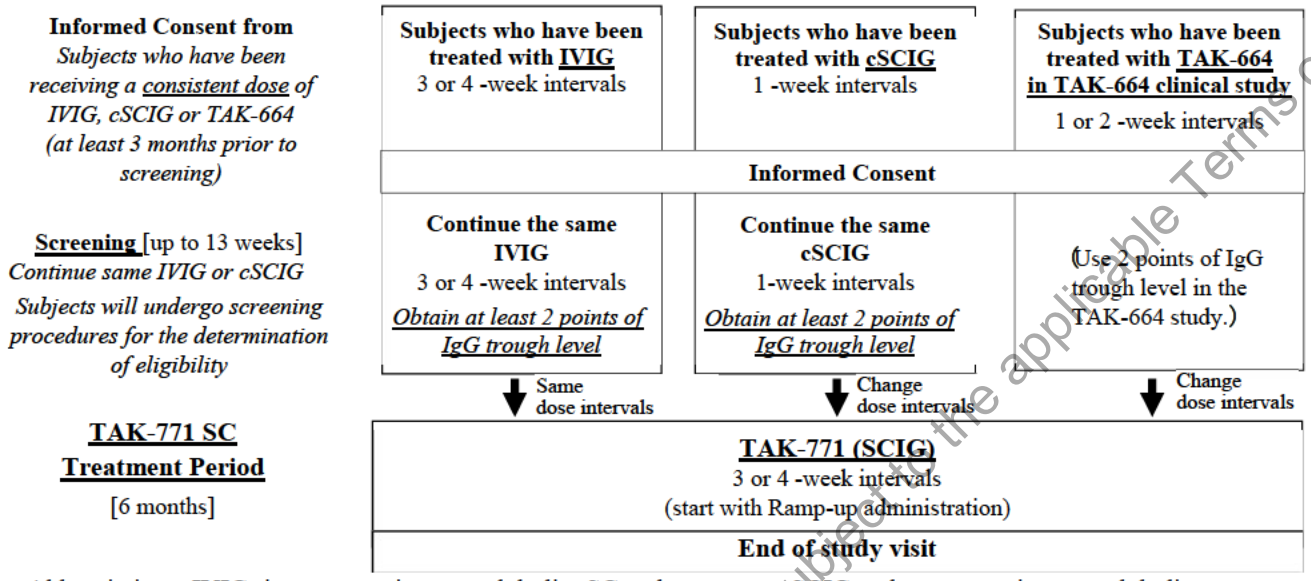
Continuous endpoints/outcome measures (e.g., change from baseline) will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value. In addition, 1st quartile (Q1) and 3rd quartile (Q3) will be summarized for safety and efficacy tables. Categorical endpoints/outcome measures (e.g., AEs) will be summarized in terms of number and percent of subjects and number of occurrences in each category.

For serum IgG, IgG subclasses (IgG1, IgG2, IgG3, and IgG4) and specific antibodies trough levels, descriptive statistics will also include geometric mean (GM) and the corresponding 2-sided 95% confidence interval (CI). No formal statistical comparison (hypothesis testing) of treatments will be performed. CIs are for descriptive purposes. Caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

For disease activity and HRQoL data, number and percentage of subjects in each category will be summarized for the endpoint of Treatment Preference at EOS/Early Termination, and raw (actual) and change from baseline values will be summarized descriptively and summaries will be provided for other endpoints.

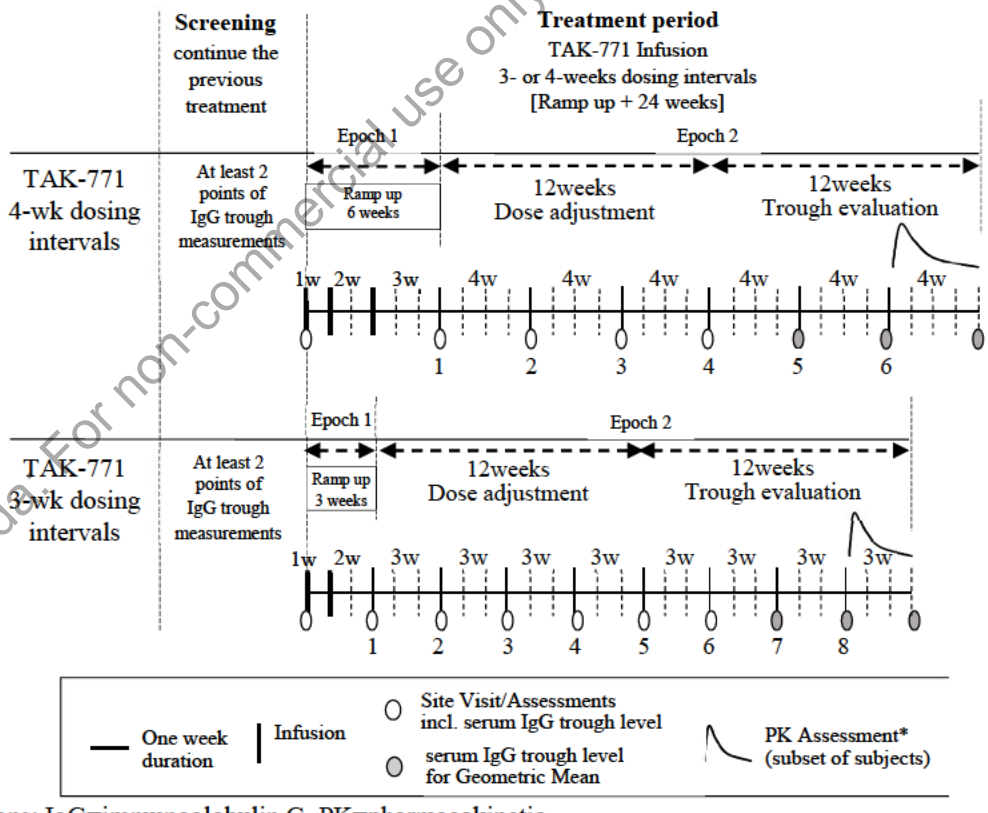
1.2 Schema

Figure 1. Study Schematic Diagram



Abbreviations: IVIG=intravenous immunoglobulin, SC=subcutaneous, SCIG=subcutaneous immunoglobulin, cSCIG=conventional subcutaneous immunoglobulin, IgG=immunoglobulin G

Figure 2. Treatment Schedule



Abbreviations: IgG=immunoglobulin G, PK=pharmacokinetic

*: Alternatively, PK assessment can be started at 1 visit earlier and completed just before the last SC infusion at the discretion of investigator.

1.3 Schedule of Activities

Table 1. Schedule of Activities for Subjects Switching from IVIG/cSCIG Treatment: 4-week Dosing Interval

Procedure	Screening period		Treatment period									
			Epoch 1 (Ramp-up)			Epoch 2 (4-week dosing interval)						EOS/Early termination visit
Visit No.	Screening visit 1[a]	Screening visit 2[a]	R-1	R-2	R-3	Visit 1[b]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[b]	Visit 6[b]	
Week	up to 13 weeks before Week 1		Week 1	Week 2	Week 4	Week 7	Week 11	Week 15	Week 19	Week 23	Week 27	Week 31
Visit allowance	-	-	±0 day	±0 day	±0 day	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent[c]	X											
Assessment of eligibility	X											
Demographic information	X											
Medical and medication history	X											
Body height	X											
Body weight	X	X[d]	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X[d]	X	X	X	X	X	X	X	X	X	X
Concomitant medication, non-drug therapies	X	X[d]	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments[e]	X	X[d]	X			X	X	X	X	X	X	X
PK assessments[f]											← X →	
Subject's own IVIG/cSCIG treatment	X	X[d]										
Investigational product treatment[g]			X	X	X	X	X	X	X	X	X	
Vital signs[h]	X	X[d]	X	X	X	X	X	X	X	X	X	X
Adverse events review	← X →											
Collection/Review diaries			X	X	X	X	X	X	X	X	X	X
Quality of life assessments			X						X			X
Treatment satisfaction assessment			X						X			X
Treatment preference												X

Table 1. Schedule of Activities for Subjects Switching from IVIG/cSCIG Treatment: 4-week Dosing Interval

Procedure	Screening period		Treatment period									
			Epoch 1 (Ramp-up)			Epoch 2 (4-week dosing interval)						EOS/Early termination visit
Visit No.	Screening visit 1[a]	Screening visit 2[a]	R-1	R-2	R-3	Visit 1[b]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[b]	Visit 6[b]	
Week	up to 13 weeks before Week 1		Week 1	Week 2	Week 4	Week 7	Week 11	Week 15	Week 19	Week 23	Week 27	Week 31
Visit allowance	-	-	±0 day	±0 day	±0 day	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Healthcare resource utilization			←	←	←	X	→	→	→	→	→	→
Self-administration proficiency[i]			X	X	X	X	X	X	X	X	X	

Abbreviations: AE=adverse event, cSCIG=conventional subcutaneous immunoglobulin, EOS=end-of-study, IgG=immunoglobulin G, IVIG=intravenous immunoglobulin, PK= pharmacokinetic, SC= subcutaneous

a. Visit frequency is dependent on the dosing frequency of subject's own IVIG/cSCIG treatment. The interval from Screening Visit 1 to Screening Visit 2 should be at least 3 weeks.
b. When TAK-771 dose is administered over multiple days as divided doses with 48 to 72 hours between doses due to the infusion volume, assessments don't need to be repeated on the second day of infusion.
c. Written and/or electronic informed consent must be obtained prior to any study procedures including screening.
d. Assessments are conducted at every visit during the screening period.
e. For laboratory assessments specific to the visits, see Table 9 in Appendix 2.
f. Alternatively, PK assessment can be started at 1 visit earlier and completed just before the last SC infusion at the discretion of investigator. See Table 13 in Appendix 2 for PK assessment schedule.
g. Subcutaneous infusion of rHuPH20 solution will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution in a sequential order at the same location. The recommended site(s) for SC infusion are the middle to upper abdomen and thighs. If more than one site are used, the infusion sites should be rotated by choosing opposite sides of the body. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localized infection. Self-administration of SC infusions at home may be allowed at the discretion of investigator after the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures are completed.
h. Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute. For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken once per administration, but will be recorded multiple times if an AE occurs. When subjects have self-infusion at home and an AE occurs, subjects (and/or caregiver) should measure vital signs by themselves and record the values on subject diary.
i. Subcutaneous infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse) or, if applicable, can be administered by the subject and/or a caregiver. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at sites, home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The proficiency check will not be required when subject has self-administration of SC infusions at home.

Table 2. Schedule of Activities for Subjects Switching from TAK-664 Treatment: 4-week Dosing Interval

Procedure	Treatment period									
	Epoch 1 (Ramp-up)			Epoch 2 (4-week dosing interval)						EOS/Early termination visit
Visit No.	**R-1**	**R-2**	**R-3**	**Visit 1[b]**	**Visit 2[b]**	**Visit 3[b]**	**Visit 4[b]**	**Visit 5[b]**	**Visit 6[b]**	
Week	**Week 1[a]**	**Week 2**	**Week 4**	**Week 7**	**Week 11**	**Week 15**	**Week 19**	**Week 23**	**Week 27**	**Week 31**
Visit allowance	**±0 day**	**±0 day**	**±0 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Informed consent[c]	X									
Assessment of eligibility[d]	X									
Demographic information	X[e]									
Medical and medication history	X[e]									
Body height	X[e]									
Body weight	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X
Concomitant medication, non-drug therapies	X[e]	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments[f]	X			X	X	X	X	X	X	X
PK assessments[g]									← X →	
Investigational product treatment[h]	X	X	X	X	X	X	X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X	X	X
Adverse events review	←				X					→
Collection/Review diaries	X	X	X	X	X	X	X	X	X	X
Quality of life assessments	X						X			X
Treatment satisfaction assessment	X[e]						X			X
Treatment preference										X

Table 2. Schedule of Activities for Subjects Switching from TAK-664 Treatment: 4-week Dosing Interval

Procedure	Treatment period									
	Epoch 1 (Ramp-up)			Epoch 2 (4-week dosing interval)						EOS/Early termination visit
Visit No.	**R-1**	**R-2**	**R-3**	**Visit 1[b]**	**Visit 2[b]**	**Visit 3[b]**	**Visit 4[b]**	**Visit 5[b]**	**Visit 6[b]**	
Week	**Week 1[a]**	**Week 2**	**Week 4**	**Week 7**	**Week 11**	**Week 15**	**Week 19**	**Week 23**	**Week 27**	**Week 31**
Visit allowance	**±0 day**	**±0 day**	**±0 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Healthcare resource utilization	←	←	←	←	←	X	→	→	→	→
Self-administration proficiency[j]	X	X	X	X	X	X	X	X	X	

Abbreviations: AE=adverse event, EOS=end-of-study, IgG=immunoglobulin G, PK= pharmacokinetic, SC= subcutaneous

a. The assessments for the Week 1 in TAK-771-3004 can be combined with the EOS/Early termination visit assessments in TAK-664 studies.
b. When TAK-771 dose is administered over multiple days as divided doses with 48 to 72 hours between doses due to the infusion volume, assessments don't need to be repeated on the second day of infusion.
c. Written and/or electronic informed consent must be obtained prior to any study procedures.
d. The latest laboratory data obtained in the TAK-664 studies will be used to determine the eligibility.
e. Data collected in the TAK-664 studies can be used if available.
f. For laboratory assessments and PK assessments specific to the visits, see Table 10 in Appendix 2.
g. Alternatively, PK assessment can be started at 1 visit earlier and completed just before the last SC infusion at the discretion of investigator. See Table 13 in Appendix 2 for PK assessment schedule.
h. Subcutaneous infusion of rHuPH20 solution will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution in a sequential order at the same location. The recommended site(s) for SC infusion are the middle to upper abdomen and thighs. If more than one site are used, the infusion sites should be rotated by choosing opposite sides of the body. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localized infection. Self-administration of SC infusions at home may be allowed at the discretion of investigator after the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures are completed.
i. Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute. For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken once per administration, but will be recorded multiple times if an AE occurs. When subjects have self-infusion at home and an AE occurs, subjects (and/or caregiver) should measure vital signs by themselves and record the values on subject diary.
j. Subcutaneous infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse) or, if applicable, can be administered by the subject and/or a caregiver. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at sites, home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The proficiency check will not be required when subject has self-administration of SC infusions at home.

Table 3. Schedule of Activities for Subjects Switching from IVIG/cSCIG Treatment: 3-Week Treatment Interval

Procedure	Screening period		Treatment period										
			Epoch 1 (Ramp-up)		Epoch 2 (3-week dosing interval)								EOS/Early termination visit
Visit No.	Screening visit 1[a]	Screening visit 2[a]	R-1	R-2	Visit 1[b]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[b]	Visit 6[b]	Visit 7[b]	Visit 8[b]	
Week	up to 13 weeks before Week 1		Week 1	Week 2	Week 4	Week 7	Week 10	Week 13	Week 16	Week 19	Week 22	Week 25	Week 28
Visit allowance	-	-	±0 day	±0 day	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent[c]	X												
Assessment of eligibility	X												
Demographic information	X												
Medical and medication history	X												
Body height	X												
Body weight	X	X[d]	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X[d]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication, non-drug therapies	X	X[d]	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments[e]	X	X[d]	X		X	X	X	X	X	X	X	X	X
PK assessments[f]												← X →	
Subject's own IVIG/cSCIG treatment	X	X[d]											
Investigational product treatment[g]			X	X	X	X	X	X	X	X	X	X	
Vital signs[h]	X	X[d]	X	X	X	X	X	X	X	X	X	X	X
Adverse events review	← X →												
Collection/Review diaries			X	X	X	X	X	X	X	X	X	X	X
Quality of life assessments			X						X				X
Treatment satisfaction assessment			X						X				X
Treatment preference													X
Healthcare resource utilization			← X →										

Table 3. Schedule of Activities for Subjects Switching from IVIG/cSCIG Treatment: 3-Week Treatment Interval

Procedure	Screening period		Treatment period										
			Epoch 1 (Ramp-up)		Epoch 2 (3-week dosing interval)								EOS/Early termination visit
Visit No.	Screening visit 1[a]	Screening visit 2[a]	R-1	R-2	Visit 1[b]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[b]	Visit 6[b]	Visit 7[b]	Visit 8[b]	
Week	up to 13 weeks before Week 1		Week 1	Week 2	Week 4	Week 7	Week 10	Week 13	Week 16	Week 19	Week 22	Week 25	Week 28
Visit allowance	-	-	±0 day	±0 day	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Self-administration proficiency[i]			X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE=adverse event, cSCIG=conventional subcutaneous immunoglobulin, EOS=end-of-study, IgG=immunoglobulin G, IVIG=intravenous immunoglobulin, PK= pharmacokinetic, SC=subcutaneous

a. Visit frequency is dependent on the dosing frequency of subject's own IVIG/cSCIG treatment. The interval from Screening Visit 1 to Screening Visit 2 should be at least 3 weeks.
b. When TAK-771 dose is administered over multiple days as divided doses with 48 to 72 hours between doses due to the infusion volume, assessments don't need to be repeated on the second day of infusion.
c. Written and/or electronic informed consent must be obtained prior to any study procedures including screening.
d. Assessments are conducted at every visit during the screening period.
e. For laboratory assessments and PK assessments specific to the visits, see Table 11 in Appendix 2.
f. Alternatively, PK assessment can be started at 1 visit earlier and completed just before the last SC infusion at the discretion of investigator. See Table 14 in Appendix 2 for PK assessment schedule.
g. Subcutaneous infusion of rHuPH20 solution will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution in a sequential order at the same location. The recommended site(s) for SC infusion are the middle to upper abdomen and thighs. If more than one site are used, the infusion sites should be rotated by choosing opposite sides of the body. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localized infection. Self-administration of SC infusions at home may be allowed at the discretion of investigator after the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures are completed.
h. Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute. For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken once per administration, but will be recorded multiple times if an AE occurs. When subjects have self-infusion at home and an AE occurs, subjects (and/or caregiver) should measure vital signs by themselves and record the values on subject diary.
i. Subcutaneous infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse) or, if applicable, can be administered by the subject and/or a caregiver. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at sites, home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The proficiency check will not be required when subject has self-administration of SC infusions at home.

Table 4. Schedule of Activities for Subjects Switching from TAK-664 Treatment: 3-Week Treatment Interval

Procedure	Treatment period										
	Epoch 1 (Ramp-up)		Epoch 2 (3-week dosing interval)								EOS/Early termination visit
Visit No.	**R-1**	**R-2**	**Visit 1[b]**	**Visit 2[b]**	**Visit 3[b]**	**Visit 4[b]**	**Visit 5[b]**	**Visit 6[b]**	**Visit 7[b]**	**Visit 8[b]**	
Week	**Week 1[a]**	**Week 2**	**Week 4**	**Week 7**	**Week 10**	**Week 13**	**Week 16**	**Week 19**	**Week 22**	**Week 25**	**Week 28**
Visit allowance	**±0 day**	**±0 day**	**±3 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Informed consent[c]	X										
Assessment of eligibility[d]	X										
Demographic information	X[e]										
Medical and medication history	X[e]										
Body height	X[e]										
Body weight	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication, non-drug therapies	X[e]	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments[f]	X		X	X	X	X	X	X	X	X	X
PK assessments[g]										← X →	
Investigational product treatment[h]	X	X	X	X	X	X	X	X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X
Adverse events review	← X →										
Collection/Review diaries	X	X	X	X	X	X	X	X	X	X	X
Quality of life assessments	X						X				X
Treatment satisfaction assessment	X[e]						X				X
Treatment preference											X
Healthcare resource utilization	← X →										

Table 4. Schedule of Activities for Subjects Switching from TAK-664 Treatment: 3-Week Treatment Interval

Procedure	Treatment period										
	Epoch 1 (Ramp-up)		Epoch 2 (3-week dosing interval)								EOS/Early termination visit
Visit No.	**R-1**	**R-2**	**Visit 1[b]**	**Visit 2[b]**	**Visit 3[b]**	**Visit 4[b]**	**Visit 5[b]**	**Visit 6[b]**	**Visit 7[b]**	**Visit 8[b]**	
Week	**Week 1[a]**	**Week 2**	**Week 4**	**Week 7**	**Week 10**	**Week 13**	**Week 16**	**Week 19**	**Week 22**	**Week 25**	**Week 28**
Visit allowance	**±0 day**	**±0 day**	**±3 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Self-administration proficiency[j]	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE=adverse event, EOS=end-of-study, IgG=immunoglobulin G, PK= pharmacokinetic, SC= subcutaneous

a. The assessments for the Week 1 in TAK-771-3004 can be combined with the EOS/Early termination visit assessments in TAK-664 studies.
b. When TAK-771 dose is administered over multiple days as divided doses with 48 to 72 hours between doses due to the infusion volume, assessments don't need to be repeated on the second day of infusion.
c. Written and/or electronic informed consent must be obtained prior to any study procedures.
d. The latest laboratory data obtained in the TAK-664 studies will be used to determine the eligibility.
e. Data collected in the TAK-664 studies can be used if available.
f. For laboratory assessments and PK assessments specific to the visits, see Table 12 in Appendix 2.
g. Alternatively, PK assessment can be started at 1 visit earlier and completed just before the last SC infusion at the discretion of investigator. See Table 14 in Appendix 2 for PK assessment schedule.
h. Subcutaneous infusion of rHuPH20 solution will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution in a sequential order at the same location. The recommended site(s) for SC infusion are the middle to upper abdomen and thighs. If more than one site are used, the infusion sites should be rotated by choosing opposite sides of the body. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localized infection. Self-administration of SC infusions at home may be allowed at the discretion of investigator after the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures are completed.
i. Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute. For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken once per administration, but will be recorded multiple times if an AE occurs. When subjects have self-infusion at home and an AE occurs, subjects (and/or caregiver) should measure vital signs by themselves and record the values on subject diary.
j. Subcutaneous infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse) or, if applicable, can be administered by the subject and/or a caregiver. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at sites, home or other suitable locations. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The proficiency check will not be required when subject has self-administration of SC infusions at home.

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Primary immunodeficiency diseases (PID) are disorders that result in increased susceptibility to recurrent infections, secondary to the underlying defects in adaptive (humoral and/or cell-mediated immunity) and/or innate immune system (Hernandez-Trujillo, 2014, Picard et al., 2018, Rosen et al., 1995). The number of known PID defects has increased in the last 20 years and the World Health Organization (WHO) currently recognizes more than 354 distinct disorders (with 344 gene defects) (Picard et al., 2018). The most recent classification of molecularly defined PIDs issued by the Expert Committee of the International Union of Immunological Societies (IUIS) (Tangye et al., 2020) distinguishes 10 PID categories according to common disease phenotypes.

Considered rare diseases until recently, PIDs may affect up to 1/1200 people worldwide according to current estimates (Bousfiha et al., 2013). In Japan, the prevalence of PIDs and number of patients are estimated as 2 to 3 per 100,000 people and 2,900 to 3,500 patients, respectively, though the accurate prevalence is not well known (Ishimura et al., 2011). In addition, it is well known that patients with PID are at high risk of developing malignancy, and, it is reported that 3.2% of patients with PID have developed malignant diseases (de la Morena and Nelson, 2014). Primary immunodeficiency diseases are specified as a designated intractable disease by Ministry of Health, Labour and Welfare in Japan.

Therapeutic options for the treatment of infections in PID with antibody production defects include standard antibiotic treatment and administration of immunoglobulin G (IgG) as a replacement therapy. Antibody replacement can be administered either intravenously or subcutaneously (Melamed et al., 2012). Therapeutic options for treatment of PID itself to correct the defect are transplantation of bone marrow-derived stem cells, and recently, gene therapy (de la Morena and Nelson, 2014, Hernandez-Trujillo, 2014, Kuo, 2018, Picard et al., 2018, Sauer et al., 2014).

Currently, the majority of IgG products are licensed for intravenous (IV) administration, though in the past several years, subcutaneous (SC) administration has gained popularity. When given weekly or every other week, subcutaneous immunoglobulin (SCIG) leads to higher trough serum IgG concentrations than monthly IV infusions (Berger, 2011, Gardulf et al., 1995, Gardulf et al., 1991). Immunoglobulin (IG) replacement therapy administered by the SC route is considered to be effective, safe and is also well accepted by subjects with PID (Gardulf and Hammarström, 1996). This route of administration may be of particular interest in patients with poor venous access such as pediatric patients (Melamed et al., 2012, Wasserman, 2012) and those patients interested in home-based therapy since it can be self-administered (Abolhassani et al., 2012, Wasserman, 2012, Zuizewind et al., 2018).

