Clinical Study Protocol

NCT Number: NCT05137717

Title: A Phase 3, Open-Label, Single-Arm Study to Assess the Efficacy, Safety, and Pharmacokinetics of Maribavir for the Treatment of Cytomegalovirus (CMV) Infection in Japanese Recipients of a Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT)

Study Number: TAK-620-3001

Document Version and Date: Amendment 1/28-Oct-2021

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.

Protocol:	TAK-620-3001
Title:	A Phase 3, Open-Label, Single-Arm Study to Assess the Efficacy, Safety, and Pharmacokinetics of Maribavir for the Treatment of Cytomegalovirus (CMV) Infection in Japanese Recipients of a Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT)
Short Title:	Open-label, Single-Arm Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Maribavir in the Treatment of CMV Infection in HSCT or SOT Recipients
Study Phase:	Phase 3
Acronym:	N/A
Drug:	Maribavir
IND Number:	Non-IND
EUDRACT Number:	Non-EUDRACT
Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka
Principal / Coordinating Investigator:	Multicenter study
Protocol History:	Amendment 1 (Version 2.0): 28 Oct 2021 Original Protocol (Version 1.0): 26 Jul 2021

PROTOCOL SIGNATURE PAGE

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Investigator's Acknowledgement

I have read this protocol for Study TAK-620-3001.

Title: A Phase 3, Open-Label, Single-Arm Study to Assess the Efficacy, Safety, and Pharmacokinetics of Maribavir for the Treatment of Cytomegalovirus (CMV) Infection in Japanese Recipients of a Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT)

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 (ICH) guidelines on Good Clinical Practice (GCP) 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

Noteworthy changes to the protocol are captured in the table below. See Appendix 13 for protocol history, including all previous amendments.

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Original Protocol: 26 Jul 2021	**Amendment Date: 28 Oct 2021**	**Global/Region/Country/Site Specific: Japan**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Standardized the deadline for reporting SAE to the sponsor/ the Emergency Reception Center for Safety Information (ERCSI) to "within 24 hours of first awareness of the event".		Emergency Contact Information, Appendix 3.4
Added cidofovir as the currently available systemic anti-CMV agents outside Japan.		Section 2.1
Deleted "and above this level, the increase in area under the concentration time curve (AUC) may be less than dose proportional".		Section 2.2.1
The description of concurrent administration with inducers of CYP3A4 and P-gp was changed as follows: • Concurrent administration of rifampin, a strong inducer of CYP3A4 and P-gp, and maribavir significantly reduced plasma concentrations of maribavir, resulting in a 60% reduction in AUC and 82% reduction in Ctrough, reduced half-life, and significantly increased clearance, most likely due to induction of hepatic and intestinal CYP3A4, and potential induction of P-gp.		Section 2.2.1
Modified the wording of an efficacy endpoint as follows: • Confirmed plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/mL		Section 1.1 Synopsis, Table 3, Section 9.5.2
Modified the wording of inclusion criterion No.5 as follows: 5. Have the current CMV infection after HSCT or SOT, either primary or reactivation, which, in the investigator's opinion, requires treatment and have any of the following. a. Asymptomatic subjects: The subjects do not have CMV tissue-invasive disease or CMV syndrome (SOT subjects only) at Baseline, as determined by the investigator according to the criteria specified by Ljungman et al., 2017. b. Resistant or refractory subjects: The subjects must have a current CMV infection that is refractory to the most recently administered of the anti-CMV treatment agent(s). Refractory is defined as documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in plasma after a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, or IV foscarnet.		Section 1.1 Synopsis, Section 5.1
[redacted]		[redacted]

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Original Protocol: 26 Jul 2021	**Amendment Date: 28 Oct 2021**	**Global/Region/Country/Site Specific: Japan**
Description of Each Change and Rationale		**Section(s) Affected by Change**
"To assess treatment-emergent breakthrough CMV infections and resistance mutations." was removed from secondary objectives and "To evaluate the recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment." was added. Accordingly, "The genotypic characterization of breakthrough infections while on maribavir treatment and CMV resistance mutations recurrences after maribavir treatment." was removed from the secondary endpoints and "Recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment" was added.		Section 1.1 Synopsis, Section 3.1.2, Section 3.2
HIV testing has been modified to be available at a local laboratory as well as central laboratory.		Section 1.1 Synopsis, Table 1 footnote k, Section 5.2, Section 8.1.1.1, Appendix 2
Specified the dose of maribavir per dose.		Table 4
Table 6 "Common Excluded Treatments and Associated Washout Period" was modified including footnotes.		Section 6.6.4
Modified the description of prohibited concomitant medications.		Section 6.6.4
Modified the description of prohibited treatment to match the revised footnote in Table 6.		Section 8.1.1
Added "CMV history" to be specified as an item to be collected at Screening Visit.		Section 8.1.1.1
Modified the description of screen failure as follows: A screen failure is a subject who has given informed consent and failed to meet the inclusion except No.4 and/or met at least 1 of the exclusion criteria and has not been administered the study treatment. However, subjects who were excluded based on the exclusion criteria of low platelet count, hemoglobin, and low neutrophil counts or liver or renal parameters can be retested once within the 14-day screening period at the investigator's discretion when other inclusion criteria are fulfilled. Screen failures may be rescreened in the future (with new informed consent and screening period) if their clinical course results in a change that deems them eligible for the trial.		Section 8.1.1.1
Modified the description of CMV genotyping as follows: • CMV DNA test: Cytomegalovirus quantification in the plasma samples taken at each visit of study treatment phase will be conducted at central specialty laboratory. Cytomegalovirus genotyping by the central specialty laboratory to assess for mutations in the UL97, UL27, and UL54 genes will be conducted at Visit 2/Study Week 0/Day 0 (Baseline). After Visit 2, CMV genotyping will be assessed in every sample that meets the criteria specified in the resistance analysis plan (see Section 8.2.2.2).		Section 8.1.2

Protocol Amendments		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Original Protocol: 26 Jul 2021	**Amendment Date: 28 Oct 2021**	**Global/Region/Country/Site Specific: Japan**
Description of Each Change and Rationale		**Section(s) Affected by Change**
Modified the wording of "recurrence or the CMV viremia recurrence" to "confirmed recurrence or the confirmed CMV viremia recurrence" for clarity.		Section 1.1 Synopsis, Section 8.2.2.1
Modified the description of CMV genotyping and phenotyping included in the efficacy endpoints to match the protocol of Study SHP620-302.		Section 1.1 Synopsis, Section 8.2.2.2
Modified the definition of rebound as follows: Rebound is defined as increase in viral DNA load for >1 $\log_{10}$ above nadir without prior clearance of viremia.		Section 1.1 Synopsis, Section 8.2.2.2
Replaced "exploratory" to "secondary" and modified as follows: Of note, the similarity between SHP620-302 study and Japan study will be based on both the primary endpoint and secondary endpoints.		Section 1.1 Synopsis, Section 9.3
Modified the description of efficacy analyses.		Section 1.1 Synopsis, Section 9.5
Added "Baseline safety analyses is defined as the last value for the assessment prior to taking the first dose of study treatment."		Section 1.1 Synopsis, Section 9.6
Added the list of CMV mutations known to confer resistance to valganciclovir, and other commercially available anti-CMV agents as Appendix 6.		Appendix 6

Minor editorial revisions (including changes for consistency and clarity) are not described in this table.

EMERGENCY CONTACT INFORMATION

When a serious adverse event (SAE) occurs through the adverse event (AE) collection period it should be reported according to the following procedure:

An SAE should be reported by the investigator to the sponsor/the Emergency Reception Center for Safety Information (ERCSI) (see Protocol Annex) within 24 hours of the first awareness of the event, along with any relevant information. The investigator should submit the detailed SAE form to the sponsor/the ERCSI appropriate personnel (see Protocol Annex) within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug
- Causality assessment

The investigator should submit the original copy of the SAE form to the sponsor.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to the study participation.

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to the sponsor 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 the sponsor licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

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

Please report the product quality complaint using the "Product Quality Complaint Data Collection Form" via the email address:

[redacted]

Telephone number (provided for reference if needed):

[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-620-3001	**Drug:** Maribavir
Title of the study: A Phase 3, Open-Label, Single-Arm Study to Assess the Efficacy, Safety, and Pharmacokinetics of Maribavir for the Treatment of Cytomegalovirus (CMV) Infection in Japanese Recipients of a Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT)	
Short title: Open-label, Single-Arm Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Maribavir in the Treatment of CMV Infection in HSCT or SOT Recipients	
Study phase: Phase 3	
Number of subjects: The study is planned to enroll approximately 44 asymptomatic subjects, and few patients with resistant or refractory CMV infection in Japan.	
Investigators: Multicenter study.	
Sites and Region: The study will be conducted in approximately 15 study sites in Japan.	
Study period (planned): 2021 to 2023	**Clinical phase:** 3

Objectives:

Primary Objectives:

- To evaluate the efficacy of maribavir in CMV viremia clearance at the end of Study Week 8 (8 weeks after start of administration) in Japanese HSCT or SOT recipients with CMV infection.
- To assess the safety and tolerability of maribavir in Japanese transplant recipients with CMV infection.

Secondary Objectives:

- To assess the maintenance of CMV viremia clearance and infection symptom control achieved at Study Week 8 (8 weeks after start of administration) , through Study Week 12 (4 weeks of post-treatment), Study Week 16 (8 weeks of post-treatment), and Study Week 20 (12 weeks of post-treatment).
- To evaluate the time to first confirmed CMV viremia clearance.
- To evaluate the recurrence of confirmed CMV viremia requiring treatment during the 12-week follow-up period in subjects who achieved confirmed viremia clearance at Study Week 8.
- To assess the time course of changes in plasma CMV viremia load from Baseline.
- To evaluate the recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.
- To assess the profile of mutations in the CMV genes conferring resistance to maribavir.
- To assess the CMV viremia clearance at cut-off value of 137 IU/mL at the end of Study Week 8.
- To characterize the pharmacokinetics (PK) of maribavir.

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Rationale:

Immunosuppressive therapies required for successful transplantation lead to an increased vulnerability to severe infections, including CMV. The number of patients with HSCT and SOT cases in Japan in 2018 were 5,673 and 2,427, respectively. In Japan, for HSCT recipients, 1 antiviral (letermovir) is approved for prophylaxis, while there are 3 approved antivirals (ganciclovir, valganciclovir, and foscarnet) for the treatment of CMV disease, which are also used as preemptive therapy agents in clinical practice. For SOT recipients, valganciclovir is approved for prophylaxis, while ganciclovir and valganciclovir are approved for CMV disease and are also used as preemptive therapy agents. The use of these anti-CMV agents is limited by their toxicities such as myelosuppression (ganciclovir and valganciclovir) and renal dysfunction (foscarnet). Clinical studies of maribavir to date demonstrate that it is not associated with myelosuppression or renal impairment and may allow longer treatment durations at a prescribed dose for patients during prolonged periods of immunosuppression following transplantation. The efficacy and safety of maribavir has been evaluated outside of Japan for the treatment of CMV infections and disease in resistant/refractory adult transplant recipients in a Phase 3 trial (completed). In addition, there is an ongoing Phase 3 study in subjects with asymptomatic CMV infection in HSCT recipients.

This study is designed to assess the efficacy, safety, and PK of maribavir, administered at 400 mg twice daily (BID)in Japanese HSCT or SOT recipients with CMV infection, including subjects with symptomatic CMV infection who are resistant or refractory to ganciclovir, valganciclovir, or foscarnet.

Investigational product, dose, and mode of administration:

Investigational product:

- Maribavir will be provided as a 200 mg tablet (oral tablet) and administered at a dose of 400 mg BID.
- No placebo or any active comparator/reference products will be used in the study.

Methodology:

Study TAK-620-3001 is a Phase 3, multicenter, open-label study to evaluate the efficacy, safety and tolerability, and PK of maribavir in Japanese HSCT or SOT recipients with CMV infection, including subjects with symptomatic CMV infection who are resistant or refractory to ganciclovir, valganciclovir, or foscarnet. The study will assess the efficacy of maribavir by measuring the plasma CMV deoxyribonucleic acid (DNA) clearance at Study Week 8. To be eligible for the study, subjects must have a documented CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Results should be available prior to the first study treatment administration to confirm subject eligibility for the study. Both samples should be taken within 14 days prior to first dose of study treatment with the second sample obtained within 5 days prior to first dose of study treatment at Visit 2/Day 0. The study will have 3 phases: (1) 2-week screening phase; (2) 8-week treatment phase; and (3) 12-week follow-up phase. Subjects will be required to visit the site up to 18 times for up to a 22-week period.

"Asymptomatic subjects" are those who do not have CMV tissue-invasive disease or CMV syndrome (SOT subjects only) at Baseline, as determined by the investigator according to the criteria specified by Ljungman et al., 2017.

"Symptomatic subjects" are those who have CMV tissue-invasive disease or CMV syndrome (SOT subjects only) at Baseline, as determined by the investigator according to the criteria specified by Ljungman et al., 2017.

"Refractory" will be defined as: documentation of failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in plasma after a 14 day or longer treatment period with intravenous (IV) ganciclovir/oral valganciclovir, or IV foscarnet. This definition applies to the current CMV infection and the most recently administered anti-CMV agent.

"Resistant" will be defined as: documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir, valganciclovir, or foscarnet.

The documentation of the resistance during screening will be based on the central specialty laboratory genotyping assay results. Plasma samples obtained at Baseline for CMV DNA genotyping will be used for the final determination of mutations in the UL97, UL27, and UL54 genes known to confer resistance to anti-CMV agent; this assessment will be based on the results from the central specialty laboratory and utilized for analysis.

Screening Phase

Subjects will be screened during an approximate 2-week screening phase which will occur from Day -14 to Day 0 in which subjects will undergo evaluation to establish eligibility. If applicable, subjects who meet eligibility requirements will undergo washout of any prohibited medications, the length of which will be specified in the eligibility criteria. Ganciclovir, valganciclovir, and foscarnet must be discontinued prior to the first dose of study treatment. Subjects receiving letermovir must discontinue 3 days prior to first dose of study treatment.

Study Treatment Phase

During the treatment phase (Day 1/Study Week 1 to Day 56/Study Week 8), maribavir will be administered twice daily.

Assessments to be performed at weekly study visits during treatment include: CMV DNA quantification testing, evaluation of symptoms suggestive of CMV disease, underlying disease assessments, graft outcomes and GVHD assessments, resolution or improvement of CMV tissue-invasive disease (symptomatic subjects only), clinical laboratory testing (hematology and chemistry), and concomitant medications and adverse event (AE) review. Pharmacokinetic sample collection, physical examination, vital sign assessment, electrocardiograms (ECGs), immunosuppressive drug level monitoring, and urinalysis will be conducted at selected visits throughout the treatment phase.

Monitoring of concomitant immunosuppressant concentration levels (eg, tacrolimus, cyclosporine, and everolimus) will be conducted at designated study time points. Cytomegalovirus DNA genotyping will be performed on samples at Baseline and in cases of rebound or lack of response to therapy.

Historical laboratory results for tests may be used for eligibility assessment (human immunodeficiency virus [HIV] or hepatitis test results) provided that these are obtained within the specified time period. The Screening and Visit 2/Day 0 visits can occur on the same day, if laboratory results are available for the determination of eligibility.

All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to study treatment administration and all clinical laboratory results required for eligibility verification must be available prior to treatment administration, including 2 separate CMV DNA assessments. Initiation of study treatment (ie, first dose) will only occur after completion of all required Visit 2/Day 0 procedures and confirmation of eligibility. This will be done under the supervision of investigator site personnel.

Depending on the time of the first dose of study treatment at Visit 2/Day 0, a second dose should be administered at Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered at Visit 2/Day 0. Study treatment will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours.

For subjects that, in the investigator's judgment, have a lack of response or are unable to tolerate treatment and require discontinuation of study treatment, alternative anti-CMV treatment may be administered as deemed necessary. Subjects who discontinue study treatment prior to Study Week 8 will complete the end of treatment procedures described for Study Week 8. These subjects will follow a modified Schedule of activities (SoA) through the remaining weekly visits of the study treatment phase and regular SoA through the 12-week follow-up phase.

Follow-up Phase

Study-specific evaluations including central specialty laboratory CMV testing and safety assessments will occur weekly for the first 4 weeks, then every 2 weeks for the final 8 weeks of the 12-week follow-up Phase. Refer to the protocol for a complete list of the evaluations.

Study Design Flow Chart

Wks = Weeks
*Visit 2A is required only for subjects receiving tacrolimus, cyclosporine, or everolimus at baseline.

CMV DNA Quantitation

Blood samples will be assessed at a central specialty laboratory for the quantification of CMV DNA in plasma using the qPCR. Central specialty laboratory plasma CMV DNA results will be reported to the investigator site as available. Additional CMV DNA testing at central specialty laboratory may be performed and collected at more frequent intervals, or additional assay methods may be used at the discretion of the investigator.

Confirmed CMV viremia clearance will be defined as plasma CMV DNA concentration below the lower limit of quantification (LLOQ) to be determined depending on the selected central specialty laboratory, in 2 consecutive postbaseline samples, separated by at least 5 days.

Confirmed recurrence or the confirmed CMV viremia recurrence will be defined as plasma CMV DNA concentration ≥LLOQ to be determined depending on the selected central specialty laboratory in 2 consecutive plasma samples at least 5 days apart, after attaining viremia clearance.

CMV Genotyping and Phenotyping

At Visit 2/Day 0 plasma samples will be obtained and tested by the central specialty laboratory to identify mutations in the viral UL97 and UL54 genes known to confer resistance to anti-CMV agents. In addition, UL27 gene will be tested. Given the urgency to treat the subjects, it is not possible to wait for this central specialty laboratory assessment prior to a subject's study treatment administration to confirm lack of resistance to any previously used agents. For asymptomatic subjects, in instances when a mutation conferring resistance to anti-CMV agents will be reported in the baseline sample analyzed by the central specialty laboratory these subjects will be excluded from the Per Protocol Set for analysis.

During the study, CMV genotyping will be conducted at the central specialty laboratory when the CMV DNA viral load is above a predefined cut off level: in cases of failure to clear CMV viremia during treatment; cases of recurrence of viremia on and off treatment; and cases of viremia rebound if >1 $\log_{10}$ above nadir while on treatment (***Rebound*** is defined as increase in viral DNA load for >1 $\log_{10}$ above nadir without prior clearance of viremia). The entire UL97, UL54, and UL27 CMV genes will be sequenced in every sample that meets the criteria for genotyping, including the baseline samples.

Additionally, virus susceptibility testing (phenotyping) could be performed on selected de-novo CMV mutations/variants of maribavir-treated subjects by recombinant phenotyping to define the association of these mutations with anti-CMV drug resistance. Details of the analysis would be specified in a resistance analysis plan.

CMV Infection Symptomatic Assessment

Cytomegalovirus tissue-invasive disease will be defined as described by Ljungman et al., 2017. The gold standard for diagnosing CMV tissue-invasive disease is the identification of CMV inclusions in the infected cells of the tissues OR identification of CMV in biopsy tissue samples. However, in some cases both diagnostic methods are required when tissue samples have a high chance of being contaminated by body fluids that shed virus (bronchoalveolar lavage [BAL], urine or stool). In some subjects, when it is not possible to obtain a tissue biopsy, a culture of CMV from body fluids or CMV DNA quantitation (for selected cases) may be used to confirm diagnosis, with a lower level of confidence in diagnosis. CMV syndrome (in SOT subjects only) will also be defined as described by Ljungman et al., 2017, and requires at least 2 of 6 signs and symptoms to be present.

All subjects will be monitored for the occurrence of CMV tissue-invasive disease and CMV syndrome throughout the study. For symptomatic subjects who present with CMV tissue-invasive disease and CMV syndrome at Baseline, the investigator will document the initial diagnosis of CMV tissue-invasive disease and CMV syndrome at Visit 2/Day 0 (ie, absence or presence at Baseline) and all serial assessments of infection status (ie, no change, improvement, worsening, or resolution) at all subsequent visits in the study.

The recurrence of symptomatic CMV infection will be defined as the presence of signs or symptoms of the CMV tissue-invasive disease or CMV syndrome (same or new symptomatology) confirmed as per Ljungman et al., 2017 after the period of resolution of symptomatic CMV infection in subjects symptomatic at Baseline.

In subjects asymptomatic at Baseline, the occurrence of new CMV tissue-invasive disease or CMV syndrome after start of study treatment will be assessed by the investigator at all scheduled study visits.

PK Assessment

Pharmacokinetic samples will be obtained for all subjects. Measurements of plasma samples for PK analysis will be conducted while the study is ongoing.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Subjects must:

1. Be able to provide written, personally signed, and dated informed consent (and assent where applicable) to participate in the study before completing any study-related procedures. When subject is below age of 20, voluntary agreement shall be obtained from a parent/both parents or legally authorized representative (LAR) using the written consent form.
2. Be Japanese with Japanese nationality, ≥16 years of age at the time of consent.
3. Be a recipient of HSCT or SOT that is functioning at the time of Screening.
4. Have a documented CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to first dose of study treatment with the second sample obtained within 5 days prior to first dose of study treatment at Visit 2/Day 0.
5. Have the current CMV infection after HSCT or SOT, either primary or reactivation, which, in the investigator's opinion, requires treatment and have any of the following.
    a. *Asymptomatic subjects:* The subjects do not have CMV tissue-invasive disease or CMV syndrome (SOT subjects only) at Baseline, as determined by the investigator according to the criteria specified by Ljungman et al., 2017.
    b. *Resistant or refractory subjects:* The subjects must have a current CMV infection that is refractory to the most recently administered of the anti-CMV treatment agent(s). Refractory is defined as documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in plasma after a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, or IV foscarnet.
6. Have all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory can be used for qualification):
    a. Absolute neutrophil count ≥1,000/mm^3 (1.0×10^9/L)
    b. Platelet count ≥25,000/mm^3 (25×10^9/L)
    c. Hemoglobin ≥8 g/dL
    d. Estimated creatinine clearance ≥30 mL/minute (estimated glomerular filtration rate by Modification of Diet in Renal Disease)
7. Have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening, if a female of childbearing potential. Urine pregnancy tests may be done per institutional requirements; however, they are not sufficient for eligibility determination. Sexually active females of childbearing potential must agree to comply with any applicable contraceptive requirements of the protocol. If male, must agree to use an acceptable method of birth control, as defined in the

protocol, during the study treatment administration period and for 90 days after the last dose of study treatment.

8. Be able to swallow tablets.
9. Have life expectancy of ≥8 weeks.
10. Weigh ≥40 kg.
11. Be willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

Exclusion Criteria:

Subjects must not:

1. Have central nervous system (CNS) CMV tissue-invasive disease or CMV retinitis as assessed by the investigator at the time of Screening and prior to administration at Visit 2/Day 0.
2. Be receiving valganciclovir, ganciclovir, foscarnet, or letermovir when study treatment is initiated, or anticipated to require 1 of these agents during the 8-week treatment period.

   NOTE: Subjects receiving letermovir must discontinue 3 days prior to first dose of study treatment. Ganciclovir, valganciclovir, and foscarnet must be discontinued prior to the first dose of study treatment.
3. Have known hypersensitivity to the active substance or to an excipient of the study treatments.
4. Have severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral medication.
5. Require mechanical ventilation or vasopressors for hemodynamic support at the time of Baseline.
6. Pregnant or nursing female.
7. Have previously completed, discontinued, or have been withdrawn from this study.
8. Have received any investigational agent (including CMV-specific T-cells) with known anti-CMV activity within 30 days before initiation of the study treatment at any time.
9. Have received any unapproved agent or device within 30 days before initiation of the study treatment.
10. Have any clinically significant medical or surgical condition that, in the investigator's opinion, could interfere with interpretation of study results, contraindicate the administration of maribavir, or compromise the safety or well-being of the subject.
11. Have previously received maribavir.
12. Have serum aspartate aminotransferase (AST) >5 times upper limit of normal (ULN) at Screening, or serum alanine aminotransferase (ALT) >5 times ULN at Screening, or total bilirubin ≥3.0 × ULN at Screening (except for documented Gilbert's syndrome), as analyzed by local or central laboratory.
13. Have known (previously documented) positive results for HIV. Subjects must have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local or central laboratory during the screening period.
14. Have active malignancy with the exception of nonmelanoma skin cancer, as determined by the investigator. Subjects who experience relapse or progression of their underlying malignancy (for which HSCT or SOT was performed), as determined by the investigator, are not to be enrolled.
15. Be undergoing treatment for acute or chronic hepatitis C.

Duration of subject participation in the study:

- Planned duration of Screening Phase: 2 weeks.
- Planned duration of Study Treatment Phase: 8 weeks.
- Planned duration of Follow-up Phase: 12 weeks.

The study will be completed in approximately 17 months.

Statistical Analysis:

Subject Populations:

- Enrolled Set: consists of all subjects who have signed an informed consent and have begun some study procedures.
- Full Analysis Set: consists of all subjects who have taken at least 1 dose of study treatment; the Full Analysis Set will be used for efficacy analyses.
- Per-Protocol Set: consists of all subjects in Full Analysis Set who do not have major predefined protocol deviations that may affect the primary efficacy assessment.
- Safety Set: consists of all subjects who have taken at least 1 dose of study treatment. The Safety Set will be used for safety analyses.
- Pharmacokinetic Set: consists of all subjects in the Safety Set who had plasma samples drawn and tested for maribavir concentrations.

Primary Endpoints:

The primary endpoints of this study are:

- Efficacy endpoint: Confirmed clearance of plasma CMV DNA (CMV viremia clearance) at the end of Study Week 8.
- Safety and tolerability assessments: treatment-emergent serious adverse events (SAEs), treatment-emergent adverse events (TEAEs) (including instances of CMV disease), maribavir dose interruptions for AEs, maribavir dose discontinuations for AEs, number of subjects with clinically significant vital signs, number of subjects with abnormal physical examination findings, number of subjects with abnormal clinical laboratory evaluations, number of subjects with clinically significant ECG parameters, and concentration of immunosuppressant drug. New onset of acute or chronic GVHD, graft rejection, or graft loss will be reported and may be assessed as AE/SAE.

Secondary Endpoints:

Secondary Efficacy Endpoints:

- The maintenance of the confirmed CMV viremia clearance and infection symptom control achieved at Study Week 8 through Study Week 12 (4 weeks of post-treatment period), Study Week 16 (8 weeks of post-treatment/follow-up phase), and Study Week 20 (12 weeks of post-treatment).
- The time to first confirmed viremia clearance at any time during the study.
- The recurrence of confirmed CMV viremia during the 12-week follow-up period in subjects with confirmed viremia clearance at Study Week 8 requiring additional anti-CMV treatment.
- The time course of changes in plasma CMV viremia load from Baseline by study week.
- Recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.
- Assessment of the profile of mutations in the CMV genes conferring resistance to maribavir.
- Confirmed plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/mL.

Secondary Pharmacokinetic Endpoint:

- Maribavir C_{min} (predose maribavir concentration)

[redacted]

Statistical Methodology:

All analyses will be descriptive.

Primary Efficacy Endpoint:

The primary efficacy endpoint of this study is confirmed clearance of plasma CMV DNA (CMV viremia clearance) at the end of Study Week 8. For clearance of CMV viremia to be declared at the end of Study Week 8 during the treatment period, the subject must have received study treatment exclusively. Confirmed CMV viremia clearance at the end of Study Week 8 is defined as plasma CMV DNA concentrations <LLOQ with the assay at a central specialty laboratory, in 2 consecutive postbaseline samples, separated by at least 5 days at Study Week 8. Subjects who take alternative anti-CMV treatment before Study Week 8 or have missing data at Study Week 8 due to early discontinuation or any other reasons will be counted as nonresponders.

Assessments of Virological Responders at Study Week 8

Scenario	CMV DNA Weeks on Study					Rationale
	Week 6	Week 7	Week 8	Week 9[a]	Response	
1	+/-	-	-	+/-/NA	Yes	2 consecutive "-" at Week 7 and Week 8
2	+/-	-	+	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
3	+/-	+	-	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
4	+/-	-	NA	-	Yes	2 consecutive "-" as shown by available data and both "-" at Week 7 and Week 9 for missing Week 8, otherwise nonresponder
5	-	NA	-	+/-/NA	Yes	2 consecutive "-" as shown by available data and both "-" at Week 6 and Week 8 for missing Week 7, otherwise nonresponder
6	-	NA	NA	-	Yes	2 consecutive "-" as shown by available data at Week 6 and Week 9 and both "-", otherwise nonresponder

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; LLOQ=lower limit of quantification; NA=not available for evaluation of study drug effect; reason could be either not assessable by lab, by starting alternative anti-CMV treatment, withdrawal from study, etc.

[a] Week 9 data, if available to evaluate effect of study drug, only to be used if Week 8 data are unavailable or missing.

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities. Only CMV DNA data evaluable for assessment of effect of study drug will be included (ie, prior to the start of alternative anti-CMV treatment if any).

"-" = CMV DNA concentration <LLOQ

"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)

Confirmed clearance of plasma CMV DNA (CMV viremia clearance) =2 consecutive postbaseline assessments of

CMV DNA target <LLOQ, separated by at least 5 days.

The proportion of subjects achieving the confirmed CMV viremia clearance at Study Week 8 and the corresponding 95% confidence intervals (CIs) will be calculated.

Other secondary efficacy endpoints and exploratory endpoints will be summarized descriptively. The

denominator for the percentages will be based on the number of subjects. Time-to-event endpoints will be summarized using Kaplan-Meier estimation. Ninety-five percent CIs for the estimated 25%, 50%, and 75% times will be presented.

Primary Safety and Tolerability Endpoints:

Safety and tolerability of maribavir for the treatment of CMV infection after HSCT or SOT will be assessed by evaluation of SAEs, TEAEs (including instances of CMV disease), AEs leading to interruptions of study treatment, AEs leading to discontinuation of study treatment, AEs leading to withdrawals from the study, number of subjects with clinically significant vital signs, number of subjects with abnormal clinical laboratory evaluations, number of subjects with clinically significant ECG parameters, and number of subjects with abnormal physical examination findings. New onset of acute or chronic GVHD, graft rejection, or graft loss will be reported and may be assessed as AE/SAE. Immunosuppression drug levels will be summarized over time.

Two observation periods are defined for the purpose of safety analyses: 1) On-treatment period: from the time of maribavir initiation through 7 days after the last dose of study treatment, and 2) Overall-study period: start of maribavir administration through the end of the study. Safety endpoints will be summarized descriptively for the on-treatment period, and overall-study period, as appropriate. Baseline assessments will be the last assessment before the first dose of the study treatment.

Treatment-emergent AEs are defined as those with a start date on or after the first dose of study treatment, or with a start date before the date of first dose of the study treatment but increasing in severity after the first dose of study treatment.

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not have a causal relationship with study drug. The PTEs will not be evaluated in the safety analysis; they will be listed as pretreatment AEs.

The number of events, incidence, and percentage of TEAEs will be displayed by preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA®) for the on-treatment period and overall-study period. Summaries in terms of severity and relationship to the study treatment will also be provided. Treatment-emergent SAEs will be summarized separately in a similar fashion. Summaries of AEs leading to interruptions of study treatment, discontinuation of study treatment, withdrawals, AEs leading to death, and SAEs will be provided.