Another major potential benefit of SCIG is the lower incidence of systemic adverse events (AEs) compared to intravenous immunoglobulin (IVIG) (Berger, 2013, Suez et al., 2016). The IG preparations currently approved for SC use in the United States (US), Canada and the European Union (EU) are formulated at 10% to 20%. The higher concentration products allow for a relatively smaller infusion volume, which may reduce the number of infusion sites and/or duration of infusion, thereby improving patient quality of life (QoL) (Wasserman, 2012).

Currently in Japan, only one product of IgG formulation for SC use (20% SCIG formulation Hizentra®) is available. The availability of additional alternative IgG formulation for SC use is highly needed for patients who do not tolerate their current SCIG. In addition, to be prepared in the event of product shortages, due to manufacturing constraints or natural disasters, stable supply of SCIG products should be secured by several companies.

2.2 Product Background and Clinical Information

The pharmacokinetics (PK) of SC administration are different from that of IV infusions, and bioavailability of IG administered subcutaneously may be lower than after IV infusions. This reduced bioavailability after SC administration may be due to the mode of absorption of large protein molecules, which cannot readily diffuse through the capillary walls and must be absorbed via the lymphatics (Supersaxo et al., 1990).

A major disadvantage of conventional SC administration is that only small volumes can be infused at each injection site, necessitating the use of multiple sites on a weekly or bi-weekly (every other week) basis. Generally, using a 16% solution, approximately 20 mL can be infused per site; an adult patient receiving 400 mg/kg body weight every 4 weeks thus would require at least 3 sites per week or 12 sites per month. Even though weekly or bi-weekly administration has the added advantage of maintaining better trough levels than monthly IV infusions, since SCIG which is currently available in Japan requires weekly injections, the requirement of multiple needle insertions in a lifelong treatment has been a deterrent for many patients with PID.

TAK-771 (10% immune globulin infusion [IGI] with rHuPH20) has been developed to address the major limitation of conventional SCIG (cSCIG) therapy and it significantly enhances SC administration in PID by offering improved bioavailability (as compared to cSCIG therapy) without requiring greater doses than those administered intravenously (Schiff et al., 2008). In addition, TAK-771 allows the SC administration of standard PID monthly dosing volumes, and the utilization of infusion rates equal to IV administration while preserving the advantages of SC administration (Schiff et al., 2008).

2.3 Study Rationale

Approximately 2,900 to 3,500 people are diagnosed with PID in Japan, and the number of diagnosed patients is increasing. Immunoglobulin replacement therapy has been widely used for patients with PID, and the administration route is commonly either monthly IV or weekly SC injection in Japan. This proposed study is designed to evaluate serum trough IgG levels, safety and tolerability, and efficacy of TAK-771 administered subcutaneously at 3- or 4-week intervals, and assesses disease activity and health-related quality of life (HRQoL) in subjects with PID in Japan. It aims to demonstrate maintenance of total IgG trough levels in PID patients after being on stable doses of TAK-771. The results from this study will extend/support the data obtained in the global pivotal study (Study 160603) and the extension study (Study 160902), in which switching from IVIG to TAK-771 in patients with PID was evaluated. Data from these global studies will be used for the regulatory submission for the approval of TAK-771 in Japan.

2.4 Benefit/Risk Assessment

The clinical program for TAK-771 includes 7 completed interventional clinical studies (160601, 160602, 160603, 160902, 161101, 170901, and 161001) in subjects with PID and healthy volunteers, and 1 completed non-interventional registry study (161301) in women exposed to treatment before or during pregnancy (pregnancy registry). These studies provide evidence demonstrating the efficacy, PK, safety and tolerability of TAK-771 in subjects with PID, healthy volunteers and pregnant women. rHuPH20 increased the bioavailability of 10% IGI administered SC normalized by area under the curve (AUC)/dose/kg body weight by approximately 20%, thus reducing the clinically effective dose. When administered at 108% of the IV dose, TAK-771 was pharmacokinetically equivalent to 10% IGI administered IV with respect to area under the curve from time 0 to time τ ($AUC_{0-\tau}$) and resulted in comparable trough IgG levels. The IgG trough levels were well above 5.0 g/L, the accepted minimum level for effective prophylaxis against infections in patients with PID (Orange et al., 2006).

TAK-771 administered over 3 years at a similar frequency to IVIG was safe with a comparable AE profile to SCIG at infusion volumes and rates equivalent to IVIG, and effectively maintained low rates of infection in patients with PID (Wasserman et al., 2015). Large infusion volumes up to 600 mL/site were well-tolerated, enabling treatment of pediatric and adult patients with PID at the same interval used for 10% IGI administered IV. When administered at 108% of the IV dose, TAK-771 resulted in a somewhat lower rate of infections per subject-year (SY) than 10% IGI administered IV or SC. Trough IgG levels were comparable for TAK-771 and 10% IGI administered IV. Protective trough levels were maintained during long-term treatment with TAK-771. TAK-771 reduced the clinically effective SC dose of 10% IGI compared to SC administration alone and resulted in decreased frequency, severity and duration of local induration. A decline in the rate of related local AEs per subject per year was observed during long-term replacement therapy with TAK-771 in subjects with PID.

TAK-771 was shown to be effective in preventing infections in patients with PID. The primary endpoint of the pivotal study 160603 was met with respect to the frequency of validated acute serious bacterial infections (ASBIs) during TAK-771 treatment. Studies 160902 and 161101 confirmed the efficacy outcomes in terms of validated ASBIs and overall infection rate. In these studies, the rate of validated ASBIs/subject/year were well below 1.0 validated ASBI/subject/year, the threshold specified as providing substantial evidence of efficacy by the Food and Drug Administration (FDA) Guidance (Food and Drug Administration, 2008) and also complies with the European Medicines Agency (EMA) Guidance (Committee for Proprietary Medicinal Products, 2002). Protection against infection was maintained during long-term TAK-771 in pivotal study 160603 and extension study 160902. The overall annual rate of infections per SY while on TAK-771 treatment in the 2 studies was 2.99 (95% CI: 2.60 to 3.42). It compare favorably to published data; 4.1 infections per SY reported from SC treatment with another 10% IgG preparation (Wasserman et al., 2010), 3.4 to 5.6 infections per SY reported in 3 studies with SC administration of 16% IgG preparation (Berger et al., 2010, Borte et al., 2011, Ochs et al., 2006), and 2.4, 2.76 and 3.3 infections per SY were reported from long-term SC treatment with a 20% IgG preparation (Borte et al., 2012, Borte et al., 2013, Hagan et al., 2010).

Overall, the clinical program for TAK-771 demonstrated the positive safety profile. In Study 160603, subjects received TAK-771 treatment for at least 1 year, and majority of subjects who received TAK-771 were treated at the same interval used previously for IV treatment (3 or 4 weeks). TAK-771 was well-tolerated at large volumes (up to 600 mL/site) and utilizing maximum flow rates significantly higher than those used for IV infusions ($p<0.0001$) as compared by Wilcoxon test stratified by subject (van Elteren's test) (van Elteren, 1960). In extension study 160902, subjects continued on TAK-771 treatment for a median of 669 days (mean 565.9 days). A decline in the rate of related AEs, both local and systemic was observed during long-term treatment with TAK-771.

The rate of adverse drug reactions (ADRs) per infusion obtained for TAK-771 compares favorably with published data on SCIG (Ochs et al., 2006). A lower rate of systemic ADRs was reported for TAK-771 than IVIG treatment; this is in line with numerous studies comparing SCIG with IVIG (Berger, 2004, Gardulf and Hammarström, 1996, Moore and Quinn, 2008). While in Study 160603 local ADRs during TAK-771 treatment, which were mostly mild and moderate in severity, were reported at a rate of 0.203 AEs per infusion, the frequency of local ADRs per infusion was as low as 0.103 during long-term treatment with TAK-771 in extension Study 160902.

The nature of ADRs was similar for 10% IGI administered SC in Studies 160601 and 160603, and for TAK-771 treatment in Studies 160603, 160902, and 161101; the most commonly reported reactions were infusion site reactions. Infusion site reactions are expected in most patients during SCIG therapy, but they are not reported to be troublesome in the majority of patients (Gardulf et al., 1995, Misbah et al., 2009, Moore and Quinn, 2008).

Across 7 completed clinical studies, 2 serious adverse events (SAEs) were reported that were considered to be related to TAK-771. These events were cases of hemolytic anemia in healthy volunteers. They were conservatively assessed by the investigator as possibly being related to TAK-771, with an alternative etiology of viral infection (H1N1 Influenza A California) which affected 10 of the 12 subjects who participated in this study and was documented by seroconversion.

There have been no serious hypersensitivity reactions, including anaphylactic reactions, attributed to rHuPH20 in the studies with TAK-771. The current clinical and safety data for TAK-771 demonstrate that exposure is safe and well-tolerated, and there has been no evidence of a lack of treatment effect when rHuPH20-reactive binding antibodies have been detected. Based upon data available to date, the incidence of the formation of anti-rHuPH20 antibodies is low, no neutralizing antibodies have been observed, no clinical signs or symptoms have been associated with positive anti-rHuPH20 antibody titers.

Based on all the above, it was considered that the benefits of TAK-771 for treatment of patients with PID outweigh the risks.

Always refer to the latest version of the TAK-771 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of TAK-771.

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), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to assess serum trough levels of total IgG when using TAK-771 as maintenance therapy in Japanese subjects with PID.

3.1.2 Secondary Objectives

The secondary objectives of this study are listed below:

- To characterize the PK profiles of TAK-771 in Japanese subjects with PID following TAK-771 administration.
- To evaluate the safety and tolerability of TAK-771 in Japanese subjects with PID.
- To evaluate the efficacy of TAK-771 in Japanese subjects with PID.
- To assess disease activity and HRQoL in Japanese subjects with PID following TAK-771 administration.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint for the study is the serum trough levels of total IgG (total serum trough IgG antibodies) measured during the trough evaluation period of Epoch 2 (administration of TAK-771).

For a detailed description of endpoints and the planned statistical analysis, refer to Section 9.

3.2.2 Secondary Endpoints

Endpoints cover PK, safety and tolerability, efficacy, and disease activity and HRQoL.

Pharmacokinetic endpoints and parameters:

- PK parameters for total serum levels of IgG and for IgG subclasses in PK assessment period in Epoch 2 (in a subset of 5 to 7 subjects aged 12 years and older), which may include but not limited to the following: maximum concentration (C_{max}), time to maximum concentration (T_{max}), AUC, half-life, apparent total clearance (CL/F), apparent volume of distribution (V_z/F), minimum concentration (C_{min})
- Serum trough levels of IgG subclasses in the trough evaluation period of Epoch 2
- Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, Haemophilus influenzae [HIB], Hepatitis B virus [HBV]) in Epoch 1 and 2

Safety and tolerability endpoints:

Safety endpoints/outcome measures:

- Occurrence of treatment-emergent adverse events (TEAEs) in Epoch 1 and 2, including but not limited to: TAK-771-related and non-related, serious, non-serious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs
- Changes in clinical laboratory parameters in Epoch 1 and 2
- Changes in vital signs and body weight in Epoch 1 and 2
  Change from baseline in vital signs and body weight, and change from pre-infusion to post-infusion in vital signs
- Development of positive titer (≥ 1:160) binding antibodies, and development of neutralizing antibodies, to rHuPH20 in Epoch 2
  Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160
  Number and percentage of subjects who develop neutralizing antibodies to rHuPH20

Tolerability endpoints/outcome measures:

- Occurrence of tolerability events related to the infusion of TAK-771 in Epoch 1 and 2.
  A tolerability event is considered to have occurred if an infusion was not tolerable, which is defined as any changes in dosing of TAK-771 such as reduction of infusion rate, interruption or discontinuation of TAK-771 due to TEAEs related to TAK-771. Number and percentage of subjects who experienced tolerability events will be measured.
- Number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1
- Percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2
- Percentage of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2

Efficacy endpoints:

- Annual rate of validated acute serious bacterial infections (ASBIs) per subject in Epoch 1 and 2
- Annual rate of all infections per subject in Epoch 1 and 2
- Healthcare Resource Utilization in Epoch 1 and 2:
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)
  - Number of acute (urgent or unscheduled) physician visits due to illness/infection
- Infusion parameters in Epoch 2, including but not limited to: number of infusions per month, number of infusion sites per infusion, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site

Disease activity and health-related quality of life endpoints:

- QoL: PEDS-QL (Varni et al., 1999), SF-36 v2 (Ware and Sherbourne, 1992), EQ-5D-3L Health Questionnaire (Shaw et al., 2005) in Epoch 1 and 2
- Treatment Satisfaction (TSQM-9) (Daly et al., 1991) in Epoch 1 and 2
- Treatment Preference at End-of-study (EOS)/Early termination

[redacted]

Endpoint details will be provided in the study Statistical Analysis Plan (SAP).

Table 5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess serum trough levels of total IgG when using TAK-771 as maintenance therapy in Japanese subjects with PID.	• The serum trough levels of total IgG (total serum trough IgG antibodies) measured during the trough evaluation period of Epoch 2 (administration of TAK-771).
Secondary	
• To characterize the PK profiles of TAK-771 in Japanese subjects with PID following TAK-771 administration.	• PK parameters for total serum levels of IgG and for IgG subclasses in PK assessment period in Epoch 2(in a subset of 5 to 7 subjects aged 12 years and older), which may include but not limited to the following: C_{max}, T_{max}, AUC, half-life, CL/F, V_z/F, C_{min} • Serum trough levels of IgG subclasses in the trough evaluation period of Epoch 2 • Trough levels of specific antibodies to clinically relevant pathogens (Clostridium tetani toxoid, HIB, HBV) in the trough evaluation period of Epoch 1 and 2
• To evaluate the safety and tolerability of TAK-771 in Japanese subjects with PID.	• Occurrence of TEAEs in Epoch 1 and 2, including but not limited to: TAK-771-related and non-related, serious, non-serious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs • Changes in clinical laboratory parameters in Epoch 1 and 2 • Changes in vital signs and body weight in Epoch 1 and 2 Change from baseline in vital signs and body weight, and change from pre-infusion to post-infusion in vital signs • Development of positive titer (≥ 1:160) binding antibodies, and development of neutralizing antibodies, to rHuPH20 in Epoch 2 • Occurrence of tolerability events related to the infusion of TAK-771 in Epoch 1 and 2 • Number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1 • Percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2 • Percentage of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2

Table 5. Objectives and Endpoints

Objectives	Endpoints
• To evaluate the efficacy of TAK-771 in Japanese subjects with PID.	• Annual rate of validated ASBIs per subject in Epoch 1 and 2 • Annual rate of all infections per subject in Epoch 1 and 2 • Health Resource Utilization: in Epoch 1 and 2 - Days not able to attend school/work or to perform normal daily activities due to illness/infection - Days on antibiotics - Number of hospitalizations due to illness/infection and length of stay (in days) - Number of acute (urgent or unscheduled) physician visits due to illness/infection • Infusion parameters in Epoch 2, including but not limited to: number of infusions per month, number of infusion sites per month, duration of individual infusions, maximum infusion rate/site, and infusion volume/site
• To assess disease activity and HRQoL in Japanese subjects with PID following TAK-771 administration.	• QoL: PEDS-QL, SF-36 v2, EQ-5D-3L Health Questionnaire in Epoch 1 and 2 • Treatment Satisfaction (TSQM-9) in Epoch 1 and 2 • Treatment Preference at EOS/Early termination
[redacted]	

4. STUDY DESIGN

4.1 Overall Design

This is a phase 3, open-label, non-controlled, multi-dose, multicenter study to evaluate serum trough levels of IgG, PK, efficacy, safety and tolerability of TAK-771 in Japanese subjects with PID, as well as to assess disease activity and HRQoL. A total of 15 subjects aged 2 years or older will be enrolled, of whom 12 subjects are expected to complete the study. Approximately 10 to 15 study sites are planned, located in Japan.

This study will enroll patients with a confirmed diagnosis of PID, who have been receiving a consistent dose of IVIG, SCIG or TAK-664[*NOTE 1] at least 3 months prior to screening. The diagnosis must be confirmed by the Medical Director prior to TAK-771 treatment.

The study consists of signing informed (e)Consent, screening, treatment period (Epoch 1: dose ramp-up period, Epoch 2: dose adjustment period and trough evaluation period), and EOS/Early termination visit.

After informed consent has been obtained, subjects will undergo screening to determine the eligibility.

Screening

Subjects who are switching from IVIG or cSCIG will enter screening period for up to 13 weeks to undergo procedures for the determination of eligibility and will continue to receive their own immunoglobulin treatment at the same dose and dosing frequency as prescribed prior to their entry into this study. During the screening period, subjects will have 2 visits to have IgG trough levels measured at least 2 timepoints, which needs to be at least 3 weeks apart. After confirming the eligibility, subjects will enter the Epoch 1 and receive the initial dosing of TAK-771 SC 1 week after the last IVIG or cSCIG administration.

Subjects who have been receiving TAK-664 and are switching from Study TAK-664-3001 or TAK-664-3002 (TAK-664 studies, hereafter) will directly move on to the treatment period without entering the screening period. To determine the eligibility, the data including the latest laboratory data and IgG trough levels collected in the TAK-664 studies will be used. After confirming the eligibility, subjects will enter the Epoch 1 and receive the initial dosing of TAK-771 SC 1 week (for subjects switching from TAK-664 weekly dosing) or 2 weeks (for subjects switching from TAK-664 bi-weekly dosing) after the last TAK-664 administration.

Epoch 1

For all subjects, TAK-771 will be started with the ramp-up infusion (3 to 6 weeks) (Section 6.3.3.1).

Epoch 2

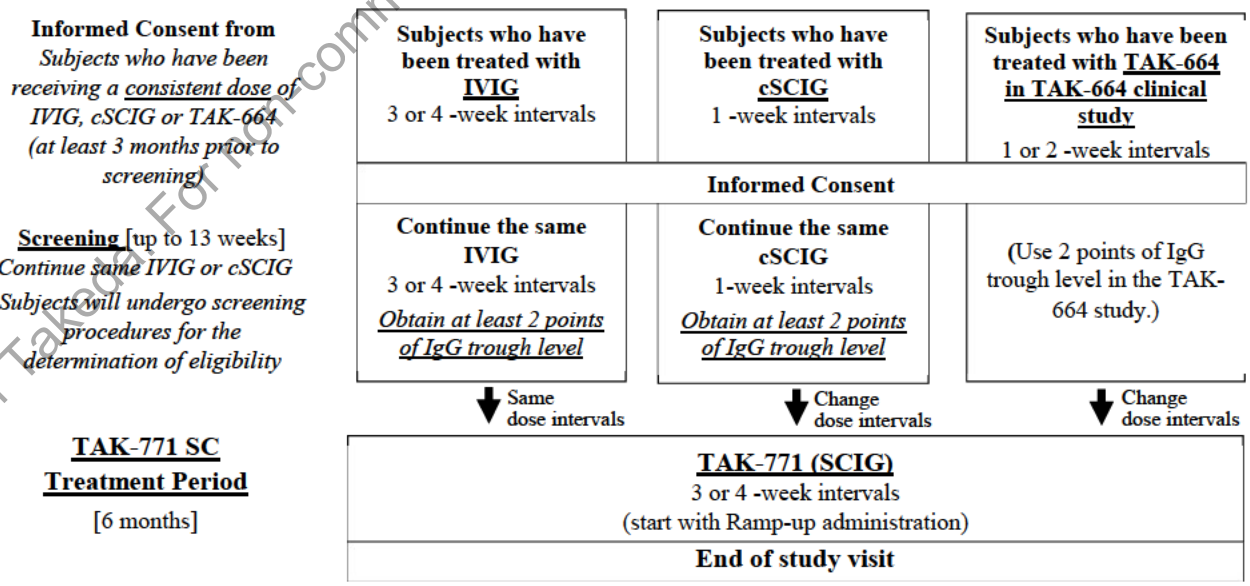
TAK-771 will be administered subcutaneously at 3- or 4-weeks dosing intervals after the ramp-up. Subjects will remain on this dosing interval until the end of 24-week treatment period.

PK assessment will be performed in 5 to 7 subjects aged 12 years and older. PK assessment will be started just before the last SC infusion (Week 27 [Visit 6] for 4-week dosing interval, and Week 25 [Visit 8] for 3-week dosing interval, depending on the subject's treatment schedule, see Figure 2) and serum samples will be collected at 7 time points in total until the EOS visit. Alternatively, PK assessment can be started at 1 visit earlier (at Week 23 [Visit 5] for 4-week dosing interval, and Week 22 [Visit 7] for 3-week dosing interval, depending on the subject's treatment schedule) and completed just before the last SC infusion at the discretion of investigator. A schedule of PK assessment is provided in Appendix 2.

All study subjects completing or exiting the study should complete the EOS/Early termination procedures. The visit will be 21 days after the last dose for 3-week dosing intervals and 28 days after the last dose for 4-week dosing intervals. This will mark the subjects' completion of the study. The recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

*NOTE 1: TAK-664 (20%IGI) is another IG preparation for SC use that is currently under development. In Japan, there are 2 ongoing clinical studies in patients with PID; pivotal study (Study TAK-664-3001) and the extension study (Study TAK-664-3002).

A schematic of the study design is shown below. A schedule of assessments is listed in Section 1.3.



Abbreviations: IVIG=intravenous immunoglobulin, SC=subcutaneous, SCIG=subcutaneous immunoglobulin, cSCIG=conventional subcutaneous immunoglobulin, IgG=immunoglobulin G

4.2 Scientific Rationale for Study Design

This is a phase 3, open-label, non-controlled study enrolling patients who have been treated with IVIG, SCIG, or TAK-664. As IgG replacement therapy has been recognized as an important treatment for patients with PID; and as the number of eligible subjects is small because of prevalence, an open-label non-controlled single-arm design was chosen and the PID patients who complete an ongoing clinical trial (TAK-664 studies) of TAK-664 (20% SCIG) are allowed to enroll this study.

4.3 Justification for Dose

The IgG dosing regimen for TAK-771 will be the same as the subject's previous monthly equivalent IVIG dose or SCIG when administered at a dosing frequency of every 3 or 4 weeks.

In the pivotal PID Phase 3 study (Study 160603), the geometric mean (GM) area under the curve over a dosing interval ($AUC_{0-\tau}$) ratio (SC/IV) for IgG was found to be 93.3%, with a 90% confidence interval (CI) of 91.4% to 95.2%. The median $AUC_{0-\tau}$ (normalized to a 1-week dosing interval) was similar after SC vs IV administration (90.5 vs 93.9 gx days/L). As expected with SC administration, the median C_{max} was lower after SC than after IV infusion (15.5 g/L vs 21.9 g/L) while the median time to reach C_{max} was longer (T_{max}: 5.0 vs 0.1 days). Clearance (or apparent clearance for SC administration) and trough concentration (C_{min}) after SC infusion were similar to the values calculated after IV infusion. The median ratio of IgG trough levels for TAK-771 was 98.5% (95% CI: 93.4%; 102.5%).

Dose conversion factor will not be applied since comparable exposure has been demonstrated between TAK-771 and IVIG at similar dose levels in previous studies; that is, subjects who has been receiving IVIG and entering the study will receive the same IgG monthly equivalent dose as their own pre-study IVIG treatment regimen that was effective in maintaining the subject's PID conditions.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 43 weeks. The study will be completed in approximately 2 years.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s).

All AEs/SAEs which had been reported until EOS/Early termination visit will be followed until resolution, medically stabilized, or 30 days after EOS/Early termination visit, whichever comes first

4.5 Sites and Regions

The study will be conducted at approximately 10 to 15 sites in Japan.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written and/or electronic 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.

1. Be a Japanese person.
2. Subject must have a documented diagnosis of a form of primary humoral immunodeficiency involving antibody formation and requiring gammaglobulin replacement, as defined according to the IUIS Committee 2017 (Picard et al., 2018). The diagnosis must be confirmed by the Medical Director prior to TAK-771 treatment.
3. Subject is 2 years or older at the time of screening/enrollment.
4. Written and/or electronic informed consent is obtained from either the subject or the subject's legally authorized representative prior to any study-related procedures and study product administration. If a subject is <18 years of age, written and/or electronic informed consent should also be obtained from the subject's legally authorized representative in addition to written informed assent by a subject if appropriate.
5. Subject has been receiving a stable clinical dose of IVIG or cSCIG, which is equivalent to approximately 200 to 600 mg/kg body weight per 3 to 4 week period for IVIG and approximately 50 to 200 mg/kg body weight per week for cSCIG based on the description in the package insert, consistently over a period of at least 3 months prior to screening, or Subject has been receiving of TAK-664 with fixed dose and dosing frequency at least 3 months prior to enrollment. That is, subject is about to complete Study TAK-664-3001 or participating in Study TAK-664-3002.
6. Subject who has been receiving IVIG or cSCIG had all serum trough levels of IgG ≥5 g/L within 1 month prior to the screening/enrollment.
7. Serum trough levels at screening/enrollment meet one of the following:
   a. IVIG-treated or cSCIG-treated subjects
      Subject who had serum trough levels of IgG ≥5 g/L at the last 2 points in screening procedure before the first administration of TAK-771.
   b. TAK-664-treated subjects
      Subject who had serum trough levels of IgG ≥5 g/L at the last 2 points in TAK-664 studies before the first administration of TAK-771.