Adverse events will be analyzed according to primary system organ classes (SOCs) and PTs. Summary tables with SOCs and PTs will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to the study treatment for the on-treatment period and overall-study period.

Usage of concomitant medications will be summarized descriptively for the on-treatment period and overall-study period. Additionally, administration of hematopoietic growth factors, blood, and blood products will be summarized.

Baseline safety analyses is defined as the last value for the assessment prior to taking the first dose of study treatment. Change from Baseline in vital signs and clinical laboratory tests during on-treatment period and overall-study period will be summarized with descriptive statistics at each assessment visit. Potentially clinically important findings will also be summarized.

Maribavir dose interruptions for any AE will be summarized. Abnormal physical examination findings will be listed. A summary of electrocardiogram findings will be provided.

PK Analysis:

The pharmacokinetic endpoint for this study is maribavir C_{min}.

Individual maribavir plasma concentrations data will be presented in a listing. Maribavir C_{min} (predose maribavir concentration) will be summarized by Visit using descriptive statistics.

In a separate analysis and report, all maribavir concentrations obtained in this study will be combined with PK data from the Phase 1, Phase 2 and Phase 3 studies in adults conducted outside Japan, and analyzed by population PK analysis approach using a nonlinear mixed effect model approach using NONMEM Version 7 or above.

Sample Size Justification:

Post-transplant (SOT/HSCT) CMV infection is a rare condition and the number of patients expected to participate in this clinical trial in Japan is anticipated to be limited. For the start of domestic development of TAK-620, Takeda conducted a feasibility assessment for the planned clinical study. Specifically, a survey on the number of patients in university or large hospitals in Japan where HSCT or SOT are performed was carried out. The number of patients with asymptomatic CMV infection was estimated to be about 44 for HSCT and about 9 for SOT, for a total of about 53 patients. Assuming a dropout rate of 15%, approximately 44 patients with asymptomatic CMV infection are expected to be enrolled. On the other hand, the number of patients with resistant or refractory CMV infection is very small, and only a few patients (approximately 3) can be expected to be enrolled at the maximum.

From the standpoint of feasibility, approximately 44 asymptomatic patients and few resistant or refractory patients are expected to be enrolled in this study.

The target number of patients with asymptomatic CMV infection should be determined from the viewpoint of evaluating the similarities in outcome between the prospective study and the overseas Phase III study (Study SHP620-302) as well as the feasibility of the new study.

For the proportion of patients who achieved CMV clearance at Week 8 in the TAK-620 group in Study SHP620-302, since the results have not been available, we can assume 68%, which was used as the estimation for sample size justification in Study SHP620-302. Regarding the proportion of patients who achieved CMV clearance at Week 8 in this study, since it is the same target population and primary endpoint as Study SHP620-302, it is appropriate to assume 68% as Study SHP620-302.

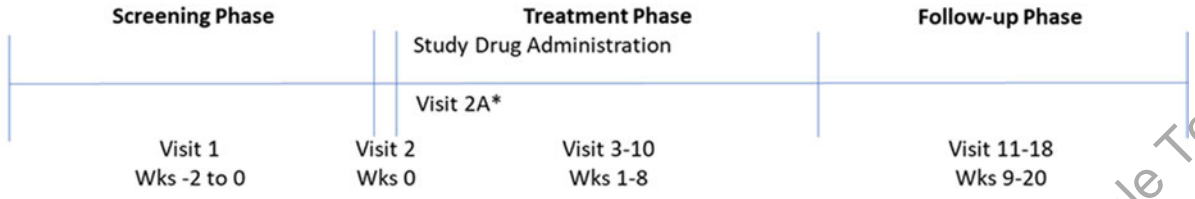
In addition, we considered it appropriate to use -15% as a reference value for the difference in the point estimate between studies based on the noninferiority margin used in 2 noninferiority studies comparing valganciclovir and ganciclovir for CMV treatment (The study reported by Chawla et al., 2012 and VICTOR study [Asberg et al., 2007]).

With a sample size of 44 in asymptomatic patients, if the true response rates for this study is the same as that of the Study SHP620-302, the probability of observing a response rate similar to that of the Study SHP620-302 is high, that is, over 95% the point estimate from this study will be above the point estimate of Study SHP620-302 minus 15%.

Of note, the similarity between SHP620-302 study and Japan study will be based on both the primary endpoint and secondary endpoints.

1.2 Schema

Figure 1. Study Schematic Diagram



Wks = Weeks
*Visit 2A is required only for subjects receiving tacrolimus, cyclosporine, or everolimus at baseline.

1.3 Schedule of Activities

Table 1. Schedule of Activities 1: Screening Phase and Study Treatment Phase

Phase	Screening Phase	Study Treatment Phase[a]									
Study Visit	**1**	**2**	**2A[b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week	**-2 to 0**	**0**	**1[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)[c]	**-14 to 0**	**0[d]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56 (±3)**
Informed consent[e]	X										
Inclusion/exclusion criteria	X	X									
Physical examination[f]		X					X				X
Height	X										
Weight	X	X			X		X		X		X
Vital signs	X	X			X		X		X		X
Medical history	X	X[g]									
Prior medications, therapies, and procedures	X	X									
12-lead ECG[h]		X									X
Hematology/Chemistry[i]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[i]		X			X		X		X		X
Pregnancy test[j]	X	X					X				X
HIV status[k]	X										
HBV, HCV test		X[l]									
CMV DNA test[m]	X	X		X	X	X	X	X	X	X	X
CMV infection symptomatic assessment[n]	X	X	X	X	X	X	X	X	X	X	X
Immunosuppressant drug concentration levels[o]		X	X	X							X
PK plasma samples[p]				X			X				X
Interactive Response Technology[q]	X	X		X	X	X	X	X	X	X	
Study treatment dispensed[r]		X		X	X	X	X	X	X	X	

Table 1. Schedule of Activities 1: Screening Phase and Study Treatment Phase

Phase	**Screening Phase**	**Study Treatment Phase[a]**									
Study Visit	**1**	**2**	**2A[b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week	**-2 to 0**	**0**	**1[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)[c]	**-14 to 0**	**0[d]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56 (±3)**
Underlying disease assessment[s]	X	X		X	X	X	X	X	X	X	X
Graft outcomes[t]	X	X		X	X	X	X	X	X	X	X
GVHD assessment (for HSCT subjects only)	X	X		X	X	X	X	X	X	X	X
Liver function assessment by Child-Pugh classification		X									
Comorbidity status evaluation		X					X				X
Concomitant medications, therapies, and procedures[u]		X	X	X	X	X	X	X	X	X	X
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; CMV=cytomegalovirus; CRF=case report form; DNA=deoxyribonucleic acid; ECG=electrocardiogram; GI=gastrointestinal; GVHD=graft-versus-host-disease; HBV=hepatitis B virus; HCV=hepatitis C virus; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HSCT=hematopoietic stem cell transplant; IRT=interactive response technology; PK=pharmacokinetic; qPCR=quantitative polymerase chain reaction; SAE=serious adverse event, SoA=schedule of activities.

[a] Subjects who permanently discontinue study treatment will complete the end of treatment procedures described for Visit 10/Study Week 8; these subjects will continue a modified SoA through the remaining weekly visits scheduled for the study treatment phase and the regular SoA through the 12-week follow-up phase. The end of treatment sample for immunosuppressant drug concentration level will be collected at the next visit scheduled 1 week after the treatment discontinuation. Subjects who discontinue study treatment early will not be asked to complete the following procedures after the end of treatment visit for subsequent visits in the study treatment phase: dispense or use of study treatment, and PK plasma sample collection. After completing the 8-week duration specified for the study treatment phase, subjects will enter the 12-week follow-up phase.

[b] Immunosuppressant drug concentration testing and Visit 2A are solely for subjects receiving immunosuppressive therapy with tacrolimus, cyclosporine, or everolimus. Visit 2A will occur at Day 4±1 day for subjects receiving immunosuppressive agent at Baseline; or 4±1 day after initiating 1 of these immunosuppressive treatments for subjects who start during the study.

[c] Permissible assessment windows: Visit 2A, ±1 day, Visit 3 (Study Week 1) +2 days, Visit 4 (Study Week 2) to Visit 6 (Study Week 4), ±2 days; Visit 7 (Study Week 5) to Visit 10 (Study Week 8), ±3 days.

[d] Screening and Visit 2/Day 0 visits can occur on the same day in the case when historical laboratory values are available for determination of the eligibility. All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to initiation of the study treatment. The test results for the samples taken at Visit 2, from central laboratory or central specialty laboratory, will not be available to be used for the screening. Initiation of study treatment (ie, first dose) will only occur after completion of all required Visit 2/Day 0 procedures, and confirmation of eligibility. This will be done under the supervision of investigator's site personnel.

Table 1. Schedule of Activities 1: Screening Phase and Study Treatment Phase

Phase	Screening Phase	Study Treatment Phase[a]									
Study Visit	**1**	**2**	**2A[b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (End of Treatment)**
Study Week	**-2 to 0**	**0**	**1[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day (permitted window)[c]	**-14 to 0**	**0[d]**	**4 (±1)**	**7 (+2)**	**14 (±2)**	**21 (±2)**	**28 (±2)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56 (±3)**

[e] Informed consent must be obtained before any study-specific procedures are performed, and the first informed consent can be obtained more than 14 days prior to Day 0. If over 14 days have passed since the first informed consent date, it must be obtained again before starting study treatment. All screening procedures will be completed within 14 days prior to initiation of study treatment, with the exception of: 1) screening clinical laboratory tests (hematology, chemistry, and pregnancy), which must be performed and verified within 3 days prior to initiation of study treatment; either central or local laboratory results for hematology/chemistry/pregnancy testing can be used for qualification, and 2) documentation of CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory qPCR or comparable quantitative CMV DNA results. Results should be available before the subject is administered study treatment to verify subject eligibility for the study. Both samples should be taken within 14 days prior to first dose of study treatment administration with the second sample obtained within 5 days prior to first dose of study treatment administration.

[f] Symptom-oriented physical examinations other than protocol-specified examinations will be performed when clinically indicated.

[g] Updated medical history at Visit 2/Day 0.

[h] Electrocardiograms other than protocol-specified ECGs will be performed when clinically indicated.

[i] Central clinical laboratory tests will be performed for all specified time points during the study with the exception of Visit 2A (for subjects receiving tacrolimus, cyclosporine, or everolimus); a local laboratory will assess potassium and magnesium at Visit 2A for these subjects. Central or local laboratory results for hematology/chemistry/pregnancy testing can be used for eligibility and their results must be available prior to initiation of the study treatment. Local laboratory hCG test results can be used for the assessment of pregnancy at Visit 2/Day 0/Study Week 0, prior to study treatment administration. Sample for hematology/chemistry/pregnancy will be taken for analyses by the central laboratory before study treatment administration at Baseline.

[j] Female subjects of childbearing potential will have serum pregnancy testing performed at a central or local laboratory. Urine test results may be performed to accommodate institutional requirements, however, are not sufficient for eligibility determination.

[k] Human immunodeficiency virus status confirmed within 3 months prior to eligibility assessment will be used for the evaluation of this criterion. If a subject is known (previously documented) to be HIV positive, this information will be used in the eligibility assessment. Local or central testing during screening will be required for the eligibility assessment for subjects for whose HIV status within the 3 months prior to study entry is unknown; negative results must be confirmed prior to study treatment administration.

[l] Hepatitis B virus and HCV historical results available within 3 months prior to study treatment initiation will be accepted. If historical values are not available, then the test will be performed at Visit 2/Day 0. The results of test do not have to be available prior to the study treatment administration.

[m] Blood samples taken at all study visits (processed to obtain plasma) for all CMV DNA tests (quantitation, genotyping) will be tested in the central specialty laboratory. The screening results from the central specialty laboratory will be utilized for eligibility assessment.

[n] Subjects with CMV tissue-invasive disease or CMV syndrome (SOT subjects only) present at Visit 2/Day 0 (Baseline) will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution. All subjects will be assessed at each visit for new tissue-invasive disease or CMV syndrome, and any new tissue-invasive disease or CMV syndrome will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution.

[o] If the subject is receiving immunosuppressant drugs (tacrolimus, cyclosporine, or everolimus) at Visit 2 (Day 0), then a blood sample to measure immunosuppressant drug concentration will be obtained at Visit 2 (Day 0) prior to study treatment administration. If the subject is not receiving immunosuppressant drugs at Day 0 but starts any time after Day 0 while still receiving study treatment, then a blood sample to measure immunosuppressant drug concentration will be obtained 4 days±1 day after initiating the

Table 1. Schedule of Activities 1: Screening Phase and Study Treatment Phase

Phase	Screening Phase	Study Treatment Phase[a]									
Study Visit	1	2	2A[b]	3	4	5	6	7	8	9	10 (End of Treatment)
Study Week	-2 to 0	0	1[b]	1	2	3	4	5	6	7	8
Study Day (permitted window)[c]	-14 to 0	0[d]	4 (±1)	7 (+2)	14 (±2)	21 (±2)	28 (±2)	35 (±3)	42 (±3)	49 (±3)	56 (±3)

immunosuppressant, and at the next scheduled study visit. Tests will be performed at a local laboratory or central laboratory. The results of the measurement of immunosuppressant concentration must be recorded on the eCRF.

[p] Pharmacokinetic samples will be taken before the morning dose of the study treatment at all 3 PK visits. A PK plasma sample will also be taken 2 to 4 hours after the morning dose of study treatment at Visit 3/Study Week 1 and Visit 10/Study Week 8. There will be no postdose PK plasma sample collected for Visit 6/Study Week 4. Additional PK plasma samples will be collected from the subjects with biopsy-proven GI GVHD with diarrhea (>300 mL/day), biopsy-proven GI GVHD with nausea and vomiting, documented acute GVHD of liver (Stage II, total bilirubin >3 mg/dL or biopsy-proven) with diarrhea (>500 mL/day), or biopsy-proven acute GVHD of the skin with diarrhea (>500 mL/day).

[q] The IRT system will be used for dispensing study treatment.

[r] All administered/dispensed study treatments will be documented on the CRFs and/or other investigational product records and may include additional information as required per applicable regulations. The disposition of unused supply of dispensed study treatment that has been prescribed to the subject will be documented in the accountability log.

[s] Underlying disease that led to HSCT or SOT, including relapse/progression, will be assessed at all visits throughout the study treatment phase.

[t] Graft outcomes (acute rejection or graft loss) will be assessed for both SOT and HSCT subjects.

[u] Includes recording of medications and transfusions of blood products. Changes in immunosuppression regimens will also be recorded.

Table 2. Schedule of Activities 2: Follow-up Phase

Phase	Follow-up Phase[a]							
Visit	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18 (End of Study)**
Study Week (Follow-up Week)[b]	**9(1)**	**10(2)**	**11(3)**	**12(4)**	**14(6)**	**16(8)**	**18(10)**	**20(12)**
Study Day (Follow-up Day), (permitted window)	**63(7), (±2)**	**70(14), (±2)**	**77(21), (±2)**	**84(28), (±2)**	**98(42), (±3)**	**112(56), (±3)**	**126(70), (±3)**	**140(84), (±3)**
Physical examination (including weight)								X
Vital signs								X
12-Lead ECG[c]								X
Hematology/Chemistry[d]		X		X		X		X
Urinalysis[d]								X
Immunosuppressant drug concentration level[e]	X							
Underlying disease assessment[f]	X	X	X	X	X	X	X	X
CMV DNA test[g]	X	X	X	X	X	X	X	X
CMV infection symptomatic assessment[h]	X	X	X	X	X	X	X	X
Graft outcomes[i]	X	X	X	X	X	X	X	X
GVHD assessment (for HSCT subjects only)	X	X	X	X	X	X	X	X
Comorbidity status evaluation				X		X		X
AE monitoring[j]	X	X	X	X	X	X	X	X
SAE monitoring[j]	X	X	X	X	X	X	X	X
Concomitant medications, therapies, and procedures[k]	X	X	X	X	X	X	X	X

AE=adverse event; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ECG=electrocardiogram; GVHD=graft-versus-host disease; HSCT=hematopoietic stem cell transplant; SAE=serious adverse event; SOT=solid organ transplant.

[a] Subjects who withdraw from the study during the follow-up phase will perform the Visit 18/Study Week 20 (Follow-up Week 12) end of study procedures.

[b] Permissible assessment windows: Study Weeks 9 to 12 (Follow-up Weeks 1 to 4) ±2 days; Study Weeks 14 to 20 (Follow-up Weeks 6 to 12) ±3 days.

[c] Electrocardiograms other than protocol-specified ECGs will be performed when clinically indicated.

[d] Clinical laboratory testing performed at a central laboratory for all specified time points during the follow-up phase.

[e] If the subject is receiving immunosuppressant drugs (tacrolimus, cyclosporine, or everolimus) on Study Day 0, then a blood sample to measure immunosuppressant drug concentration will be obtained at the Follow-up Week 1 post-treatment follow-up visit (ie, 1 week [±2 days] after discontinuation of study treatment). If the subject is not receiving immunosuppressant drugs at Day 0, but starts any time after Day 0 while still receiving study treatment, then a blood sample to measure immunosuppressant drug concentration will be obtained at the Follow-up Week 1 post-treatment follow-up visit (ie, 1 week [±2 days] after discontinuation of study treatment). Tests will be performed at a local laboratory or central laboratory. The results of the measurement of immunosuppressant concentration must be recorded on the eCRF.

[f] Underlying disease that led to HSCT or SOT, including relapse/progression, will be assessed at all visits throughout the follow-up phase.

Table 2. Schedule of Activities 2: Follow-up Phase

Phase	Follow-up Phase[a]							
Visit	11	12	13	14	15	16	17	18 (End of Study)
Study Week (Follow-up Week)[b]	9(1)	10(2)	11(3)	12(4)	14(6)	16(8)	18(10)	20(12)
Study Day (Follow-up Day), (permitted window)	63(7), (±2)	70(14), (±2)	77(21), (±2)	84(28), (±2)	98(42), (±3)	112(56), (±3)	126(70), (±3)	140(84), (±3)

[g] Blood sample taken at all study visits (processed to obtain plasma), for all CMV DNA tests (quantitation, genotyping) during the follow-up phase will be tested in the central specialty laboratory.

[h] Subjects with CMV tissue-invasive disease or CMV syndrome (SOT subjects only) present at Visit 2/Day 0 (Baseline) will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution. All subjects will be assessed at each visit for new tissue-invasive disease or CMV syndrome, and any new tissue-invasive disease or CMV syndrome will have serial assessments at all subsequent visits for infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) until resolution.

[i] Graft outcomes (acute rejection or graft loss) will be assessed for in both SOT and HSCT subjects.

[j] Serious adverse events and nonserious AEs deemed related to the study treatment will be monitored and recorded through Visit 18/Study Week 20/Follow-up Week 12 (end of study). Nonserious AEs will be recorded through 30 days after the last dose of study treatment.

[k] All medications, therapies, and procedures used to treat AEs will be recorded through Visit 18/Study Week 20/Follow-up Week 12 (end of study).

2. INTRODUCTION

2.1 Indication and Current Treatment Options

Cytomegalovirus (CMV) is a beta herpes virus that commonly infects humans; serologic evidence of prior infection can be found in 40% to 100% of various adult populations (de la Hoz et al., 2002). However, serious disease occurs almost exclusively in individuals with compromised immune systems. Cytomegalovirus remains a significant problem for patients undergoing various types of transplants that are associated with the use of potent immunosuppressive chemotherapy, including hematopoietic stem cell transplants (HSCT) and solid organ transplants (SOT) (de la Hoz et al., 2002; Razonable and Emery, 2004).

Cytomegalovirus can cause multiorgan disease in recipients of stem cell transplants, including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis, and the disease can develop both early and late after the transplantation procedure (Boeckh et al., 2003; Boeckh and Ljungman, 2009; Krause et al., 1997; Zaia et al., 1997).

In addition to the direct effects that manifest as CMV organ disease or symptomatic infection, CMV also is known to have several potential indirect effects. These indirect effects include an increased incidence of opportunistic infections, an association between CMV and graft-versus-host disease (GVHD) predominately in patients with HSCT, and associations between CMV and graft rejection or other allograft pathology in patients with SOT, and reduced patient survival (Rubin, 1989; Hodson et al., 2005; Ljungman et al., 2006). These effects are believed to be mediated by the virus's ability to modulate the immune system, either directly or secondary to the host antiviral response through regulation of cytokine, chemokine, and/or growth factor production.

Cytomegalovirus prevention strategies (prophylaxis or preemptive therapy) for various high-risk transplant subjects exist, however, CMV infection or disease can still occur within the early (initial approximate 3 months) or later post-transplantation time periods (Boeckh et al., 2003; Legendre and Pascual, 2008). Cytomegalovirus viremia is considered 1 of the most important predictors of development of CMV disease (Emery et al., 2000; Humar et al., 1999). In kidney transplant recipients, the highest incidence of symptomatic CMV infection (syndrome) or disease occurs in CMV-seronegative recipients who receive a kidney from a CMV-seropositive donor (Paya et al., 1989; Kanj et al., 1996; Singh et al., 2004; Winston et al., 1995).

Although the currently available systemic anti-CMV agents, intravenous (IV) or oral ganciclovir, oral valganciclovir (a prodrug of ganciclovir with improved bioavailability), IV foscarnet, and IV cidofovir (not approved in Japan) are generally effective, their use is limited by their respective toxicities; bone marrow suppression caused by ganciclovir/valganciclovir and renal impairment caused by foscarnet or cidofovir (not approved in Japan) (Boeckh et al., 2003;

Ljungman et al., 2001; Reusser et al., 2002; Salzberger et al., 1997). These toxicities are of particular concern in transplant patients, in whom the bone marrow has been ablated or significantly suppressed (patients with HSCT), who receive ongoing immunosuppressants to prevent organ rejection (patients with SOT) or GVHD (in patients with HSCT), or who may require the use of other therapies that are potentially toxic to the kidneys or other organs (patients with SOT and HSCT).

Regardless of currently available antiviral strategies that exist for various high-risk transplant subjects, the adverse effects of these strategies have led to low use of prophylaxis in the HSCT recipients who continue to remain at risk for CMV infection within the early (initial approximate 3 months) or later post-transplantation time periods (Boeckh et al., 2003; Legendre and Pascual, 2008).

In contrast, preemptive strategies are widely preferred as a prevention method by transplant centers and include close surveillance of target viral deoxyribonucleic acid (DNA) concentration (CMV viremia), which varies depending on host's risk for CMV disease, current immunosuppression, and treatment center practice. Cytomegalovirus viremia is considered 1 of the most important predictors of development of CMV disease (Emery et al., 2000; Humar et al., 1999).

In Japan, for HSCT recipients, 1 antiviral (letermovir) is approved for prophylaxis while there are 3 approved antivirals (ganciclovir, valganciclovir, and foscarnet) for the treatment of CMV disease, which are also used as preemptive therapy agents in clinical practice. For SOT recipients valganciclovir is approved for prophylaxis, while ganciclovir and valganciclovir are approved for CMV disease. The use of these anti-CMV agents is limited by their toxicities. Also, development of antiviral resistance to these anti-CMV agents is an ongoing clinical problem leading to graft loss and even mortality for some transplant patients.

Maribavir is currently under development for the treatment of CMV infection or disease, including those resistant or refractory to ganciclovir, valganciclovir, or foscarnet, in transplant recipients (HSCT and SOT). Based on clinical studies completed to date, maribavir does not appear to cause bone marrow suppression or renal toxicities and therefore may offer a safer option for CMV treatment in patients with HSCT.

2.2 Product Background and Clinical Information

Maribavir is a potent and selective, orally bioavailable antiviral drug with a novel mechanism of action against CMV (Chulay et al., 1999) and has a favorable nonclinical and clinical safety profile. It is a potent member of a class of drugs, the benzimidazole ribosides (Williams et al., 2003). In side-by-side in vitro assays it is 3- to 20-fold more potent than

ganciclovir and at least 100-fold more potent than foscarnet (Biron et al., 2002; Drew et al., 2006).

Unlike currently available anti-CMV agents that inhibit CMV DNA polymerase, maribavir inhibits the CMV UL97 serine/threonine kinase by competitively inhibiting the binding of adenosine triphosphate (ATP) to the kinase ATP-binding site (Biron et al., 2002; Williams et al., 2003; Krosky et al., 2003; Wolf et al., 2001; Kern et al., 2004); the dominant phenotypic inhibitory effect of maribavir is on viral DNA assembly and egress of viral capsids from the nucleus of infected cells (Biron et al., 2002). Except for ganciclovir, maribavir does not antagonize the effects of other antiviral (anti-CMV) agents. Since ganciclovir is dependent on its initial phosphorylation by the viral UL97 kinase, maribavir may antagonize its clinical efficacy. Maribavir is active in vitro against and clinically against strains of CMV that are resistant to ganciclovir or foscarnet.

2.2.1 Pharmacokinetics, Metabolism, and Drug-Drug Interactions

Results from the Phase 1 studies demonstrated that following oral administration, maribavir was rapidly and well absorbed with mean peak plasma concentrations generally achieved between 1 and 3 hours postdose. After administration of single and multiple doses (both twice daily [BID] and 3 times daily regimens) over 28 days, total maribavir plasma concentrations increased with increasing dose proportionally up to 1,600 mg (single dose) and 2,400 mg (multiple doses), respectively. At dose levels ≥900 mg BID, there was no apparent increase in maximum concentration (C_{max}) levels. Maribavir demonstrates time-independent pharmacokinetics (PK). Pharmacokinetic data obtained in Phase 2 studies were similar to the data observed in healthy volunteers.

Administration of maribavir in conjunction with food resulted in a 28% decrease in C_{max} and prolonged time to maximum concentration from 1.5 hours to 2.0 hours without a significant effect on area under the concentration-time curve (AUC) when compared with administration under fasting conditions. Bioavailability of a 100 mg tablet was unaffected by crushing the tablet or changes in gastric pH. Maribavir was bound to plasma proteins, namely human serum albumin, lipoproteins, and alpha-1-acid-glycoprotein. The fraction of unbound maribavir was estimated at approximately 1.5% in healthy subjects. Following 400 mg BID doses, the elimination half-life of maribavir was estimated to be 3.87 hours in healthy subjects and 4.32 hours in transplant patients based on noncompartmental analysis. Maribavir is metabolized primarily in the liver through CYP3A4 pathway with the formation of the primary metabolite, VP 44469. Renal clearance is a minor route of elimination of maribavir.

A mass balance study in healthy male and female subjects following administration of a single 400 mg oral dose of [^{14}C] maribavir resulted in fecal recovery of radiolabel that averaged about

14% and recovery of radiolabel in the urine that averaged about 61%. In plasma, the predominant drug-related species was unchanged maribavir, representing approximately 88% of total radioactivity and VP 44469 represented approximately 12% during the first 24 hours.

In vitro studies indicated that CYP3A4 (a hepatic metabolizing enzyme) is the primary enzyme involved in the formation of VP 44469 from maribavir; CYP1A2 may also be involved in VP 44469 formation. In vitro studies also demonstrated that maribavir is not an inhibitor of CYP3A4, CYP2A6, CYP2B6, CYP2C8, CYP2D6, or CYP2E1. It is potentially a weak inhibitor of CYP1A2, 2C9, and 2C19. VP 44469 is not an inhibitor of CYP enzymes.

Maribavir is a substrate as well as an inhibitor of P-glycoprotein (P-gp: a transporter protein). Clinical studies conducted to evaluate the potential of drug-drug interactions demonstrated the following:

- Concomitant administration of maribavir (400 mg BID) with tacrolimus, a substrate of CYP3A4 and P-gp, resulted in increased tacrolimus C_{max}, AUC, and plasma concentration at the end of a dosing interval (C_{trough}) by 38%, 51%, and 57%, respectively.
- Maribavir did not have a clinically significant effect on the activity of CYP1A2, CYP3A, CYP2C9, CYP2C19 or CYP2D6.
- Concurrent administration of rifampin, a strong inducer of CYP3A4 and P-gp, and maribavir significantly reduced plasma concentrations of maribavir, resulting in a 60% reduction in AUC and 82% reduction in C_{trough}, reduced half-life, and significantly increased clearance, most likely due to induction of hepatic and intestinal CYP3A4, and potential induction of P-gp.
- Concomitant administration of antacid had no effect on maribavir exposure.
- Concomitant administration of ketoconazole increased maribavir AUC and C_{max} by 53% and 10%, respectively.

No clinically relevant impact on maribavir PK related to age (18 to 79 years), sex, race (Caucasian, Black, Asian or others), ethnicity (Hispanic/Latino, or non-Hispanic/Latino), or weight (36 to 141 kg) were identified based on population PK analysis. Transplant types (eg, HSCT versus. SOT) or between SOT types (liver, lung, kidney, or heart) or presence of gastrointestinal (GI) GVHD do not impact PK of maribavir.

The effect of renal impairment on maribavir PK was evaluated in a single dose (400 mg) study with 12 subjects with normal renal function (creatinine clearance >80 mL/minute), 10 subjects with mild/moderate renal impairment (creatinine clearance 30 to 80 mL/minute), and 9 subjects with severe renal impairment (creatinine clearance <30 mL/minute). Mean PK parameter

estimates based on total or unbound plasma drug concentrations for subjects with normal renal function, mild/moderate renal impairment, and severe renal impairment were similar. Based on the results from this study, renal impairment does not affect the PK of maribavir; dose adjustment for subjects with mild to severe renal impairment is not needed. There is no experience with the use of maribavir in subjects receiving peritoneal dialysis or hemodialysis. Due to the high plasma protein binding of maribavir, dialysis is unlikely to reduce plasma concentrations of maribavir significantly.

The effect of hepatic impairment on the PK of maribavir was evaluated in a single dose study (200 mg) with 10 subjects with normal hepatic function and 10 subjects with moderate hepatic impairment based on a Child-Pugh Class B classification. Moderate hepatic impairment results in a modest increase in total plasma maribavir C_{max} and AUC values (and modestly reduced clearance values) when compared with subjects with normal hepatic function. However, C_{max} and AUC values based on unbound plasma concentrations of maribavir were comparable among these groups.

The population PK analysis conducted based on relevant Phase 1, 2 and 3 studies showed that the steady-state area under the concentration-time curve from time 0 extrapolated to infinite time ($AUC_{0-\infty}$), C_{max}, and C_{trough} were 27%, 5%, and 70% higher, respectively, in transplant patients than in healthy subjects likely due to the decreased liver/kidney function in transplant patients and their multiple concomitant medications which could impact the disposition of maribavir. The apparent differences in exposure between healthy subjects and transplant patients are not considered clinically significant.

2.2.2 Efficacy

Once the safety and tolerability of maribavir was established across a wide range of doses (up to 2,400 mg/day for 28 days) in 15 Phase 1 studies, the clinical development plan focused on maribavir as an anti-CMV agent for the prevention of CMV disease in transplant patients.

Results from the Phase 3 trials for CMV prevention, where maribavir was administered at 100 mg BID for up to 12 weeks in HSCT recipients and up to 14 weeks in liver transplant recipients, failed to show reduction in the incidence of endpoint adjudication committee confirmed CMV disease within 6 months following HSCT when compared with placebo (Study 1263-300), and failed to show noninferiority to ganciclovir with respect to the incidence of endpoint adjudication committee confirmed CMV disease within 6 months following liver transplantation (Study 1263-301).

Maribavir was used for treatment of CMV infections in 6 transplant recipients (5 SOT, 1 HSCT) under individual emergency investigational new drug (EIND) applications in the United States (US) (Avery et al., 2010). All patients had previously been treated with multiple other anti-CMV drugs, and 4 out of 6 had known genotypic CMV resistance to 1 or more of those CMV drugs. For all 6 patients, oral maribavir treatment was initiated at a dose of 400 mg BID. In 2 patients, the dose was increased to 800 mg BID. The duration of treatment was individualized for each patient based on response.

Maribavir appeared to be safe and well-tolerated, as it was administered for prolonged periods of time (4 out of 6 patients were dosed >6 months). Three patients reported 7 serious adverse events (SAEs), all of which were considered to be unrelated to maribavir.

Within 6 weeks of starting maribavir treatment, all subjects had a >1 $\log_{10}$ decrease in blood CMV DNA, and 4 of the 6 patients had no detectable CMV. Cytomegalovirus viremia persisted in 2 patients despite dosing >6 months; 1 of these patients had unusually low exposure to maribavir based on trough blood levels. The other patient in whom CMV viremia persisted had a very high baseline CMV DNA level. The genotypic analysis for this patient revealed the presence of UL97 maribavir-resistance mutations T409M and H411Y (Strasfeld et al., 2010).

Subsequently, in Europe, more than 200 patients received maribavir through a named patient program (NPP), and in France, through the authorized therapeutic-use procedure. Data from only a small subset of the French NPP were reported. These data were consistent with the US EIND experience. Additional details regarding these patients are available in the SHP620 (Maribavir) Investigator's Brochure Edition 20.0 04Feb21.

The data obtained from the small number of patients in EIND and NPP, suggested that maribavir was associated with a reduction in CMV DNA in the blood in the majority of subjects, and could be useful for the treatment of CMV infections including those that are resistant or refractory to currently available anti-CMV therapies. As a result, 2 Phase 2 studies were conducted to assess the safety, tolerability, and anti-CMV activity of maribavir for treatment of CMV infections: Study SHP620-202 in transplant recipients with CMV infections or disease that are resistant or refractory to treatment with anti-CMV agents conducted in the US and Study 1263-203 (SHP620-203) in transplant recipients with wild-type CMV infections who do not have CMV organ disease (asymptomatic) conducted in Europe. In these studies subjects received maribavir at 1 of 3 dose strengths: 400, 800, or 1,200 mg BID. Both studies demonstrated favorable anti-CMV activity of maribavir and showed that maribavir was well-tolerated.

The primary efficacy endpoint for Study SHP620-202 was confirmed undetectable plasma CMV DNA within the 6 weeks after starting study drug treatment, defined as 2 consecutive postbaseline, on treatment undetectable results (<200 copies/mL) separated by at least 5 days.

Overall, 67% of subjects achieved confirmed undetectable plasma CMV DNA within 6 weeks. Among maribavir groups, there was no strong evidence of dose strength differentiation in the proportion of subjects achieving the endpoint. Among subjects with ≥1 investigator-reported CMV genetic mutation associated with resistance to ganciclovir/valganciclovir or foscarnet at Baseline, 43/71 (61%) achieved confirmed undetectable plasma CMV DNA within 6 weeks after starting treatment with maribavir.

Secondary efficacy endpoints for Study SHP620-202 included CMV recurrence, defined as achievement of undetectable plasma CMV DNA in at least 2 consecutive samples separated by at least 5 days at any time after Day 1, followed by detectable plasma CMV DNA in at least 2 consecutive samples separated by at least 5 days. Overall, 30/86 (35%) maribavir subjects had a CMV recurrence at any time during the study (Note: Percentage is based on the number of subjects achieving undetectable CMV DNA). Twenty-four of the 30 subjects had a CMV recurrence while on study drug. Thirteen of these 24 subjects developed UL97 mutations previously described to confer resistance to maribavir that were not present prior to study drug dosing. The remaining 6 maribavir subjects had a CMV recurrence after the end of treatment with study drug.

The primary efficacy endpoint for Study SHP620-203 was confirmed undetectable plasma CMV DNA within 3 and 6 weeks after starting study drug treatment, defined as 2 consecutive postbaseline, on treatment undetectable results (<200 copies/mL) separated by at least 5 days. The proportion of subjects with undetectable plasma CMV DNA within 3 and 6 weeks after starting study drug treatment was numerically higher in the maribavir group than the valganciclovir group. Among the 3 maribavir dose strength groups, there was no difference in the proportion of subjects achieving the endpoint. In the subgroup of subjects whose transplant type was HSCT, a numerically higher percentage of subjects in the overall maribavir group (75%) than the valganciclovir group (48%) achieved confirmed undetectable plasma CMV DNA within 6 weeks. Although the percentage of subjects with high baseline plasma CMV DNA (≥10,000 copies/mL) was similar between the overall maribavir and valganciclovir groups (34% versus 33%), a numerically higher percentage of maribavir subjects (77%) achieved confirmed undetectable plasma CMV DNA within 6 weeks compared with valganciclovir (65%).

Secondary efficacy endpoints for Study SHP620-203 included CMV recurrence; this was assessed within 6 weeks after starting study drug treatment and within the study participation period. Overall, 22/98 (22%) maribavir subjects and 5/28 (18%) valganciclovir subjects experienced a CMV recurrence within the study participation period (Note: Percentages are based on the number of subjects achieving undetectable CMV DNA). Four of the 22 maribavir subjects recurred while on study drug (2 subjects each in the 400 mg BID and 800 mg BID groups).

All 4 of these subjects developed UL97 mutations previously described to confer resistance to maribavir that were not present prior to study drug dosing. The remaining 18 maribavir subjects and all 5 valganciclovir subjects experienced a CMV recurrence after the end of study drug treatment.

Phase 3 registration trials were planned based on the results from these Phase 2 studies for CMV treatment.

The primary objective for the recently completed Study SHP620-303 was to compare the efficacy of maribavir to investigator assigned treatment (IAT) in CMV viremia clearance at the end of Study Week 8 in transplant recipients who were resistant or refractory to prior anti-CMV treatment. Maribavir was superior to IAT in achieving confirmed CMV viremia clearance in transplant recipients. The proportion of maribavir-treated subjects who achieved confirmed CMV viremia clearance at Week 8 was more than 2-fold higher than subjects who received standard-of-care treatment with IAT in the randomized set (maribavir: 55.7%; IAT: 23.9%).

The key secondary objective of this study was to compare the efficacy of the 2 study treatment arms on CMV viremia clearance and CMV tissue-invasive disease and CMV syndrome improvement or resolution at the end of Study Week 8, and maintenance of this treatment effect through Study Week 16. Forty-four (18.7%) maribavir-treated subjects and 12 (10.3%) subjects in the IAT group were responders not only for virologic response, but also for CMV infection symptom control at the end of Week 8 and maintained the treatment effect through Week 16 (adjusted difference in proportions [95% confidence interval (CI)]: 9.5 [2.02, 16.88], p=0.013).

Study SHP620-303 concluded that maribavir was an efficacious treatment for subjects with post-transplant CMV infection and disease. The effect of maribavir on viral clearance was superior to conventional therapy, demonstrating superiority to IAT in achieving CMV viremia clearance at Week 8 in post-transplant recipients with refractory CMV infection, including resistant CMV (SHP620-303 [Maribavir] Clinical Study Report).

2.2.3 Safety

Maribavir has been administered across a broad range of oral doses from 50 mg to 2,400 mg/day. Clinical safety experience has been obtained from 16 Phase 1 studies in adult healthy volunteers, special populations (subjects with renal and hepatic impairment, and stable renal transplant recipients), and human immunodeficiency virus (HIV)-infected subjects.

Maribavir had a favorable safety and tolerability profile in both the Phase 2 and Phase 3 trials for CMV prophylaxis. Adverse events (AEs) were most commonly associated with GI disorders (eg, diarrhea, dysgeusia, nausea, and vomiting). These events were generally of mild or moderate intensity. There were no signals of clinically significant effects of maribavir on vital signs, electrocardiogram (ECG) parameters, or laboratory findings in the studies conducted for CMV prophylaxis.

In both Phase 2 studies for treatment of CMV infection (Studies SHP620-202 and SHP620-203), subjects received maribavir at 1 of 3 dose strengths: 400, 800, or 1,200 mg BID, and both studies demonstrated that maribavir was well-tolerated. In Study SHP620-202, treatment-emergent AEs (TEAEs) that occurred were events already observed in previous studies (ie, dysgeusia, GI events, elevated immunosuppressant drug levels, and rash) and there were no additional safety concerns raised from this study. In Study SHP620-203, TEAEs that occurred at a higher frequency in maribavir subjects compared with valganciclovir were events already observed in previous studies with maribavir (ie, dysgeusia, GI events, and elevated immunosuppressant drug levels). Analyses of clinical laboratory, vital signs, and ECG data did not identify any clinically meaningful differences across the maribavir treatment groups.

Data from Study SHP620-303 showed that maribavir treatment was not associated with treatment-limiting toxicities, in contrast to the currently available anti-CMV therapies. The incidence of neutropenia was lower for maribavir-treated subjects than for ganciclovir/valganciclovir-treated subjects. Maribavir had a lower incidence of overall hematologic TEAEs compared with ganciclovir/valganciclovir (28.2% versus 42.9%). Maribavir did not appear to cause nephrotoxicity. The incidence of selected TEAEs associated with renal disorders was half the rate for maribavir-treated subjects (15.8%) compared with foscarnet-treated subjects (31.9%). The AE profile was consistent across subgroups of subjects based on age, sex, race, region, transplant type, resistance (resistant or not resistant), presence or absence of symptomatic infection, and presence of renal impairment at Baseline (SHP620-303 [Maribavir] Clinical Study Report).

To date, maribavir has shown an overall favorable safety profile in placebo-controlled studies, open-label studies, and in studies that compared maribavir with other CMV therapies (ganciclovir, valganciclovir) for prophylaxis and for CMV treatment in patients with HSCT and SOT. Treatment effect on viral load reduction (confirmed undetectable plasma CMV DNA: 67% of subjects within 6 weeks in Study SHP620-202; 60.5% of subjects in 3 weeks and 77.3% of subjects in 6 weeks in Study SHP620-203) seen in Phase 2 treatment studies coupled with acceptable safety and tolerability establish the positive benefit-risk profile and warrant further investigation of maribavir in the treatment of CMV infections in transplant recipients.

Refer to the latest version of the maribavir IB (SHP620 [Maribavir] Investigator's Brochure Edition 20.0 04Feb21) and clinical study report of SHP620-303 study (SHP620-303 [Maribavir] Clinical Study Report) for the most detailed and most current information regarding the drug metabolism, PK, efficacy, and safety (including the adverse drug reactions) of maribavir.

2.3 Study Rationale

Immunosuppressive therapies required for successful transplantation lead to an increased vulnerability to severe infections, including CMV. The number of patients with HSCT and SOT cases in Japan in 2018 were 5,673 and 2,427, respectively (The Japanese Data Center for Hematopoietic Cell Transplantation [Internet]. Japan. Annual change in the number of reports by transplant type. 2019 [cited 2021 Apr 16]. Available from: http://www.jdchct.or.jp/data/report/2019/2-1.pdf.; Japanese society for clinical renal transplantation, 2019; The Japanese liver transplantation society, 2019; The Japanese society for heart transplantation, 2019; The Japanese pancreas and islet transplantation association working group for pancreas transplantation, 2019; The Japanese society of lung and heart-lung transplantation, 2019).

In Japan, for HSCT recipients, 1 antiviral (letermovir) is approved for prophylaxis, while there are 3 approved antivirals (ganciclovir, valganciclovir, and foscarnet) for the treatment of CMV disease, which are also used as preemptive therapy agents in clinical practice. For SOT recipients, valganciclovir is approved for prophylaxis, while ganciclovir and valganciclovir are approved for CMV disease and are also used as preemptive therapy agents. The use of these anti-CMV agents is limited by their toxicities such as myelosuppression (ganciclovir and valganciclovir) and renal dysfunction (foscarnet). Clinical studies of maribavir to date demonstrate that it is not associated with myelosuppression or renal impairment and may allow longer treatment durations at a prescribed dose for patients during prolonged periods of immunosuppression following transplantation.

The efficacy and safety of maribavir has been evaluated outside of Japan for the treatment of CMV infections and disease in resistant/refractory adult transplant recipients in a Phase 3 trial (completed). In addition, there is an ongoing Phase 3 study in subjects with asymptomatic CMV infection in HSCT recipients. Study SHP620-303 was recently completed.

This study is designed to assess the efficacy, safety, and PK of maribavir, administered at 400 mg BID in Japanese HSCT or SOT recipients with CMV infection, including subjects with symptomatic CMV infection who are resistant or refractory to ganciclovir, valganciclovir, or foscarnet.

2.4 Benefit/Risk Assessment

Maribavir is a potent and selective, orally bioavailable benzimidazole riboside antiviral drug with a novel mechanism of action against human cytomegalovirus being developed for the treatment of CMV infection or disease, including those resistant or refractory to ganciclovir, valganciclovir, or foscarnet, in transplant patients.

In 2 Phase 2 treatment studies (SHP620-202 and SHP620-203), maribavir at doses ≥400 mg BID was effective in treating CMV infection resistant or refractory to ganciclovir/valganciclovir or foscarnet and treatment effect was comparable to valganciclovir in the study of patients with asymptomatic CMV infection.

To date, maribavir has been safe and well-tolerated in 1,806 subjects in placebo-controlled studies, open-label studies, and in studies that compared maribavir with other CMV therapies (ganciclovir and valganciclovir) for prophylaxis and for CMV treatment in transplant patients. Treatment effect on viral load reduction (confirmed undetectable plasma CMV DNA: 67% of subjects within 6 weeks in Study SHP620-202; 60.5% of subjects in 3 weeks and 77.3% of subjects in 6 weeks in Study SHP620-203) seen in Phase 2 treatment studies and SHP620-303 treatment study, coupled with acceptable safety and tolerability, establish the positive benefit-risk profile and warrant continuation of maribavir development (SHP620 [Maribavir] Investigator's Brochure Edition 20.0 04Feb21).

Refer to the latest version of the IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety (including the adverse drug reactions) of maribavir.

2.5 Compliance Statement

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

The responsibilities of the study sponsor and investigators are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the efficacy of maribavir in CMV viremia clearance at the end of Study Week 8 (8 weeks after start of administration) in Japanese HSCT or SOT recipients with CMV infection.
- To assess the safety and tolerability of maribavir in Japanese transplant recipients with CMV infection.

3.1.2 Secondary Objectives

- To assess the maintenance of CMV viremia clearance and infection symptom control achieved at Study Week 8 (8 weeks after start of administration), through Study Week 12 (4 weeks of post-treatment), Study Week 16 (8 weeks of post-treatment), and Study Week 20 (12 weeks of post-treatment).
- To evaluate the time to first confirmed CMV viremia clearance.
- To evaluate the recurrence of confirmed CMV viremia requiring treatment during the 12-week follow-up period in subjects who achieved confirmed viremia clearance at Study Week 8.
- To assess the time course of changes in plasma CMV viremia load from Baseline.
- To evaluate the recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.
- To assess the profile of mutations in the CMV genes conferring resistance to maribavir.
- To assess the CMV viremia clearance at cut-off value of 137 IU/mL at the end of Study Week 8.
- To characterize the PK of maribavir.

[redacted]

3.2 Study Endpoints

Table 3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of maribavir in CMV viremia clearance at the end of Study Week 8 (8 weeks after start of administration) in Japanese HSCT or SOT recipients with CMV infection.	• Confirmed clearance of plasma CMV DNA (CMV viremia clearance) at the end of Study Week 8.
• To assess the safety and tolerability of maribavir in Japanese transplant recipients with CMV infection.	• Safety and tolerability assessments: treatment-emergent SAEs, TEAEs (including instances of CMV disease), maribavir dose interruptions for AEs, maribavir dose discontinuations for AEs, number of subjects with clinically significant vital signs, number of subjects with abnormal physical examination findings, number of subjects with abnormal clinical laboratory evaluations, number of subjects with clinically significant ECG parameters, and concentration of immunosuppressant drug. New onset of acute or chronic GVHD, graft rejection, or graft loss will be reported and may be assessed as AE/SAE.
Secondary	
	Efficacy Endpoints
• To assess the maintenance of CMV viremia clearance and infection symptom control achieved at Study Week 8 (8 weeks after start of administration), through Study Week 12 (4 weeks of post-treatment), Study Week 16 (8 weeks of post-treatment), and Study Week 20 (12 weeks of post-treatment).	• The maintenance of the confirmed CMV viremia clearance and infection symptom control achieved at Study Week 8 through Study Week 12 (4 weeks of post-treatment period), Study Week 16 (8 weeks of post-treatment/follow-up phase), and Study Week 20 (12 weeks of post-treatment).
• To evaluate the time to first confirmed CMV viremia clearance.	• The time to first confirmed viremia clearance at any time during the study.
• To evaluate the recurrence of confirmed CMV viremia requiring treatment during the 12-week follow-up period in subjects who achieved confirmed viremia clearance at Study Week 8.	• The recurrence of confirmed CMV viremia during the 12-week follow-up period in subjects with confirmed viremia clearance at Study Week 8 requiring additional anti-CMV treatment.

Table 3. Objectives and Endpoints

Objectives	Endpoints
• To assess the time course of changes in plasma CMV viremia load from Baseline.	• The time course of changes in plasma CMV viremia load from Baseline by study week.
• To evaluate the recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.	• Recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment
• To assess the profile of mutations in the CMV genes conferring resistance to maribavir.	• Assessment of the profile of mutations in the CMV genes conferring resistance to maribavir.
• To assess the CMV viremia clearance at cut-off value of 137 IU/mL at the end of Study Week 8.	• Confirmed plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/mL.
	Pharmacokinetic Endpoint
• To characterize the PK of maribavir.	• Maribavir C_{min} (predose maribavir concentration)
[redacted]	

AE(s)=adverse event(s), CMV=cytomegalovirus, C_{min}=minimum concentration, DNA=deoxyribonucleic acid, ECG=electrocardiogram, GVHD=graft-versus-host disease, HSCT=hematopoietic stem cell transplant, PK=pharmacokinetic, SAE=serious adverse event, SOT=solid organ transplant, TEAE=treatment-emergent adverse event.

4. STUDY DESIGN

4.1 Overall Design

This is a Phase 3, multicenter, open-label study to evaluate the efficacy, safety and tolerability, and PK of maribavir in Japanese HSCT or SOT recipients with CMV infection, including subjects with symptomatic CMV infection who are resistant or refractory to ganciclovir, valganciclovir, or foscarnet. The study will assess the efficacy of maribavir by measuring the plasma CMV DNA clearance at Study Week 8. To be eligible for the study, subjects must have a documented CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Results should be available prior to the first study treatment administration to confirm subject eligibility for the study. Both samples should be taken within 14 days prior to first dose of study treatment with the second sample obtained within 5 days prior to first dose of study treatment at Visit 2/Day 0.

As shown in Figure 1, the study will have 3 phases: (1) 2-week screening phase; (2) 8-week treatment phase; and (3) 12-week follow-up phase. Subjects will be required to visit the site up to 18 times for up to a 22-week period.

Screening Phase:

As presented in the Schedule of activities (SoA) (Table 1), subjects will be screened from Day -14 to Day 0 to establish eligibility for study participation. If applicable, subjects who meet eligibility requirements will undergo washout of any prohibited medications, the length of which is specified in Table 6.

Study Treatment Phase:

Once all screening assessments following informed consent (and assent where applicable) are completed and eligibility is confirmed, the subject will receive maribavir 400 mg BID for 8 weeks starting at Visit 2/Day 0.

Assessments to be performed at weekly study visits during treatment include: CMV DNA quantification testing, evaluation of symptoms suggestive of CMV disease, underlying disease assessments, graft outcomes and GVHD assessments, resolution or improvement of CMV tissue-invasive disease (symptomatic subjects only), clinical laboratory testing (hematology and chemistry), and concomitant medications and AE review. Pharmacokinetic sample collection, physical examination, vital sign assessment, ECGs, immunosuppressive drug level monitoring, and urinalysis will be conducted at selected visits throughout the treatment phase. Monitoring of concomitant immunosuppressant concentration levels (eg, tacrolimus,

cyclosporine, and everolimus) will be conducted at designated study time points. Cytomegalovirus DNA genotyping will be performed on samples at Baseline and in cases of rebound, or lack of response to therapy.

Historical laboratory results for tests specified in the SoA (Table 1) may be used for eligibility assessment (HIV or hepatitis test results) provided that these are obtained within the specified time period. The Screening and Visit 2/Day 0 visits can occur on the same day, if laboratory results are available for the determination of eligibility.

All Visit 2/Day 0 procedures and screening laboratory results needed to confirm eligibility must be completed and documented prior to study treatment administration and all clinical laboratory results required for eligibility verification must be available prior to treatment administration, including 2 separate CMV DNA assessments. Initiation of study treatment (ie, first dose) will only occur after completion of all required Visit 2/Day 0 procedures and confirmation of eligibility. This will be done under the supervision of investigator site personnel. If the baseline sample analyzed by central specialty laboratory reports mutation, then the subject will continue receiving treatment but will be excluded from the Per-Protocol Set for analysis.

All subjects will perform study-specific evaluations weekly during the 8-week study treatment phase (Table 1).

Depending on the time of the first dose of study treatment at Visit 2/Day 0, a second dose should be administered at Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered at Visit 2/Day 0. Study treatment will then be administered (preferably) every 12 hours (q12h). When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours.

For subjects that, in the investigator's judgment, have a lack of response or are unable to tolerate treatment and require discontinuation of study treatment, alternative anti-CMV treatment may be administered as deemed necessary. Subjects who discontinue study treatment prior to Study Week 8 will complete the end of treatment procedures described for Study Week 8 in the SoA. These subjects will follow a modified SoA through the remaining weekly visits of the study treatment phase and regular SoA through the 12-week follow-up phase.

All subjects who complete the study treatment phase through Visit 10/Study Week 8 will enter the 12-week follow-up phase.

Follow-up Phase:

Study-specific evaluations including central specialty laboratory CMV testing and safety assessments will occur weekly for the first 4 weeks, then every 2 weeks for the final 8 weeks of

the 12-Week Follow-up Phase. Refer to SoA 2 (Table 2). See Section 7 for details regarding discontinuation and withdrawal.

If a subject is unable to travel to the site for the follow-up visits, AEs and SAEs collection may be completed by telephone follow-up call on the day of the scheduled visit. It is recommended that the end of study visit be completed at the site if the subject is able to travel.

4.2 Scientific Rationale for Study Design

This study will assess the efficacy and safety of maribavir for the treatment of CMV infection in HSCT or SOT recipients. In Japan, for HSCT recipients, 1 antiviral (letermovir) is approved for prophylaxis, while there are 3 approved antivirals (ganciclovir, valganciclovir, and foscarnet) for the treatment of CMV disease, which are also used as preemptive therapy agents in clinical practice. For SOT recipients, valganciclovir is approved for prophylaxis, while ganciclovir and valganciclovir are approved for CMV disease. However, the use of these anti-CMV agents is limited by their toxicities; treatment with maribavir may address the unmet medical need for this population. In HSCT recipients, when CMV replication is detected above the predefined threshold during the monitoring of CMV infection, the pre-emptive treatment is generally given for a minimum of 2 weeks with further extension until CMV becomes undetectable. There is a difference in practice regarding the minimum duration of therapy. Valganciclovir (previously ganciclovir) is often used for preemptive therapy, although foscarnet can be used as well (Busca et al., 2007; Reusser et al., 2002). However, foscarnet is associated with nephrotoxicity, and requires IV hydration and frequent electrolyte monitoring (Reusser et al., 2002). Ganciclovir or valganciclovir use is associated with bone marrow toxicities that specifically in the HSCT recipients are a considerable clinical issue.

In the SHP620-202 study (HSCT and SOT recipients with resistant or refractory CMV infections), the majority of maribavir subjects achieved confirmed undetectable plasma CMV DNA levels by Week 6 of study drug treatment, while CMV recurrence occurred at rates not unexpected for a population with such an overwhelmingly severe illness and concurrent lack of host immune responsiveness. A fixed duration, 8-week treatment regimen, in this Phase 3 study will account for a longer duration of treatment need in patients of certain transplant types (ie, lung transplant) consistent with clinical practice as well as the prolonged period of immunosuppression/vulnerability in this patient population; furthermore, in the context of a clinical trial, the 8-week treatment duration will allow standardization of the duration of treatment for measuring the primary efficacy endpoint.

The clearance of CMV viremia (plasma CMV DNA clearance) is considered a surrogate marker that correlates with direct clinical benefit for the treatment of CMV infection or disease. While no registration trials for the treatment of established CMV infection in transplant patients have

been conducted, the VICTOR study (Asberg et al., 2007) of IV ganciclovir versus oral valganciclovir for the treatment of CMV disease in SOT recipients demonstrated that clearance of CMV viremia was highly correlated with resolution of CMV disease. This correlation was further evidenced with the subsequent analysis of VICTOR study plasma samples using the COBAS® AmpliPrep/COBAS® TaqMan® CMV Test, a test calibrated to the World Health Organization International Standard for Human CMV for Nucleic Acid Amplification Techniques. These findings, together with the maribavir Phase 2 study results, support a primary efficacy endpoint weighted on the CMV viremia clearance to demonstrate the efficacy of maribavir for the treatment of CMV infections. Clinicians consider CMV viremia clearance when evaluating the success of therapy hence the CMV plasma/blood monitoring protocols are employed in patients with high-risk of CMV infection or reactivation of latent CMV infection, and information of the viral load guides the decision for preemptive treatment in the absence of the symptomatic disease.

Primary endpoint based on CMV viremia clearance will be assessed at the end of Study Week 8 as on treatment clearance is the most relevant assessment to determine antiviral treatment effect. Assessment of treatment effect off therapy will be measured as key secondary and secondary endpoints. Although important from the clinical standpoint, recurrence of CMV DNA after treatment is more influenced by other factors such as host immune status, other comorbidities, and immunosuppressive treatments for prevention of transplant rejection than by the effectiveness of the anti-CMV drug treatment.

4.3 Justification for Dose

Results from the 2 Phase 2 studies, SHP620-202 (HSCT and SOT recipients with resistant or refractory CMV infections) and SHP620-203 (HSCT and SOT recipients with asymptomatic CMV infection) demonstrated comparable efficacy across the 400 mg BID, 800 mg BID, and 1,200 mg BID maribavir dose groups in the clearance of CMV viremia within up to 6 weeks after starting the study drug treatment. In both Phase 2 studies, the most common TEAEs included dysgeusia, events of nausea, vomiting, and diarrhea, and elevated immunosuppressant drug concentration levels. These comparable efficacy and slightly better safety profile with the 400 mg dose support the further evaluation of 400 mg BID maribavir for the treatment of CMV.

Currently available maribavir PK, PK modeling and extrapolation of systemic exposure from adults, and safety and tolerability data in adults support the administration of the 400 mg BID dose in adolescents who weigh ≥35 kg and are able to swallow tablets. The expression of CYP3A4, which is the primary enzyme for maribavir metabolism in the liver, occurs during the first weeks of life (Lu and Rosenbaum, 2014). The expression of CYP1A2, which is also involved with maribavir metabolism, the last enzyme to develop, is present by 13 months of life.

By 1 to 2 years of age, all the isoenzyme activities are similar to those of adults. Therefore, the bioavailability, clearance and systemic exposure of maribavir in adolescent subjects is not expected to be substantially different from adults at the same oral dose.

In a Phase 1 single dose PK study, subjects of Japanese descent showed 10% higher C_{max} and 25% higher AUC compared to their age, sex and body mass index matched non-Hispanic, Caucasian subjects following oral administration of 400 mg maribavir. The population PK analysis suggested that race (Caucasian, Black, Asian, or others) did not have any clinically significant impact on the PK of maribavir. Compared to the exposure in Caucasian SOT or HSCT patients, AUC and C_{max} were 4% lower and 4% higher, respectively, in Asian patients. Therefore, the exposure in Japanese patients is not expected to be clinically significantly different from that in Caucasian patients (TAK-620-1020 [Maribavir] Clinical Study Report).

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 22 weeks (screening phase: 2 weeks; study treatment phase: 8 weeks; follow-up phase: 12 weeks). Follow-up visits will occur weekly for the first 4 weeks (Follow-up Weeks 9 to 12), followed by visits every 2 weeks for the last 8 weeks (Follow-up Weeks 12 to 20) of this 12-week follow-up phase. The study will be completed in approximately 17 months.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessments. This includes the follow-up visit or contact, whichever is later (refer to Section 8.1.3 for the defined follow-up period for this protocol).

4.5 Sites and Regions

The study will be conducted in approximately 15 study sites in Japan.

5. STUDY POPULATION

The study is planned to enroll 44 asymptomatic subjects, and few patients with resistant or refractory CMV infection in Japan.

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

5.1 Inclusion Criteria

The subject will be considered eligible for the study if the subject meets all of the criteria below.

Subjects must:

1. Be able to provide written, personally signed, and dated informed consent (and assent where applicable) to participate in the study before completing any study-related procedures. When subject is below age of 20, voluntary agreement shall be obtained from a parent/both parents or legally authorized representative (LAR) using the written consent form.
2. Be Japanese with Japanese nationality, ≥16 years of age at the time of consent.
3. Be a recipient of HSCT or SOT that is functioning at the time of Screening.
4. Have a documented CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to first dose of study treatment with the second sample obtained within 5 days prior to first dose of study treatment at Visit 2/Day 0.
5. Have the current CMV infection after HSCT or SOT, either primary or reactivation, which, in the investigator's opinion, requires treatment and have any of the following.
   a. *Asymptomatic subjects:* The subjects do not have CMV tissue-invasive disease or CMV syndrome (SOT subjects only) at Baseline, as determined by the investigator according to the criteria specified by Ljungman et al., 2017.
   b. *Resistant or refractory subjects:* The subjects must have a current CMV infection that is refractory to the most recently administered of the anti-CMV treatment agent(s). Refractory is defined as documented failure to achieve >1 $\log_{10}$ (common logarithm to base 10) decrease in CMV DNA level in plasma after a 14 day or longer treatment period with IV ganciclovir/oral valganciclovir, or IV foscarnet.
6. Have all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory can be used for qualification):

a. Absolute neutrophil count ≥1,000/mm^3 (1.0 × 10^9/L)
b. Platelet count ≥25,000/mm^3 (25 × 10^9/L)
c. Hemoglobin ≥8 g/dL
d. Estimated creatinine clearance ≥30 mL/minute (estimated glomerular filtration rate by Modification of Diet in Renal Disease)

7. Have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening, if a female of childbearing potential. Urine pregnancy tests may be done per institutional requirements; however, they are not sufficient for eligibility determination. Sexually active females of childbearing potential must agree to comply with any applicable contraceptive requirements of the protocol. If male, must agree to use an acceptable method of birth control, as defined in the protocol, during the study treatment administration period and for 90 days after the last dose of study treatment.
8. Be able to swallow tablets.
9. Have life expectancy of ≥8 weeks.
10. Weigh ≥40 kg.
11. Be willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

5.2 Exclusion Criteria

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

Subjects must not:

1. Have central nervous system (CNS) CMV tissue-invasive disease or CMV retinitis as assessed by the investigator at the time of Screening and prior to administration at Visit 2/Day 0.
2. Be receiving valganciclovir, ganciclovir, foscarnet, or letermovir when study treatment is initiated, or anticipated to require 1 of these agents during the 8-week treatment period.