8. Subject is willing and able to comply with the requirements of the protocol.
9. Subject is willing and able to comply with use of digital tools and applications.

5.2 Exclusion Criteria

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

1. Subject has a known history of or is positive at screening/enrollment for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2
   For subjects who are switching from TAK-664 studies, the eligibility will be reconfirmed after result of the specialty test conducted at Week 1 become available.
2. Abnormal laboratory values at screening/enrollment meeting any one of the following criteria (abnormal tests may be repeated once to determine if they are persistent):
   a. Persistent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN) for the testing laboratory*NOTE 2
   b. Persistent severe neutropenia (defined as an absolute neutrophil count [ANC] $\leq 500/mm^3$) *NOTE 2
3. Subject has presence of renal function impairment defined by eGFR <60 mL/min/1.73m^2. *NOTE 2
4. Subject has been diagnosed with, or had a malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) unless the disease-free period prior to screening exceeds 5 years.
5. Subject is receiving anti-coagulation therapy or has a history of thrombotic episodes (including deep vein thrombosis, myocardial infarction, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening/enrollment or a history of thrombophilia.
6. Subject has abnormal protein loss (protein losing enteropathy, nephrotic syndrome)
7. Subject has anemia that would preclude phlebotomy for laboratory studies according to standard practice at the site.
8. Subject has an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IVIG, SCIG, and/or Immune Serum Globulin infusions
9. Subject has immunoglobulin A (IgA) deficiency (serum IgA less than 0.07 g/L) and history of hypersensitivity, or history of confirmed anti-IgA antibodies, or both.

10. Subject is on preventative (prophylactic) systemic antibacterial antibiotics at doses sufficient to treat or prevent bacterial infections, and cannot stop these antibiotics at the time of screening/enrollment[*NOTE 3].
11. Subject has active infection and is receiving antibiotic therapy for the treatment of infection at the time of screening/enrollment[*NOTE 3] or had a serious bacterial infection within the 3 months prior to screening/enrollment
12. Subject has a bleeding disorder, or a platelet count less than 20,000/μL[*NOTE 2], or in the opinion of the investigator, would be at significant risk of increased bleeding or bruising as a result of SC therapy.
13. Subject has total protein >9 g/dL[*NOTE 2] or myeloma, or macroglobulinemia (IgM) or paraproteinemia.
14. Subject has a known allergy to hyaluronidase
15. Women of childbearing potential who meet any one of the following criteria:
    a. Subject presents with a positive pregnancy test.
    b. Subject is breast-feeding.
    c. Subject intends to begin nursing during the course of the study.
    d. Subject does not agree to employ adequate birth-control measures (e.g. intrauterine device, diaphragm or condom [for male partner] with spermicidal jelly or foam, or birth-control pills/patches) throughout the course of the study. See Section 5.4.1 and Appendix 4 for adequate birth-control measures.
16. Subject has participated in another clinical study and has been exposed to an investigational product or device within 30 days prior to study enrollment, (exception: TAK-664 studies).
17. Subject is scheduled to participate in another non-observational (interventional) clinical study involving an investigational product or device during the course of the study.
18. Subjects who experiences clinically significant AEs in TAK-664 studies and it may worsen by participating in this study
19. Subject has severe dermatitis that would preclude adequate sites for safe product administration

*NOTE 2: For subjects who are switching from TAK-664 studies, the latest laboratory data obtained in the TAK-664 studies will be used to determine the eligibility.

*NOTE 3: The exceptional use of antibiotics is allowed. See Section 6.8.4 for the details.

5.3 Restrictions

Not applicable

5.4 Reproductive Potential

There are limited data available on the use of TAK-771 during pregnancy. Study 161301 (pregnancy registry) reported that TAK-771 given during pregnancy was not associated with labor and delivery complications. Two minor birth defects (cleft lip without cleft palate and talipes calcaneovalgus) were reported in 2 infants in the TAK-771 Arm and assessed as unrelated with treatment. Please see the IB addendum for the detailed information.

There are limited safety data available on the use of TAK-771 in breast-feeding women.

The effects of TAK-771 on fertility have not been established.

5.4.1 Female Contraception

Sexually active females of childbearing potential should use an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If used, hormonal contraceptives should be administered according to the package insert. Any female of childbearing potential who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 30 days following the last dose of investigational product.

Female subjects should be either:

- Premenarchal and either Tanner stage 1 or less than age 9 years,
- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years),
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of childbearing potential with a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test conducted at screening for subjects switching from IVIG or cSCIG treatment, and at pre-infusion at Week 1 for subjects switching from TAK-664 studies. If subjects switching from TAK-664 studies have a result of pregnancy test conducted at EOS/Early termination visit, it can be used to determine the pregnancy. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the Week 1, plus condoms. Note: If subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days. See Appendix 4 for contraceptive guidance.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is TAK-771 (10% IGI with rHuPH20).

Immune Globulin Infusion 10% (Human) - 10% IGI

The 10% IGI component of TAK-771 manufactured from human plasma by employing a modified Cohn-Oncley cold alcohol fractionation process, as well as cation and anion exchange chromatography. Screening against potentially infectious agents (such as HIV, hepatitis A virus [HAV], HBV, HCV, hepatitis E virus [HEV], and Parvovirus B19 [B19V]) begins with the donor selection process and continues throughout plasma collection and preparation. To further improve the margin of safety, three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent treatment, nanofiltration, and incubation at a low pH and elevated temperature in the final formulation.

The finished medicinal product, 10% IGI, is a purified, functionally intact IgG solution formulated with 0.25 M glycine (for a stabilizing effect) at 10% w/v protein concentration and a pH of 4.6 to 5.1.

The preparation is an isotonic solution containing approximately 100 mg of protein per mL, of which at least 98% is IgG with an IgG subclass distribution representative of native human plasma. The product contains no preservatives.

Recombinant Human Hyaluronidase - rHuPH20

rHuPH20 drug product is supplied as a sterile, clear, colorless, ready-for-use solution in the label strength of 160 U/mL, containing the additional excipients sodium chloride, sodium phosphate, human albumin, ethylenediaminetetraacetic acid disodium, calcium chloride, and sodium hydroxide and/or hydrochloric acid added for pH adjustment. rHuPH20 solution contains 0.1% human albumin with an approximate pH of 7.4 and osmolality of 290 to 350 mOsm. rHuPH20 solution is preservative-free. rHuPH20 solution provides for high margins of safety with respect to viruses, due to comprehensive virus testing at the Master Cell Bank, Working Cell Bank and bulk harvest stage, effective virus reduction during the purification process, and the use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process.

Additional information is provided in the current IB.

6.2 Non-investigational Product

For subjects switching from IVIG or cSCIG treatment, the IVIG or cSCIG product administered during screening period is an approved IG product procured locally, which is administered as per local product label. Additional information is provided in the appropriate product package label. The IVIG or cSCIG will not be managed by interactive response technology (IRT) and will not be provided by the sponsor as investigational product.

The IVIG or cSCIG used in screening period will be the same IG preparation being administered to the patient prior to enrollment in the study and will be sourced by the sites. The lot number of IVIG or cSCIG used for the study should be recorded in electronic case report form (eCRF) by clinical site personnel.

6.3 Administration of Investigational Product

6.3.1 Interactive Response Technology for Investigational Product Management

This is an open-label, non-controlled study where all subjects will be enrolled to receive TAK-771. Individual subject numbers are automatically assigned to all subjects via the IRT as they consent to take part in the study. Within each study site (numbered uniquely within a protocol), the subject number is assigned according to the sequence of subject presentation for study participation.

Interactive response technology will be used for study drug supply management, inventory management, supply ordering, study drug expiration tracking, temperature excursion reporting, and return of study drug.

Details for the handling of study drug will be described in the pharmacy manual.

6.3.2 Allocation of Subjects to Treatment

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

Individual subject treatment is automatically assigned by the IRT. Subjects will be assigned to receive the next available medication ID number allocated to each study site. The medication ID number will be entered onto the eCRF.

6.3.3 Dosing

Subcutaneous infusion of rHuPH20 solution will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution at the same location. The recommended site(s) for SC infusion are the middle to upper abdomen and thighs.

If more than one site are used, the infusion sites should be rotated by choosing opposite sides of the body. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localized infection.

rHuPH20 and 10% IGI solutions for administration must be prepared according to separate written procedures which will be provided in infusion manuals.

6.3.3.1 Dosing in Epoch 1 (Ramp-up Period)

This study employs a dose ramp-up schedule until the subject's full-dose is reached in order to increase the SC infusion volume gradually. Dosing during ramp-up period for tolerated doses are shown in Table 6 for 4-week dosing interval regimen and Table 7 for 3-week dosing interval regimen.

Table 6 Subjects with 4-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/4 of full dose
Week 2	2nd. infusion	1/2 of full dose
Week 4	3rd. infusion	3/4 of full dose
Week 7 and the following 4-week intervals	4th. infusion and the following infusions	full dose

Table 7 Subjects with 3-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/3 of full dose
Week 2	2nd. infusion	2/3 of full dose
Week 4 and the following 3-week intervals	3rd. infusion and the following infusions	full dose

Subjects who are switching from IVIG treatment (every 3 or 4 weeks):

The first administration of investigational product will take place 1 week after the last IVIG administration at screening. If the first administration of investigational product is tolerated, each week interval will be increased by 1 week until the planned dosing intervals (every 3 or 4 weeks).

Investigational product should be administered with the same dose of IgG and frequency (every 3 or 4 weeks) as previous IVIG treatment, after the initial ramp-up.

Subjects who are switching from cSCIG treatment (Weekly):

The first administration of investigational product will take place 1 week after the last cSCIG administration at screening. If the first administration of investigational product is tolerated, each week interval will be increased by 1 week until the planned dosing intervals (every 3 or 4 weeks).

The dosing interval (every 3 or 4 weeks) can be chosen by investigator considering subject preference and tolerability. The IG dose should be calculated on the basis of weekly equivalents from cSCIG treatment, that is to say the 3- or 4-weeks investigational product dose is calculated by multiplying cSCIG weekly dose by 3 or 4.

Subjects who are switching from TAK-664 studies (weekly or bi-weekly):

The first administration of investigational product will take place 1 week (for subjects switching from TAK-664 weekly dosing) or 2 weeks (for subjects switching from TAK-664 bi-weekly dosing) after the last TAK-664 administration in the TAK-664 studies, the first interval should be the same as the TAK-664 treatment. If the first administration of investigational product is tolerated, each week interval will be increased by 1 week until the planned dosing intervals (every 3 or 4 weeks). The dosing interval (every 3 or 4 weeks) can be chosen by investigator considering subject preference and tolerability. The IG dose should be calculated on the basis of weekly equivalents from TAK-664 treatment, that is to say the 3- or 4-weeks investigational product dose is calculated by multiplying TAK-664 weekly dose by 3 or 4.

6.3.3.2 Dosing in Epoch 2

6.3.3.2.1 rHuPH20

Dose: 80 U/g IgG (rHuPH20 drug product: 160 U/mL)

Dosing Frequency: Same as 10% IGI

Mode of Administration: For the initial 2 administrations in the study, infuse rHuPH20 solution at 60 to 120 mL/h/site as tolerated (or a total of 120 to 240 mL/h at 2 infusion sites or 180 to 360 mL/h at 3 infusion sites). For subsequent administrations, rHuPH20 solution infusion rate may be increased as tolerated by the subject and at the discretion of the investigator, but not to exceed 300 mL/h/site (or not to exceed a total of 600 mL/h at 2 infusion sites or 900 mL/h at 3 infusion sites).

6.3.3.2.2 10% IGI

Dose: The total amount of IgG administered per month will be maintained as equivalent to that of previous IG treatment. The dose will be adjusted, if needed, to maintain an IgG trough level ≥5 g/L.

Dosing Frequency: Every 3 or 4 weeks after the initial ramp-up. It should be the same as the previous IVIG treatment for subjects switching from IVIG treatment and can be chosen by the investigator considering subject preference and tolerability.

Mode of Administration: SC infusion, to be administered via an infusion pump (Sapphire™ Multi-Therapy, See Section 6.9) at 1, 2, or 3 infusion sites per infusion day.

Maximum Infusion Rate

For the initial 2 infusions in the study, the maximum infusion rate should be 80 mL/h and 240 mL/h per site, for subjects <40 kg and ≥40 kg body weight, respectively.

Step-wise increases are suggested in subsequent infusions with rate increases of up to 300 mL/h per infusion site (or up to a total of 600 mL/h over 2 sites if bifurcated needle set is used, or up to a total of 900 mL/h if trifurcated needle set is used) for subjects weighing ≥40 kg. For subjects weighing <40 kg, infusion rates of up to 160 mL/h per infusion site (or up to a total of 320 mL/h and 480 mL/h over 2 and 3 sites if bifurcated and trifurcated needle set is used, respectively).

Table 8. 10% IGI Infusion Rates

	First 2 Infusions		Subsequent 2 or 3 Infusions	
	subjects <40 kg	subjects ≥40 kg	subjects <40 kg	subjects ≥40 kg
Intervals	**Rate per site**	**Rate per site**	**Rate per site**	**Rate per site**
5 to 15 minutes	5 mL/h	10 mL/h	10 mL/h	10 mL/h
5 to 15 minutes	10 mL/h	30 mL/h	20 mL/h	30 mL/h
5 to 15 minutes	20 mL/h	60 mL/h	40 mL/h	120 mL/h
5 to 15 minutes	40 mL/h	120 mL/h	80 mL/h	240 mL/h
Remainder of infusion	80 mL/h	240 mL/h	160 mL/h	300 mL/h

Volume of Infusion Per Site

10% IGI solution may be administered at a volume of up to 600 mL per infusion site for subjects ≥40 kg or up to 300 mL per infusion site for subjects <40 kg, as tolerated. On a given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg.

If a subject's total IgG dose on a given day exceeds 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg, or exceeds the SC maximum infusion volume the subject can tolerate, the TAK-771 dose may be administered over multiple days as divided doses with 48 to 72 hours between doses (eg, Day 1 and Day 3 of a given infusion cycle) to allow absorption of infusion fluid at infusion site(s).

6.3.3.2.3 Location of the Infusion Procedures

Initial SC infusions (during the ramp-up period and, at a minimum, the first full-dose infusion) will be administered at the study site, and to provide training to the subject (and/or, as applicable, a caregiver who may assist the subject with self-administration) on self-infusion procedures. At the investigator's discretion, the remainder of the SC infusions may take place at the study site or other suitable location. Self-administration of SC infusions at home may be allowed at the discretion of investigator after the training, evaluation and verification of subject's (and/or caregiver's) proficiency in self-infusion procedures are completed.

6.3.3.2.4 Monitoring Subject Treatment Compliance

Subcutaneous infusions will be administered by an appropriately trained healthcare professional (eg, infusion nurse) or, if applicable, can be administered by the subject and/or a caregiver. Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee, must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions at sites, home or other suitable locations. A healthcare professional (eg, infusion nurse) may be present to observe the subject's self-administration. A proficiency checklist will be completed by the investigator/designee once training begins and until the subject's (and/or caregiver's) proficiency is demonstrated. The proficiency check will not be required when the subject has self-administration of SC infusions at home.

6.3.4 Dose Modification

The dose (in milligrams IgG per kg body weight) should remain stable throughout the study. In order to maintain the same dose in mg/kg when there has been an increase in body weight (kg), it will be necessary to increase the absolute dose (in g or mg) administered.

The dose of TAK-771 should be based on the most current weight measurement (taken at a site visit) - if the subject´s weight has increased by more than 5% compared to that the current dose of TAK-771 was determined based on, the absolute dose (in g or mg) should be adjusted at the next possible infusion. If there is a weight decrease, regardless of the percentage, the dose of TAK-771 should not be changed.

Serum trough levels of IgG ≥ 5 g/L are targeted to be maintained throughout the study. If levels fall below 5 g/L, the subject's dose must be adjusted to maintain minimum trough levels of 5 g/L. If the dose is adjusted because IgG levels are below 5 g/L, a trough level should be reevaluated at the next infusion and the dose should be readjusted if necessary. The dose in mg/kg may be increased during the study if clinically indicated (e.g. increased incidence of infections, low IgG trough level [<5 g/L]) at the investigator´s discretion.

If such an event arises, the sponsor should be informed, the rationale for such dose adjustment should be documented in the patient file, and the adjusted dose should be entered in the eCRFs.

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

6.4.1 Labeling

The product will be labeled according to the regulatory requirements for clinical studies.

6.4.2 Packaging

rHuPH20 drug product (160 U/mL) will be supplied as a clear, colorless, ready-for-use sterile liquid preparation in single-use glass vials. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

10% IGI will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials. 10% IGI is a clear or slightly opalescent and colorless or pale yellow solution. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

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

6.4.3 Storage

TAK-771 must be stored under refrigerated conditions (2° to 8°C). Do not freeze the product. Do not use if expiration date is exceeded.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy. The pharmacist will enter the unique subject identifier on the investigational product vial/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation.
The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.5 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol. This delegation must be documented in the applicable study delegation of authority form.

The site may use an alternative method for dispensing. If permitted by country or local regulations and ethics committees (ECs), the investigational product can be shipped from the site directly to the subject's home address via courier. Subjects must be provided with instructions on how to receive, store, and ultimately return investigational/sponsor-supplied treatments.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer/dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered/dispensed medication will be documented in the subject's source and/or other investigational product record. The investigator is responsible for ensuring the retrieval of all study supplies from subjects. Due to the health/safety concerns with returning the investigational product container, the investigator must request that subjects keep the empty investigational product packaging after use and return it for drug accountability purposes.

No investigational product stock or returned inventory from a study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated contract research organization [CRO]). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IRT) do not require a shipment form. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.6 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the investigational product, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

6.7 Subject Compliance

For study procedures that are to be performed under the direct supervision of the investigator/healthcare professional (eg, infusion nurse) at the study site or infusion center, no separate procedures will be used to monitor subject compliance.

The procedure to monitor treatment compliance is provided in Section 6.3.3.2.4.

6.8 Prior and Concomitant Therapy

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 30 days prior to signing of informed (e)Consent (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact must be recorded in the subject's source document and appropriate eCRF.

6.8.1 Prior Treatment

Prior treatment includes all treatment taken within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) of the date of signing of informed (e)Consent until the date of the first dose of investigational product. For subjects switching from TAK-664 studies, the records of all treatment (including investigational product the subject received) that were collected during the TAK-664 studies will be used in this study. Prior treatment information must be recorded in the subject's source document and appropriate eCRF.

6.8.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and study completion/termination, inclusive. Concomitant treatment information must be recorded in the subject's source document and appropriate eCRF.

6.8.3 Permitted Treatment

Treatments not listed in Section 6.8.4 are considered allowable.

6.8.4 Prohibited Treatment

The following medications are not permitted during the course of the study:

- Requirement for all antibiotic therapy must be documented as an AE. Prophylactic treatment with systemic antibacterial antibiotics is not allowed during the study, with 3 exceptions shown in below.
  - Use of antibiotics for a period of up to 72 hours if required due to trauma or a scheduled procedure
  - Use of anti-viral/fungal/protozoal drug for infections which are not treated by IG (e.g trimethoprim/sulfamethoxazole twice a week)
  - Low-dose continuous administration of macrolides which are used for anti-inflammatory effects (e.g. For adults (≥15 years old): erythromycin 400 mg/day; clarithromycin 200 mg/day, For children (<15 years old): erythromycin 10 mg/kg/day; clarithromycin 5 mg/kg/day)
  - The use of systemic prophylactic antibacterial antibiotics by a subject will be considered a protocol deviation (except for trauma or a scheduled procedure as described above). However, prophylaxis for viral, fungal or protozoal infections (e.g. trimethoprim/sulfamethoxazole twice a week for pneumocystis) which are not treated by IG can be used and should be recorded as concomitant medication.
- Other IgG products after first exposure to study drug
- Hyper immune serum
- Immunosuppressive drugs following transplantation
- For subjects who are switching from IVIG treatment:
  Subjects who are prone to AEs occurring in conjunction with infusions of IVIG products are often pre-medicated with antihistamines, antipyretics, and/or steroids. In this study, however, pre-medications should be avoided, if possible, for both IV and SC infusions. Subjects should only receive pre-medication (acetaminophen/non-steroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and antihistamines) prior to IV infusions if the same AE(s) were seen prior to the study with 2 or more IVIG preparations. In addition, should an AE occur during or following 2 or more infusions during this study, pre-medications can be used for subsequent IV or SC infusions. The use of these medications must be recorded in the concomitant medication record. Reactions that occur during the IV infusions do not necessitate automatic pretreatment for the SC infusions.

- For subjects who are switching from cSCIG treatment or TAK-664 studies:
  In this study, subjects should not receive pre-medication for SC infusions unless an adverse reaction of at least moderate severity, not resolving with a reduction in the infusion rate, occurs during or after at least 2 infusions. Should this occur, subjects may be pretreated with antipyretics, corticosteroids or antihistamines at the discretion of the investigator. Topical local anesthetics may be used if the needle insertion was intolerable in prior infusions. Subjects who have a history of using topical anesthetics may use these topical anesthetics for SC infusions. The use of such pre-medications must be recorded on the concomitant medication record.

6.9 Devices Used in Clinical Trial

In this study, 'Device Used in Clinical Trial' is defined as below:

Device name	SapphireTM Multi-Therapy
Type	Infusion pump
Manufacturer	Q Core Medical Ltd.

6.9.1 Marketing approval

Sapphire Multi-Therapy has not yet been approved for marketing in Japan.

Administration of TAK-771 using Sapphire Multi-Therapy has already been evaluated for the compatibility with the drug and the mechanical suitability by Sponsor in Europe and the US where TAK-771 had been approved and marketed.

6.9.2 Indications for Use

Sapphire Multi-Therapy will be used for administration of TAK-771 and to adjust the administration rate and volume of TAK-771 for SC infusion.

6.9.3 Usage Instructions and Warnings

For the usage instructions and warnings of Sapphire Multi-Therapy, see the User Manual (Q Core Medical, 2021) that will be provided to investigators.

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 evaluation listed for EOS/Early termination visit will be performed as completely as possible. 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.

Subjects who prematurely discontinue the study will not be replaced.

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.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other

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.

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

8.1 Study Periods

The study consists of signing informed (e)Consent, screening period (up to 13 weeks), treatment period (Epoch 1: 3 to 6 weeks of dose ramp-up period, Epoch 2: 12 weeks of dose adjustment period and 12 weeks of trough evaluation period), and EOS/Early termination visit. Tabulated schedules of study procedures are provided for 4-week dosing interval regimen in Table 1 (for subjects switching from IVIG or cSCIG) and Table 2 (for subjects switching from TAK-664), and for 3-week dosing interval regimen in Table 3 (for subjects switching from IVIG or cSCIG) and Table 4 (for subjects switching from TAK-664). Study assessments are detailed in Section 8.2.

8.1.1 Screening

Any subject who provides informed (e)Consent /assent (i.e., signs and dates the informed consent form [ICF]/assent) is considered a subject in the study. If a subject is <18 years of age, the informed (e)Consent should also be signed and dated by the subject's legally authorized representative in addition to written and/or electronic informed assent by a subject if appropriate.

The written and/or electronic informed consent for all procedures and assessments for the conduct of the study must be obtained prior to any study-related procedure.

Every single subject who enters the study will get a unique subject identification code.

Subjects who are switching from IVIG or cSCIG treatment:

Subjects will be screened up to 13 weeks prior to the initial dose of investigational product. Subjects will continue to receive their own IG treatment at the same dose and dosing frequency as prescribed prior to their entry into this study.