   NOTE: Subjects receiving letermovir must discontinue 3 days prior to first dose of study treatment. Ganciclovir, valganciclovir, and foscarnet must be discontinued prior to the first dose of study treatment.
3. Have known hypersensitivity to the active substance or to an excipient of the study treatments.
4. Have severe vomiting, diarrhea, or other severe GI illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral medication.
5. Require mechanical ventilation or vasopressors for hemodynamic support at the time of Baseline.

6. Pregnant or nursing female.
7. Have previously completed, discontinued, or have been withdrawn from this study.
8. Have received any investigational agent (including CMV-specific T-cells) with known anti-CMV activity within 30 days before initiation of the study treatment at any time.
9. Have received any unapproved agent or device within 30 days before initiation of the study treatment.
10. Have any clinically significant medical or surgical condition that, in the investigator's opinion, could interfere with interpretation of study results, contraindicate the administration of maribavir, or compromise the safety or well-being of the subject.
11. Have previously received maribavir.
12. Have serum aspartate aminotransferase (AST) >5 times upper limit of normal (ULN) at Screening, or serum alanine aminotransferase (ALT) >5 times ULN at Screening, or total bilirubin ≥3.0 × ULN at Screening (except for documented Gilbert's syndrome), as analyzed by local or central laboratory.
13. Have known (previously documented) positive results for HIV. Subjects must have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local or central laboratory during the screening period.
14. Have active malignancy with the exception of nonmelanoma skin cancer, as determined by the investigator. Subjects who experience relapse or progression of their underlying malignancy (for which HSCT or SOT was performed), as determined by the investigator, are not to be enrolled.
15. Be undergoing treatment for acute or chronic hepatitis C.

5.3 Restrictions

There will be no special restrictions for subjects participating in this study. Subjects are to maintain their normal diets, medications (except those listed in Section 6.6.4), and activities of daily life as determined by the investigator.

5.4 Reproductive Potential

5.4.1 Female Contraception

There is no clinical experience with maribavir in pregnant subjects.

All female subjects of childbearing potential will be tested and should have negative serum human chorionic gonadotropin pregnancy test results prior to administration of study treatment. They must agree to abstain from sexual activity that could result in pregnancy or agree to use an acceptable method of contraception. Females of childbearing potential who are not currently

sexually active must agree to use an acceptable contraception, as defined below, if they become sexually active during the study period and for 90 days after the last dose of the study treatment. If hormonal contraceptives are used, they should be administered according to the package insert and in conjunction with another acceptable method of contraception. Sexually active females of childbearing potential should be using an acceptable method of contraception, as defined below.

Methods of contraception that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods for females of childbearing potential and are presented below:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral) stabilized for at least 30 days prior to the Screening visit (Visit 1), plus condoms.
  Note: Since hormonal contraception may be susceptible to interaction with the study treatment in the study, which may reduce the efficacy of the contraception method, this method must be supplemented with a barrier method (preferably male condom).
- Intrauterine devices (all types) or intrauterine hormone-releasing systems plus condoms.
  Note: contraception methods that in the context of the clinical trial facilitation group (CTFG) guidance are considered to have lower user dependency.
- Bilateral tubal occlusion.
- Vasectomized male partner is a highly effective birth control method provided that partner is the sole sexual partner of the female study participant who is of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. Note: the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Female subjects 16 years of age and older, who are amenorrheic for reasons other than menopause (12 consecutive months of spontaneous amenorrhea in subjects with previous normal menstruation), including subjects who did not yet have the menarche, would be allowed to participate provided they agree to abstinence or an acceptable form of contraception.

Female subjects who are postmenopausal (12 consecutive months of spontaneous amenorrhea) or surgically sterile (having undergone 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and are at least 6 weeks post

sterilization do not need a pregnancy test performed prior to administration of study treatment and do not have to agree to the use of acceptable methods of contraception.

5.4.2 Male Contraception

Per CTFG, male subjects will be required to use a condom in conjunction with a highly effective method of birth control for their female partners of childbearing age. Both male participants and their female partners must use this form of birth control from the time prior to first dosing until 90 days after the last dose of study treatment. For male subjects, sexual intercourse with pregnant partners should also be avoided during the course of the study unless condoms are used from the time prior to the first dose until 90 days after the last dose of study treatment. Male subjects must not donate sperm until 90 days after the last dose of study treatment.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is maribavir, which will be provided in a 200 mg tablet (oral tablet) form. Additional information is provided in the current maribavir IB.

No placebo or any active comparator/reference products will be used in the study.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive response technology (IRT) will be employed in this study to assign subject numbers, manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, site assignments, and return of study treatment. The IRT provider will provide a user manual and training to each site, with detailed instructions on use of the IRT.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. All subjects will be assigned the same study treatment.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site, the subject number is assigned to subjects by the IRT system according to the sequence of presentation for study participation.

6.2.3 Dosing

Initiation of the study treatment (ie, first dose) will occur at Visit 2/Day 0 only after completion of all required procedures and confirmation of eligibility. The first dose should be administered under the supervision of the investigator's site personnel.

Depending on the time of the first dose of the study treatment at Visit 2/Day 0, a second dose should be administered at Visit 2/Day 0 provided that doses can be separated by a minimum of 8 hours; otherwise, only 1 dose should be administered at Visit 2/Day 0. The study treatment will then be administered (preferably) q12h. When q12h dosing is not feasible, the doses should be separated by a minimum of 8 hours.

Maribavir 200 mg tablets will be provided for daily dosing. Subjects will take the maribavir 400 mg BID dose for 8 weeks of the study treatment phase. There are no dose modifications for maribavir.

Table 4. Study Treatment Dosing-Standard Regimen

Regimen	AM	PM
Maribavir (400 mg, BID)	400 mg (2 tablets of 200 mg)	400 mg (2 tablets of 200 mg)

BID=twice daily.

6.2.4 Unblinding the Treatment Assignment

Not applicable.

6.2.5 Dose Modification

Not applicable.

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

6.3.1 Labeling

Labels containing study information and study treatment kit number are applied to the study treatment container.

All study treatment product will be labeled with a minimum of the following: protocol number, study treatment kit number, dosage form, storage conditions,the statements “For clinical trial use only” and other information that may be required by the local laws.

Additional labels may not be added without the sponsor’s prior full agreement.

6.3.2 Packaging

The study treatment, maribavir, is packaged in 40-count white 60cc square high-density polyethylene bottles with child-resistant cap and foil induction seal.

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

6.3.3 Storage

The head of clinical trial site has overall responsibility for ensuring that study treatment is stored in a secure, limited-access location. Maribavir tablets will be stored at controlled room temperature (15°C to 30°C or 59°F to 86°F). 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 or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the study treatment bottle/carton labels as they are distributed.

Study treatment must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study treatment 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 study treatment 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 study treatment that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the study treatment only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the study treatment carrying his/her treatment assignment. All administered/dispensed medication

will be documented in the subject's source, electronic case report form (eCRF) and/or other study treatment record and may include additional information as required per applicable regulations. The investigator is responsible for ensuring the retrieval of all study supplies from subjects. The disposition of the dispensed study treatment and study treatment lost by the subject or site staff will be documented in the accountability log. The destruction of the unused study treatment at the site is not allowed by the sponsor.

No study treatment or returned inventory from a Takeda-sponsored 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.

With the written agreement of the sponsor, at the end of the study all unused study treatment, subject-returned study treatment, and empty/used study treatment packaging will be returned to a sponsor specified designation. Should local, state or national laws prohibit the return of unused study treatment, subject-returned study treatment, and empty/used study treatment packaging to the sponsor designated locations, it may be destroyed at the site or a local facility once the sponsor has reviewed and approved the site's standard operating procedure. In this case, Certificates of Destructions identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of study treatment must be in accordance with local, state, and national laws.

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

6.5 Subject Compliance

Subjects must be instructed to bring their unused study treatment, empty/used study treatment packaging at every visit. Drug accountability must be assessed at the container/packaging level for unused study treatment or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form. The number of tablets prescribed and the number of tablets returned will be documented on the CRFs.

6.6 Prior and Concomitant Therapy

All non-study treatment including but not limited to herbal treatments and vitamins received within 30 days prior to the Screening visit (Visit 1) and through the final study contact (including

protocol-defined follow-up period) must be recorded in the subject's source document and eCRF.

6.6.1 Prior Treatment

Prior treatment information must be recorded in the subject's source document and eCRF page and will include the following presented in Table 5.

Table 5. Prior Medications, Therapies, and Procedures

Time Period (Prior to Visit 2/Study Week 0/Day 0)	Category	Prior Medications, Therapies, and Procedures
Medications/procedures administered/performed for transplant related reason from their start or date of transplant (whichever is first) to the first dose of study treatment at Visit 2/Day 0	Induction therapy for transplant*	Including but not limited to: • Pre-transplant irradiation • Chemotherapy agents • Lymphocyte depleting and nondepleting therapies, including monoclonal, polyclonal, and anti-thymocyte globulin preparations.
	Anti-CMV prophylaxis and treatment*	Including, but not limited to: • Ganciclovir • Valganciclovir • Foscarnet • CMV immune globulin (CMV-IGIV***, Cytogam®***) • Leflunomide*** • IVIG • Artesunate*** • CMV-specific T-cell transfer*** (considered investigational) • Letermovir
All medications within 3 months prior to the first dose of study treatment at Visit 2/Study Week 0/Day 0	Transplant maintenance, rejection treatment, and other adjuvant/related therapy	Including, but not limited to: • Systemic steroids • Tacrolimus, cyclosporine, everolimus, sirolimus***, mycophenolate • GVHD prophylaxis and treatment • Antirejection medications including T-cell depleting therapies*** • Photopheresis
	Hematopoietic growth factors	-
	Blood or blood product transfusions	-
	Other anti-infective agents	• Prophylaxis and/or treatment of viral, bacterial and fungal infections

Table 5. Prior Medications, Therapies, and Procedures

Time Period (Prior to Visit 2/Study Week 0/Day 0)	Category	Prior Medications, Therapies, and Procedures
Within 30 days or 5 half-lives (whichever is longer)	All other	• All other prescription medications • All other OTC medications • All herbal supplements**
Any therapeutic or diagnostic intervention performed within 30 days prior to the first dose of study treatment at Visit 2/Study Week 0/Day 0		Including, but not limited to: • Biopsies (along with the results obtained) • Dialysis • X-rays, CT scans, MRI, ultrasound imaging (along with significant findings).

CMV=cytomegalovirus, CMV-IGIV=Cytomegalovirus Immune Globulin Intravenous, CT=computed tomography, GVHD=graft-versus-host disease, IVIG=intravenous immunoglobulin, MRI=Magnetic resonance imaging, OTC=over-the-counter.
* Subjects for whom transplant was performed >3 months from the time of Screening, limited (no dose data) information for induction therapy will be collected. Similarly, for anti-CMV treatment data older than >3 month prior to Screening will be recorded in more limited manner (dose prescribed, major interruptions, overall treatment duration).
** If half-life is unknown, report use within 30 days prior to study.
*** Leflunomide is not approved for anti-CMV prophylaxis and treatment in Japan. Sirolimus and T-cell depleting therapies are not approved for transplant maintenance and rejection treatment in Japan. Other medications are not approved in Japan.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment (including medication) taken between the dates of the first dose of the study treatment and the end of the follow-up period, inclusive. A concomitant procedure is any therapeutic and diagnostic intervention (eg, surgery/biopsy) or diagnostic assessment (bacterial cultures, imaging such as X-ray, computed tomography scans) performed between the dates of the first dose of the study treatment and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the subject's source document.

6.6.3 Permitted Treatment

All concomitant treatment information must be recorded on the subject's source document and appropriate eCRF page.

Additional treatment strategies may complement the use of the study treatments, eg, reducing or modifying the immunosuppressant drug (tacrolimus, cyclosporine, or everolimus) use, or use of hemopoietic growth factors as needed for neutropenia.

Of note, changes in the net state of immunosuppression can influence response to treatment of CMV infection, therefore, whenever possible, investigators should maintain a stable regimen of immunosuppressant drugs during the study treatment administration period, particularly through Visit 10/Study Week 8. Note that the sample for the assessment of immunosuppressant agent concentration is included in the SoA as maribavir was found to impact the metabolism of some immunosuppressive agents. Any changes in immunosuppression regimens due to the concomitant administration with maribavir or other reasons must be recorded in the CRF.

Maribavir is specifically intended to treat human CMV infections. Maribavir is not active in vitro against most non-CMV herpes virus infections, including herpes simplex virus (HSV type 1 and type 2) and varicella zoster virus (VZV). At Baseline, investigators will assess subjects to determine whether prophylaxis for these viruses is appropriate according to institutional guidelines or standard practices; the need for continued prophylaxis or initiation of prophylaxis will be assessed. If considered appropriate, permitted medications to use for this purpose include systemic acyclovir, valaciclovir, or famciclovir. Choice of medication, dose, and duration of such therapy is at the discretion of the investigator based on a given subject's clinical condition (eg, net state of immunosuppression, risk factors, and other medications). These medications (acyclovir, valaciclovir, or famciclovir) also can be used to treat any HSV or VZV infection that may occur during the study. Antifungal and antibacterial medications will be allowed as deemed appropriate by the investigator for prophylaxis or treatment.

Although potent inhibitors of CYP3A4 (such as ketoconazole) could increase blood levels of maribavir, they are likely to be associated with minimal increased risk given the safety profile of maribavir demonstrated at up to 1,200 mg BID in Phase 2 studies.

The following concomitant medications should be taken with caution:

Maribavir has the potential to inhibit CYP2C19 and P-gp and therefore, may increase the concentration of drugs that are substrates of CYP2C19 and P-gp. For drugs with narrow therapeutic window, the increase in drug concentration may lead to toxicity. A drug interaction study showed that maribavir (400 mg BID) when administered with tacrolimus, resulted in increased tacrolimus $C_{max,}$ AUC, and C_{trough} by 38%, 51%, and 57%, respectively. Therefore, monitoring tacrolimus blood concentration and tacrolimus-associated AEs, and the appropriate dose adjustment of tacrolimus is recommended when maribavir and tacrolimus are used concomitantly. Conversely, after a period of coadministration, discontinuation of maribavir could lead to reduced blood levels of tacrolimus and potentially reduced therapeutic effect. Similarly, for drugs that are substrates of CYP2C19 or P-gp and have narrow therapeutic window, careful monitoring is recommended both after initiation of maribavir (when substrate levels may increase) and after discontinuation of maribavir (when substrate levels may decrease).

6.6.4 Prohibited Treatment

The washout periods of common prior treatments that are excluded medications in this study are presented in Table 6.

Table 6. Common Excluded Treatments and Associated Washout Period

Treatment	Minimum Number of Days Before First Dose			
	Prior to the first dose of study treatment	3 days	14 days	30 days
Artesunate*	X	-	-	
Ganciclovir, valganciclovir, and foscarnet	X	-		-
Letermovir	-	X	-	-
Leflunomide*	-	-	X	-
Any investigational anti-CMV agent	-	-		X
Any unapproved agent or device	-	-		X
CMV vaccine*	Any time before or during the study.			

CMV=Cytomegalovirus
* Leflunomide is not approved for anti-CMV prophylaxis and treatment in Japan. Artesunate and CMV vaccine are not approved in Japan.

Treatments not listed above are considered allowable.

Besides the medications indicated in Table 6, concomitant use of any of the following medications is prohibited in all subjects during the study.

- Strong CYP3A inducers: avasimibe, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort (Hypericum perforatum), phenobarbital, primidone, mitotane, enzalutamide, apalutamide, bosentan, efavirenz.
- Herbal medications known to have potential toxicities or drug interactions, eg, Ginkgo biloba or Piper methysticum (kava).

Potent inducers of CYP3A4 and CYP3A4/P-gp (such as rifampin, rifabutin, or phenobarbital) could reduce blood levels of maribavir, potentially reducing its antiviral activity. Use of alternate agents with less enzyme induction potential should be considered during administration of maribavir.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If the subject discontinues the study treatment but does not withdraw consent, regardless of the reason, the evaluations listed for Visit 10/Study Week 8 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 study treatment, and the total amount of the study treatment administered must be recorded in the source documents.

These subjects will follow a modified SoA through the remaining weekly visits scheduled for the study treatment phase and the regular SoA through the 12-week follow-up phase. The end of treatment sample for immunosuppressant drug concentration level will be collected at the next visit scheduled 1 week after the treatment discontinuation. Subjects who discontinue study treatment early will not be asked to complete the following procedures after the end of treatment visit for subsequent visits in the treatment phase: dispense or use of any study treatment, and PK plasma sample collection. After completing the 8-week duration specified for the study treatment phase, subjects will enter the 12-week follow-up phase.

Subjects who discontinue 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 and the CRF. 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:

- AE
- CMV CNS infection*
- Protocol deviation
- Withdrawal of consent (by subject or by parent or both parents/LAR for pediatric subject)
- Pregnancy
- Lost to follow-up
- Lack of efficacy

- Sponsor decision
- Death
- Other (the investigator must specify on the CRF)

*Maribavir does not cross the blood-brain barrier. If a subject in the study develops CMV CNS infection (eg, meningo-encephalitis) then the subject will discontinue study treatment in order to be treated for this condition.

The end of study treatment and the end of study date for each subject (ie, the date of completion of the study or premature withdrawal from the study) will be recorded in the CRF.

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible. Subjects who withdraw consent during the study treatment phase will be asked to undergo all end of treatment evaluations and procedures listed for Visit 10/Study Week 8, if they agree; no further follow-up will be performed.

Subjects who withdraw from the study during the follow-up phase will undergo all end of study evaluations and procedures listed for Visit 18/Study Week 20 (Follow-up Week 12) as soon as possible and whenever possible, if they agree, prior to initiation of any nonstudy anti-CMV treatment (as deemed by the investigator); no further follow-up will be performed.

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 (office visit or telephone contact). 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 return to the site for final safety evaluations and return any unused study treatment.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

Refer to Table 1 for SoA for the screening and study treatment phase and Table 2 for the SoA for the follow-up phase. Study assessments are detailed in Section 8.2.

8.1.1 Screening Period

Prior to initiation of any study procedures, the informed consent (and assent where applicable) to participate in the study must be obtained from a subject or the subject's parent or legal guardian if the subject is <20 years of age.

Subjects will be screened during an approximate 2-week screening phase which will occur from Day -14 to Day 0 in which subjects will undergo evaluation to establish eligibility. To be eligible for the study, subjects must have a documented CMV infection with a screening value of >455 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by a central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to first dose of study treatment with the second sample obtained within 5 days prior to first dose of study treatment at Visit 2/Day 0. If applicable, subjects who meet eligibility requirements will undergo washout of any prohibited medications, the length of which will be specified in the eligibility criteria. Ganciclovir, valganciclovir, and foscarnet must be discontinued prior to the first dose of study treatment. Subjects receiving letermovir must discontinue 3 days prior to first dose of study treatment.

8.1.1.1 Screening Visit (Visit 1/Study Week -2/Day -14 to Day 0)

As specified in Table 1, the screening procedures will include:

- Informed consent
- Inclusion/Exclusion criteria (see Section 5.1 and Section 5.2)
- Height and body weight
- Vital signs (see Section 8.2.3.3)
- Medical history, including transplant history (eg, underlying disease that led to HSCT or SOT, including relapse/progression) and CMV history
- Prior medication, therapies, and procedures, including any prior anti-CMV medication used to treat the current CMV infection (see Section 6.6)
- Hematology/Chemistry (see Section 8.2.3.4)

- Serum pregnancy test for all females of childbearing potential (see Section 8.2.3.5). Additional urine pregnancy tests may be done per institutional requirements. Urine pregnancy test results are not sufficient for eligibility determination.
- HIV status: Historical results for HIV tests performed within 3 months prior to the eligibility assessment (screening) will be acceptable. If no HIV test result within 3 months is available, the subject must have testing done locally or centrally during the screening period and have the results available prior to administration of study treatment. Negative results must be confirmed prior to study treatment administration.
- CMV DNA test (quantitation): Documentation of CMV infection with CMV DNA in 2 consecutive samples separated by at least 1 day as determined by a central specialty laboratory qPCR or comparable quantitative CMV DNA results. The DNA results with the first sample should be available within 14 days prior to administration of study treatment at Visit 2/Study Week 0/Day 0. The second sample must be taken within 5 days prior to administration of study treatment. The laboratory used for DNA quantification should be central specialty laboratory.
- Symptomatic CMV infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) assessment
- Interactive response technology (see Section 6.2.1)
- Graft outcomes (acute rejection or graft loss in both SOT and HSCT subjects) and GVHD (for HSCT subjects only) assessments

At Screening, either central or local laboratory results for hematology/chemistry/pregnancy testing can be used for qualification; for CMV DNA quantification, only central laboratory results can be used.

A screen failure is a subject who has given informed consent and failed to meet the inclusion except No.4 and/or met at least 1 of the exclusion criteria and has not been administered the study treatment. However, subjects who were excluded based on the exclusion criteria of low platelet count, hemoglobin, and low neutrophil counts or liver or renal parameters can be retested once within the 14-day screening period at the investigator's discretion when other inclusion criteria are fulfilled. Screen failures may be rescreened in the future (with new informed consent and screening period) if their clinical course results in a change that deems them eligible for the trial.

The Screening and Visit 2/Study Week 0/Day 0 visits can occur on the same day, if laboratory results are available for the determination of eligibility.

8.1.2 Study Treatment Period

Visit 2/Study Week 0/Day 0 (Baseline) to Visit 10/Study Week 8/Day 56 (End of Treatment)

Permissible assessment windows during the 8-week study treatment phase are: Visit 2A, ±1 day; Visit 3 (Study Week 1) +2 days; Visit 4 (Study Week 2) to Visit 6 (Study Week 4), ±2 days; and Visit 7 (Study Week 5) to Visit 10 (Study Week 8), ±3 days.

As specified in Table 1 the following assessments will be performed during the study treatment phase:

- Administration of study treatment at Visit 2/Study Week 0/Day 0 (Baseline)
- Physical examination at Visit 2/Study Week 0, Visit 6/Study Week 4, and Visit 10/Study Week 8 (see Section 8.2.3.1)
- Weight at Visit 2/Study Week 0, Visit 4/Study Week 2, Visit 6/Study Week 4, Visit 8/Study Week 6, and Visit 10/Study Week 8 (see Section 8.2.3.1)
- Vital signs at Visit 2/Study Week 0, Visit 4/Study Week 2, Visit 6/Study Week 4, Visit 8/Study Week 6, and Visit 10/Study Week 8 (see Section 8.2.3.3)
- Review of medical history and prior medication at Visit 2/Study Week 0
- 12-lead ECG at Visit 2/Study Week 0 and Visit 10/Study Week 8 (see Section 8.2.3.6)
- Hematology/Chemistry tests will be done at all the visits from Visit 2/Study Week 0 to Visit 10/Study Week 8. For subjects receiving tacrolimus, cyclosporine, or everolimus; a local laboratory will assess potassium and magnesium at Visit 2A (see Section 8.2.3.4).
- Urinalysis will be done at Visit 2/Study Week 0, Visit 4/Study Week 2, Visit 6/Study Week 4, Visit 8/Study Week 6, and Visit 10/Study Week 8 (see Section 8.2.3.4).
- Pregnancy test at Visit 2/Study Week 0, Visit 6/Study Week 4, and Visit 10/Study Week 8 (see Section 8.2.3.5)
- Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) test at Visit 2/Study Week 0
- Underlying disease that led to HSCT or SOT, including relapse/progression, will be assessed at all visits throughout the study treatment phase, except Visit 2A.
- CMV DNA test: Cytomegalovirus quantification in the plasma samples taken at each visit of study treatment phase will be conducted at central specialty laboratory. Cytomegalovirus genotyping by the central specialty laboratory to assess for mutations in the UL97, UL27, and UL54 genes will be conducted at Visit 2/Study Week 0/Day 0

(Baseline). After Visit 2, CMV genotyping will be conducted in every sample that meets the criteria specified in the resistance analysis plan (see Section 8.2.2.2).

- Symptomatic CMV infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) will be assessed at all visits until resolution for subjects with CMV tissue-invasive disease or CMV syndrome (SOT subjects only) present at Visit 2/Study Week 0/Day 0 (Baseline).
- Development of new tissue-invasive disease or CMV syndrome will be assessed at all visits. Any new tissue-invasive disease or CMV syndrome status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) will be assessed at all visits until resolution.
- Immunosuppressant drug concentration levels for subjects receiving immunosuppressant will be measured at Visit 2/Study Week 0/Day 0 (Baseline), Visit 2A/Day 4, Visit 3/Study Week 1/Day 7, and Visit 10/Study Week 8/Day 56 (see Section 8.2.3.4). If maribavir is discontinued early during the treatment phase, immunosuppressant drug concentration should also be measured 1 week after the discontinuation.
- Pharmacokinetic sample collection will be as follows: at Visit 3/Study Week 1/Day 7 (predose and between 2 to 4 hour postdose); at Visit 6/Study Week 4/Day 28 (only predose); and at Visit 10/Study Week 8/Day 56 (predose and between 2 to 4 hour postdose) (see Section 8.2.4.1).
- IRT at all visits through the study treatment phase, except Visit 2A/Study Week 1 and Visit 10/Study Week 8
- Study treatment is dispensed at every visit, except Visit 2A/Study Week 1 and Visit 10/Study Week 8 (Week 0 through Week 7).
- Graft outcomes (acute rejection or graft loss in both SOT and HSCT subjects) and GVHD (for HSCT subjects only) assessments will be done at all visits through the study treatment phase, except Visit 2A/Study Week 1.
- Hepatic function grading will be assessed according to the Child-Pugh classification (see Appendix 5 and Section 8.2.1.2) at Visit 2/Study Week 0.
- Comorbidity status evaluation at Visit 2/Study Week 0, Visit 6/Week 4, and Visit 10/Week 8
- Concomitant medications, therapies, and procedures will be assessed through the study treatment phase.
- AE/SAE monitoring will be assessed throughout the study treatment phase.

For subjects who permanently discontinue study treatment early but do not withdraw consent, refer to Section 7.1 regarding modified schedule of assessments.

8.1.3 Follow-up Period

Visit 11/Study Week 9/Follow-up Week 1 to Visit 18/Study Week 20/Follow-up Week 12 (End of Study)

The follow-up period for this protocol is 84 days or 12 weeks (post-treatment Visits 11 to 18). The permissible assessment windows for the visits are: Study Weeks 9 to 12 (Follow-up Weeks 1 to 4) ±2 days; Study Weeks 14 to 20 (Follow-up Weeks 6 to 12) ±3 days.

As specified in Table 2 study evaluation include:

- Physical examination (including weight) at Visit 18/Study Week 20
- Vital signs at Visit 18/Study Week 20
- 12-lead ECG at Visit 18/Study Week 20
- Hematology/Chemistry tests will be done at Visit 12/Study Week 10, Visit 14/Study Week 12, Visit 16/Study Week 16, and Visit 18/Study Week 20.
- Urinalysis at Visit 18/Study Week 20
- Immunosuppressant drug concentration levels at Visit 11/Study Week 9, if treatment continued until Study Week 8 (drug concentration level to be measured 1 week after the end of the study treatment).
- Underlying disease that led to HSCT or SOT, including relapse/progression, will be assessed at all visits throughout the follow-up phase.
- CMV DNA test: all CMV DNA tests (quantitation, genotyping) at all visits during the follow-up phase will be tested in the central specialty laboratory.
- Symptomatic CMV infection status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) will be assessed at all visits until resolution during the follow-up for subjects with CMV tissue-invasive disease or CMV syndrome (SOT subjects only) present at Visit 2/Day 0 (Baseline).
- Development of new tissue-invasive disease or CMV syndrome will be assessed at all visits during the follow-up. Any new tissue-invasive disease or CMV syndrome status (no change, improvement, worsening, or resolution of disease/syndrome and associated symptoms) will be assessed at all visits until resolution.

- Graft outcomes (acute rejection or graft loss in both SOT and HSCT subjects) and GVHD (for HSCT subjects only) assessments will be done at all visits through the follow-up phase.
- Comorbidity status evaluation at Visit 14/Study Week 12, Visit 16/Study Week 16, and Visit 18/Study Week 20.
- Concomitant medications, therapies, and procedures will be assessed through the follow-up phase.
- AE/SAE monitoring will be assessed through the follow-up phase according to Section 8.2.3.2.

All AEs and SAEs that are not resolved at the time of end of study (Visit 18/Study Week 20/Follow-up Week 12) will be followed to closure (see Appendix 3.2). If a subject is withdrawn from the study, all Follow-up Week 12 (end of study procedures) must be performed as soon as possible after discontinuation.

Subjects who have a CMV tissue-invasive disease or CMV syndrome (SOT subjects only) at Visit 2/Day 0 (Baseline) and who have no change, worsening, or improvement of disease/syndrome and associated symptoms at the time of end of study (Visit 18/Study Week 20/Follow up Week 12) will be followed until the resolution.

Subjects who develop new CMV tissue-invasive disease or CMV syndrome during the treatment period and who have no change, worsening or improvement of disease/syndrome and associated symptoms at the time of end of study (Visit 18/Study Week 20/Follow up Week 12) will be followed until the resolution.

8.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.2 Study Assessments

All study evaluations and procedures are specified in SoA 1 (Table 1) and SoA 2 (Table 2).

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including sex, age, race, and ethnicity will be collected prior to the subject receiving the first dose of study treatment.

8.2.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents.

8.2.1.2 Medical and Medication History

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

A medical history will be taken during the screening period and updated at Visit 2/Study Week 0/Day 0 as specified in Table 1. All medical history findings that have been present/active within the 2 years prior to enrollment at Visit 2/Study Week 0/Day 0 will be recorded regardless of clinical relevance or presence at study start. Medical history finding that have not been present/active within the 2 years prior to enrollment will be recorded if deemed clinically relevant by the investigator to the conduct of the study. Medical history related to the transplant (including the disease/diseases leading to transplant) and CMV infection will be recorded without a time limit. The medical history should include any history of allergic reactions to drugs.

Specific information regarding the subject's transplant history that will be collected, including but not limited to, are: the number of past transplants prior to the current transplant; the type of transplant and details for each, such as cell source and type for HSCT or organ for SOT; the human leukocyte antigen (HLA) matching level. The date and the history of the current transplant including complications, transplant related infections, induction and maintenance therapy received for transplant, history of relevant viral serology, history of antiviral prophylaxis, and status of the transplant at Baseline.

Specific information regarding the subject's CMV infection will be collected (when available). The collected information will include but will not be limited to: CMV serology of donor and recipient, CMV infection episodes with viral loads and/or treatment, CMV resistance information (sequencing data), prophylactic treatment, if utilized. More details will be specified in the study manual.

Subjects will be classified into 1 of the following categories with respect to hepatic function, based on baseline clinical and laboratory assessments (see Appendix 5). This information will primarily be utilized in the interpretation of the PK data for which the samples will be collected at the specified visits in the study:

- No chronic liver disease
- Chronic liver disease - Child-Pugh Class A
- Chronic liver disease - Child-Pugh Class B
- Chronic liver disease - Child-Pugh Class C

8.2.2 Efficacy

8.2.2.1 CMV DNA Quantitation (CMV infection)

Blood samples collected will be assessed at a central specialty laboratory for the quantification of CMV DNA in plasma using qPCR. Central specialty laboratory plasma CMV DNA results will be reported to the investigator site as available. Additional CMV DNA tests at central specialty laboratories may be performed and collected at more frequent intervals, or additional assay methods may be used at the discretion of the investigator. These results will also be collected when available.

Confirmed CMV viremia clearance will be defined as plasma CMV DNA concentration below the lower limit of quantification (LLOQ) to be determined depending on the selected central specialty laboratory, in 2 consecutive postbaseline samples, separated by at least 5 days.

Confirmed recurrence or the confirmed CMV viremia recurrence will be defined as plasma CMV DNA concentration ≥LLOQ to be determined depending on the selected central specialty laboratory in 2 consecutive plasma samples at least 5 days apart, after attaining viremia clearance. Every attempt should be made by the investigators to collect the 2 consecutive plasma samples and monitor results to confirm recurrence prior to initiating alternative available therapy.

8.2.2.2 CMV Genotyping and Phenotyping

At Visit 2/Day 0 plasma samples will be obtained and tested by the central specialty laboratory to identify mutations in the viral UL97 and UL54 genes known to confer resistance to anti-CMV agents. In addition, UL27 gene will be tested. Given the urgency to treat the subjects, it is not possible to wait for this central specialty laboratory assessment prior to a subject's study treatment administration to confirm lack of resistance to any previously used agents. For asymptomatic subjects, in instances when a mutation conferring resistance to anti-CMV agents will be reported in the baseline sample analyzed by the central specialty laboratory these subjects will be excluded from the Per-Protocol Set for analysis.

During the study, CMV genotyping will be conducted at the central specialty laboratory when the CMV DNA viral load is above a predefined cut off level: in cases of failure to clear CMV viremia during treatment; cases of recurrence of viremia on and off treatment; and cases of viremia rebound if >1 $\log_{10}$ above nadir while on treatment (***Rebound*** is defined as increase in viral DNA load for >1 $\log_{10}$ above nadir without prior clearance of viremia). The entire UL97, UL54, and UL27 CMV genes will be sequenced in every sample that meets the criteria for genotyping, including the baseline samples.

Additionally, virus susceptibility testing (phenotyping) could be performed on selected de-novo CMV mutations/variants of maribivir-treated subjects by recombinant phenotyping to define the association of these mutations with anti-CMV drug resistance. Details of the analysis would be specified in a resistance analysis plan.

The list of CMV mutations known to confer resistance to valganciclovir, and other commercially available anti-CMV agents (ganciclovir, foscarnet, and cidofovir [not approved in Japan]) is presented in Appendix 6.

8.2.2.3 CMV Infection Symptomatic Assessment

Cytomegalovirus tissue-invasive disease will be defined as described by Ljungman et al., 2017. The gold standard for diagnosing CMV tissue-invasive disease is the identification of CMV inclusions in the infected cells of the tissues OR identification of CMV in biopsy tissue samples. However, in some cases both diagnostic methods are required when tissue samples have a high chance of being contaminated by body fluids that shed virus (bronchoalveolar lavage [BAL], urine or stool).

In some subjects, when it is not possible to obtain a tissue biopsy, a culture of CMV from body fluids or CMV DNA quantitation (for selected cases) may be used to confirm diagnosis, with a lower level of confidence in diagnosis. CMV syndrome (in SOT subjects only) will also be defined as described by Ljungman et al., 2017, and requires at least 2 of 6 signs and symptoms to be present (see Appendix 7 for full description of criteria).

All subjects will be monitored for the occurrence of CMV tissue-invasive disease and CMV syndrome throughout the study. For symptomatic subjects who present with CMV tissue-invasive disease and CMV syndrome at Baseline, the investigator will document the initial diagnosis of CMV tissue-invasive disease and CMV syndrome at Visit 2/Day 0 (ie, absence or presence at Baseline) and all serial assessments of infection status (ie, no change, improvement, worsening, or resolution) at all subsequent visits in the study.

The recurrence of symptomatic CMV infection will be defined as the presence of signs or symptoms of the CMV tissue-invasive disease or CMV syndrome (same or new symptomatology) confirmed as per Ljungman et al., 2017 after the period of resolution of symptomatic CMV infection in subjects symptomatic at Baseline.

In subjects asymptomatic at Baseline, the occurrence of new CMV tissue-invasive disease or CMV syndrome after start of study treatment will be assessed by the investigator at all scheduled study visits.

8.2.2.4 Graft Outcomes

History of the current transplant and its status at screening and baseline will be collected for all transplant types, including dates of transplant, graft complications, and use of antirejection therapies for prophylaxis or treatment of graft rejection.

Assessment of the transplant throughout the study will include the status of the graft function, the presence of the episode(s) of acute rejection, or development of other relevant complications (eg, new onset diabetes). The outcome of graft loss is a clinical determination that the graft irreversibly and irrevocably ceases functioning (eg, in case of renal transplant, with the subject returning to permanent dialysis if dialysis-dependent prior to transplant or return to insulin dependency in the case of pancreas transplant) as determined by the investigator.

Detailed information will be collected in separate CRF forms for SOT (by organ) or HSCT, as specified in the study manual.

8.2.2.5 Graft-versus-host-disease (GVHD) Assessments

Graft-versus-host-disease is a well-recognized complication of transplantation, much more frequently in HSCT transplants. Graft-versus-host-disease occurs when the donor cells (the "graft") recognizes the patient being transplanted (the "host") as being foreign, ie, when donor T lymphocytes respond to mismatched protein antigens expressed in host T-cells. It presents in an acute and chronic form.

The most influential protein mismatches are HLAs and the incidence of acute GVHD is directly related to the degree of mismatch between HLA proteins expressed by the HSCT donor and recipient (Loiseau et al., 2007). Even in patients that receive HLA-matched (HLA-A/B/C/DRB1) grafts, however, GVHD arises in approximately 40% of patients due to differences in minor histocompatibility antigens and requires systemic therapy. Acute GVHD that typically occurs in first 100 days after transplant includes: erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus or cholestatic liver disease.

Chronic GVHD typically occurs later (>100 days after transplant) and is manifested on skin, appendages, mouth, eyes, lungs, genitalia, esophagus, and connective tissues. Chronic GVHD diagnosis is supported by histologic evidence of GVHD from any affected site. The diagnosis might be difficult as negative histological findings do not exclude the existence of chronic GVHD, and similarity to other conditions that often occur in patients with HSCT (such as mycophenolate mofetil [MMF] toxicity or the presence of GI CMV tissue-invasive disease).

Investigators are expected to consider recommendations for diagnosis provided in guidance in Appendix 9 and Appendix 10 (Jagasia et al., 2015; Shulman et al., 2015). Detailed information

on GVHD and its grading, at Baseline and during the study will be collected in separate eCRF forms.

Assessment of absence or presence of acute GVHD will be done at Baseline, and if present, grading will be performed according to published guidelines provided in Appendix 8 (Harris et al., 2016); acute or chronic GVHD present at Baseline will also be followed throughout the study treatment phase, at every study visit, utilizing the same diagnosis until resolution (during the duration of the study) as indicated in Table 1 and Table 2.

8.2.2.6 Comorbidity Status

Transplant subjects often have multiple other comorbidities, resulting from their immunosuppressed status (co-infections, GVHD, transplant malfunctioning due to rejection), toxicities from therapies for maintenance of the transplant or reactivation of the baseline disease for which they had been transplanted (malignancy for example), and other concomitant diseases resulting in very diverse population that might be enrolled into the study. The comorbidity assessment will be conducted at timepoints specified in Table 1 and Table 2.

Comorbidity assessment will utilize Karnofsky Performance Status (KPS) scale for subjects (Peus et al., 2013; Schag et al., 1984). Karnofsky Performance Status is a valuable tool for measurement of and comparison between the functional statuses of individual subjects. Refer to Appendix 11 for the KPS performance status scale.

8.2.3 Safety

8.2.3.1 Physical Examination

A physical examination will be performed by the investigator. A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, neck, lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

Symptom-oriented physical examinations other than protocol-specified examinations will be performed when clinically indicated.

Abnormalities identified at the Screening visit (Visit 1) will be documented in the subject's source documents and medical history CRF. Changes after the Screening visit (Visit 1) will be captured as AEs on the AE eCRF page, as deemed clinically relevant by the investigator and at subsequent study visits will be recorded in the subject's source documents.

The investigator or designee will perform physical examinations at time points specified in Table 1 and Table 2. Body weight and height will be measured at time points specified in the SoA.

8.2.3.2 Adverse Events

At each 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 consent is signed through 30 days after the dose of study treatment. Following the 30-day capture period for all AEs, only those AEs deemed related to study treatment or other protocol-mandated procedures and all SAEs (regardless of causality assessment) will be collected through the end of the study (Visit 18/Study Week 20/Follow-up Week 12). Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.3.3 Vital Signs

Vital signs include pulse rate, respiration rate, blood pressure and temperature.

Measurement of vital signs is always performed prior to drawing the blood samples at the timepoints specified in Table 1 and Table 2. The investigator will assess whether a change from Baseline (Visit 2/Study Week 0/Day 0) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.2.3.4 Clinical Laboratory Tests

Clinical laboratory tests (hematology, chemistry, urinalysis, HBV, HCV, and pregnancy) will be performed by a central laboratory at the time points specified in Table 1 and Table 2. Immunosuppressant drug concentration testing will solely be done for subjects receiving immunosuppressive therapy with tacrolimus, cyclosporine, or everolimus (see Table 1 and Table 2). During screening, clinical laboratory tests will be performed by the central laboratory, however local laboratory results if available might be utilized for the assessment of the eligibility. If local laboratory results are used for the assessment of the eligibility, the reference ranges must be provided. However, for CMV DNA quantitation results, only central laboratory results will be used to confirm eligibility. At Baseline (Visit 2/Study Week 0/Day 0) blood samples will be taken for CMV DNA quantitation and genotyping, hematology and chemistry, and tested in the central specialty laboratory. All clinical laboratory assays will be performed according to the central laboratory's standard procedures. Reference ranges will be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out of range pathological changes. 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. Clinically significant finding should be reported as an AE unless signs of already reported conditions exist. Abnormal clinical laboratory values that 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.

8.2.3.5 Pregnancy Test

Aserum hCG pregnancy test will be performed on all females of childbearing potential at the Screening visit (Visit 1), Baseline visit (Visit 2/Study Week 0/Day 0), Visit 6/Study Week 4/Day 28 and end of study treatment visit (Visit 10/Study Week 8/Day 56); if pregnancy is suspected; or on withdrawal of the subject from the study. Urine pregnancy tests may be done per institutional requirements; however, they are not sufficient for eligibility determination.

8.2.3.6 Electrocardiogram

A 12-lead ECG will be performed at Visit 2/Study Week 0/Day 0, Visit 10/Study Week 8/Day 56 (end of treatment visit), Visit 18/Study Week 20/Day 84 (end of study visit), and at any additional time during the study, if clinically indicated. Each ECG will include heart rate, RR Duration, PR duration, QT duration, QRS duration. The corrected QT interval (QTc) will be calculated using the Fridericia's formula. The investigator will be responsible for providing the interpretation for all ECGs in terms of clinical significance to the subject.

8.2.4 Other

8.2.4.1 Clinical Pharmacology

For subjects entered to study treatment, the PK plasma samples will be collected on each of the study days specified in Table 1. The predose PK plasma sample will be obtained at all 3 PK visits. The postdose PK plasma samples at Visit 3/Study Week 1/Day 7 and at Visit 10/Study Week 8/Day 56 will be obtained any time between 2 to 4 hours after the morning dose. Any episode of vomiting occurring within 2 to 4 hours after the morning dose and before the postdose PK plasma sample collection must be documented.

The following will be recorded in the CRF:

- Date and time of the last dose of study treatment before the predose PK plasma sample
- Date and time of the predose PK plasma sample
- Date and time of the last dose of study treatment before the postdose PK plasma sample
- Date and time of the 2 to 4 hours postdose PK plasma sample
- Date and time of vomiting within 2 to 4 hours after the morning dose and before the postdose PK plasma sample collection

If a subject had study treatment interrupted for 2 consecutive days prior to the morning maribavir dose on a PK visit, no PK plasma sample will be collected. If a subject has completed the

predose PK plasma sample collection but has missed the morning dose of maribavir on the day of the PK visit, then no postdose PK plasma sample will be collected.

Additional PK plasma samples will be collected from the subjects with biopsy-proven GI GVHD with diarrhea (>300 mL/day), biopsy-proven GI GVHD with nausea and vomiting, documented acute GVHD of liver (Stage II, total bilirubin >3 mg/dL or biopsy-proven) with diarrhea (>500 mL/day), or biopsy-proven acute GVHD of the skin with diarrhea (>500 mL/day).

8.2.4.2 Pharmacodynamics

Not applicable.

8.2.4.3 Genetics

Not applicable.

8.2.4.4 Health-related Quality of Life

Not applicable.

8.2.4.5 Healthcare Resource Utilization

Not applicable.

8.2.5 Volume of Blood to Be Drawn from Each Subject

The volume of blood drawn from each subject during the study is provided in the Protocol Annex.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

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

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy, safety, and PK data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, study treatment exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed. A separate population PK analysis and report will be generated and a data analysis plan for the population PK analysis will be produced separately.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using statistical analysis system (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

Post-transplant (SOT/HSCT) CMV infection is a rare condition and the number of patients expected to participate in this clinical trial in Japan is anticipated to be limited. For the start of domestic development of TAK-620, Takeda conducted a feasibility assessment for the planned clinical study. Specifically, a survey on the number of patients in university or large hospitals in Japan where HSCT or SOT are performed was carried out. The number of patients with asymptomatic CMV infection was estimated to be about 44 for HSCT and about 9 for SOT, for a total of about 53 patients. Assuming a dropout rate of 15%, approximately 44 patients with asymptomatic CMV infection are expected to be enrolled. On the other hand, the number of patients with resistant or refractory CMV infection is very small, and only a few patients (approximately 3) can be expected to be enrolled at the maximum.

From the standpoint of feasibility, approximately 44 asymptomatic patients and few resistant or refractory patients are expected to be enrolled in this study.

The target number of patients with asymptomatic CMV infection should be determined from the viewpoint of evaluating the similarities in outcome between the prospective study and the overseas Phase III study (Study SHP620-302) as well as the feasibility of the new study.

For the proportion of patients who achieved CMV clearance at Week 8 in the TAK-620 group in Study SHP620-302, since the results have not been available, we can assume 68%, which was used as the estimation for sample size justification in Study SHP620-302. Regarding the proportion of patients who achieved CMV clearance at Week 8 in this study, since it is the same target population and primary endpoint as Study SHP620-302, it is appropriate to assume 68% as Study SHP620-302.

In addition, we considered it appropriate to use -15% as a reference value for the difference in the point estimate between studies based on the noninferiority margin used in 2 noninferiority studies comparing valganciclovir and ganciclovir for CMV treatment (The study reported by Chawla et al., 2012 and VICTOR study [Asberg et al., 2007]).

With a sample size of 44 in asymptomatic patients, if the true response rates for this study is the same as that of the Study SHP620-302, the probability of observing a response rate similar to that of the Study SHP620-302 is high, that is, over 95% the point estimate from this study will be above the point estimate of Study SHP620-302 minus 15%.

Of note, the similarity between SHP620-302 study and Japan study will be based on both the primary endpoint and secondary endpoints.

9.4 Statistical Analysis Sets

Statistical analysis sets are as follows:

- Enrolled Set: consists of all subjects who have signed an informed consent and have begun some study procedures.
- Full Analysis Set: consists of all subjects who have taken at least 1 dose of study treatment; the Full Analysis Set will be used for efficacy analyses.
- Per-Protocol Set: consists of all subjects in Full Analysis Set who do not have major predefined protocol deviations that may affect the primary efficacy assessment.
- Safety Set: consists of all subjects who have taken at least 1 dose of study treatment. The Safety Set will be used for safety analyses.
- Pharmacokinetic Set: consists of all subjects in the Safety Set who have plasma samples drawn and tested for maribavir concentrations.

9.5 Efficacy Analyses

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, interquartile ranges (Q1, Q3), minimum, maximum. Categorical and count variables will be summarized by the number and the percent of subjects in each category. The denominator for the percentages will be based on the number of subjects in the analysis set unless otherwise specified. Time-to-event endpoints will be summarized using Kaplan-Meier estimation. Ninety-five percent confidence intervals (CIs) for the estimated 25%, 50%, and 75% times will be presented.

The baseline value for efficacy variables is defined as the last available value before or on the first dose date of study drug at Visit 2/Study Week 0/Day 0.

9.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is confirmed clearance of plasma CMV DNA (CMV viremia clearance) at the end of Study Week 8.

For clearance of CMV viremia to be declared at the end of Study Week 8 during the treatment period, the subject must have received study treatment exclusively.

Confirmed CMV viremia clearance at the end of Study Week 8 is defined as plasma CMV DNA concentrations <LLOQ with the assay at a central specialty laboratory, in 2 consecutive postbaseline samples, separated by at least 5 days at Study Week 8. Subjects who take alternative anti-CMV treatment before Study Week 8 or have missing data at Study Week 8 due to early discontinuation or any other reasons will be counted as nonresponders.

Assessments of virological responders at Study Week 8 are described with examples in Table 7.

Table 7. Assessments of Virological Responders at Study Week 8

Scenario	CMV DNA Weeks on Study					Rationale
	Week 6	Week 7	Week 8	Week 9[a]	Response	
1	+/-	-	-	+/-/NA	Yes	2 consecutive "-" at Week 7 and Week 8
2	+/-	-	+	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
3	+/-	+	-	+/-/NA	No	Not 2 consecutive "-" at Week 7 and Week 8
4	+/-	-	NA	-	Yes	2 consecutive "-" as shown by available data and both "-" at Week 7 and Week 9 for missing Week 8, otherwise nonresponder
5	-	NA	-	+/-/NA	Yes	2 consecutive "-" as shown by available data and both "-" at Week 6 and Week 8 for missing Week 7, otherwise nonresponder
6	-	NA	NA	-	Yes	2 consecutive "-" as shown by available data at Week 6 and Week 9 and both "-", otherwise nonresponder

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; LLOQ=lower limit of quantification; NA=not available for evaluation of study drug effect; reason could be either not assessable by lab, by starting alternative anti-CMV treatment, withdrawal from study, etc.

[a] Week 9 data, if available to evaluate effect of study drug, only to be used if Week 8 data are unavailable or missing.

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.

Only CMV DNA data evaluable for assessment of effect of study drug will be included (ie, prior to the start of alternative anti-CMV treatment if any).

"-" = CMV DNA concentration <LLOQ

"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)

Confirmed clearance of plasma CMV DNA (CMV viremia clearance) =2 consecutive postbaseline assessments of

CMV DNA target <LLOQ, separated by at least 5 days.

Statistical Methodology for Primary Efficacy Endpoint:

The proportion of subjects achieving the confirmed CMV viremia clearance at Study Week 8 and the corresponding 95% exact CI will be calculated for the Full Analysis Set.

This analysis is also performed for the Per-Protocol Set.

Details of the analysis will be specified in the statistical analysis plan.

9.5.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- The maintenance of the confirmed CMV viremia clearance and infection symptom control achieved at Study Week 8 through Study Week 12 (4 weeks of post-treatment period), Study Week 16 (8 weeks of post-treatment/follow-up phase), and Study Week 20 (12 weeks post-treatment).
- The time to first confirmed viremia clearance at any time during the study.
- The recurrence of confirmed CMV viremia during the 12-week follow-up period in subjects with confirmed viremia clearance at Study Week 8 requiring additional anti-CMV treatment.
- The time course of changes in plasma CMV viremia load from Baseline by study week.
- Recurrence of CMV viremia during study treatment and in the follow-up period after the subject is discontinued from study treatment.
- Assessment of the profile of mutations in the CMV genes conferring resistance to maribavir.
- Confirmed plasma CMV DNA at the end of Study Week 8 to be less than 137 IU/mL.

Statistical Methodology for Secondary Efficacy Endpoint:

Secondary efficacy endpoints will be summarized descriptively. The denominator for the percentages will be based on the number of subjects in the Full Analysis Set, unless specified otherwise. Time-to-event endpoints will be summarized using Kaplan-Meier estimation. Ninety-five percent CIs for the estimated 25%, 50%, and 75% times will be presented.

Details of the analysis will be specified in the statistical analysis plan and the resistance analysis plan.

9.5.3 Pharmacokinetic Analyses

The pharmacokinetic endpoint for this study is maribavir C_{min}.

Individual maribavir plasma concentrations data will be presented in a listing. Maribavir C_{min} (predose maribavir concentration) will be summarized by Visit using descriptive statistics.

In a separate analysis and report, all maribavir concentrations obtained in this study will be combined with PK data from the Phase 1, Phase 2 and Phase 3 studies in adults conducted outside Japan, and analyzed by population PK analysis approach using a nonlinear mixed effect model approach using NONMEM Version 7 or above.

[redacted]

9.6 Safety Analyses

Safety and tolerability of maribavir for the treatment of CMV infection after HSCT or SOT will be assessed by evaluation of TEAEs (including instances of CMV disease), SAEs, AEs leading to interruption of study treatment, AEs leading to discontinuation of study treatment, AEs leading to withdrawal from the study, number of subjects with clinically significant vital signs, number of subjects with abnormal clinical laboratory evaluations, number of subjects with clinically significant ECG parameters, and number of subjects with abnormal physical examination findings. New onset of acute or chronic GVHD, graft rejection, or graft loss will be reported and may be assessed as AE/SAE. Immunosuppression drug levels will be summarized over time.

Two observation periods are defined for the purpose of safety analyses: 1) On-treatment period: from the time of maribavir initiation through 7 days after the last dose of study treatment, and 2) Overall-study period: start of maribavir administration through the end of the study. Safety endpoints will be summarized descriptively for the on-treatment period, and overall-study period, as appropriate. Baseline assessments will be the last assessment before the first dose of the study treatment.

Treatment-emergent AEs are defined as those with a start date on or after the first dose of study treatment, or with a start date before the date of first dose of study treatment but increasing in severity after the first dose of study treatment.

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not have a causal relationship with study drug. The PTEs will not be evaluated in the safety analysis; they will be listed as pretreatment AEs.

The number of events, incidence, and percentage of TEAEs will be displayed by preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA®) for the on-treatment period and overall-study period. Summaries in terms of severity and relationship to study treatment will also be provided. Treatment-emergent SAEs will be summarized separately in a similar fashion. Summaries of AEs leading to interruptions of study treatment, discontinuation of study treatment, withdrawals, AEs leading to death, and SAEs will be provided.

Adverse events will be analyzed according to primary system organ classes (SOCs) and PTs. Summary tables with SOCs and PTs will be generated presenting the number and percentage of subjects by AE, severity, seriousness, and relationship to study treatment for the on-treatment period and overall-study period.

Usage of concomitant medications will be summarized descriptively for the on-treatment period and overall-study period. Additionally, administration of hematopoietic growth factors, blood, and blood products will be summarized.

Baseline safety analyses is defined as the last value for the assessment prior to taking the first dose of study treatment. Change from Baseline in vital signs and clinical laboratory tests during on-treatment period and overall-study period will be summarized with descriptive statistics at each assessment visit. Potentially clinically important findings will also be summarized.

Maribavir dose interruptions for any AE will be summarized. Abnormal physical examination findings will be listed. A summary of ECG findings will be provided.