The following procedures and assessments will be performed during the screening period:

- Availability of signed informed (e)Consent
- Assessment of eligibility
- Demographic information
- Body height and weight
- Medical and Medication history
- Physical examination
- Vital signs (see Section 8.2.4.4)

- Clinical laboratory assessments (see Table 9 for 4-week dosing interval regimen and Table 11 for 3-week dosing interval regimen)
- Serum IgG
  Immunoglobulin G trough levels will be measured at least 2 points. The time interval between measurement of IgG trough levels should be at least 3 weeks. The last 2 values measured in the screening period, which become available before the initial administration of investigational product, will be used to assess the eligibility.
- Specialty tests
- Concomitant medication and non-drug therapies
- Adverse events
- Pregnancy test

Subjects who are switching from TAK-664 studies:

Subjects who are switching from TAK-664 studies will directly move on to the treatment period without entering the screening period. The eligibility will be determined based on the data including the latest laboratory data and IgG trough levels collected in the TAK-664 studies. For IgG trough levels, the latest 2 values measured in the TAK-664 studies and available at the enrollment will be used to assess the eligibility.

Screen failure

A screen failure is a subject who has given informed (e)Consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered investigational product(s). The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All relevant screening data will be collected and reported, regardless of screening outcome.

Subjects who fail to meet eligibility criteria may be re-screened; they will be assigned a different subject identification code at re-screening.

8.1.2 Treatment Period

Eligible subjects will move on to the treatment period and receive investigational product.

8.1.2.1 Epoch 1 (Ramp-up Period)

Investigational product administration will be started with the ramp-up infusion.

The following procedures and assessments will be performed at the study site before the investigational product is administered.

- Physical examination
- Body weight
- Vital signs (see Section 8.2.4.4)
- Clinical laboratory assessments (Week 1 only, see Table 9 and Table 10 for 4-week dosing interval regimen and Table 11 and Table 12 for 3-week dosing interval regimen)
- Serum IgG (Week 1 only)
- Anti-rHuPH20 antibody (Week 1 only)
- Retention samples (Week 1 only)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries
- Quality of life and treatment satisfaction assessments (see Section 8.2.5.3)
- Healthcare Resource Utilization (see Section 8.2.5.4)
- Investigational product treatment
  Collection of Infusion related data e.g.: lot number, start and stop time, infusion site, maximum infusion rate achieved (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

For subjects who are switching from TAK-664 studies, the following procedures and assessments will also be performed at Week 1 prior to the initial dose of investigational product. The assessments for the Week 1 can be combined with the EOS/Early termination visit assessments in TAK-664 studies, and data collected in the TAK-664 studies can be used if available:

- Availability of signed informed (e)Consent
- Assessment of eligibility
- Demographic information
- Body height
- Medical and Medication history
- Specialty tests (the eligibility will be reconfirmed after the result become available)
- Pregnancy test

8.1.2.2 Epoch 2 (24-week Treatment Period)

Investigational product will be administered subcutaneously at 3- or 4-week intervals after the ramp-up. The number of study site visits during the treatment period will vary across subjects, depending on their dosing intervals of investigational product

The following procedures and assessments will be performed at the study site (detailed scheduled provided in Table 1 and Table 2 for 4-week dosing interval regimen and in Table 3 and Table 4 for 3-week dosing interval regimen):

- Physical examination
- Body weight
- Vital signs (see Section 8.2.4.4)
- Clinical laboratory assessments (see Table 9 and Table 10 for 4-week dosing interval regimen and Table 11 and Table 12 for 3-week dosing interval regimen)
- Serum IgG
- Anti-rHuPH20 antibody (only at Week 19 for 4-week dosing interval regimen and Week 16 for 3-week dosing interval regimen)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries
- Quality of life and treatment satisfaction assessments (see Section 8.2.5.3)
- Healthcare Resource Utilization (see Section 8.2.5.4)
- Investigational product treatment
  Collection of Infusion related data e.g.: lot number, start and stop time, infusion site, maximum infusion rate achieved (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.
- Self-administration proficiency (See Section 6.3.3.2.4)

8.1.3 End-of-Study/Early Termination Visit

All subjects completing or exiting the study should complete the EOS/Early termination procedures. The visit will be 21 days after the last dose for 3-week dosing intervals and 28 days after the last dose for 4-week dosing intervals.

The following procedures and assessments will be performed at the study site (see Table 1 and Table 2 for 4-week dosing interval regimen and Table 3 and Table 4 for 3-week dosing interval regimen):

- Physical examination
- Body weight
- Vital signs (see Section 8.2.4.4)
- Clinical laboratory assessments (see Table 9 and Table 10 for 4-week dosing interval regimen and Table 11 and Table 12 for 3-week dosing interval regimen)
- Serum IgG
- Anti-rHuPH20 antibody (Testing is not required if the subject enroll the extension study)
- Concomitant medication and non-drug therapies
- Adverse events
- Collection/review of patient diaries
- Quality of life, treatment satisfaction and treatment preference assessments (see Section 8.2.5.3)
- Healthcare Resource Utilization (see Section 8.2.5.4)

8.1.4 Follow-up Period

There is no follow-up period.

8.1.5 Additional Care of Subjects After the Study

An extension study is planned, to offer continuation of treatment and for the additional collection of treatment-related data. The subjects who complete the treatment period can be enrolled in the extension study.

8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

8.2.1.1 Demographics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of investigational product.

8.2.1.2 Medical and Medication History

Medical and medication history will be collected and recorded in the subject's source documents and appropriate eCRF.

At screening, the subject's medical history will be described for the following body systems or surgery, and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) prior to signing of informed (e)Consent until study completion/termination will be recorded on the concomitant medications and non-drug therapies case report forms (CRFs). For subjects switching from TAK-664 studies, the records of all treatment (including investigational product the subjects received) that were collected during the TAK-664 studies will be used as prior treatment in this study.

8.2.2 Pharmacokinetics

8.2.2.1 Serum IgG Trough Levels

Serum IgG trough levels (total serum levels of IgG and IgG subclasses IgG1, IgG2, IgG3, and IgG4) will be determined according to the schedule described in Table 9 through Table 12 in Appendix 2 by using standard assay methods for the determination of total IgG concentration and IgG subclasses.

The blood drawing for the IgG trough level determination will always take place before the infusion is administered.

8.2.2.2 Pharmacokinetic Profiles

PK parameters for total serum levels of IgG and for IgG subclasses (IgG1, IgG2, IgG3, and IgG4) will be evaluated in a subset of 5 to 7 subjects aged 12 years and older.

The parameters to be assessed may include but not limited to: C_{max}, T_{max}, AUC, half-life, CL/F, V_z/F, and C_{min}.

For a schedule of PK testing, see Table 13 and Table 14 in Appendix 2 for 4-week and 3-week dosing interval regimen, respectively. Subjects who divided the dosing in multiple days will not be eligible for PK profile sampling.

8.2.2.3 Specific Antibodies

Specific antibody tests (quantitative method) to Clostridium tetani toxoid, HIB and HBV will be performed at Week 1, PK troughs (just before infusion), and the EOS/Early termination visit. The test at PK troughs (just before infusion) is not required for subjects who are not included in the PK profile assessment.

For a schedule of specific antibody testing, see Table 9 through Table 12 in Appendix 2.

8.2.3 Efficacy

8.2.3.1 Acute Serious Bacterial Infection Rate

Infections will be reported as AEs and the number and types of infections will be determined. Acute serious bacterial infections will include bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that are caused by a recognized bacterial pathogen. The diagnostic criteria for ASBIs are included in Appendix 5.

The ASBI rate will be calculated as the mean number of ASBIs per subject per year.

8.2.3.2 Infections

1. The annual rate of all infections per subject.
   All infections will be reported as AEs and the number and types of infections will be determined.
2. Days not able to attend school/work or to perform normal daily activities due to illness/infection.
   Days not able to attend school/work or to perform normal daily activities due to illness/infection, will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.
3. Days on antibiotics
   Days on antibiotics will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.
4. Number of hospitalizations due to illness/infection and length of stay (in days)
   Admissions to a hospital as an inpatient and the number of days in hospital will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.
5. Number of acute (urgent or unscheduled) physician visits due to illness/infection
   Acute (urgent or unscheduled) physician visits due to illness/infection, will be collected using diaries or other source data options throughout the study and will be transcribed to eCRFs.

8.2.4 Safety

8.2.4.1 Physical Examination

At screening and subsequent scheduled study visits at the site (as described in Section 1.3, Section 8.1.1 and Section 8.1.2), a physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening visits, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease (described in Appendix 3), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

8.2.4.2 Body Height and Weight

Body height will be measured at screening and recorded in the subject's source documents and appropriate eCRF.

Body weight will be measured at each screening and study visits including the EOS/Early termination visit, and recorded in the subject's source documents and the appropriate eCRF.

8.2.4.3 Adverse Events

At each screening and study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed (e)Consent is signed. Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.4.4 Vital Signs

Vital signs include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Blood pressure measurements will be taken after subjects remain sitting in an upright position for at least one minute.

Vital signs will be measured at each screening and study visits including the EOS/Early termination visit. For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken once per administration, but will be recorded multiple times if an AE occurs. When subjects have self-infusion at home and an AE occurs, subjects (and/or caregivers) should measure vital signs by themselves and record the values on the subject diary.

Guidance for self-measurement and documentation of vital signs will be given to subjects (and/or caregiver) by the investigator/designee.

Vital sign values are to be recorded on the appropriate eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

The investigator will assess whether a change from baseline (baseline is defined as the last value before the initial dose) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.2.4.5 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. 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. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

A complete list of the clinical laboratory tests to be performed is provided in Appendix 2.

8.2.4.5.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell {WBC} count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. In addition, ANCs will be determined by laboratory calculation.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, serum total bilirubin, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine, creatinine phosphokinase (CPK), glucose, haptoglobin, lipase.

Blood will be obtained for assessment of hematology and clinical chemistry including IgG and IgG subclasses at baseline, distinct study visits, and at EOS/Early termination visit. IgG and IgG subclasses will also be measured for PK purposes. This will only be performed in subjects aged 12 years and older. For a schedule of laboratory test blood drawings, see Appendix 2.

These assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, processed through a central laboratory.

8.2.4.5.2 Anti-rHuPH20 Antibodies

Blood samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected at baseline, in the mid of the study and, if subject is not enrolling the extension study, at EOS/Early termination visit. For a schedule of blood sample drawings, see Appendix 2. Blood samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected and processed according to directions provided in the laboratory manual. At each collection timepoint, plasma samples will be collected into separate tubes labeled for binding antibodies and neutralizing antibodies. All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection assay (also known as the Screening and Confirmatory Binding Assay). Samples with binding antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies using a validated assay based on neutralization of rHuPH20 activity at the central laboratory.

The test results (titers, and binding or neutralizing) will be assessed for clinical significance by the investigator in the Electronic Data Capture (EDC) database but are not to be reported as AEs.

8.2.4.5.3 Immunogenicity Panel

At Week 1 predose, samples will be collected for the following tests to be conducted: 50% hemolytic complement activity of serum (CH50), serum complement component 3 (C3), serum complement component 4 (C4), Complement 1q (C1q) binding assay, and circulating immune complex (CIC) Raji cell assay.

All subjects will have anti-rHuPH20 antibody testing in pre-identified central laboratories for anti-rHuPH20 binding antibodies, and neutralizing antibodies will also be measured for subjects with an anti-rHuPH20 binding antibody titer ≥160 (Section 8.2.4.5.2). If a subject has a positive titer ≥10,000 at any time during the study, characterization of antibodies may be performed (include antibodies cross reacting with Hyal 1, 2, and 4). When there is more than one samples from a same subject has a positive titer ≥10,000, the cross-reactivity analyses for each subject at the peak titer sample will be analyzed, not more than a one-time point from the same subject in a given study. If the cross-reactivity data is going to be included in any interim Safety Data Analysis deliverable/milestone, the highest titer sample of the subject observed by the time of data cut-off for interim analysis will be used for analysis. At any time during the course of the study, subjects who have (a) two consecutive anti-rHuPH20 binding antibody titers of ≥1:160 which are elevated from the subject's baseline titers, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin or rHuPH20 will be asked to return to the study site as soon as possible to undergo an additional panel of testing.

That panel assesses CH50, serum C3, serum C4, C1q binding assay and CIC Raji cell assay.

For a schedule of laboratory test blood drawings, see Appendix 2.

8.2.4.5.4 Urinalysis

Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

For a schedule of laboratory test sample drawings, see Appendix 2. These assessments will be performed at the central laboratory.

A urine pregnancy test will be performed at the study site for females of childbearing potential as indicated in Appendix 2 (see also Sections 5.4 and Section 8.2.4.6).

8.2.4.5.5 Specialty Tests

Specialty tests include: HBsAg, PCR for HCV and PCR for HIV-1/2. For a schedule of laboratory test blood drawings, see Appendix 2. These assessments will be performed at the central laboratory.

Additional specialty tests may be performed if required to establish the etiology of an AE or of abnormal laboratory results, such as tests for HIV, HAV, HBV, HCV, HEV, or B19V (see also Section 8.2.4.5.7.2).

8.2.4.5.6 Hemolysis Tests

Scheduled tests will only be performed in subjects aged 12 years and older, in order to avoid multiple blood drawings in small children.

Tests for hemolysis:

1. If hemolysis tests are scheduled when routine hematology and clinical chemistry are already being assessed at the visit, then tests for hemolysis will consist of:
    - direct antiglobulin test (Coombs-test or AGT)
    - urine hemosiderin
2. If hemolysis tests are scheduled when routine hematology and clinical chemistry are Not being assessed at the visit, then tests for hemolysis will consist of:
    - direct antiglobulin test (Coombs-test or AGT)
    - urine hemosiderin
    - hemoglobin

- lactate dehydrogenase
- serum haptoglobin

In addition, these assessments (item 2 above) should be performed within 72 hours of being informed of the hemoglobin level if there is a decrease of hemoglobin ≥2 g/dL compared to the previous visit, unless there is a clear alternative explanation (which has been documented on the appropriate eCRF).

For a schedule of laboratory test blood drawings, see Appendix 2.

8.2.4.5.7 Assessment of Laboratory Values

8.2.4.5.7.1 Toxicity Grading Scale

The investigator will be asked to assess each abnormal laboratory value as described in Section 8.2.4.5.7.2. In addition, the sponsor will evaluate laboratory values for abnormalities according to a 5-point (Grades 0-4) toxicity grading scale provided in Appendix 6.

The Common Toxicity Criteria of the (Eastern Cooperative Oncology Group, 2006) will be used to grade the following laboratory values: ALP, ALT, AST, BUN, hemoglobin, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and WBC count. Grading for LDH will use the same thresholds as defined for ALT and AST. Sodium and potassium will be graded using the thresholds taken from the WHO toxicity grading system (World Health Organization, 2003).

8.2.4.5.7.2 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value (with the exception of total IgG, IgG subclasses and specific antibodies) is to be recorded on the laboratory form. For each abnormal laboratory value, the investigator will determine whether the value is also considered an AE (see definition in Appendix 3). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE CRF. If the abnormal value was not deemed an AE because it was due to a lab error, was due to a pre-existing disease (described in Appendix 3.1), was not clinically significant, was a symptom of a new/worsened condition already recorded as an AE, or was due to another issue that will be specified, the investigator will record the justification on the laboratory form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any positive seroconversion result for HIV, HAV, HBV, HCV, HEV, or B19V shall be re-tested and confirmed.

8.2.4.6 Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at screening for subjects switching from IVIG or cSCIG treatment, and at pre-infusion at Week 1 for subjects switching from TAK-664 studies; if pregnancy is suspected; or on withdrawal of the subject from the study. If subjects switching from TAK-664 studies have a result of pregnancy test conducted at EOS/Early termination visit in the TAK-664 studies, it can be used to determine the pregnancy; no need to repeat the test in this study.

All pregnancies are reported from the time informed (e)Consent is signed until EOS/Early termination visit. See Appendix 3.8 for the pregnancy reporting.

8.2.5 Other

8.2.5.1 Pharmacodynamics

Not applicable

8.2.5.2 Genetics

Not applicable

8.2.5.3 Disease Activity and Health-related Quality of Life

Paper questionnaire or electronic collection device will be used to capture the QoL/treatment satisfaction data.

8.2.5.3.1 Quality of Life

A QoL assessment will be performed at Week 1, 12 weeks after the ramp-up in treatment period (Week 19 for 4-week dosing interval regimen and Week 16 for 3-week dosing interval regimen), and at the EOS/Early termination visit.

Quality of life will be analyzed separately for the age groups of 2 to 7 years (PEDS-QL, observer: parent), 8 to 13 years (PEDS-QL, observer: subject), and 14 years and older (SF-36, observer: subject). Additionally, all subjects will complete the EQ-5D-3L Health Questionnaire, analyzed separately for the age groups: 2 to 11 years EQ-5D-3L (observer: parent) and 12 years and older EQ-5D-3L (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation. In the event that the language/age group is not available, the assessment in the closest language/age group will be used.

8.2.5.3.2 Treatment Satisfaction

Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be assessed at Week 1, 12 weeks after the ramp-up in treatment period (Week 19 for 4-week dosing interval regimen and Week 16 for 3-week dosing interval regimen), and at the EOS/Early termination visit.

Data will be analyzed separately for the age groups of 2 to 12 years (observer: parent) and 13 years and older (observer: subject). Age will be defined as the age at screening. The observer should remain constant for the duration of subject participation. In the event that the language/age group is not available, the assessment in the closest language/age group will be used.

8.2.5.3.3 Treatment Preference

Treatment preference will be assessed at the EOS/Early termination visit.

Treatment preference will be analyzed separately for the age groups of 2 to 13 years (observer: parent) and 14 years and older (observer: subject). Age will be defined as the age at screening.

8.2.5.4 Healthcare Resource Utilization

Days not able to attend school/work or to perform normal daily activities due to illness/infection, days on antibiotics, number of hospitalizations due to illness/infection and length of stay (in days) and number of acute (urgent or unscheduled) physician visits due to illness/infection will be collected as described in Section 8.2.3.2.

8.2.6 Volume of Blood to Be Drawn from Each Subject

The volume of blood to be drawn from each subject for laboratory assessments will be specified in the laboratory manual.

8.2.7 Retention of Bioavailability and Bioequivalence Testing Samples

Retention samples should be taken prior to the first infusion at Week 1. For subjects 12 years or older, approximately 2.5 mL serum and 2 mL plasma will be taken and stored frozen at –70°C or below at the central lab in the event further testing is needed. For children younger than 12 years of age, approximately 2 mL of plasma will be obtained.

8.2.8 Subject Diary

A subject diary will be provided to each subject at enrollment to record the following information throughout the study period:

- Occurrence of AEs (including infections). The investigator will provide guidance for the subject/caregiver regarding identification and documentation of AEs

- Concomitant medication use
- Days not able to attend school/work or to perform normal daily activities due to illness/infection
- Number of hospitalizations, indication for the hospitalization (infection or non-infection) and days hospitalized
- Number of acute physician visits (office and emergency room) due to infection or other illnesses

TAK-771 infusion related data should be recorded in the subject diary when subjects have self-administration of SC infusions at home. Vital signs self-measured should also be recorded in the subject diary when subjects have self-infusion at home and an AE occurs. The investigator will provide guidance for the subject/caregiver regarding self-measurement and documentation of vital signs. The subject diary will serve as a source record and remain at the study site. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment. Entries in the subject diaries will be transcribed or entered into the appropriate collection device. Any entry on the eCRF that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

8.2.9 Product Administration

TAK-771 infusion related data will be collected and recorded in the eCRF. The data to be collected includes but not limited to: lot number, start and stop time, infusion site, maximum infusion rate achieved (mL/h) and changed rate if there is, total infusion volume (mL), infusion completion, and the reason if infusion is not completed as planned.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The SAP will provide the statistical methods and definitions for the analysis of the PK, efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock. Specifications for the corresponding tables, figures, and listings (TFLs) will be provided separately, in the study TFL shells document.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513) version 9.4 or higher

9.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

No interim analysis, adaptive design, or data monitoring committee is planned for this study.

9.3 Sample Size and Power Considerations

The planned total sample size for this study is 15 subjects (enrolled).

Of the 15 subjects to be enrolled, 12 subjects are expected to complete treatment period of the study, assuming a dropout rate of 20%. Subjects who prematurely discontinue the study will not be replaced. The number of subjects expected to complete treatment period (12 subjects) is considered adequate for the evaluation of serum trough IgG levels, safety and tolerability, and efficacy of TAK-771, as well as for the assessment of disease activity and HRQoL.

This study is not designed for statistical hypothesis testing and therefore the sample size is not based on statistical considerations such as study power, but instead mainly on consideration of the small size of the Japanese patient population with PID, a group of rare diseases. In Japan, the estimated prevalence of PIDs is 2 to 3 per 100,000 people and the estimated number of people affected is 2,900 to 3,500. Of the number of PID patients (2,900 to 3,500), an estimated 1,450 to 1,750 would be potential targets for IG replacement therapy. In clinical practice, most patients requiring a switch to SCIG (as is required by the study design) are already being treated with the approved SCIG product (Hizentra®). In the Hizentra® New Drug Application review report, the estimated number of patients who could receive IG replacement therapy was 1,155, which is lower than the estimated 1,450 to 1,750 patients.

Even if both patients who are treated with IVIG or Hizentra® can participate in this study, the number of potentially eligible patients for the planned study is extremely limited, making it infeasible to enroll a large sample size. Therefore, the applicant made the study design that PID patients who complete ongoing clinical trials (TAK-664 studies) of TAK-664 (20% SCIG) are able to enroll in this study.

Based on feasibility and the sponsor's clinical experience with IgG products, a total sample size of 15 subjects (12 completers) is considered suitable for providing adequate estimates of trough levels (study primary objective), as well as adequate estimates of safety and tolerability, efficacy, disease activity and HRQoL (secondary objectives).

9.4 Statistical Analysis Set(s)

Analysis of serum trough levels of IgG, efficacy, safety and tolerability, and disease activity and HRQoL data will be based on the following analysis sets (analysis populations), as defined:

- Enrolled Set: All enrolled subjects who have signed informed (e)Consent and are assigned to subject identification codes.
  Baseline summaries (e.g., subject disposition) will be based on the Enrolled Set.
- Full Analysis Set (FAS): All enrolled subjects who received investigational drug at least once.
  Analysis of efficacy, disease activity and HRQoL will be based on the FAS.
- Safety Analysis Set (SAS): All enrolled subjects who received investigational drug at least once.
  Analysis of safety, tolerability and product administration will be based on the SAS.
- Pharmacokinetic Analysis Set (PKAS): All enrolled subjects who received investigational drug at least once, have had at least 1 evaluable serum IgG concentration, and no major protocol deviations or events that would affect the serum IgG concentration analysis results.
  Analysis of serum IgG trough concentrations will be based on the PKAS and analysis of PK profiles will be based on the subset of 5 to 7 subjects aged 12 years and older in the PKAS.

9.5 Pharmacokinetic Analyses

The primary PK endpoint is the serum trough levels of total IgG (total serum trough IgG antibodies) measured during the trough evaluation period of Epoch 2 (administration of TAK-771).

The secondary PK endpoints are:

- PK parameters for total serum levels of IgG and for IgG subclasses in the PK assessment period of Epoch 2 (in a subset of 5 to 7 subjects aged 12 years and older)
- Serum trough levels of IgG subclasses in the trough evaluation period of Epoch 2
- Trough levels of specific antibodies to Clostridium tetani toxoid, HIB, and HBV in Epoch 1 and 2.

All PK data will be summarized using the following descriptive statistics: number of subjects (n), mean, median, standard deviation (SD), minimum value, maximum value. For serum IgG, IgG subclasses and specific antibodies trough levels, descriptive statistics will also include GM and the corresponding 2-sided 95% CI. No formal statistical comparison (hypothesis testing) of treatments will be performed. CIs are for descriptive purposes only and caution should be exhibited in their interpretation as this study is not designed for hypothesis testing.

9.6 Efficacy Analysis

Assessment of efficacy is a secondary objective of the study. Efficacy endpoint data (defined below) will be analyzed using descriptive statistics: number of subjects (n), mean, median, SD, minimum value, maximum value, 1st quartile (Q1) and 3rd quartile (Q3). It will be summarized by Epoch and overall treatment period.

- Annual rate of validated ASBIs per subject
- Annual rate of all infections per subject
- Healthcare Resource Utilization:
  - Days not able to attend school/work or to perform normal daily activities due to illness/infection
  - Days on antibiotics
  - Number of hospitalizations due to illness/infection and length of stay (in days)
  - Number of acute (urgent or unscheduled) physician visits due to illness/infection

9.7 Safety Analyses

Assessment of safety and tolerability is a secondary objective of this study. Safety and tolerability endpoints (defined below) will be summarized using descriptive statistics (n, mean, median, SD, minimum value, maximum value, Q1, and Q3) for continuous endpoints/outcome measures, and by Epoch and overall treatment period where applicable. Categorical endpoints/outcome measures of safety and tolerability will be summarized in terms of number and percent of subjects and number of occurrences in each category.

- Occurrence of TEAEs, including but not limited to: TAK-771-related and non-related, serious, non-serious, severe, local and systemic TEAEs, as well as TEAEs leading to premature discontinuation from study, and infusion-associated TEAEs
- Occurrence of tolerability events related to the infusion of TAK-771
  An infusion is considered tolerable if the infusion rate was not reduced, or the infusion was not interrupted or stopped, due to a TEAE related to TAK-771 infusion. A tolerability event is considered to have occurred if an infusion was not tolerable. Tolerability events will be measured in terms of the number and percentage of subjects for which the infusion was not tolerable.
- Changes in clinical laboratory parameters
- Changes in vital signs and body weight.
  Change from baseline in vital signs and body weight, and change from pre-infusion to post-infusion in vital signs
- Development of positive titer (≥ 1:160) binding antibodies, and development of neutralizing antibodies, to rHuPH20
  Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160
  Number and percentage of subjects who develop neutralizing antibodies to rHuPH20

Baseline is defined as the last non-missing value before the initial dose of investigational drug.

9.7.1 Analysis of Adverse Events

9.7.1.1 Definitions

Treatment-emergent adverse events, defined as AEs with onset after date-time of first dose of investigational drug, or medical conditions present prior to the start of investigational drug but increased in severity or relationship after date-time of first dose of investigational drug.

Non-TEAEs, defined as AEs with onset before date-time of first dose of investigational drug, or medical conditions present prior to the start of investigational drug but did not increase in severity or relationship after date-time of first dose of investigational drug.

Related TEAEs, defined as TEAEs causally related to investigational product.

9.7.1.2 Handling of Recurrent Adverse Events and Other Adverse Event Situations

Multiple Severities and Relationships: Subject with multiple severities of the same AE, the maximum severity (most serious severity) will be used in analysis, and similarly with multiple relationships of the same AE, the worst relationship will be used. If a subject experiences multiple severities of the same AE (e.g., 3 occurrences: 1 mild, 1 moderate, 1 severe) all categorized under the same causality assessment (e.g., all related to investigational drug), the AE with the maximum severity (AE that is severe) will be used in analysis.

Related AEs: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible. Relationship (causality) to study procedures should also be determined for all AEs. The relationship should be assessed as "Related" if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as "Not Related".

Recurrent AEs: If more than 1 AE occurs within the same preferred term (PT) for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational drug. For example, if a subject experienced a mild headache not related to the investigational drug, and a moderate headache related to investigational drug, then the subject will be counted once for headache using the moderate headache related to investigational drug.

Details on data handling conventions will be provided in the study SAP.

9.7.1.3 Occurrence and Number of Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or higher and then reported by MedDRA system organ class (SOC) and PT, and overall. Only TEAEs will be analyzed. Non-TEAEs will be listed only.

Note: Hereafter, TEAE and AE are used interchangeably.

The following summaries will be provided:

- Number and percentage of subjects with TEAEs by SOC and PT, and overall
- Number of TEAEs by SOC and PT, and overall

The following approaches will be used, where applicable:

- Overall summary: Overall summary will include, but not limited to: Any TEAE, local TEAE, related TEAE, severe TEAE, severe related TEAE, serious TEAE, serious related TEAE, and TEAE leading to discontinuation, and any TEAE leading to death.
- Summaries by SOC and PT: In the summaries, SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the Total column (i.e., the Total column will be sorted in descending order after the sorting by SOC and PT).
- Summaries by PT only: In the summaries, PT will be sorted in decreasing frequency in the table Total column.
- If more than 1 TEAE occurs within the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational drug. For example, if a subject experienced a mild headache not related to the investigational drug, and a moderate headache related to investigational drug, then the subject will be counted once for headache using the moderate headache related to investigational drug.
- In AE incidence summaries, subjects with multiple events in the same category will be counted only once in the AE category. Subjects with events in more than one category will be counted once in each of the categories.
- In AE count summaries, multiple occurrences of the same AE will be counted multiple times.

9.7.1.4 Adverse Events per Infusion, per Subject, per Subject-Year

The following summaries will be provided:

- Number of AEs per infusion, by SOC and PT
- Number of AEs per subject, by SOC and PT
- Number of AEs per SY, by SOC and PT

Per infusion is number of events divided by total number of infusions administered; per subject is number of events divided by total number of subjects; per SY is number of events divided by total number of days of exposure, converted into years.

AEs per SY summary adjusts for differences in subjects' durations in the study.

For number of AEs, multiple occurrences of the same AE in the same subject will be counted multiple times.

Number of AEs and AEs per 1000 SYs will be provided for all AEs (if analyzable), by primary SOC and PT.

The following calculations apply, where applicable:

- AEs per infusion = number of AEs / total number of infusions administered to subjects in the analysis set
- AEs per subject = number of AEs / total number of subjects in the analysis set
- AEs per SY = number of AEs / total number of days of exposure, i.e., the sum of duration of treatment for all subjects in the analysis set, converted into years
- AEs per 1000 SYs = 1000 x (Total Number of AEs in the study for all subjects / Total SYs in the study)

Total SYs will be calculated by summing subjects' durations in the study. Each subject's duration will be calculated as: (last date in study – date of initial dose of investigational drug + 1) / 365.25. If the subject's last date is missing, then the date of last dose of investigational drug will be used if available.

9.7.1.5 Tolerability

The following summaries will be provided:

- Number (percentage) of subjects for whom the infusion rate was reduced for tolerability concerns or for AEs
- Number (percentage) of subjects for whom the infusion was interrupted for tolerability concerns or for AEs
- Number (percentage) of subjects for whom the infusion was stopped for tolerability concerns or for AEs
- Number (percentage) of subjects for whom the infusion rate was reduced or interrupted or stopped for tolerability concerns or for AEs

- Number of weeks to reach final dose interval (3 weeks or 4 weeks) in Epoch 1
- Percentage of subjects who achieve a treatment interval of 3 or 4 weeks in Epoch 2
- Percentage of subjects who maintain a treatment interval of 3 or 4 weeks in Epoch 2

9.7.2 Clinical Laboratory Data

Baseline is defined as the last non-missing value before initial dose of study drug.

Raw (actual) clinical laboratory values (in SI units) and changes in raw values from baseline at each post-baseline assessment time point will be summarized as continuous variables.

Shift from baseline (shift table) to each post-baseline assessment time point will be provided for categorical variables. Summaries of shift-from-baseline will be produced for each laboratory parameter that has a reference range, using the categories: low (below the lower limit of the reference range), normal (within the reference range), high (above the upper limit of the reference range), and missing. Missing data will not be imputed. In addition, shift-from-baseline summaries will be produced by toxicity grade.

9.7.3 Vital Signs and Body Weight

Raw (actual) vital signs and body weight, and changes in raw values from baseline at each post-baseline assessment time point will be summarized as appropriate. For vital signs, change from pre-infusion to post-infusion will also be summarized as appropriate.

9.7.4 Antibodies

Number and percentage of subjects who develop anti-rHuPH20 binding antibody titers of ≥1:160 in Epoch 2 will be summarized. Samples with anti-rHuPH20 binding antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies, and the number and percentage of subjects who develop neutralizing antibodies to rHuPH20 in Epoch 2 will be summarized.

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9.8 Other Analyses

9.8.1 Disease Activity and Health-related Quality of Life Analyses

All disease activity and HRQoL data (defined below) will be listed in the subject data listing(s). For the endpoint of Treatment Preference at EOS/Early Termination, number and percentage of subjects in each category will be summarized. For other endpoints shown below, raw (actual) and change from baseline values will be summarized descriptively, and summaries will be provided.

- QoL: PEDS-QL (Varni et al., 1999), SF-36 v2 (Ware and Sherbourne, 1992), EQ-5D-3L Health Questionnaire (Shaw et al., 2005) in Epoch 1 and 2
- Treatment Satisfaction (TSQM-9) (Daly et al., 1991) in Epoch 1 and 2

9.8.2 Product Administration

Infusion parameters in Epoch 2 will be summarized descriptively. The parameters may include but not limited to the following:

- Number of infusions per month
- Number of infusion sites per infusion
- Number of infusion sites per month
- Duration of individual infusion
- Maximum infusion rate/site
- Infusion volume/site

Endpoint details will be provided in the study SAP.

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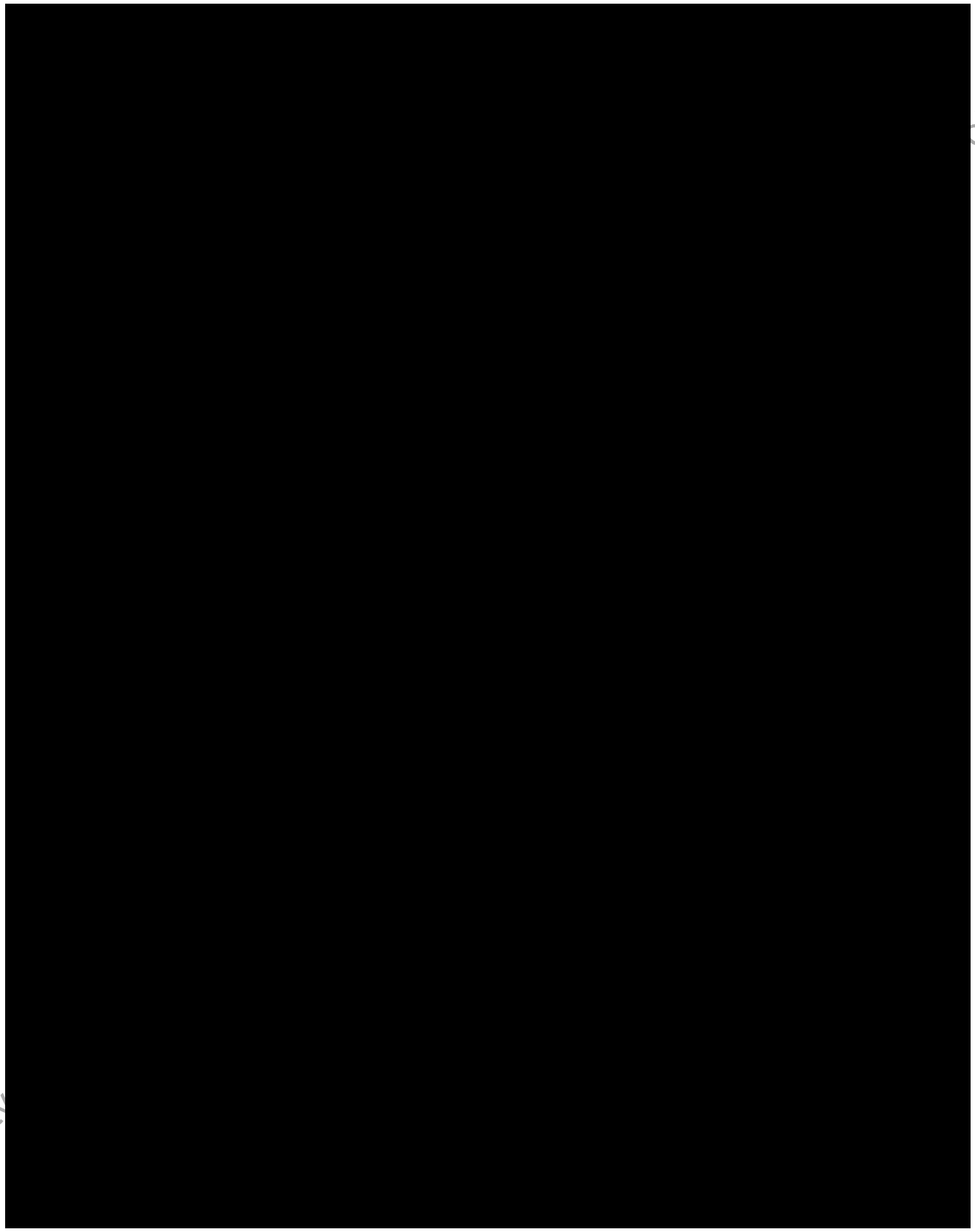