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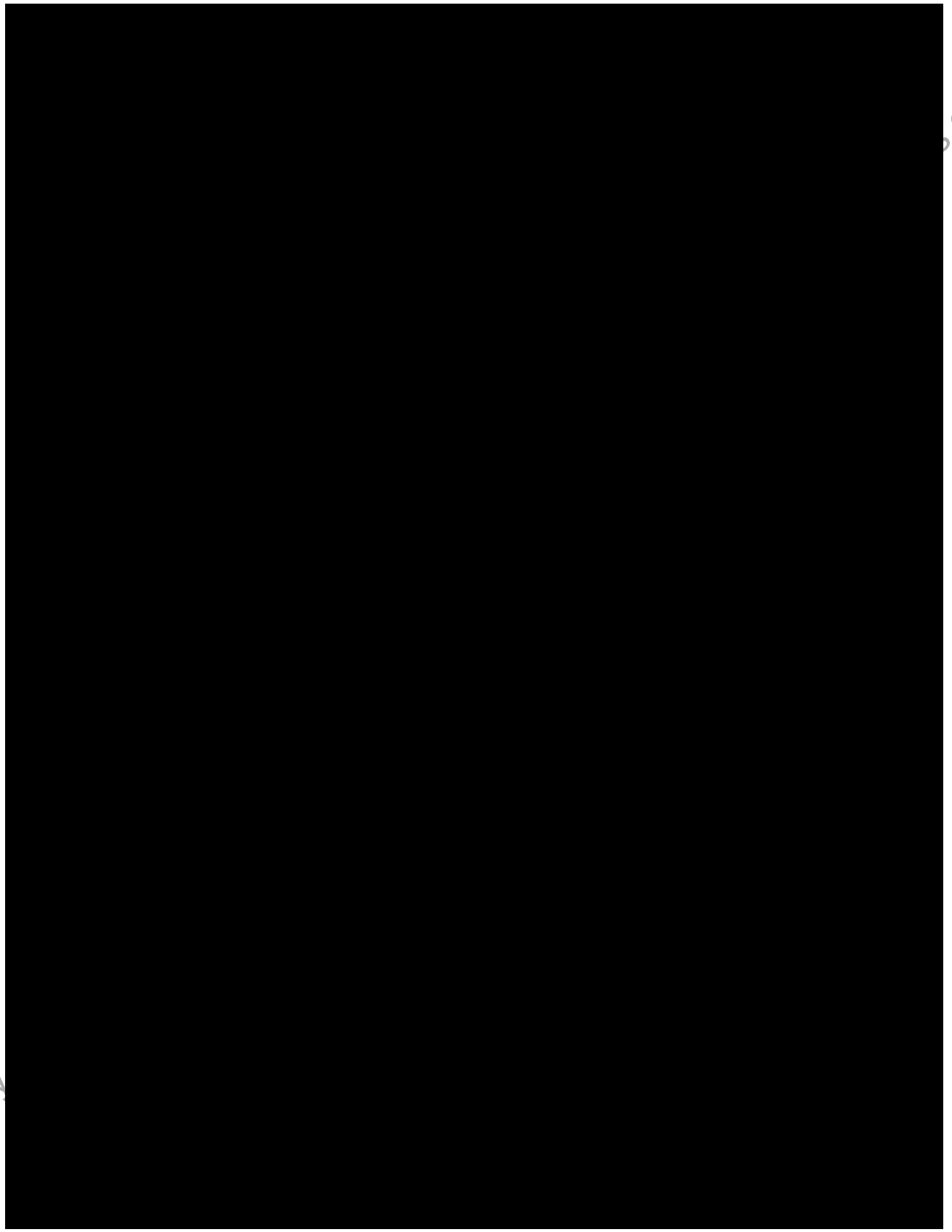
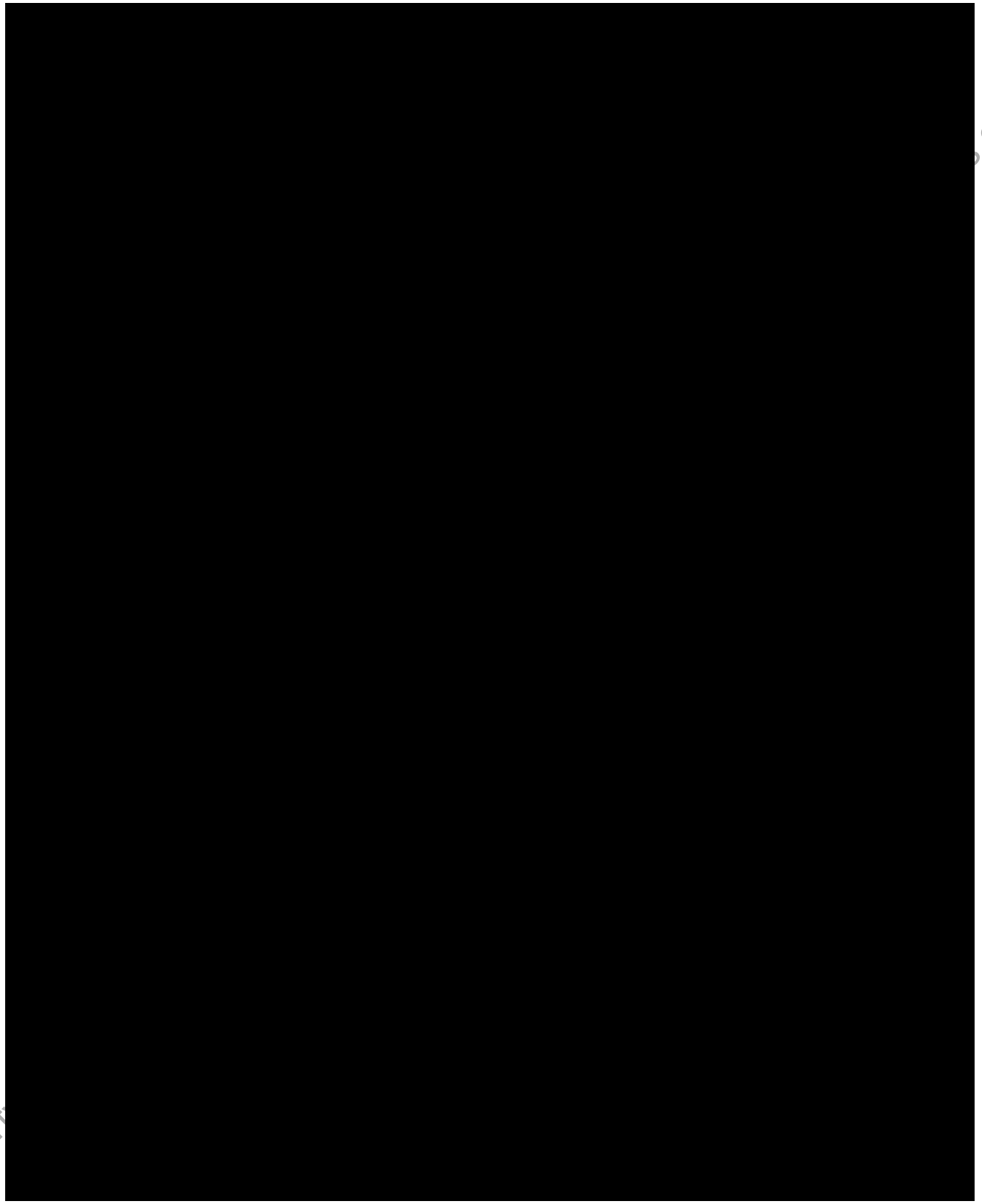
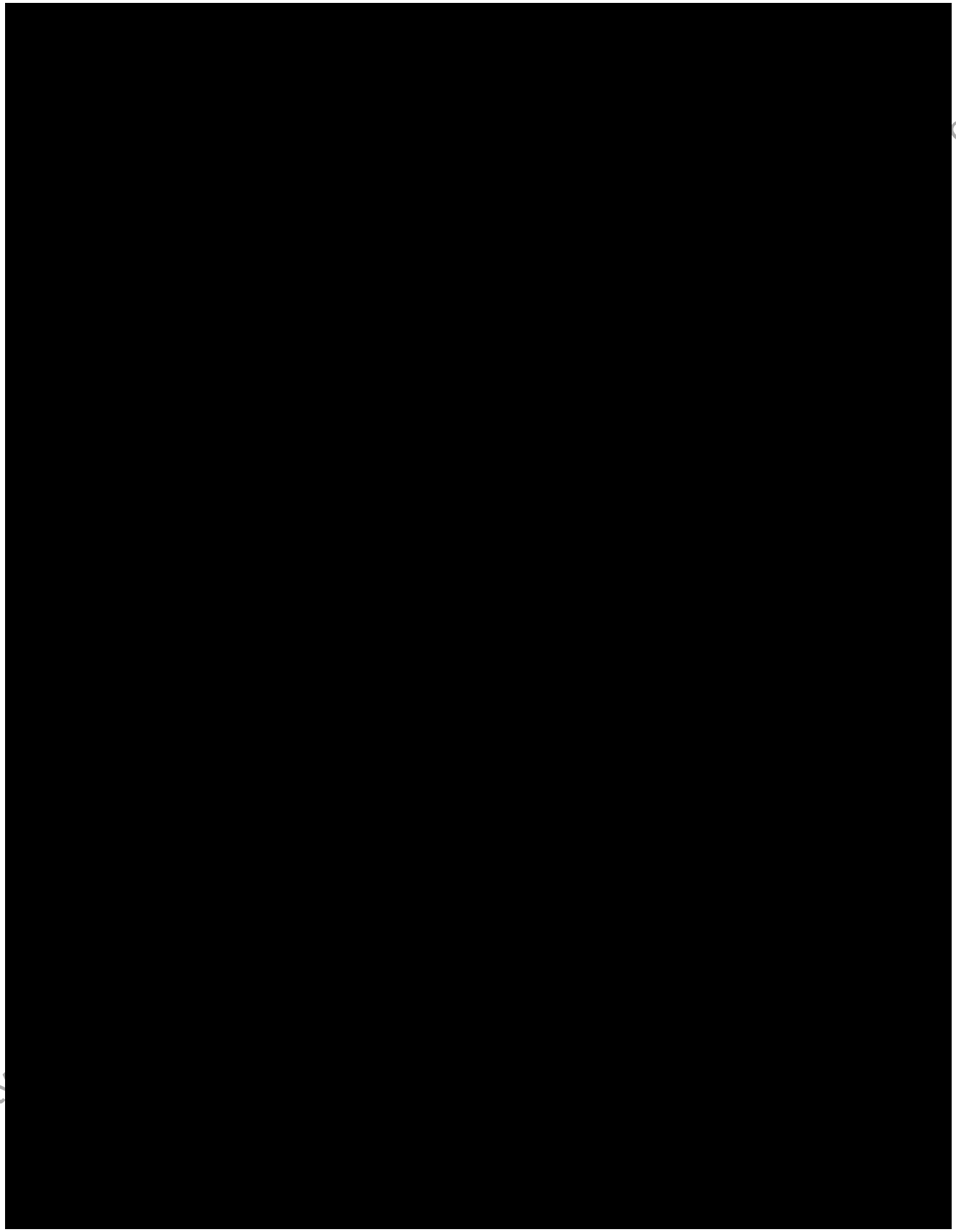
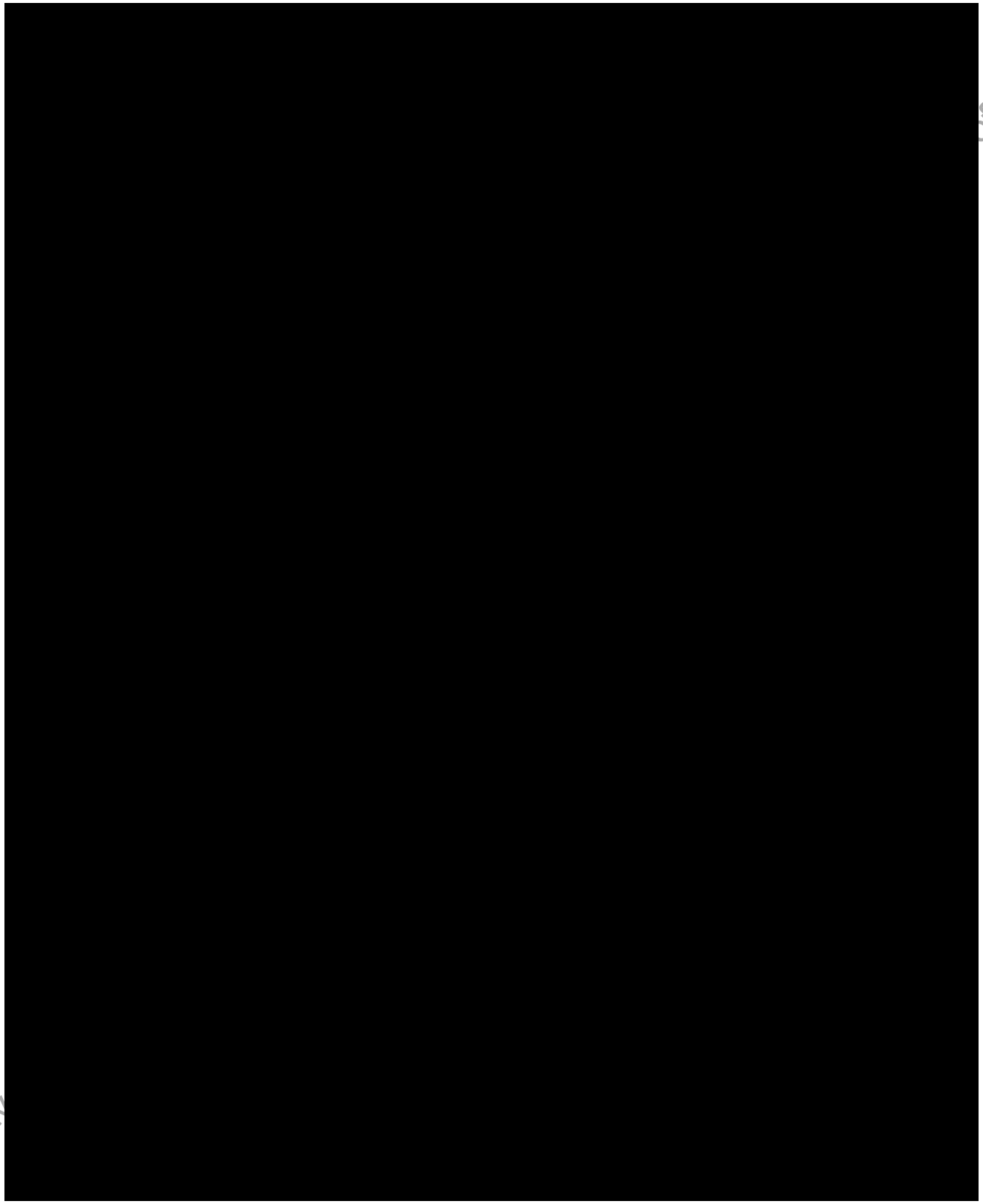
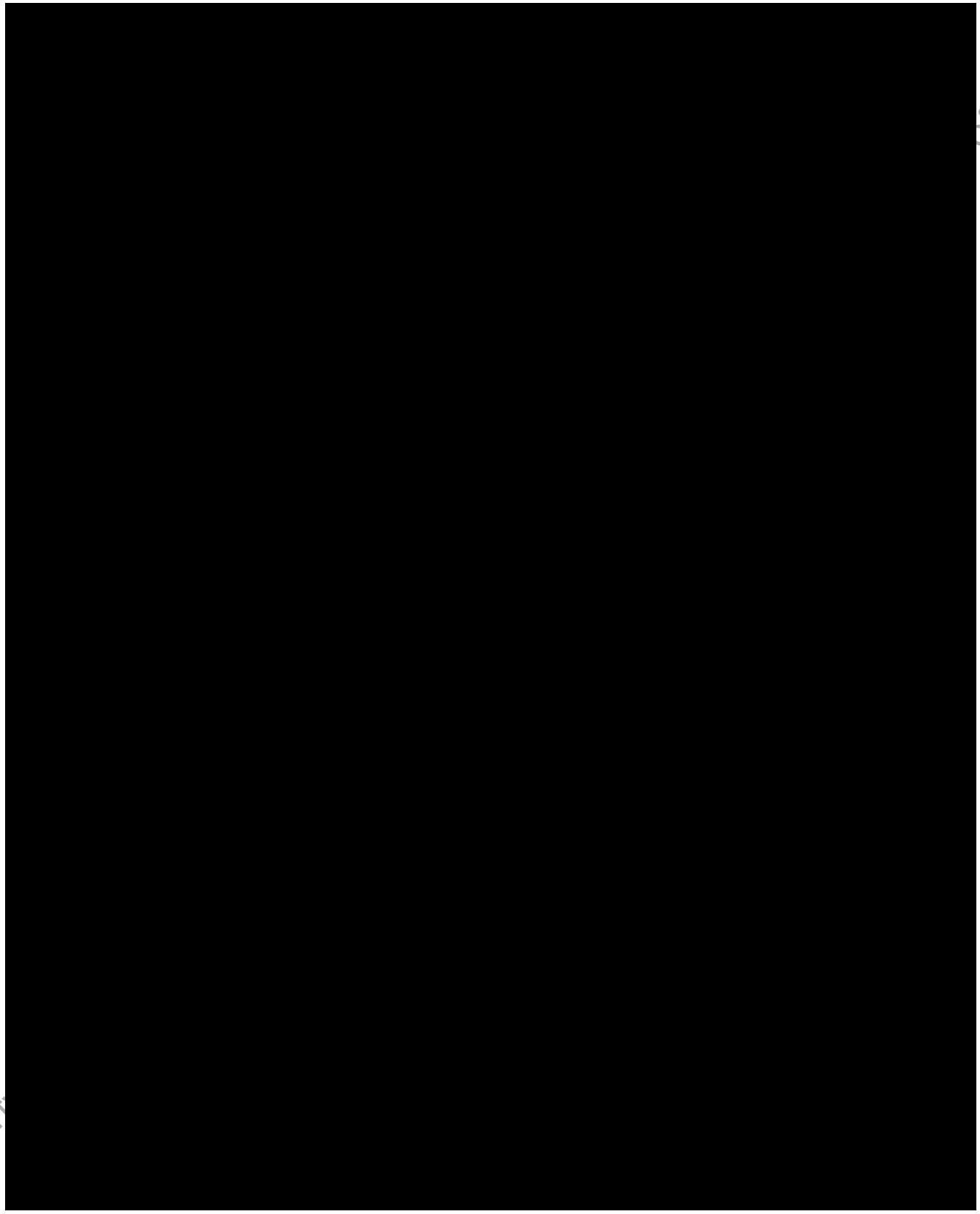
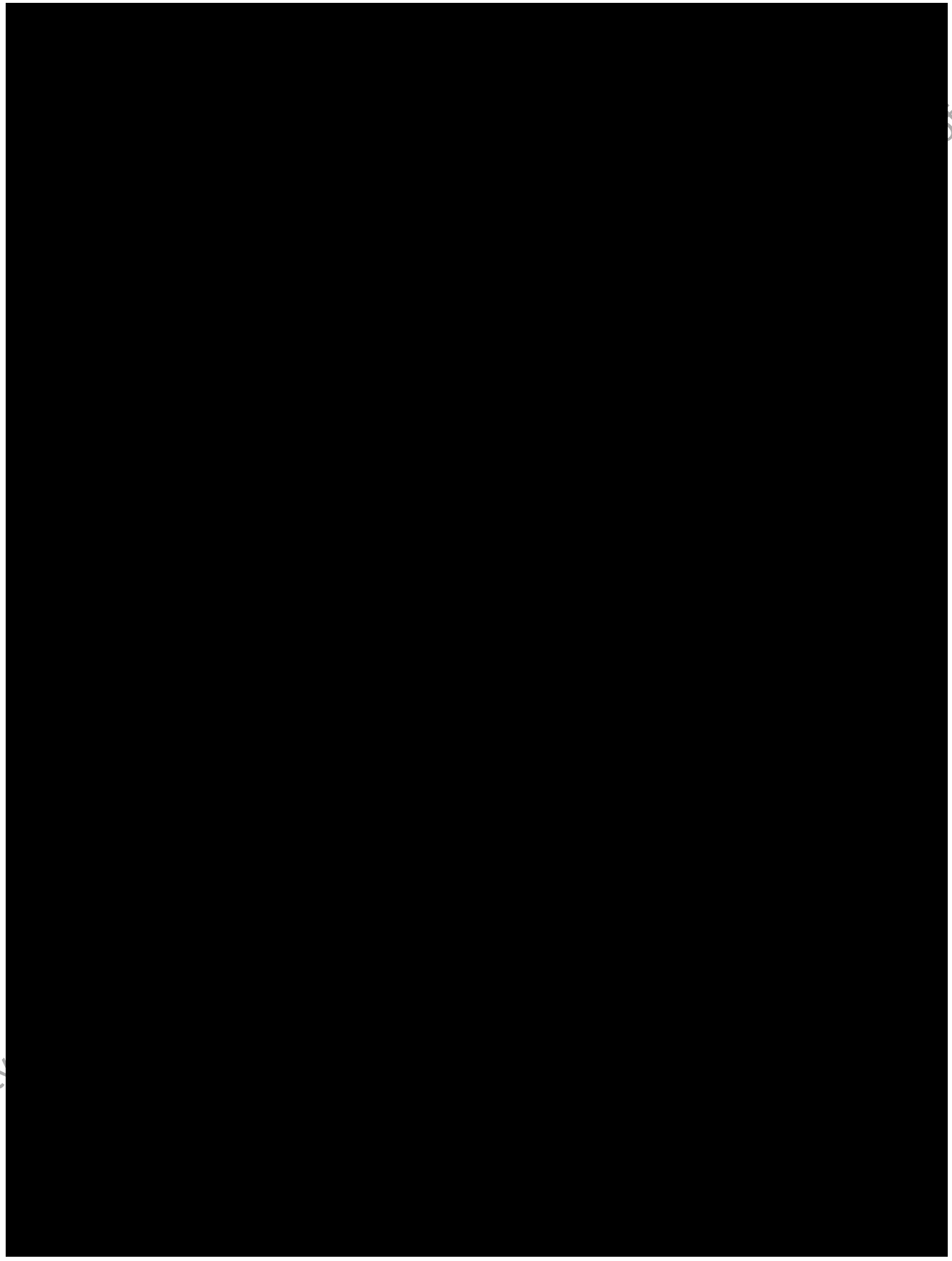