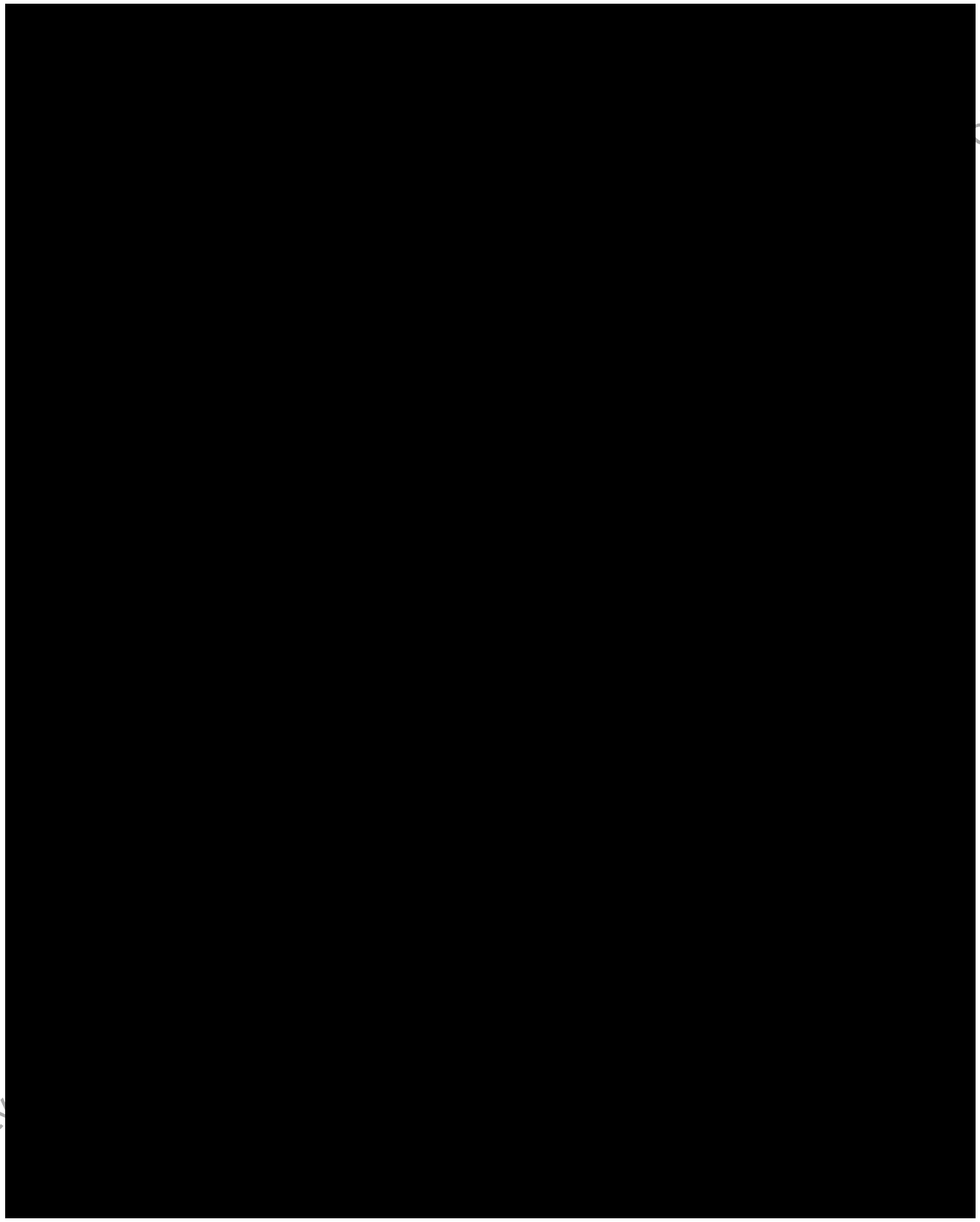

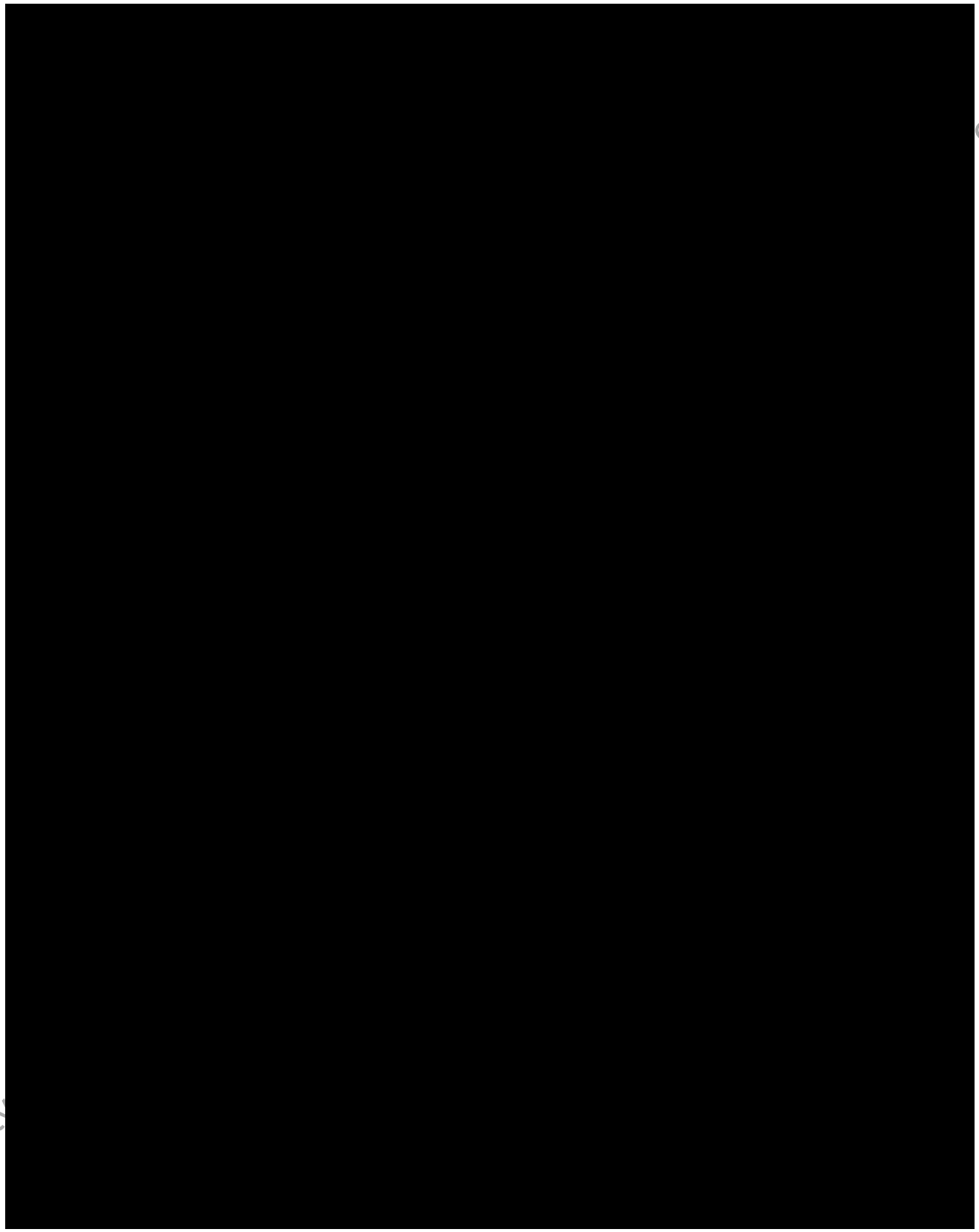

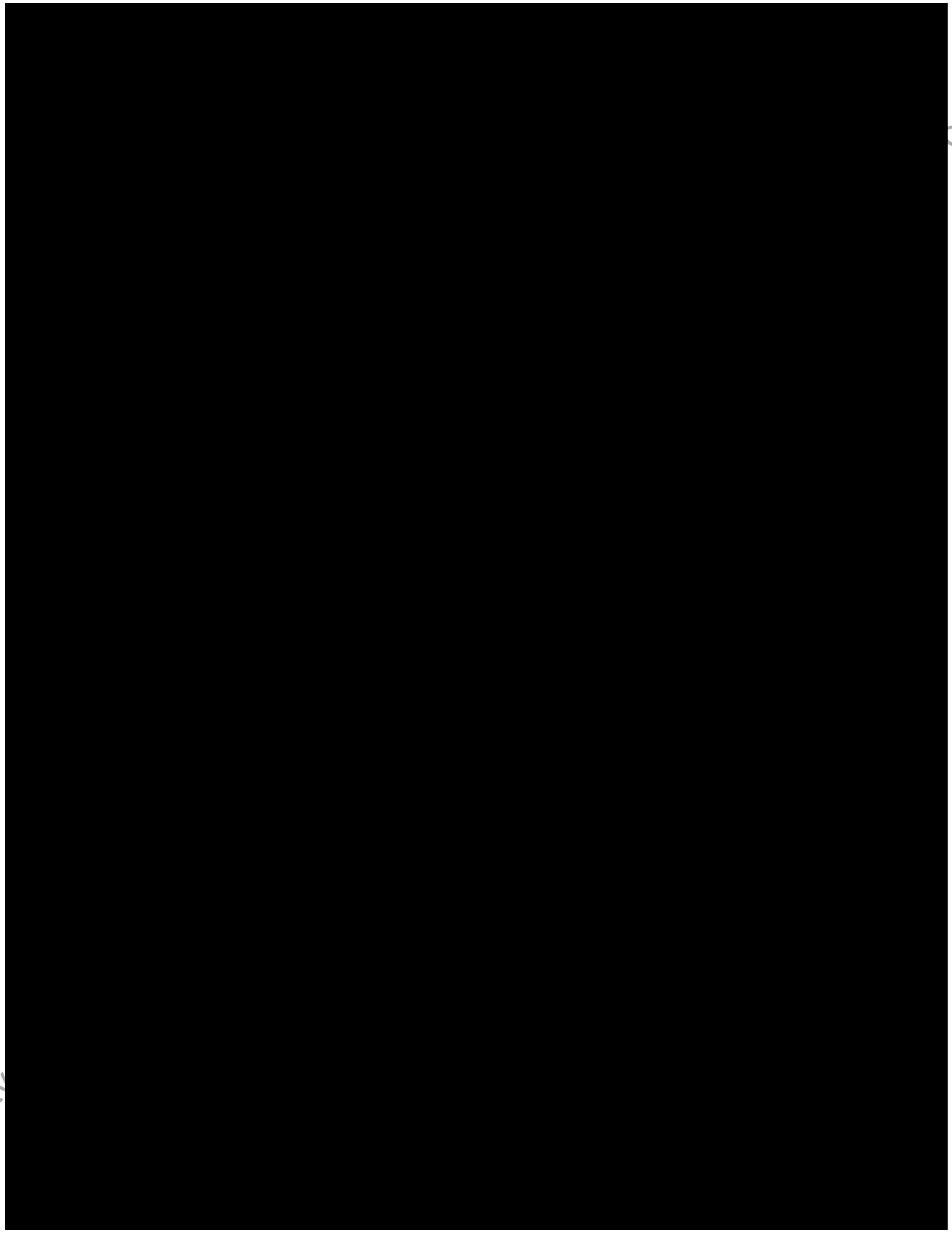

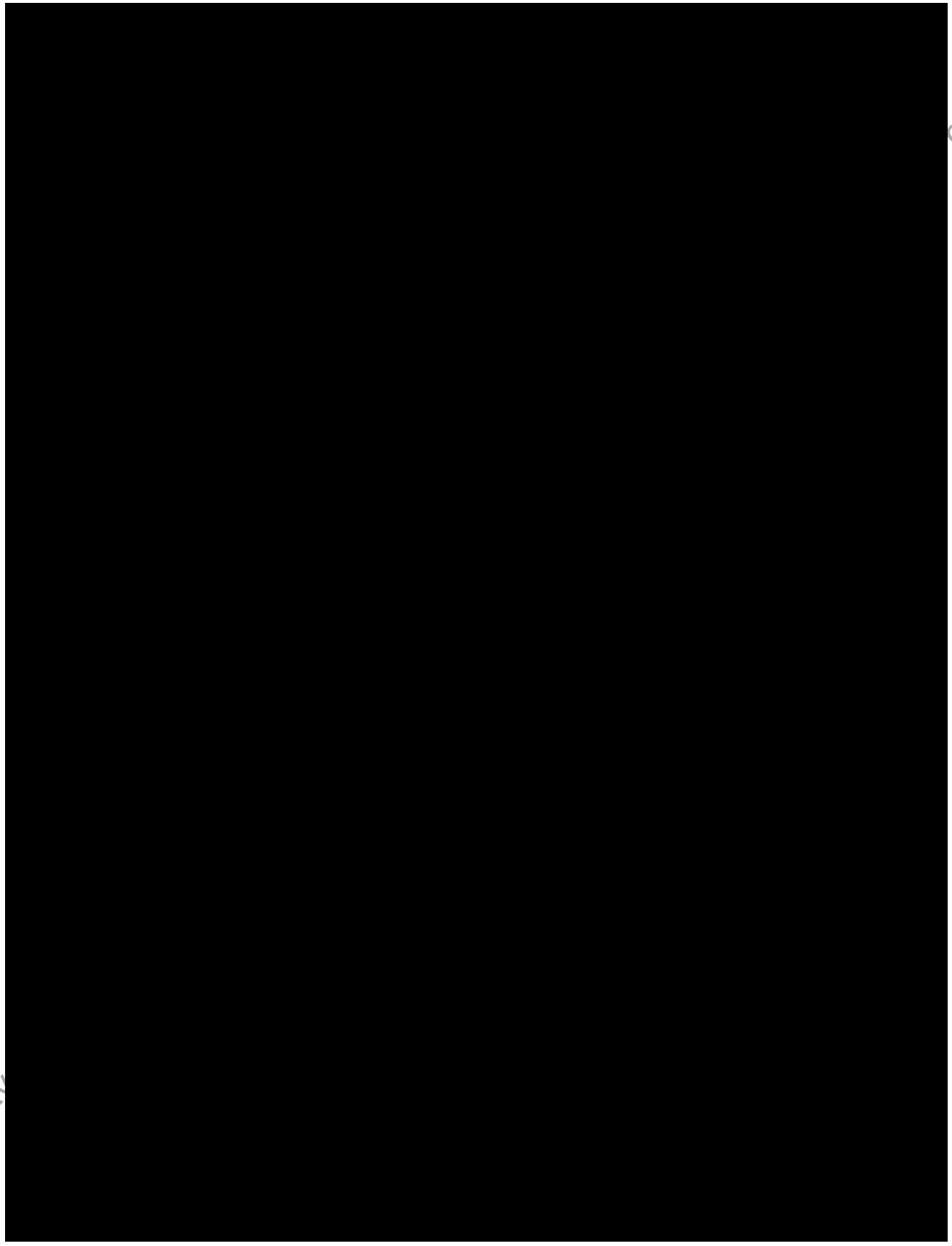

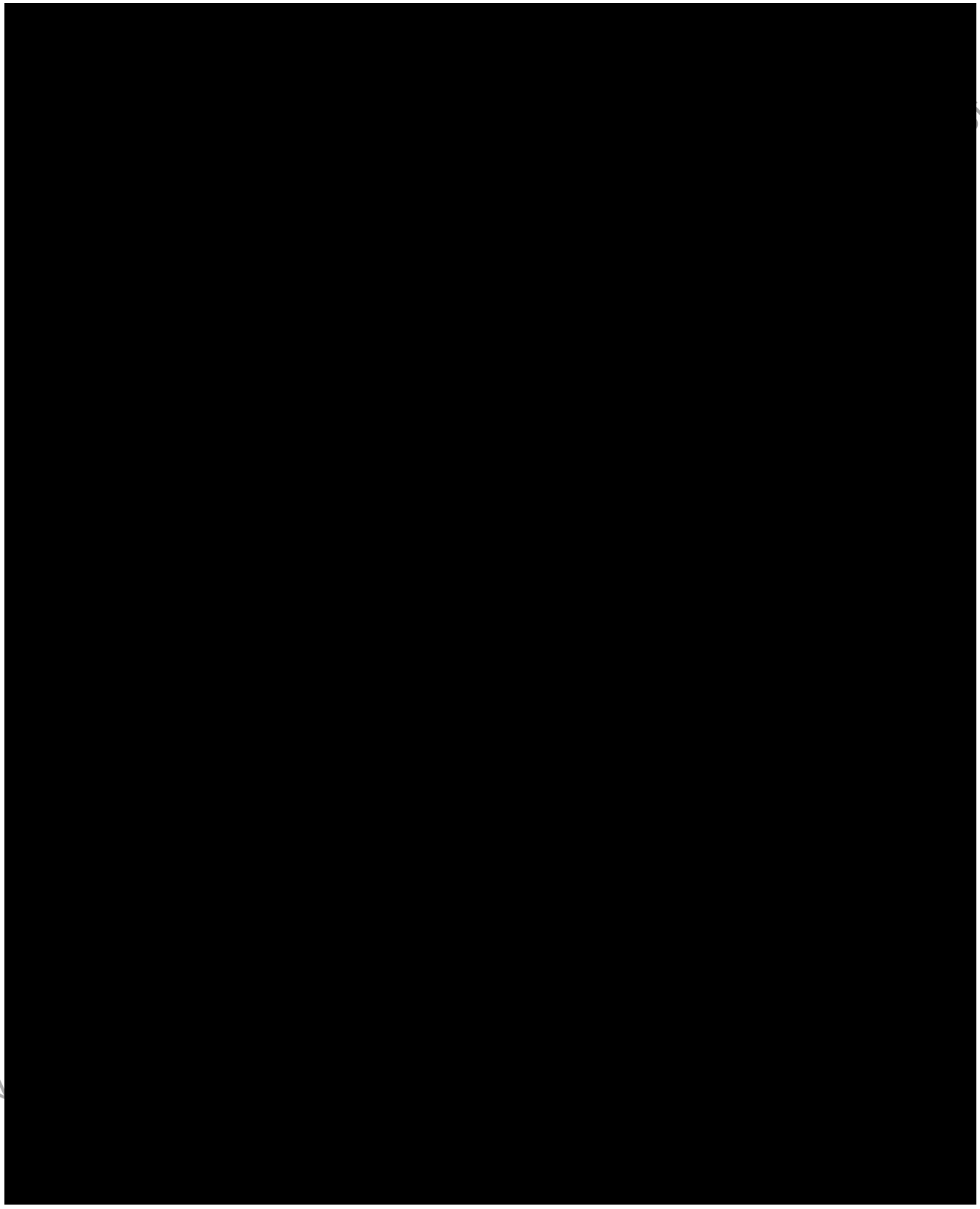

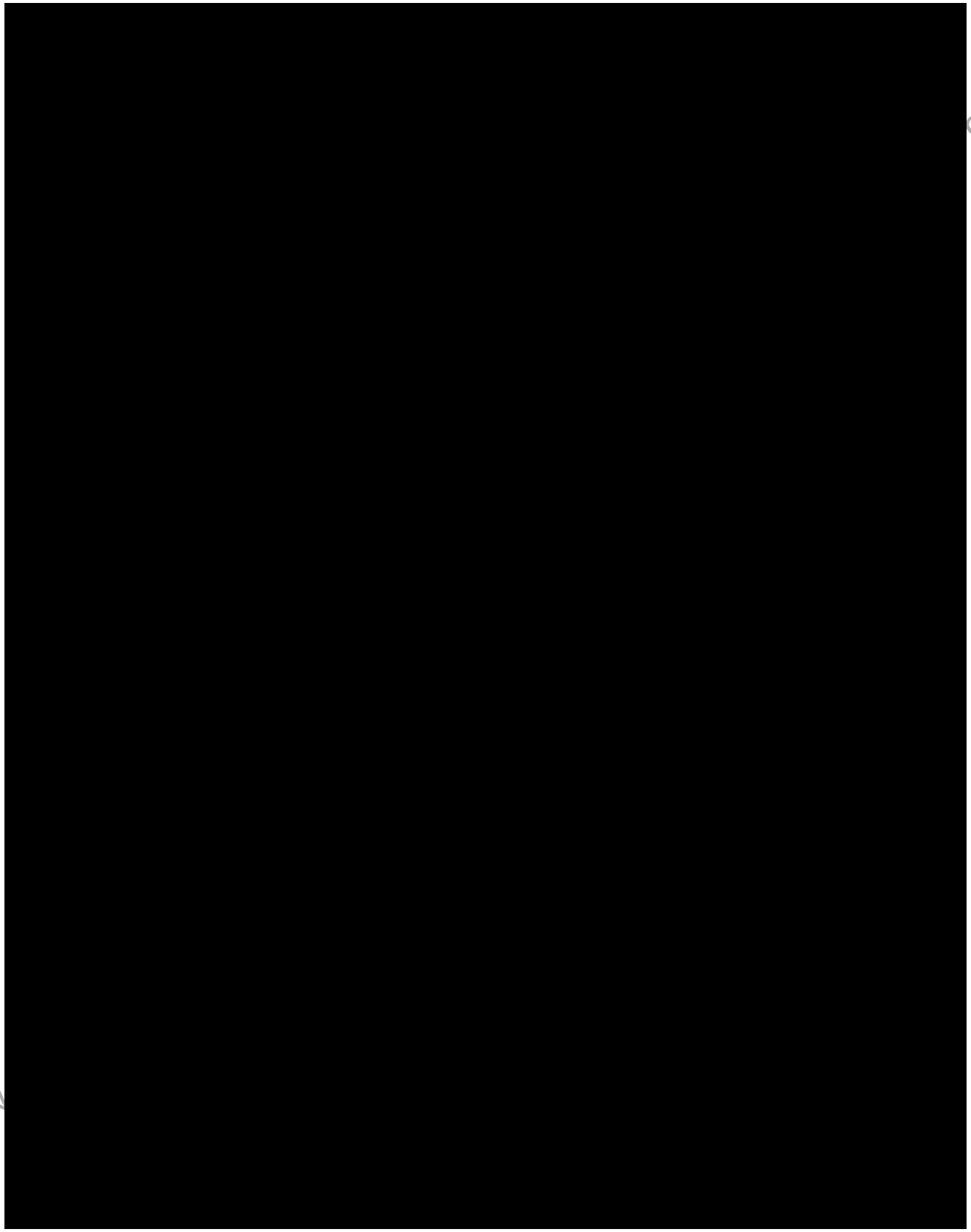

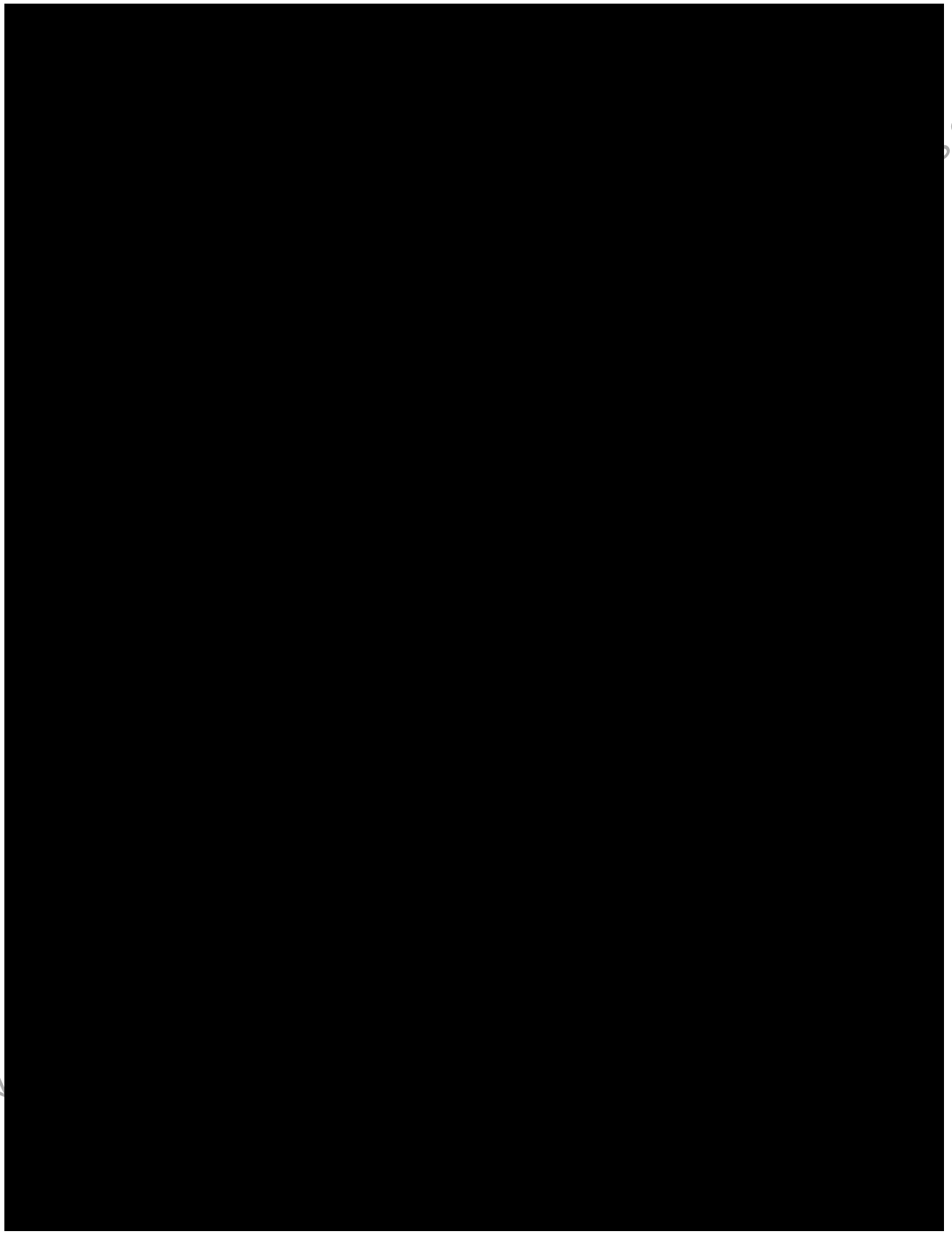

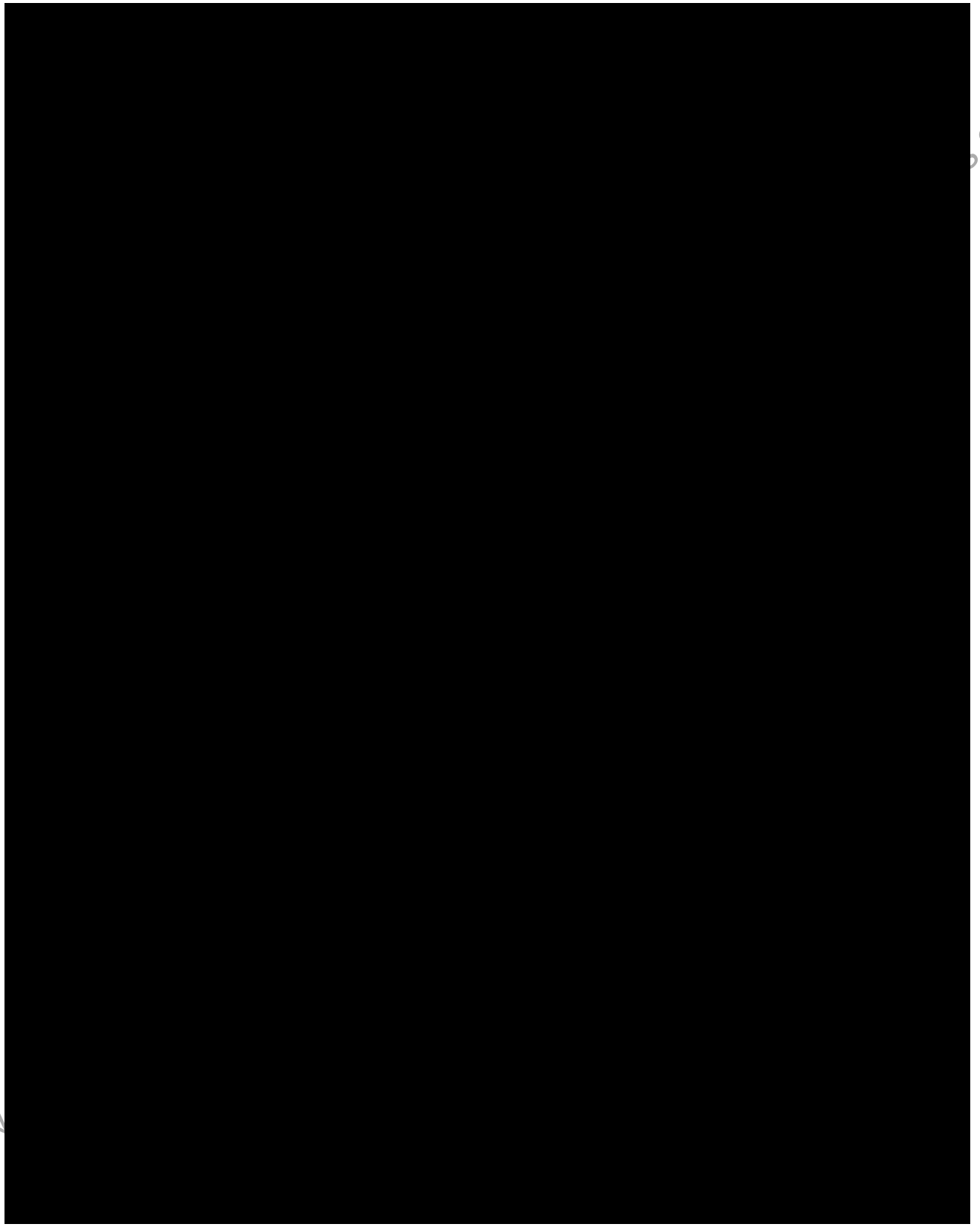

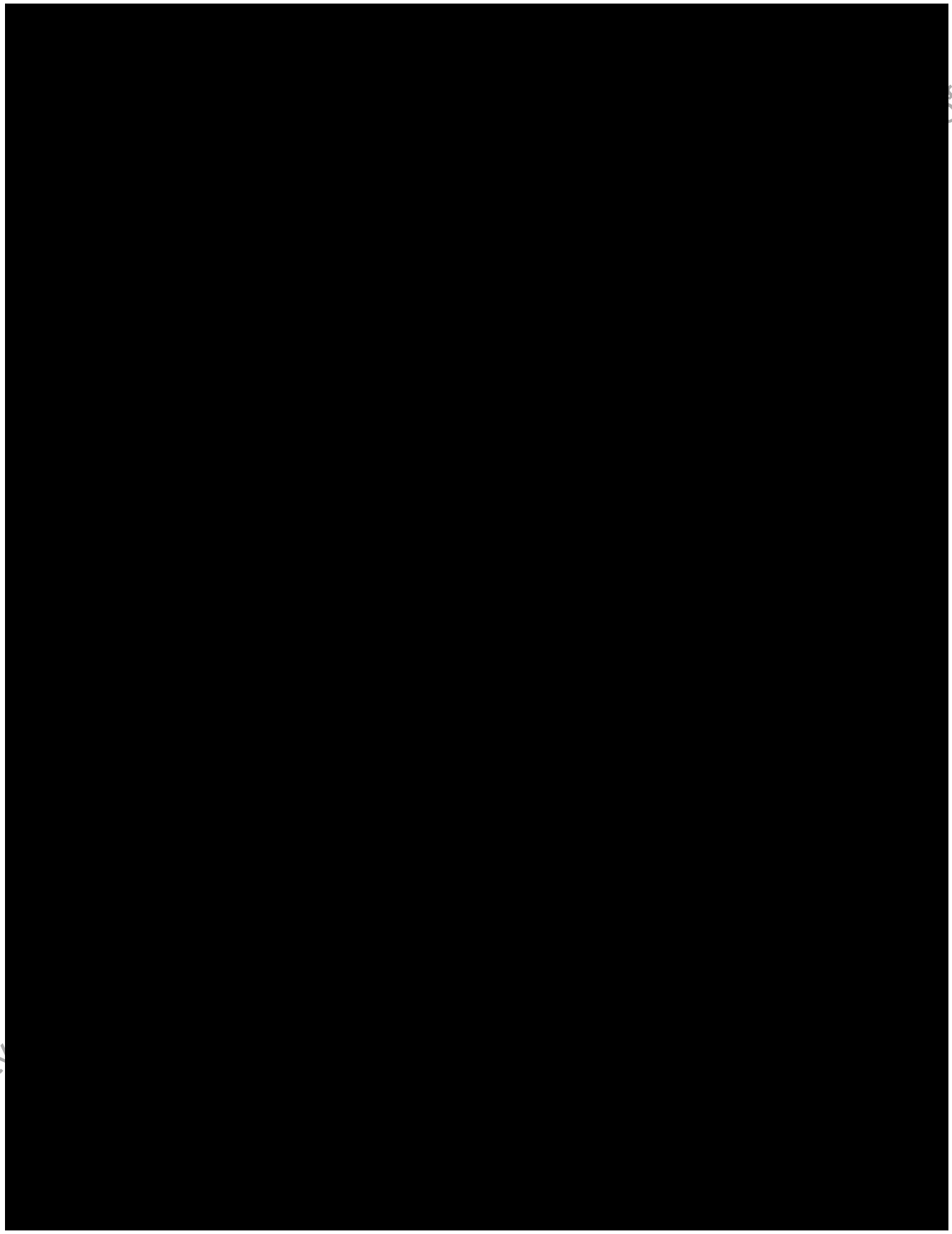

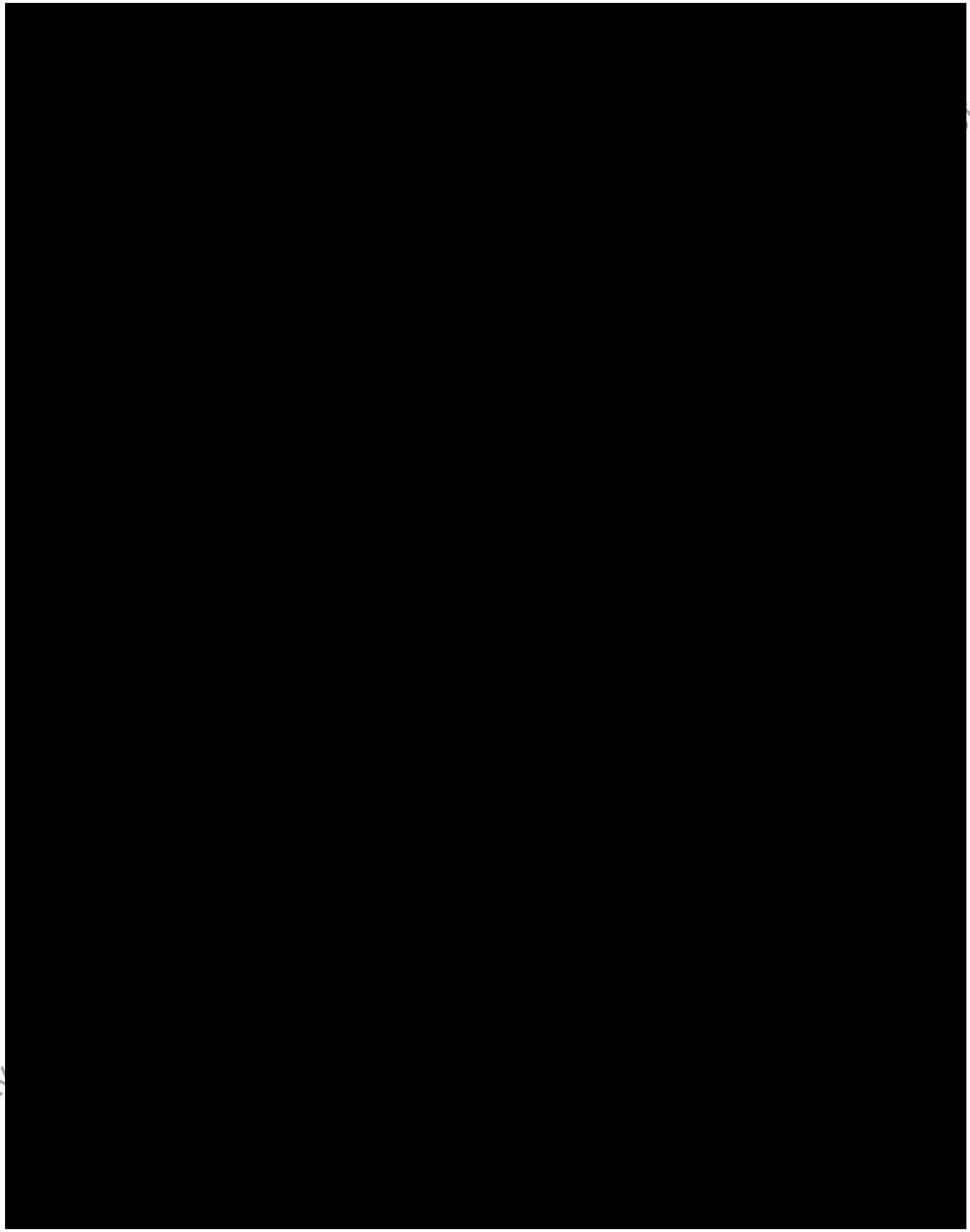

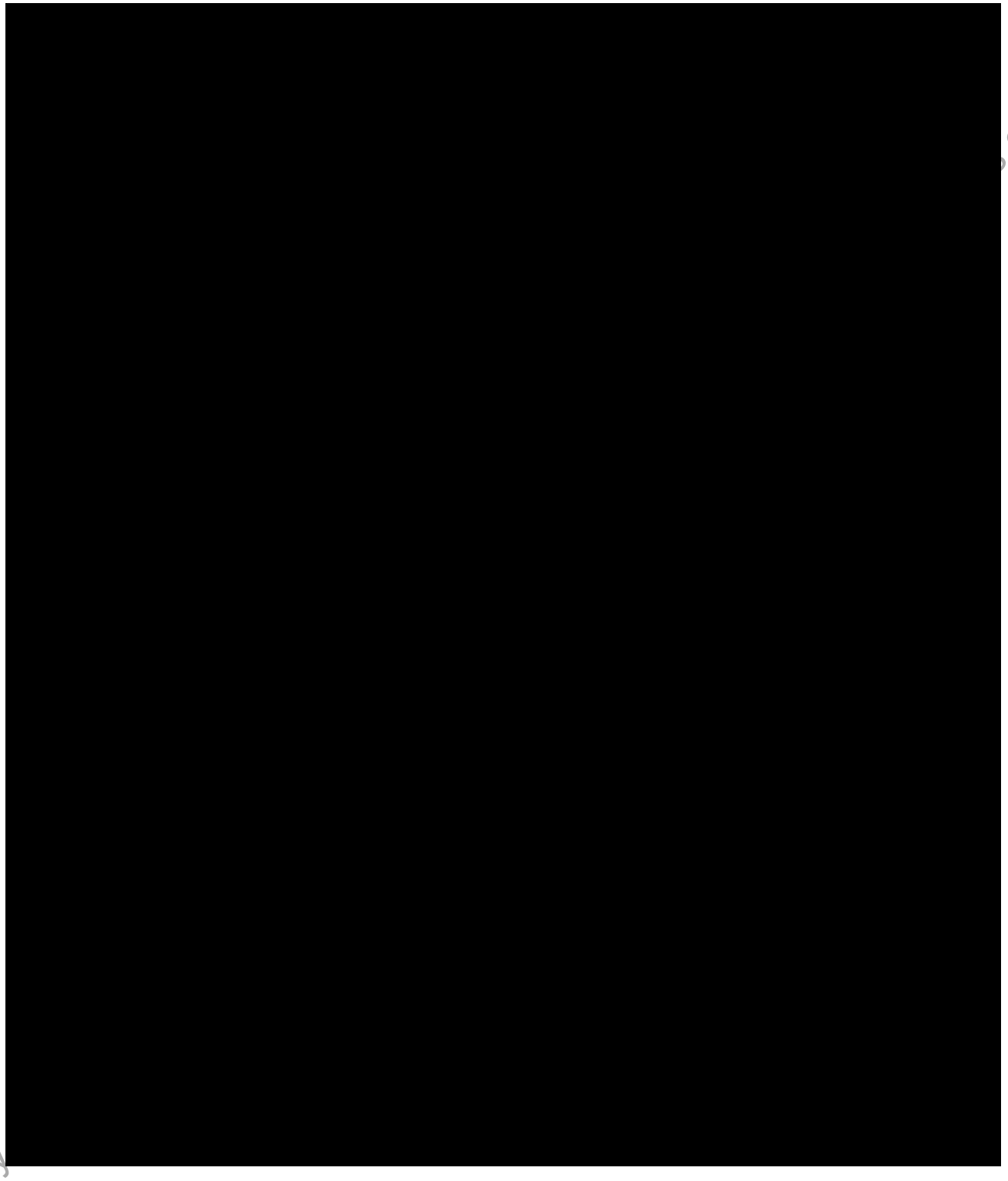

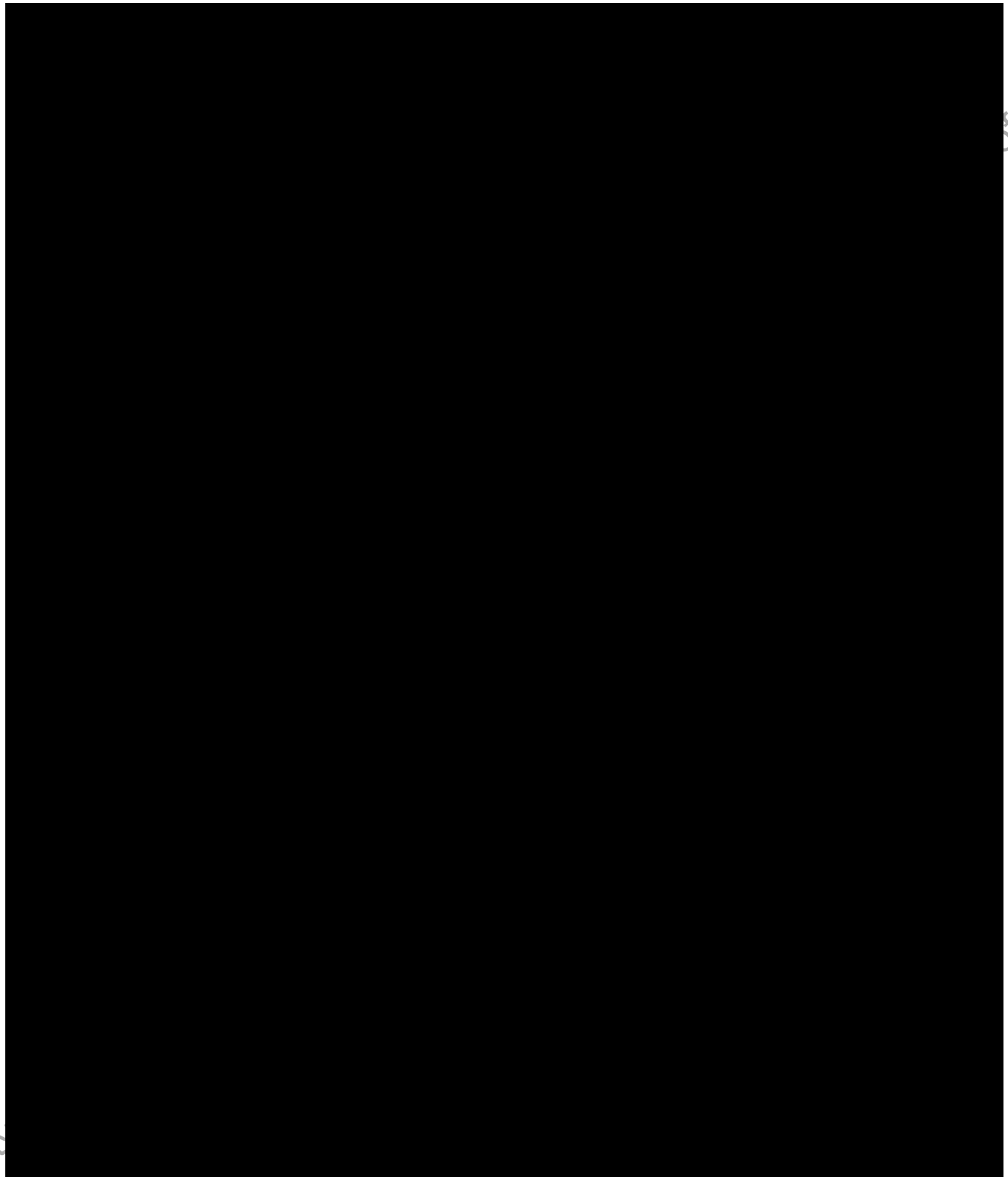

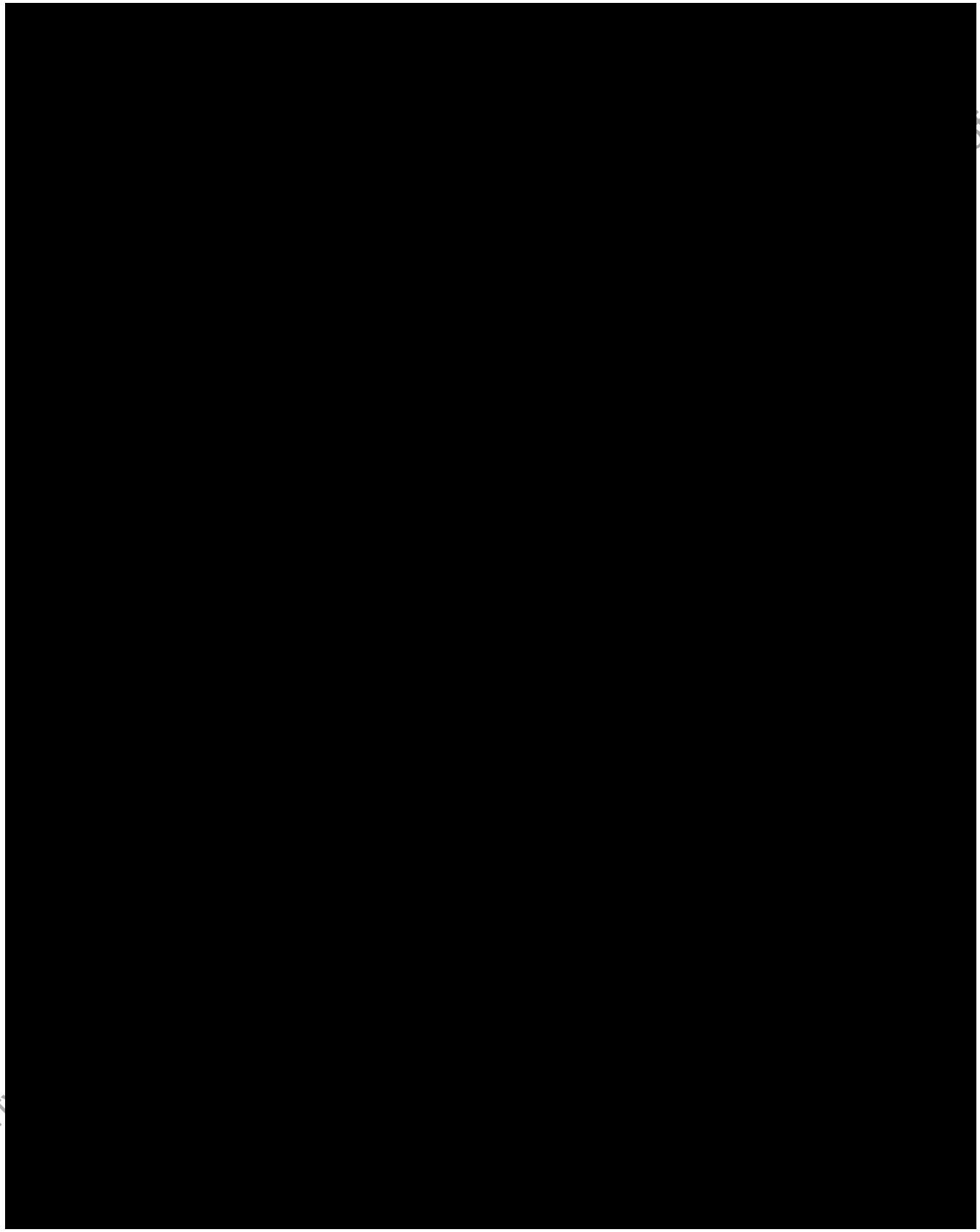

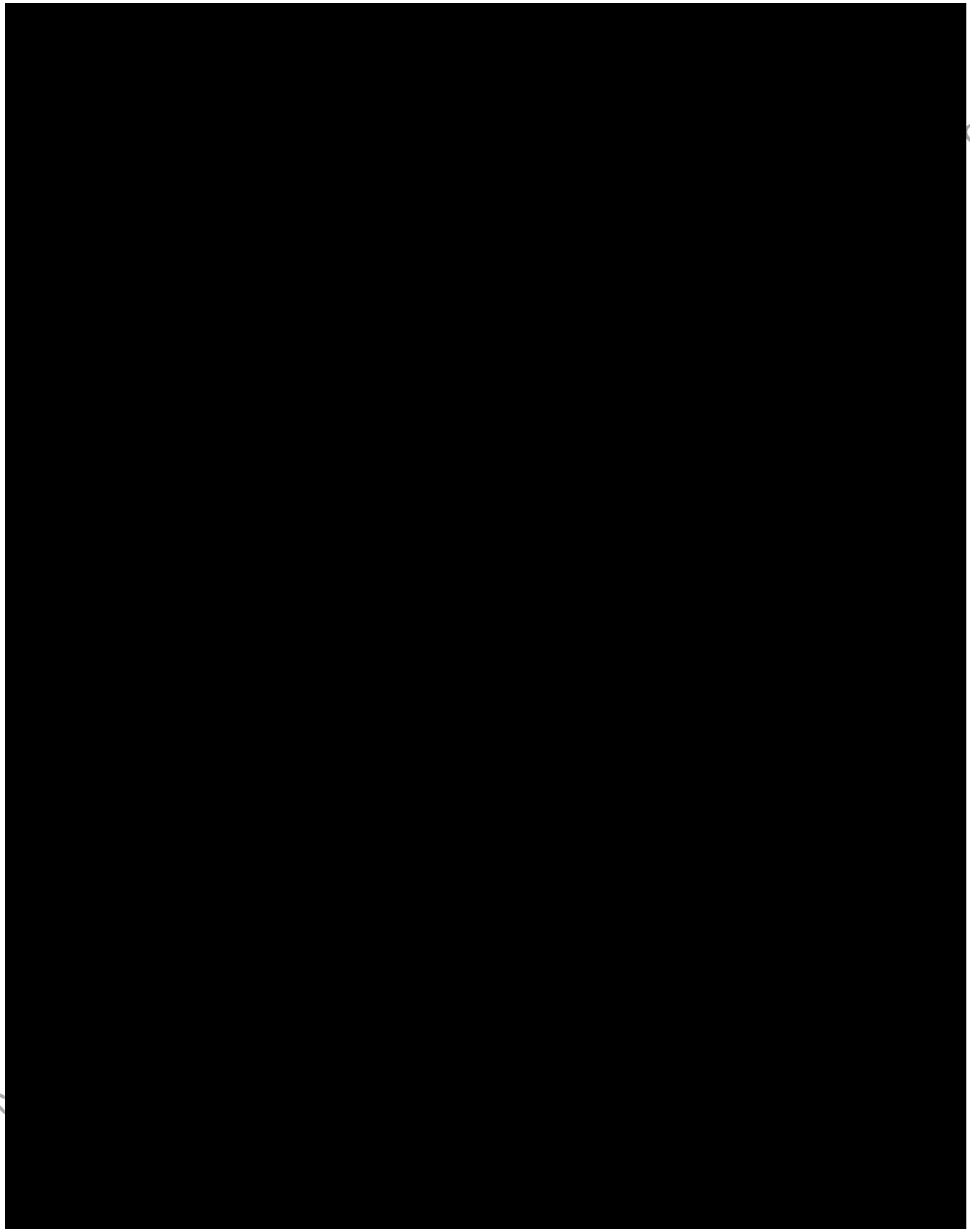

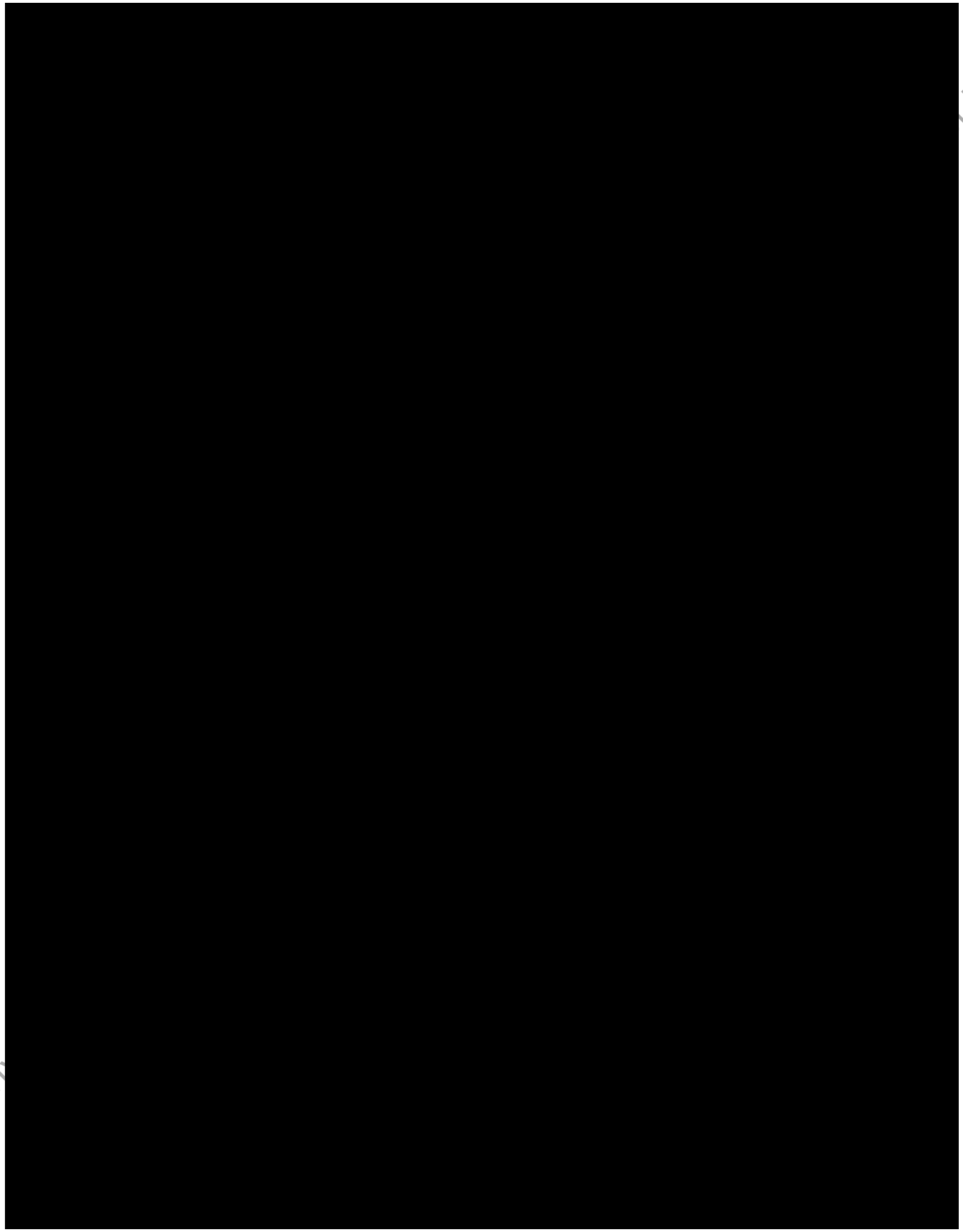

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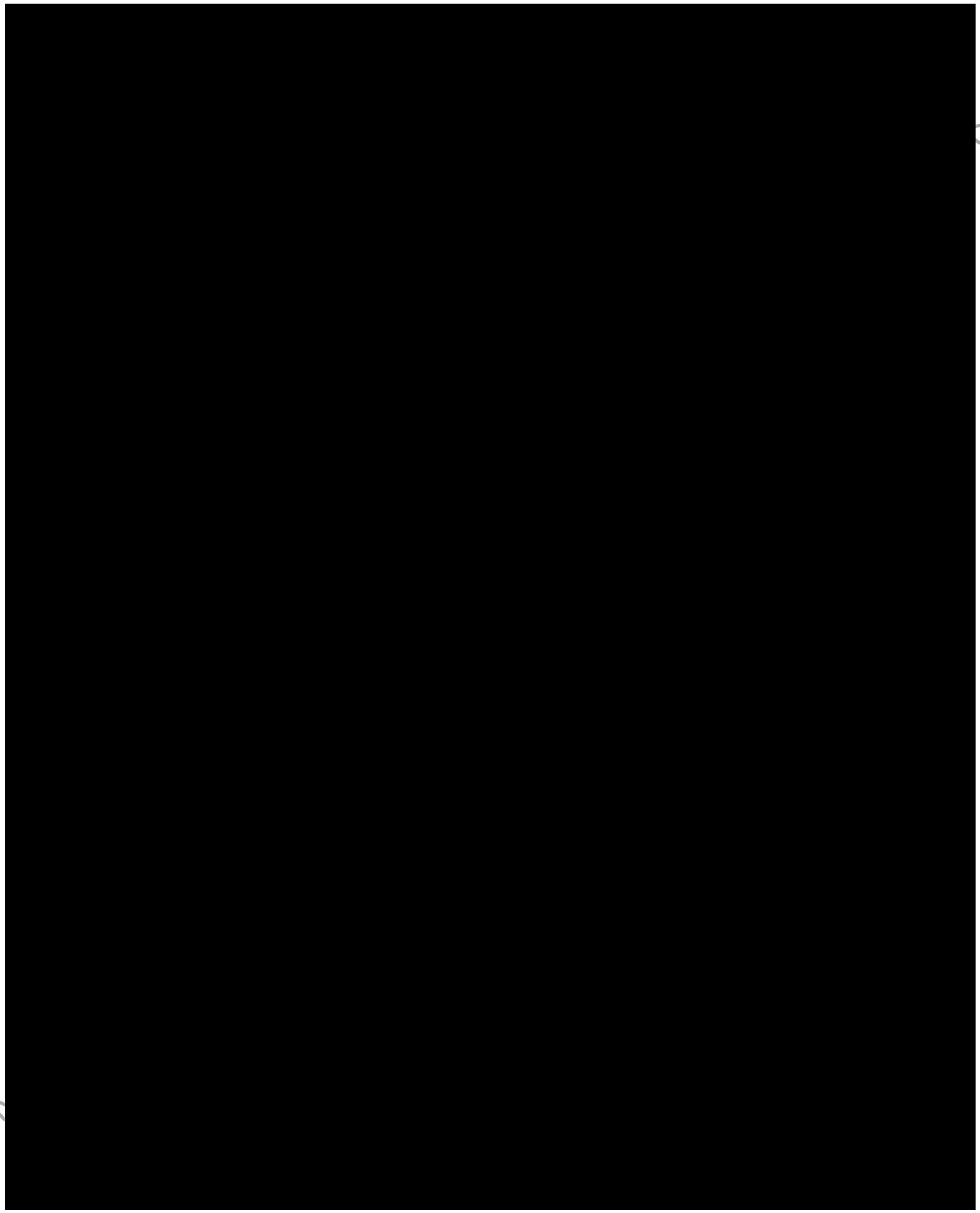