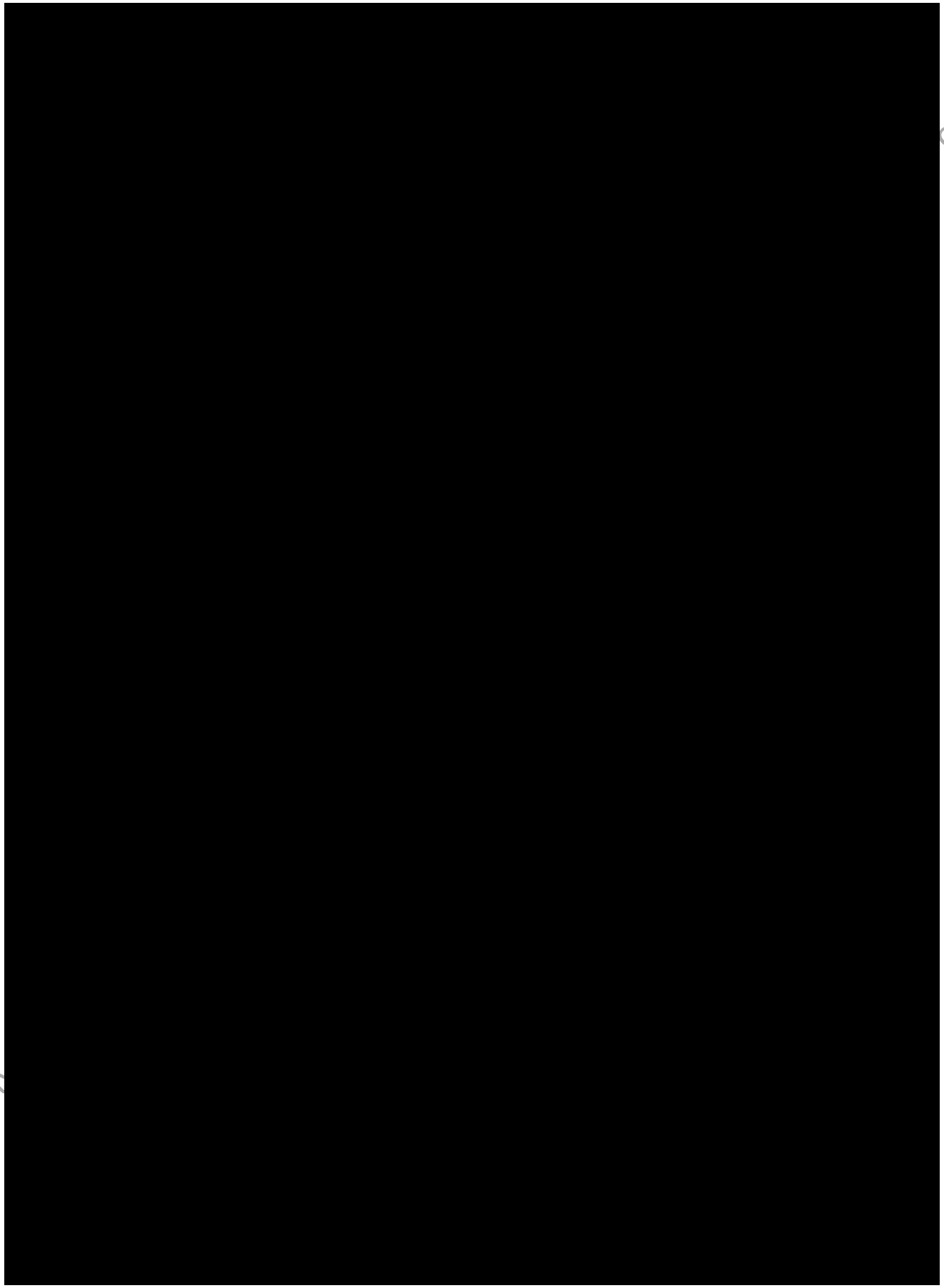


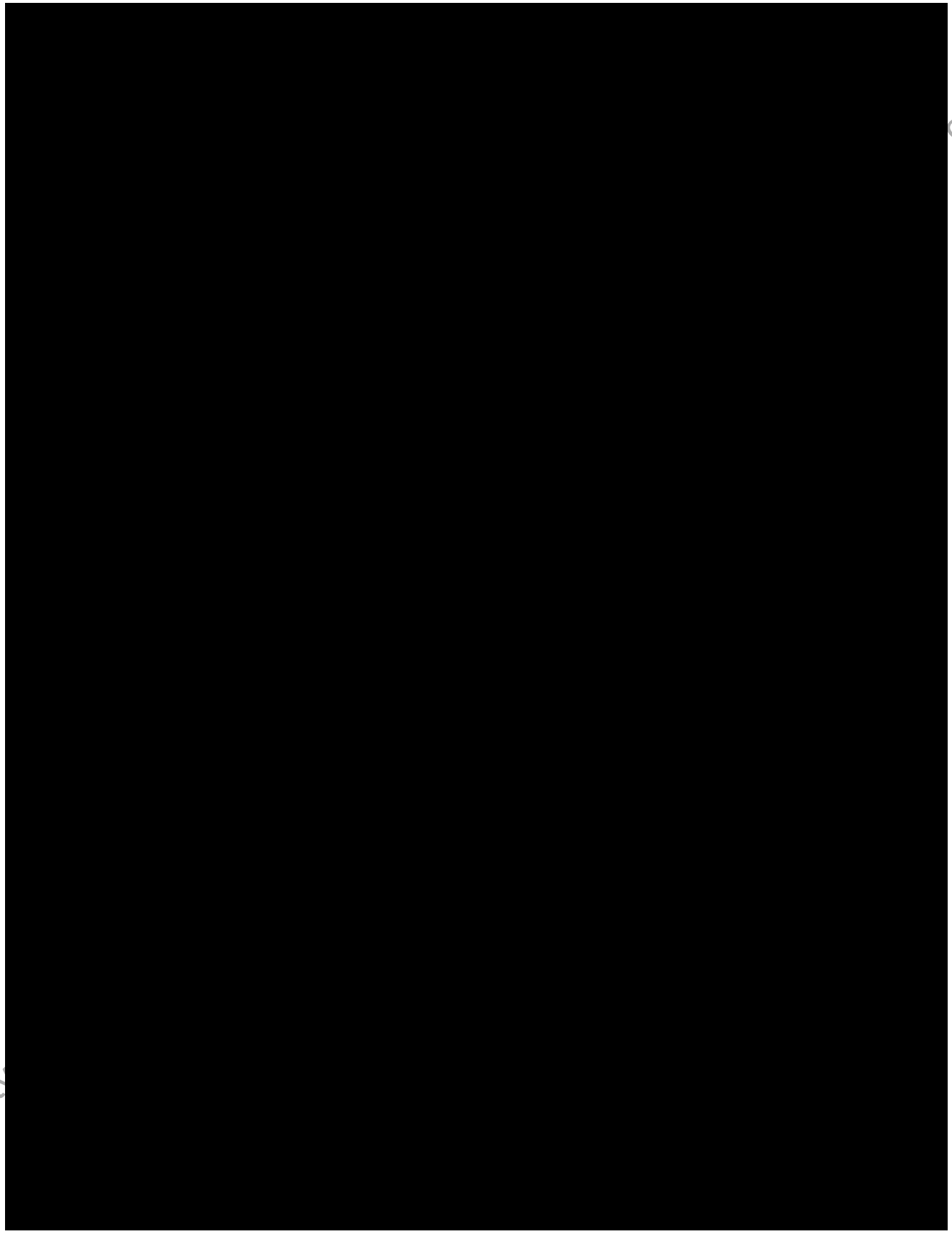


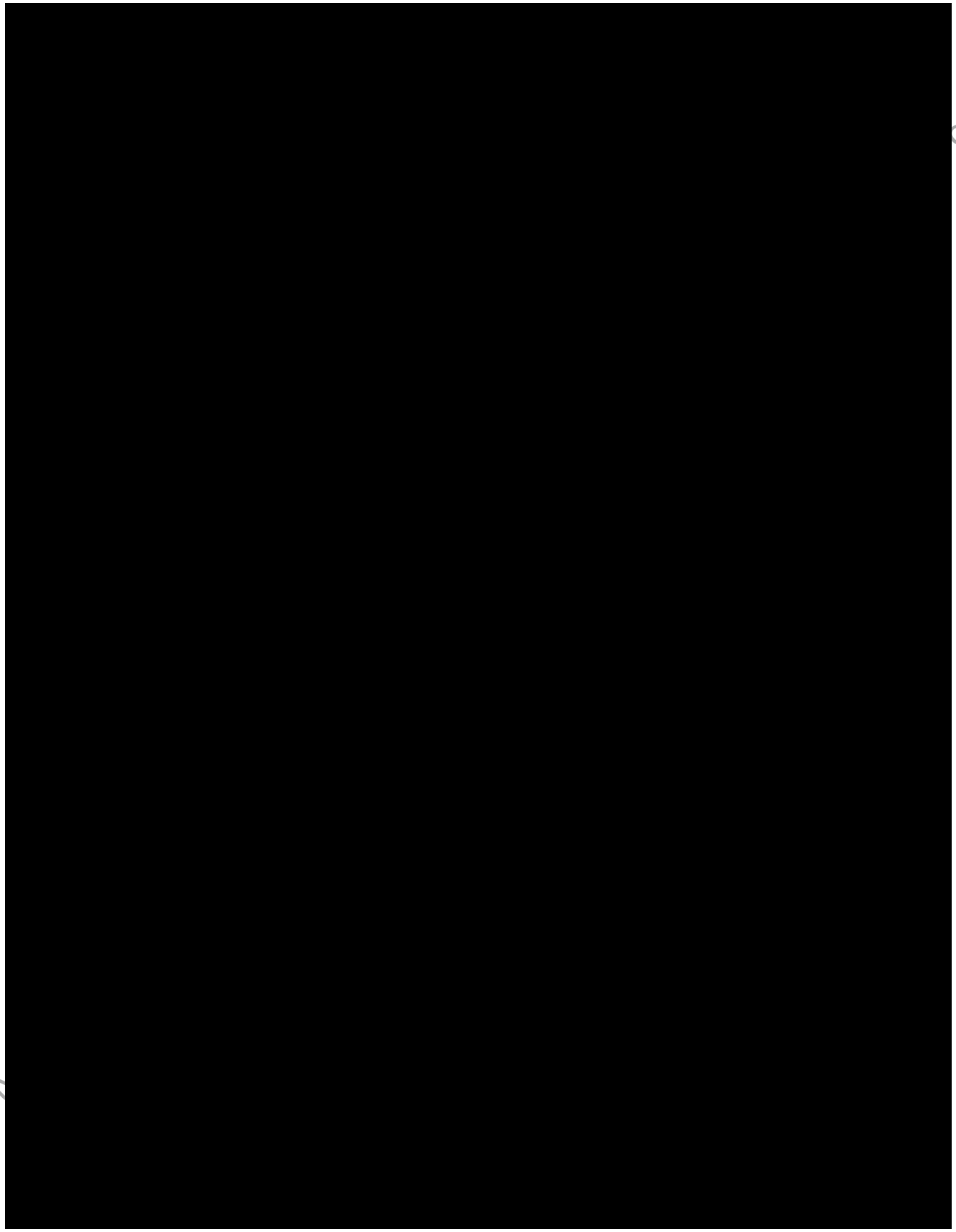


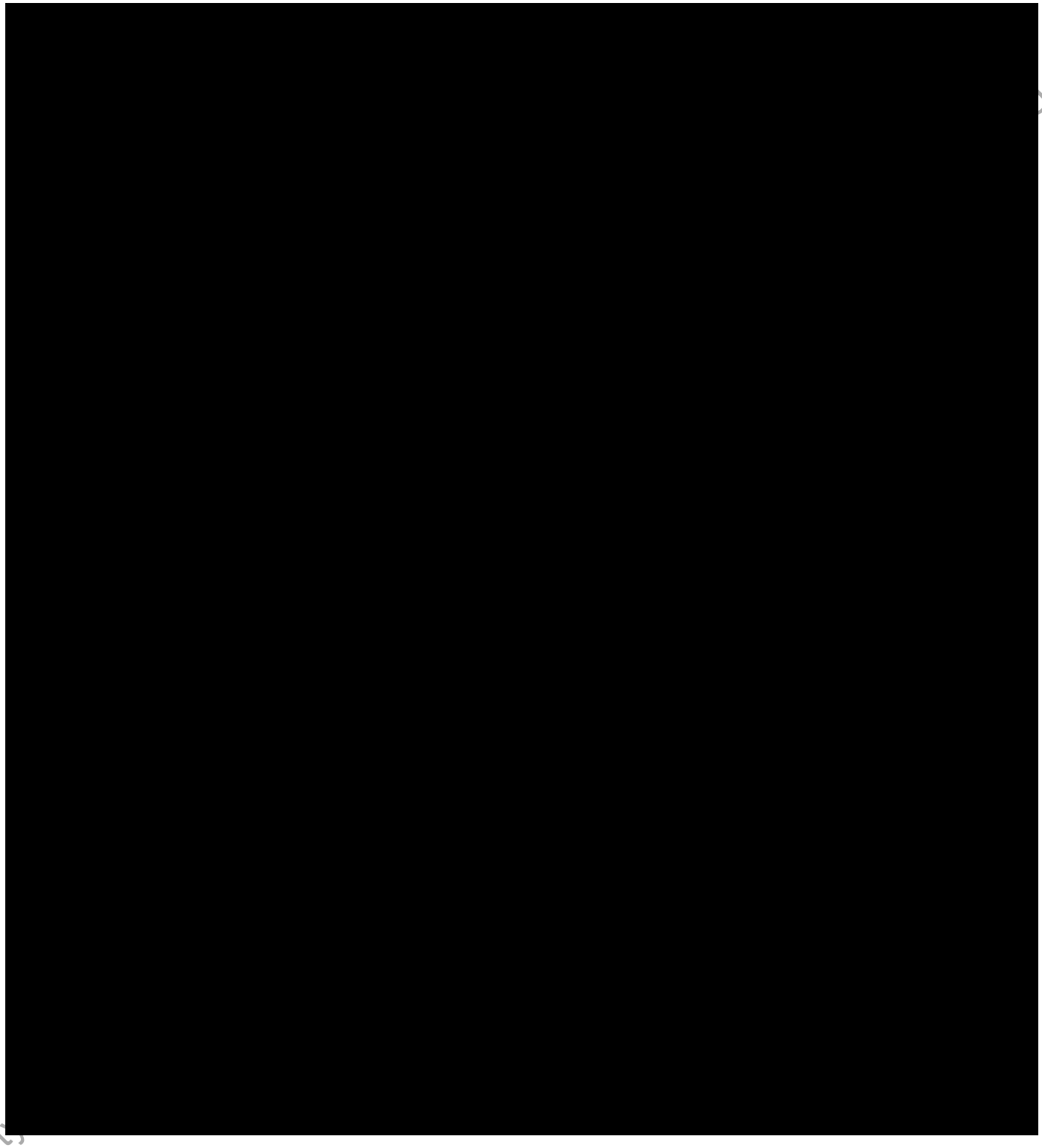


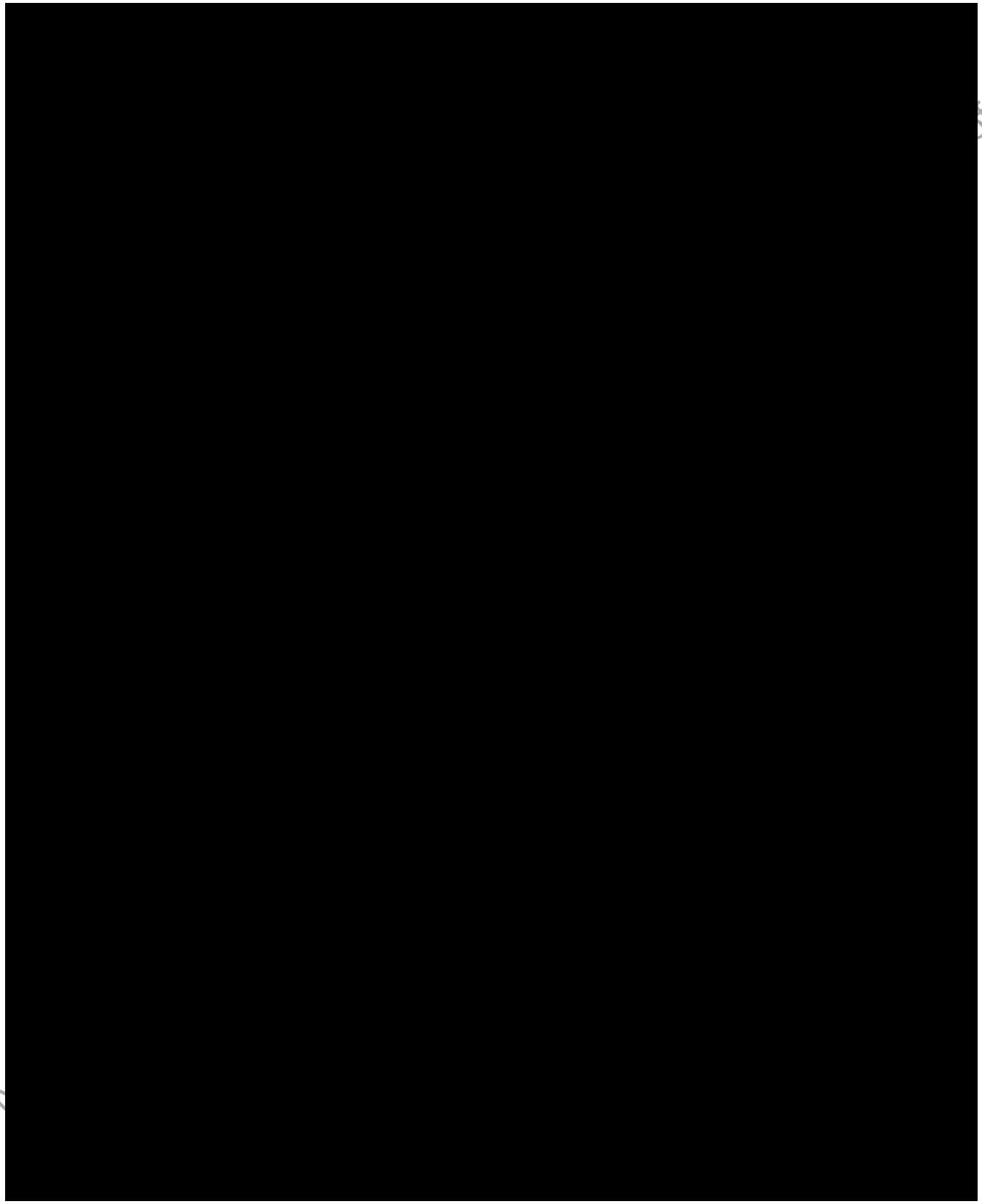


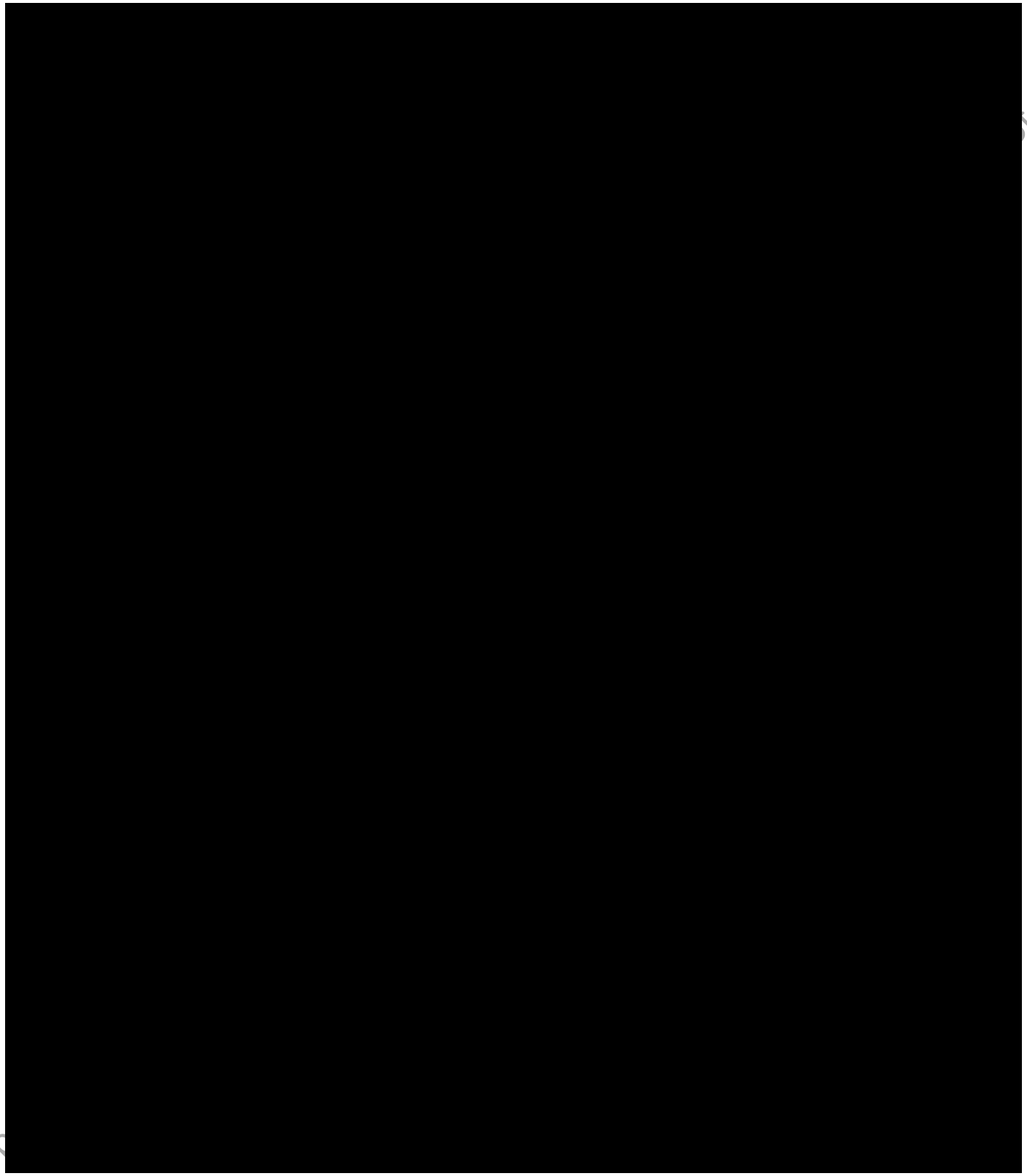


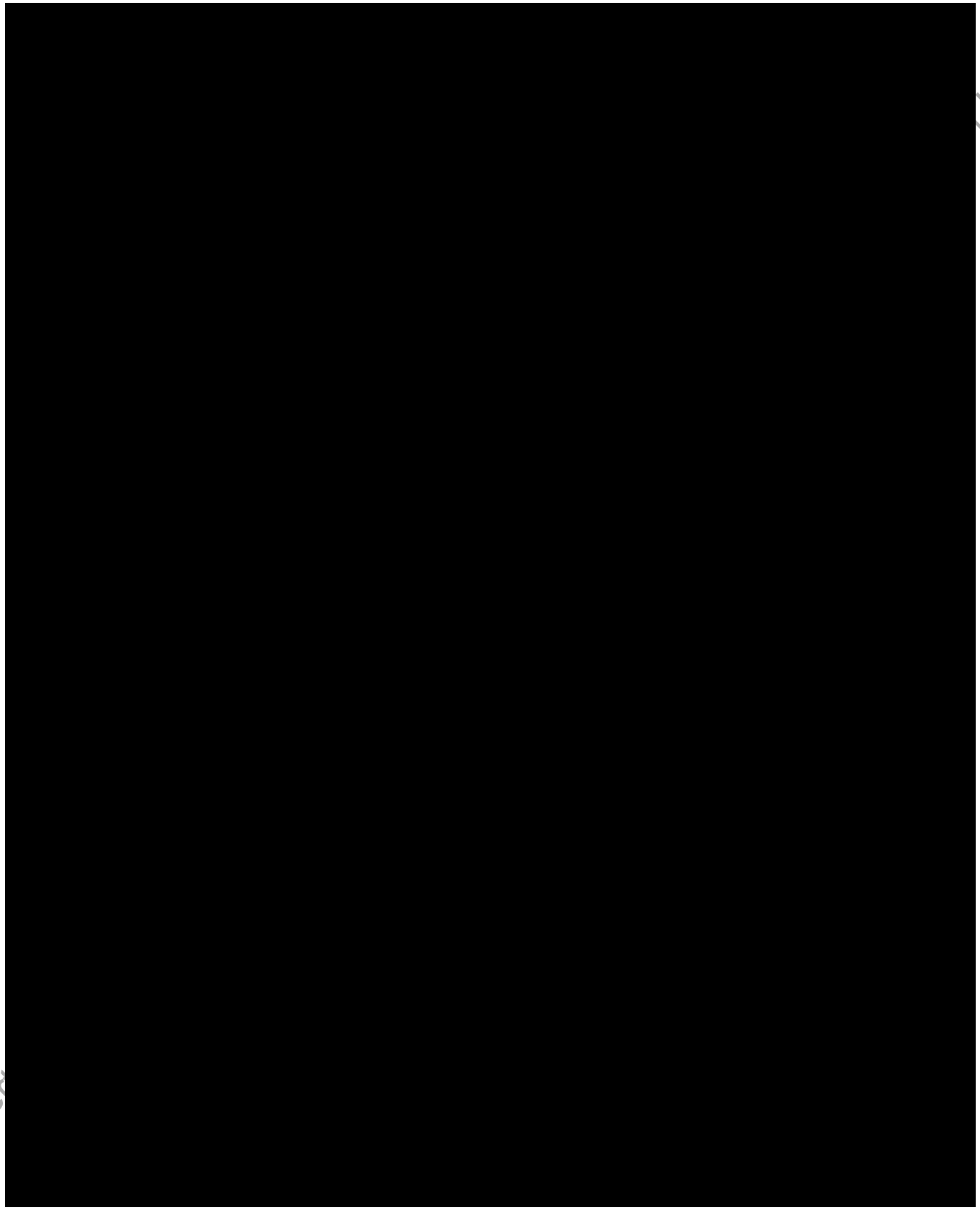


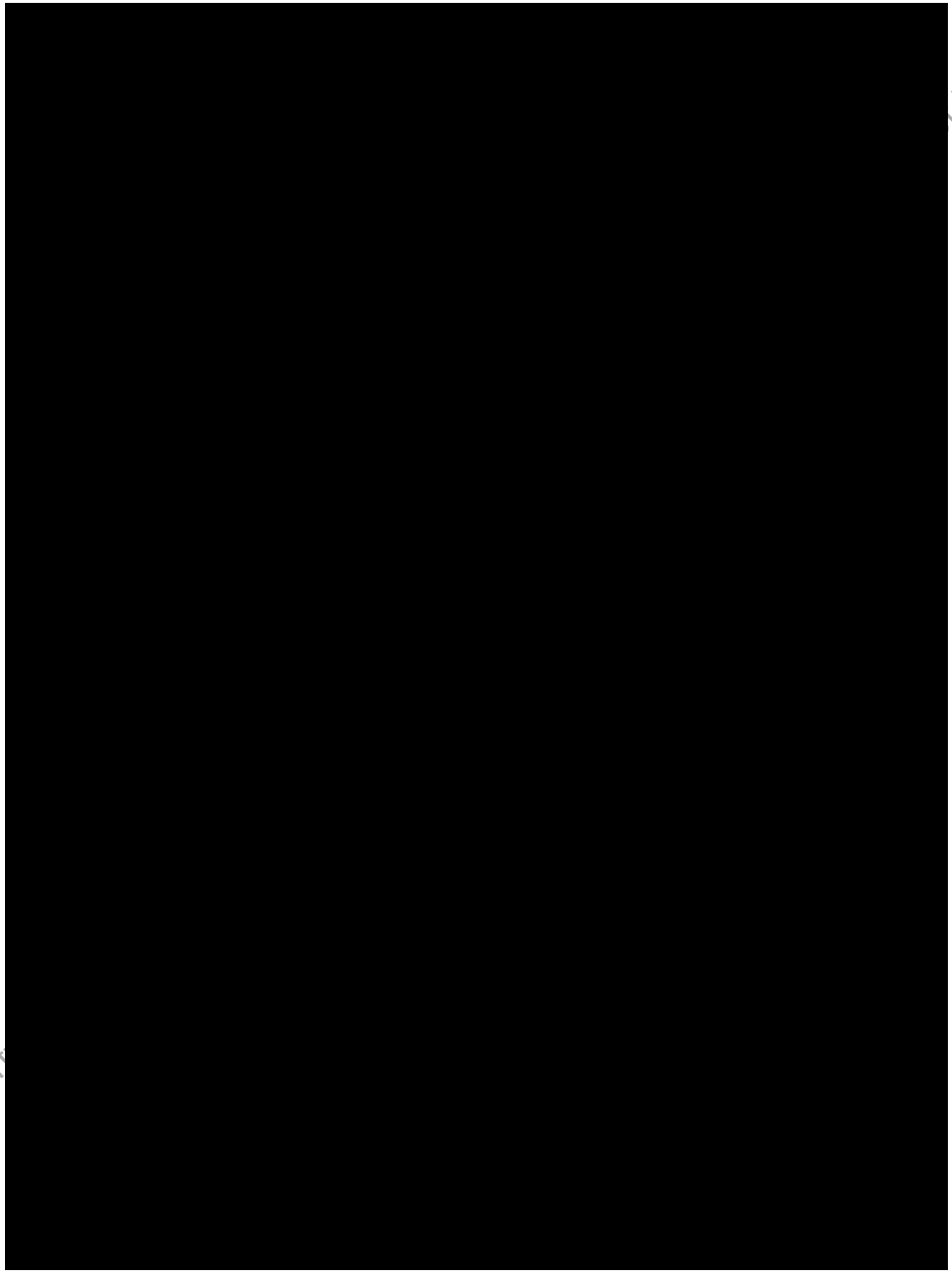


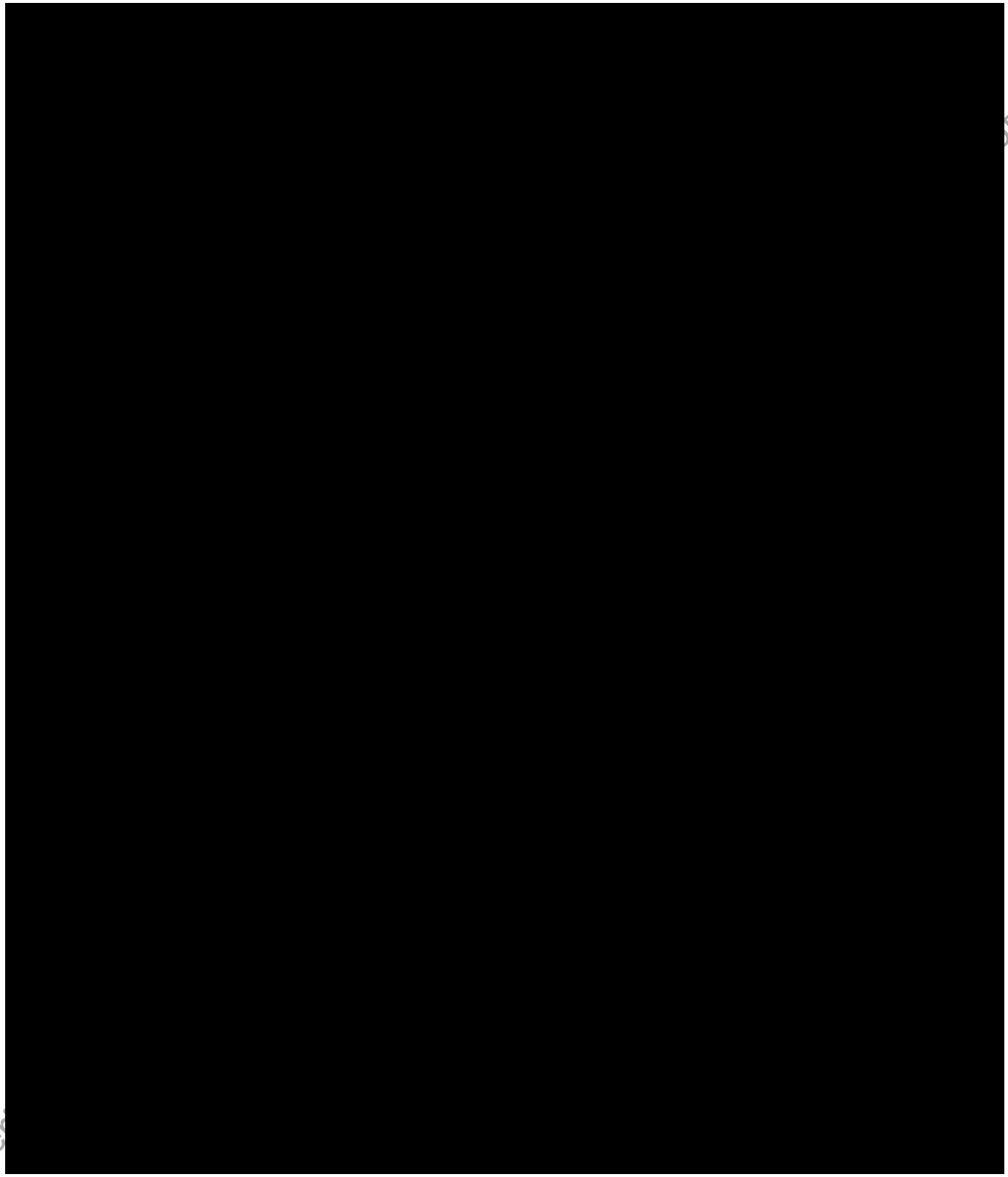


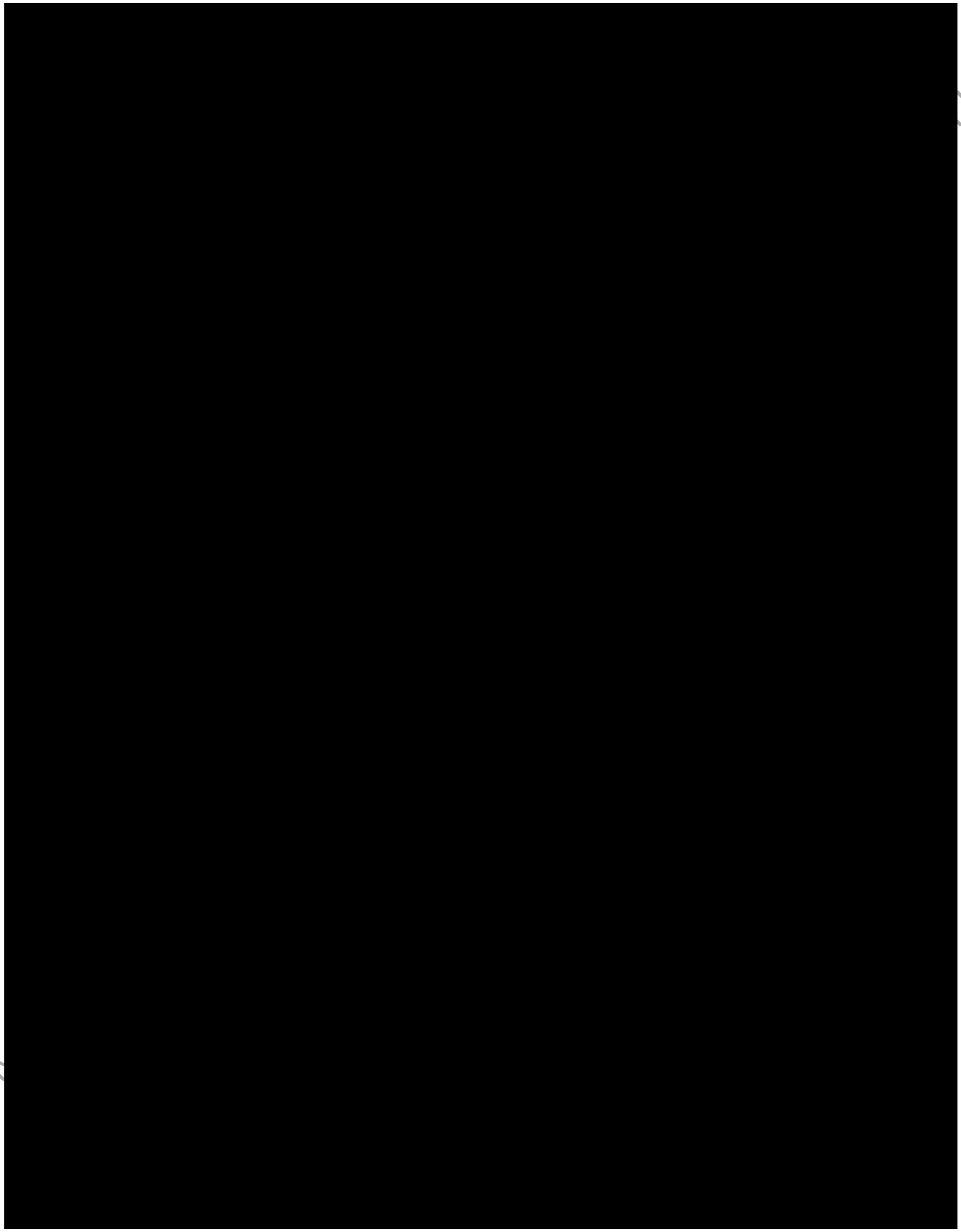