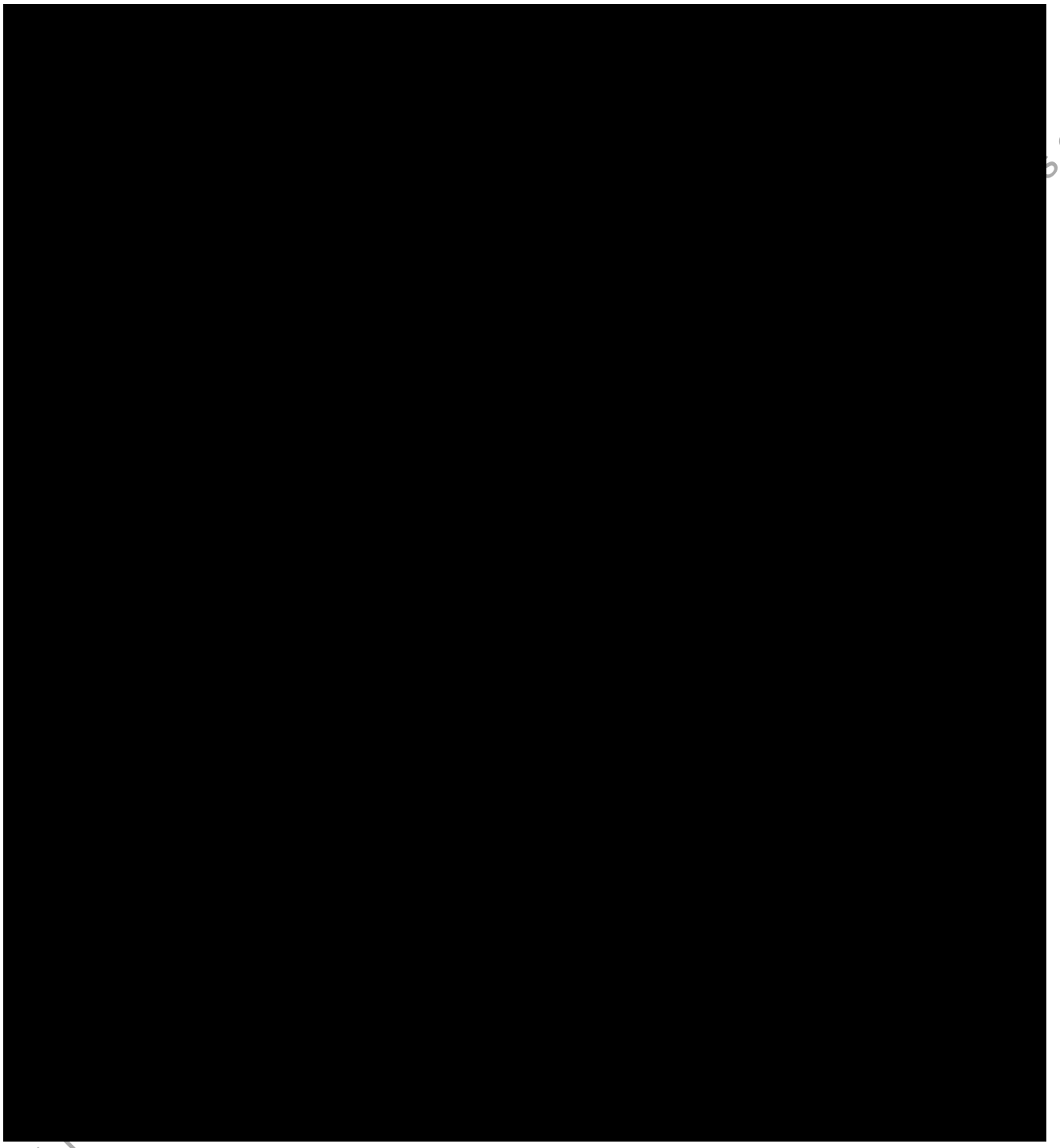

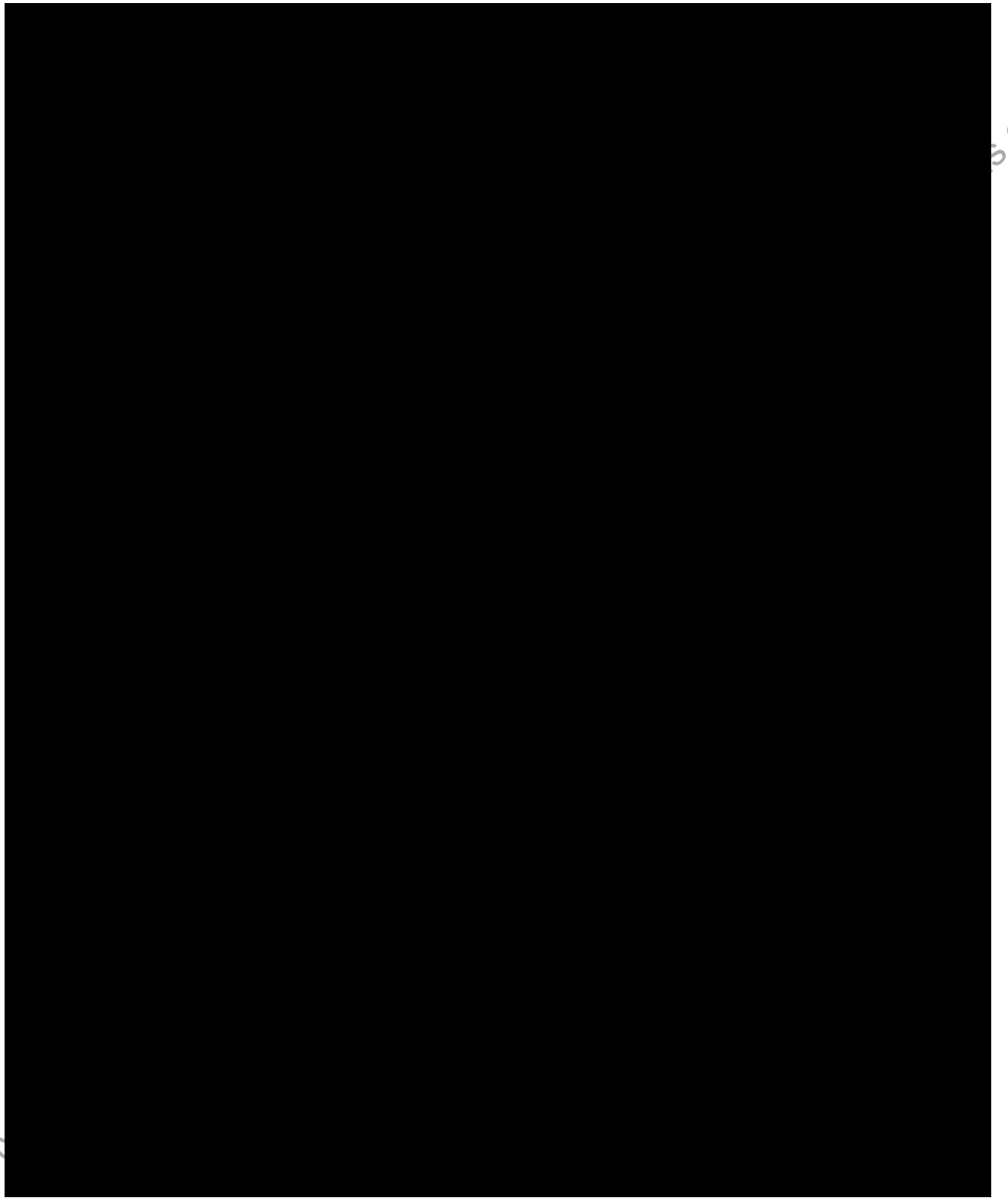

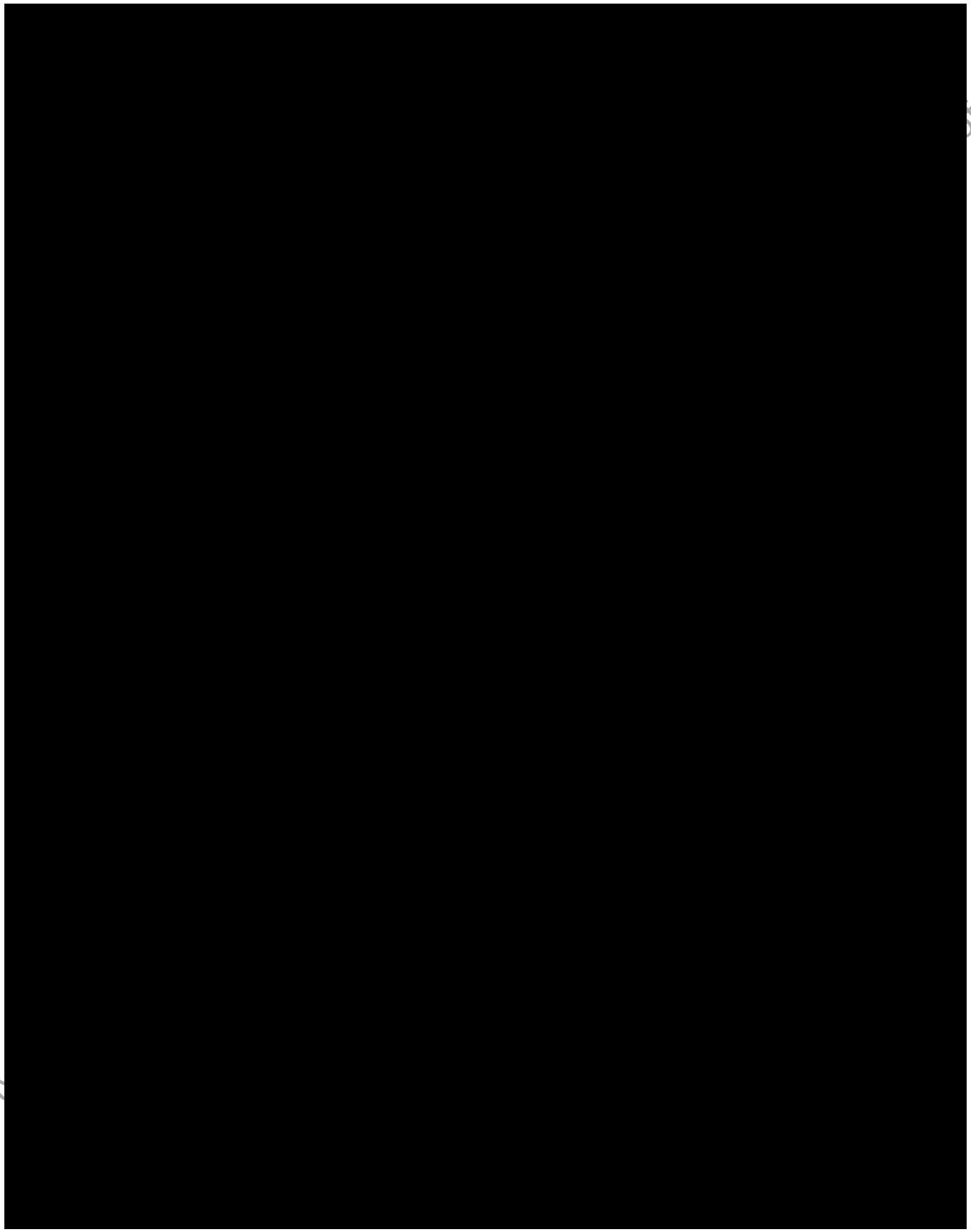

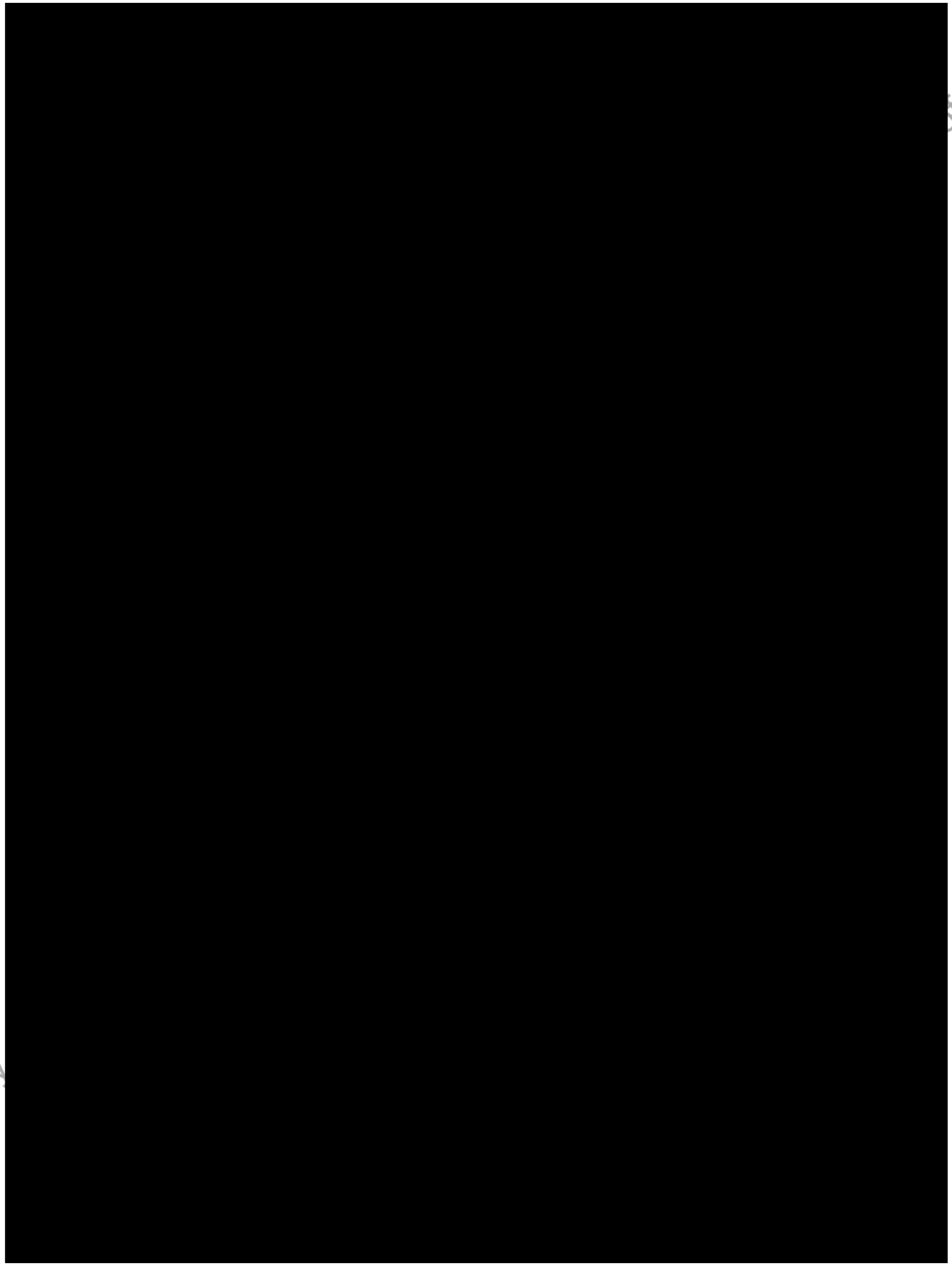

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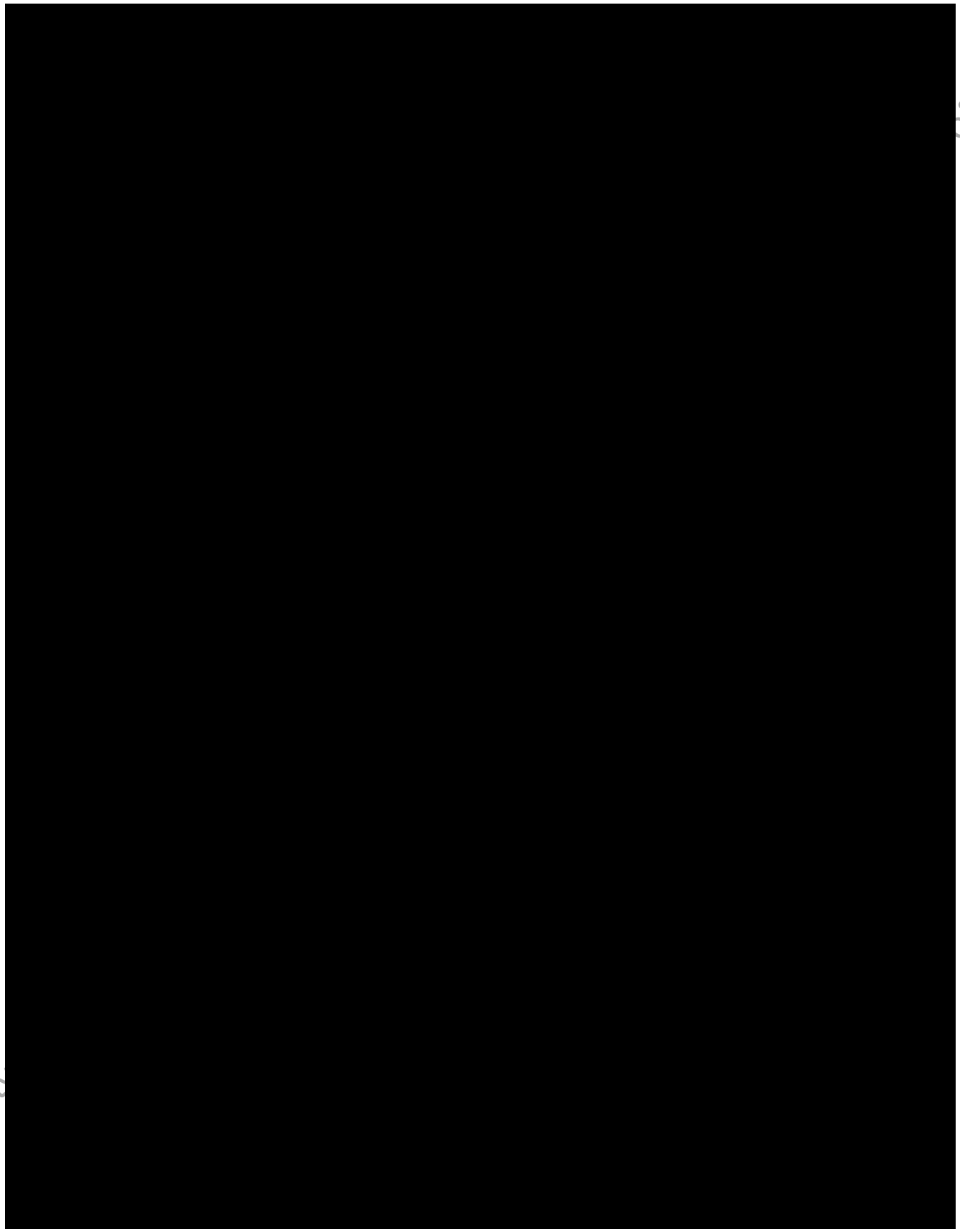

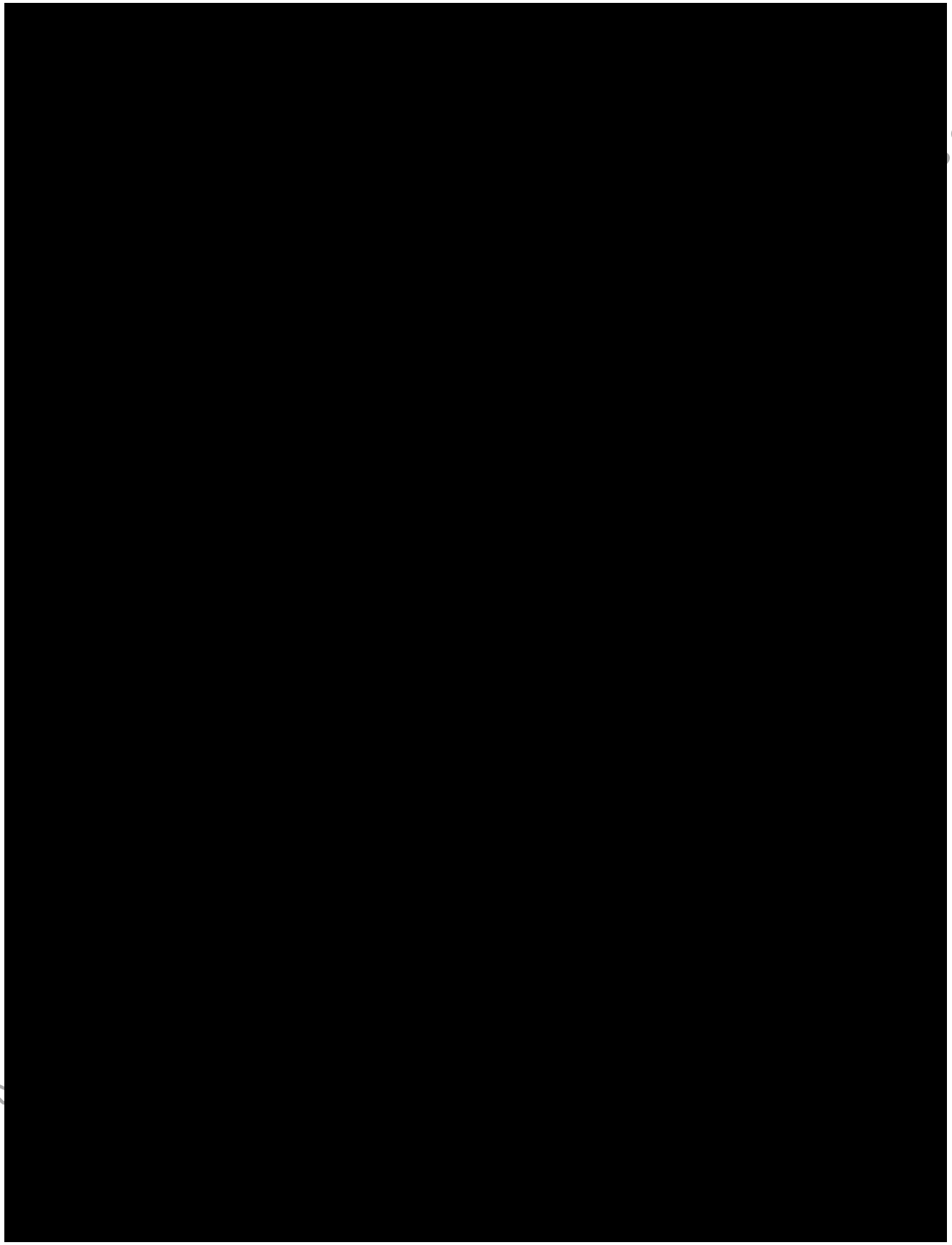

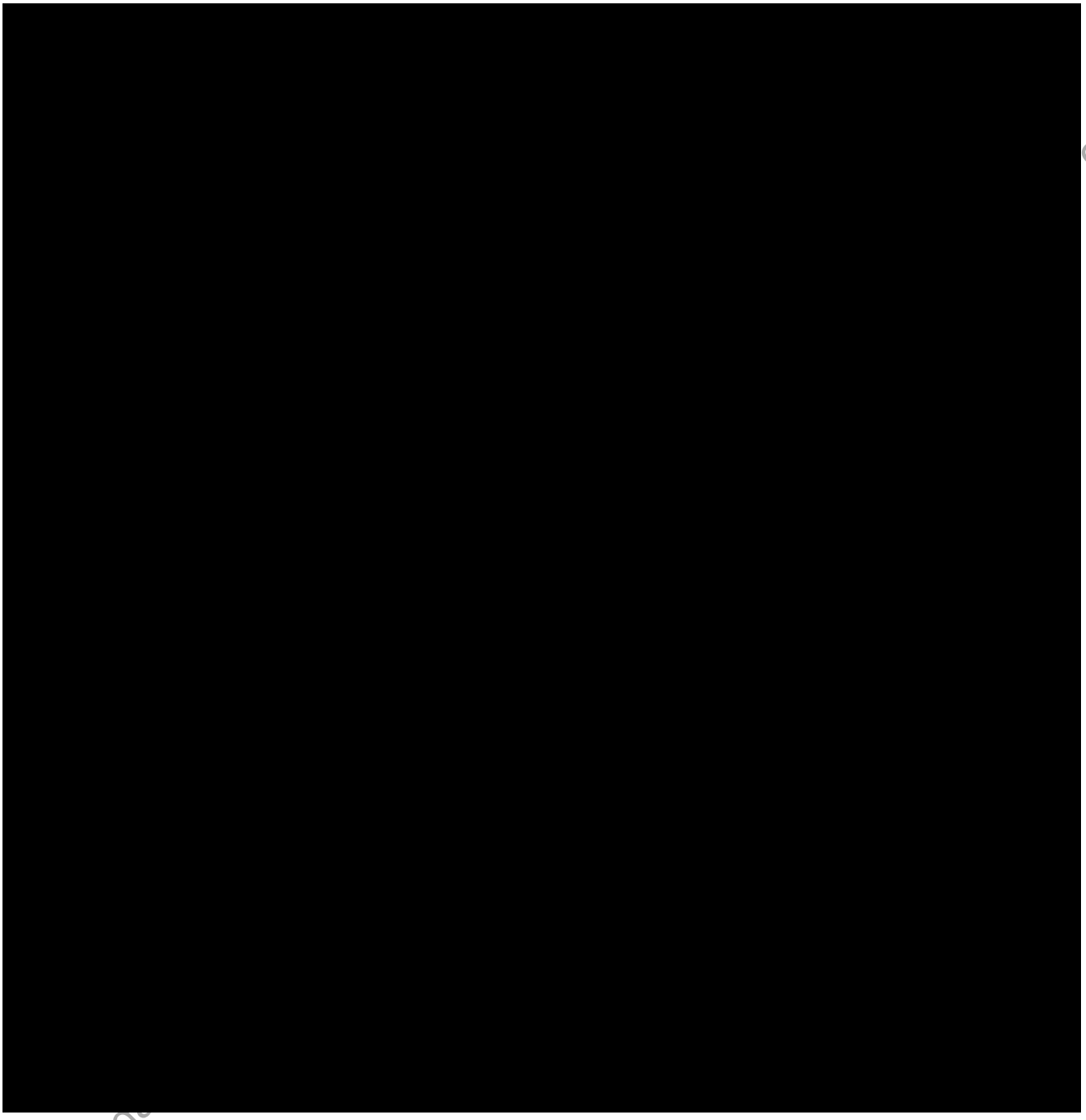

APPENDIX 9 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Amendment 1	19 May 2022	Japan
Original Protocol	13 July 2021	Japan