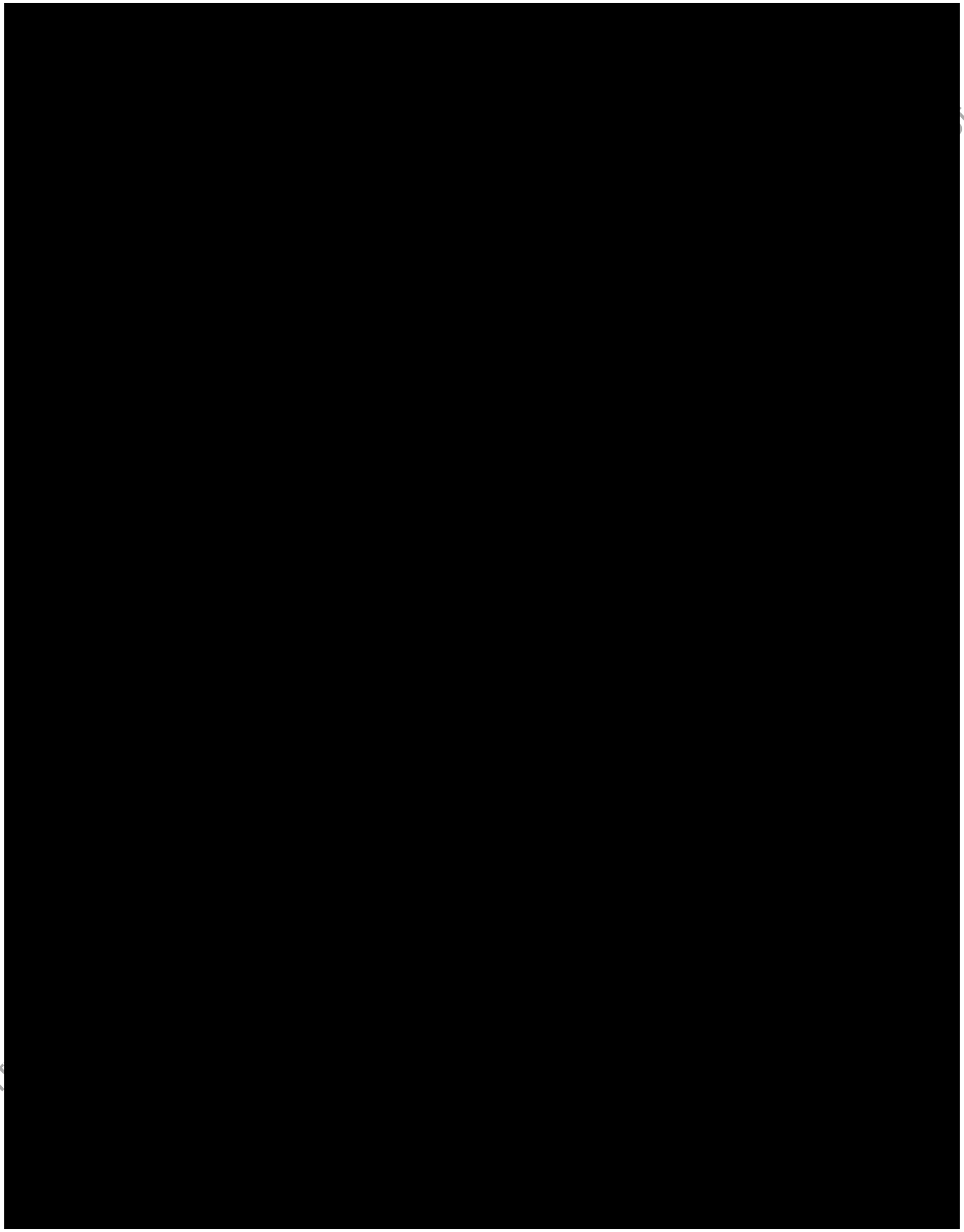


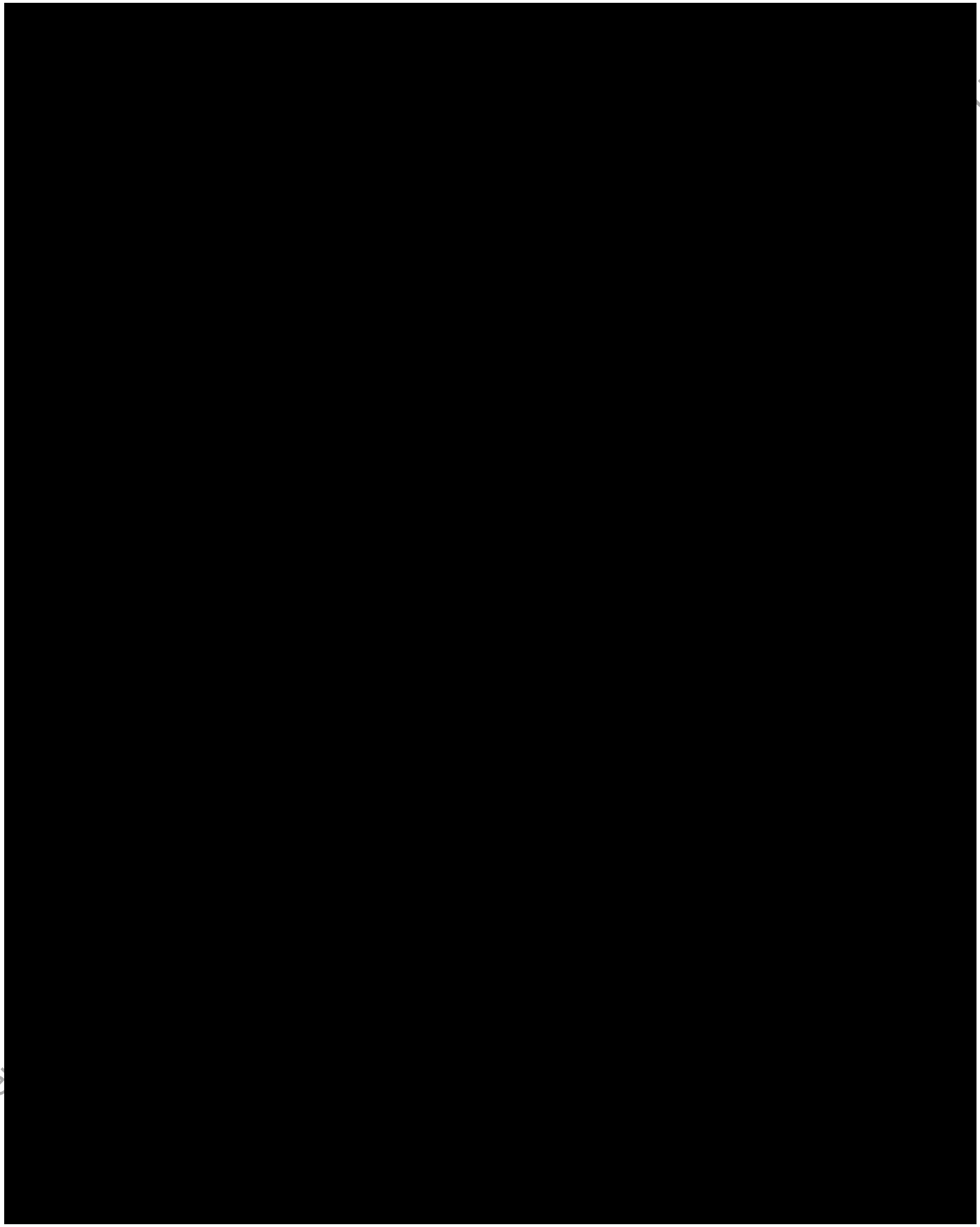


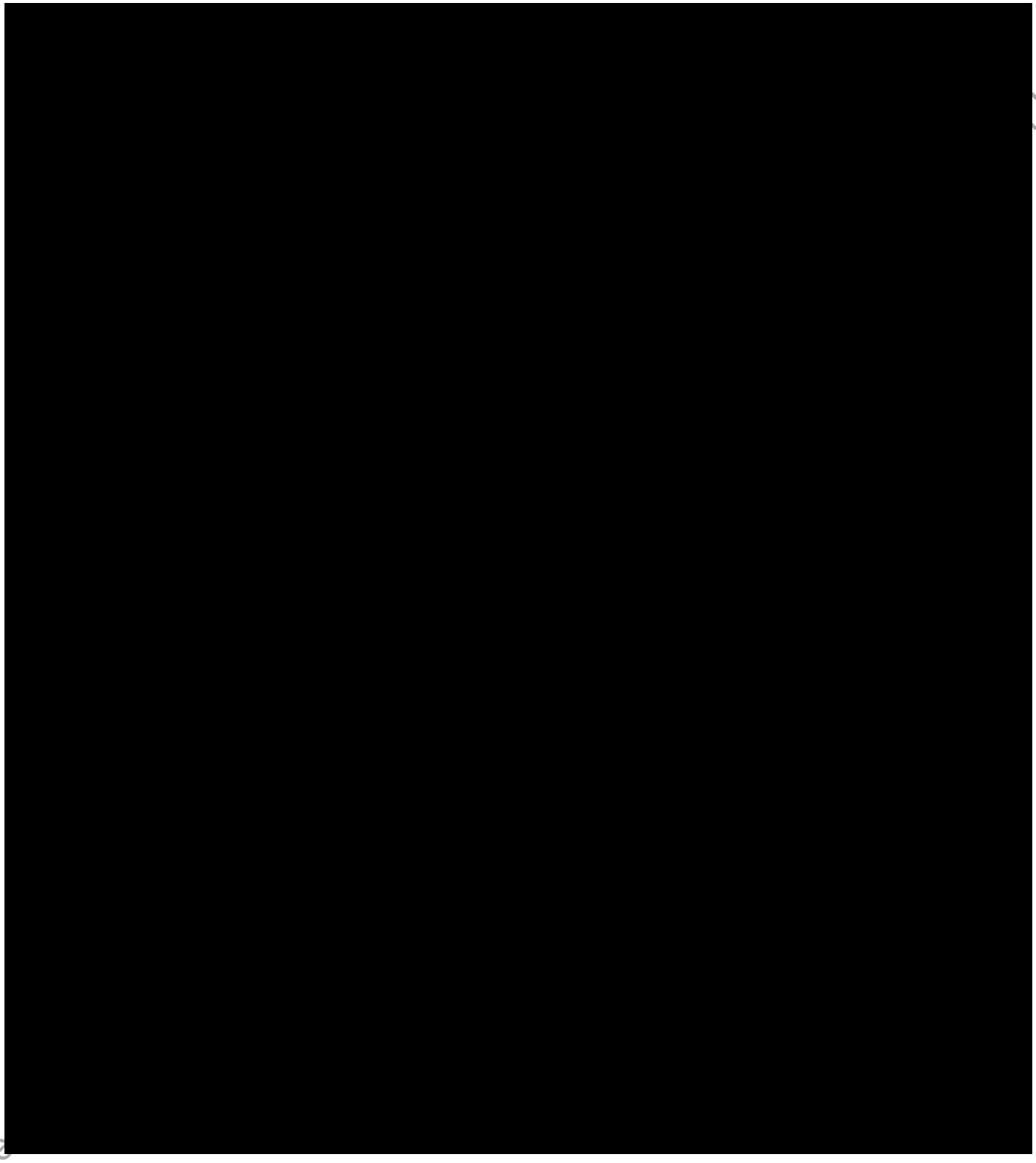


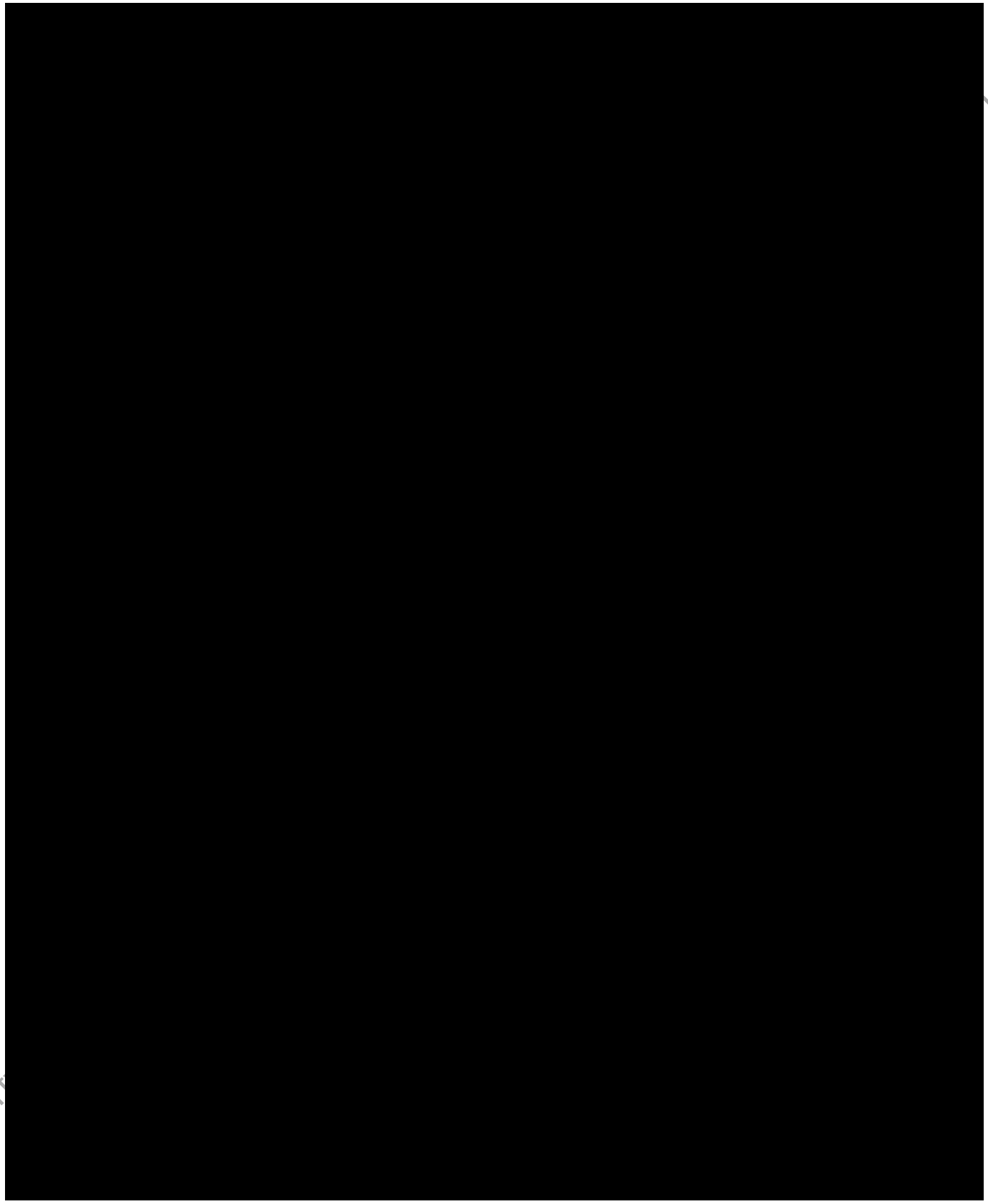


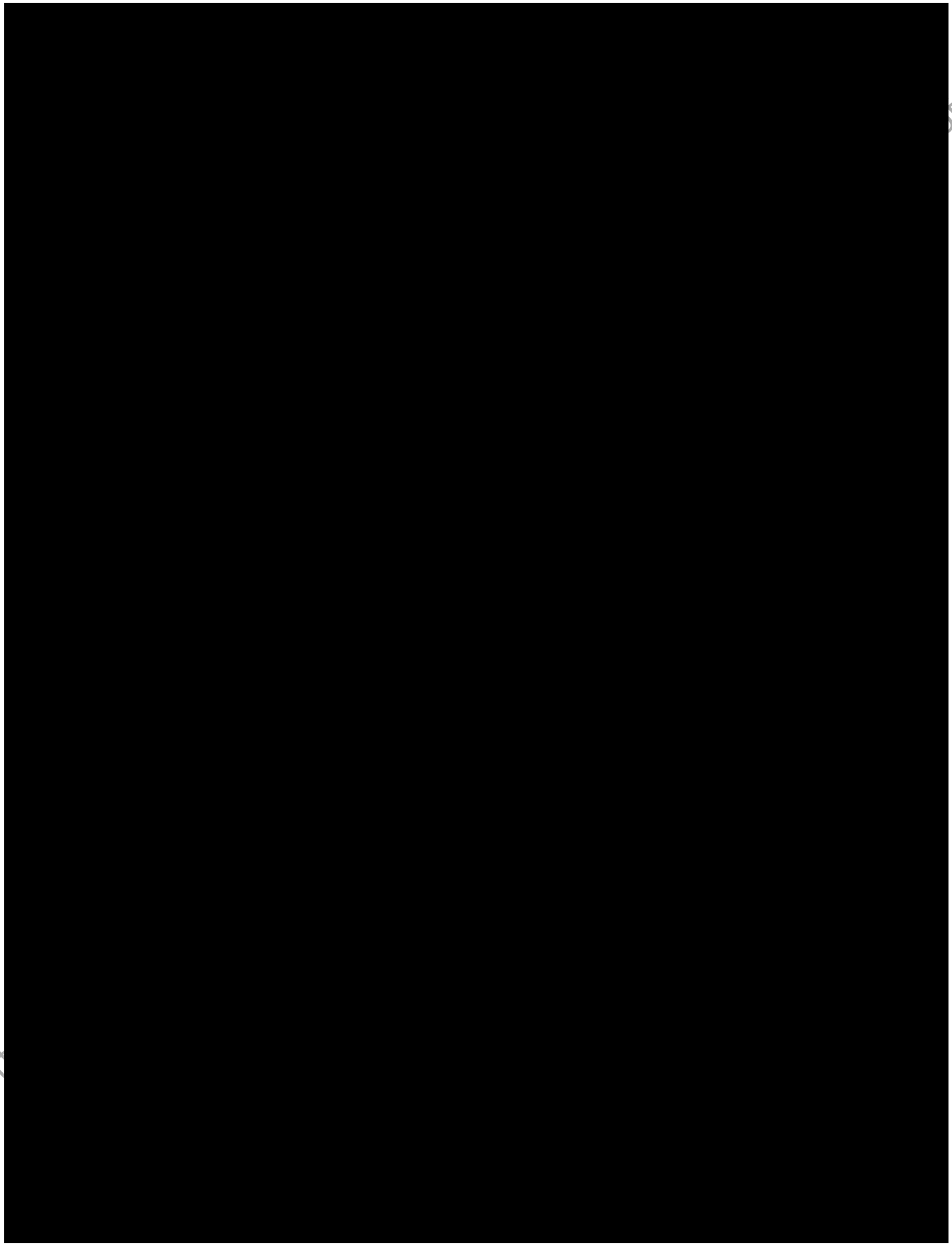


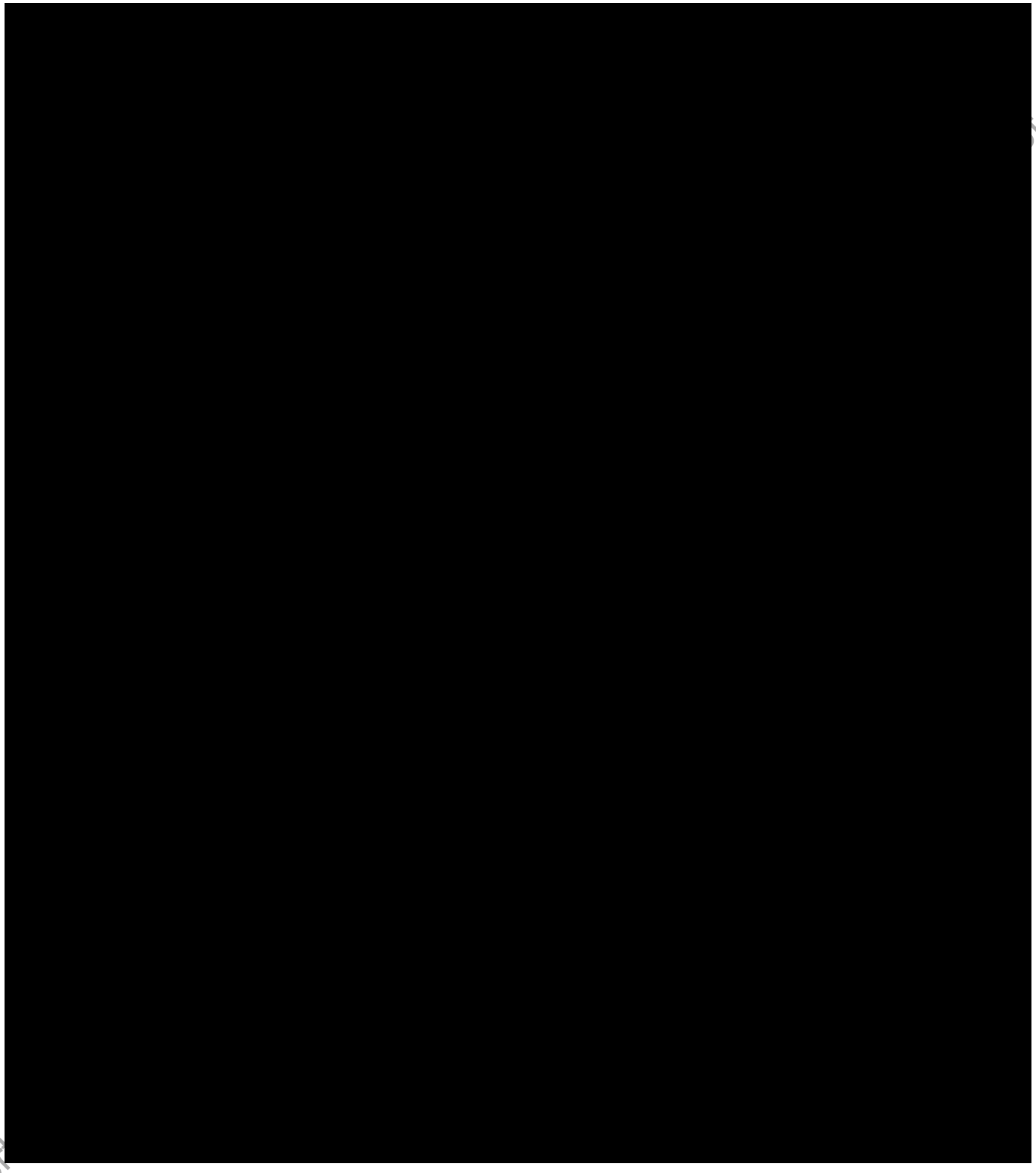


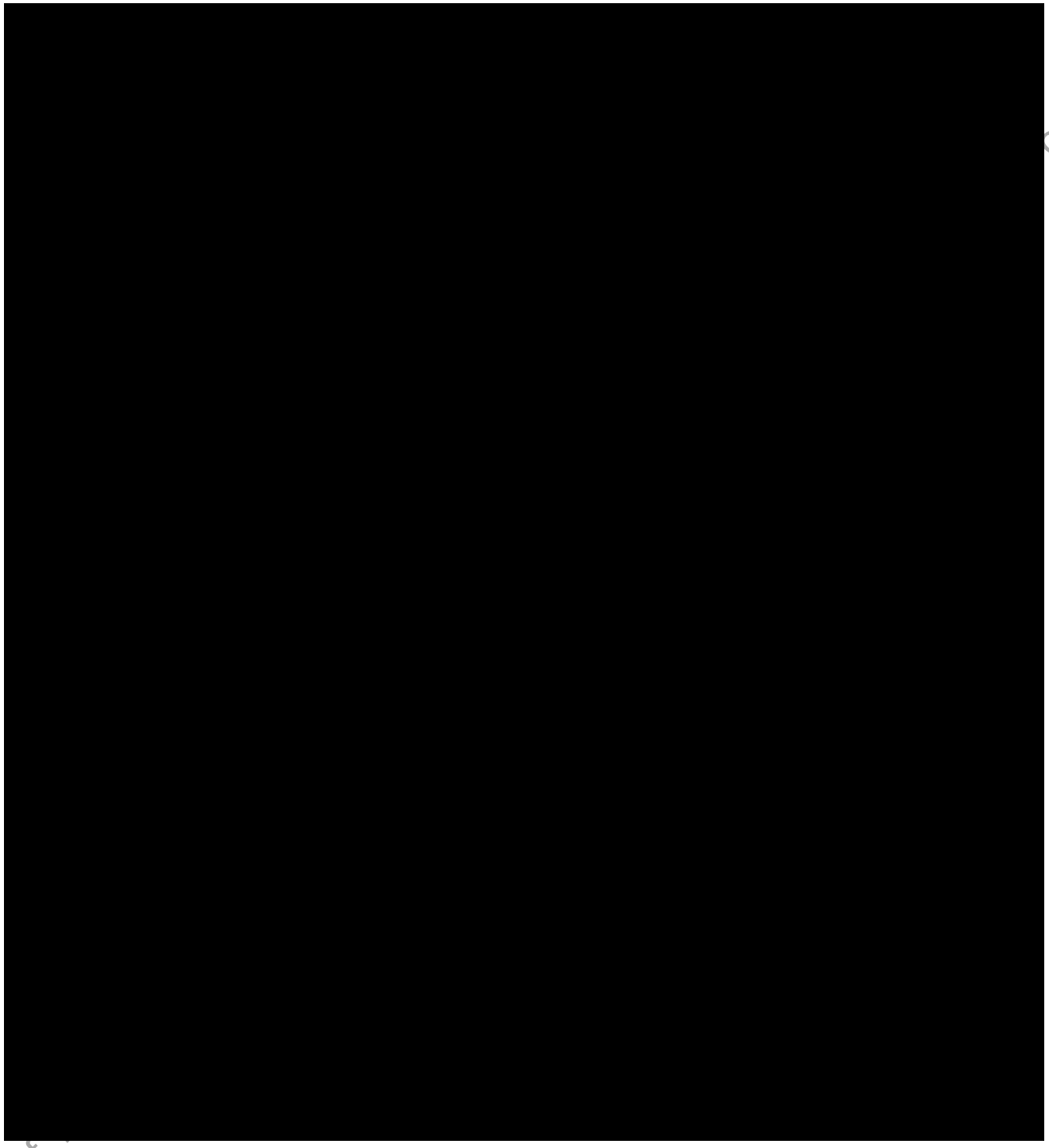


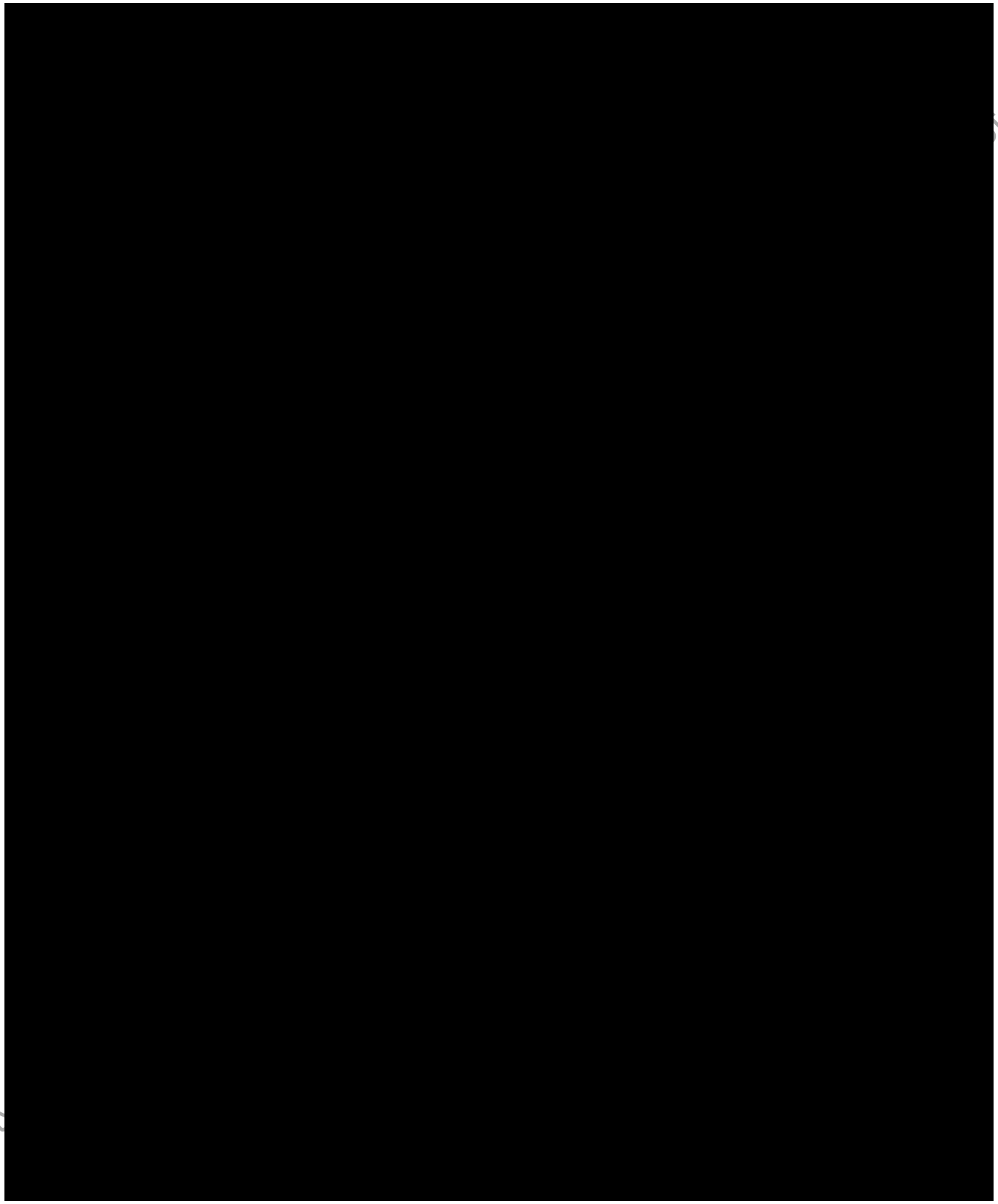


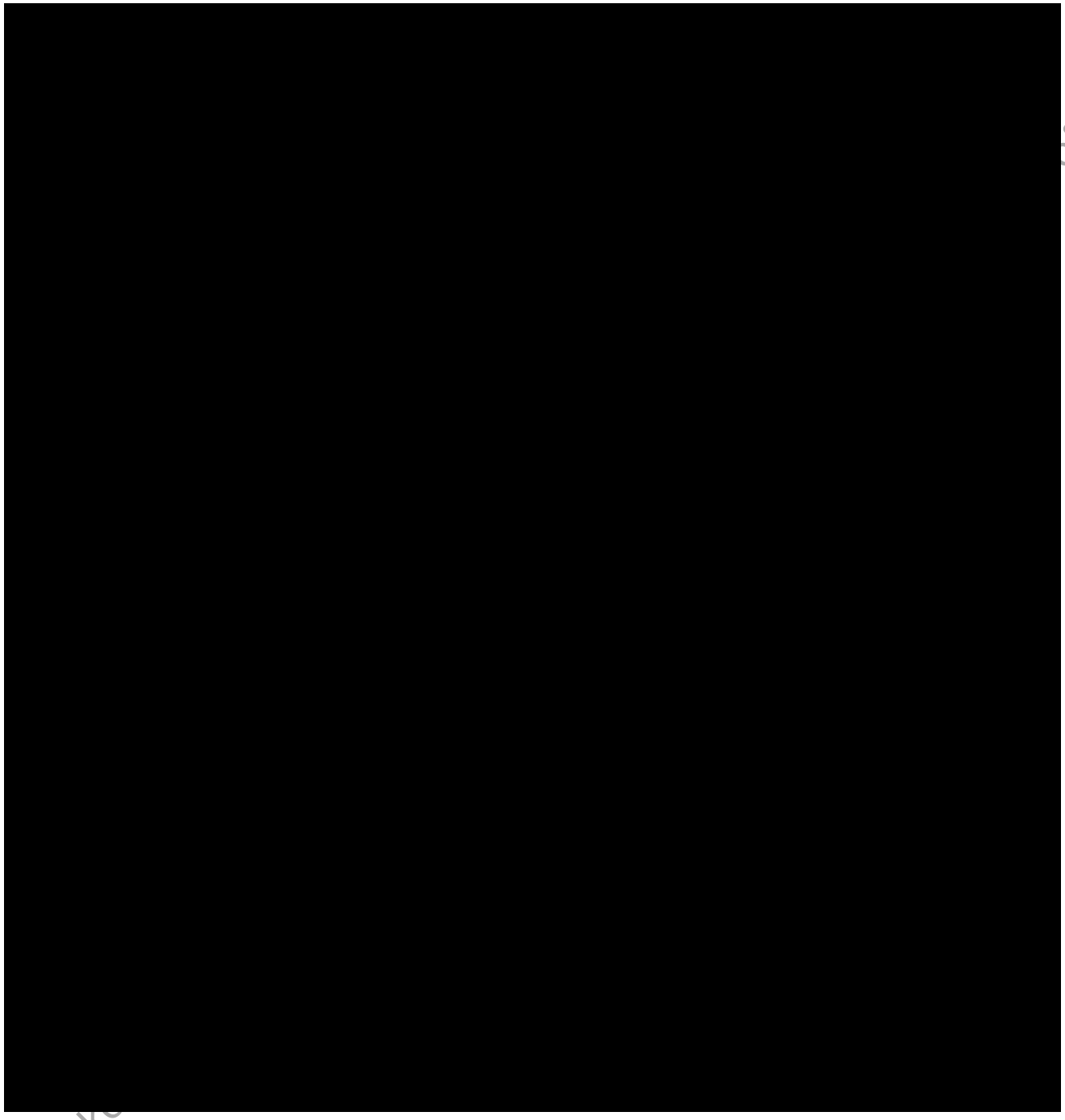


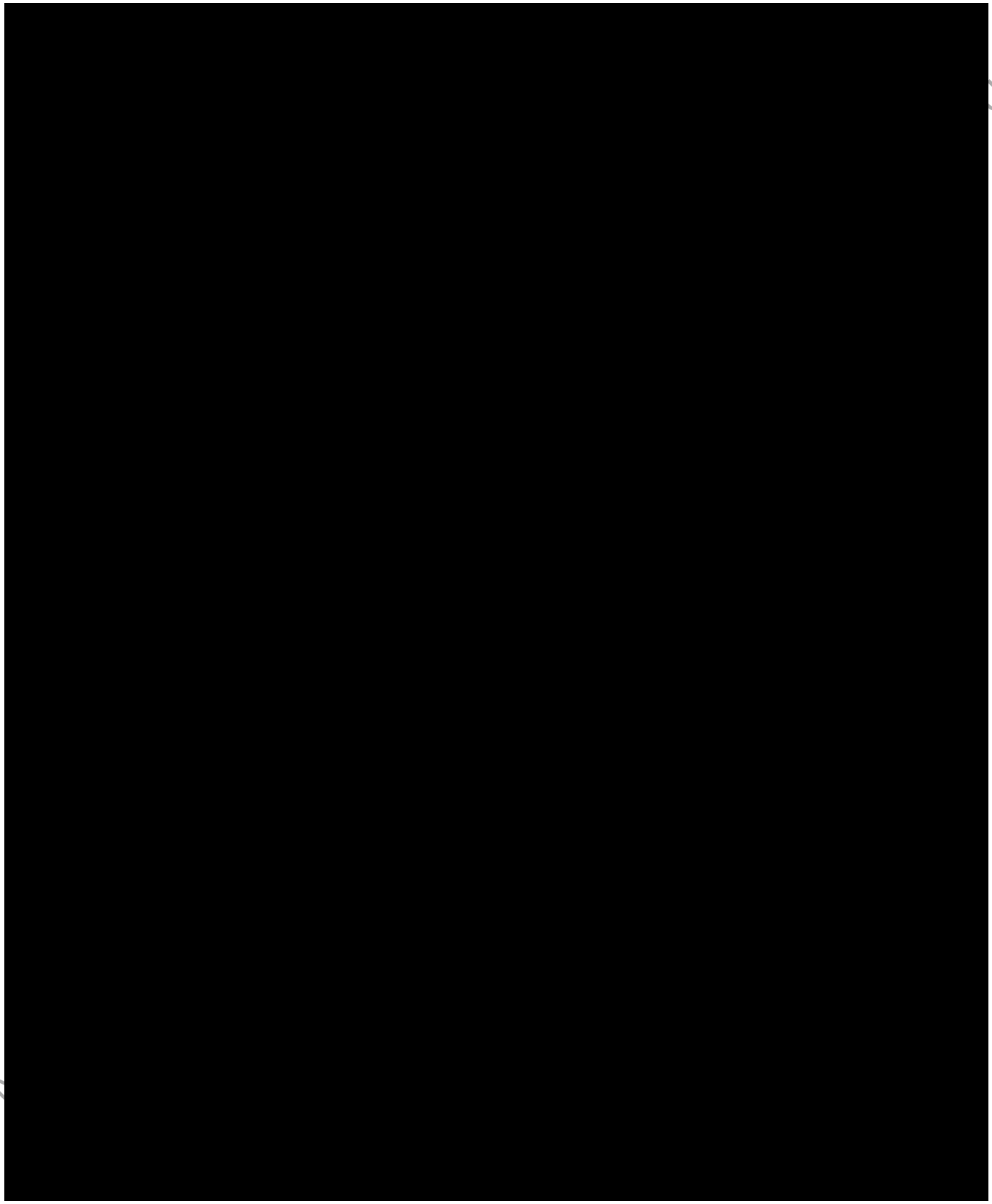


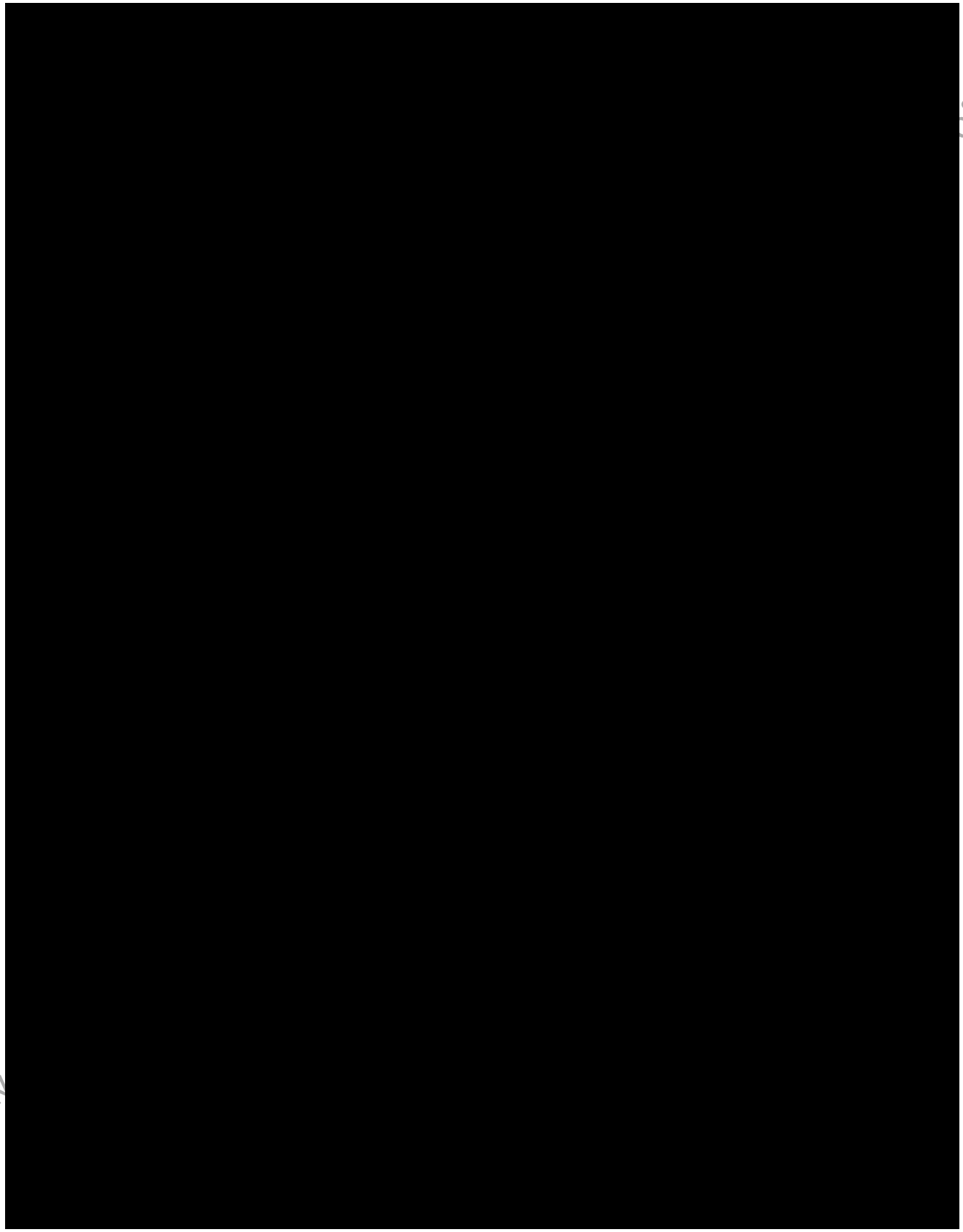


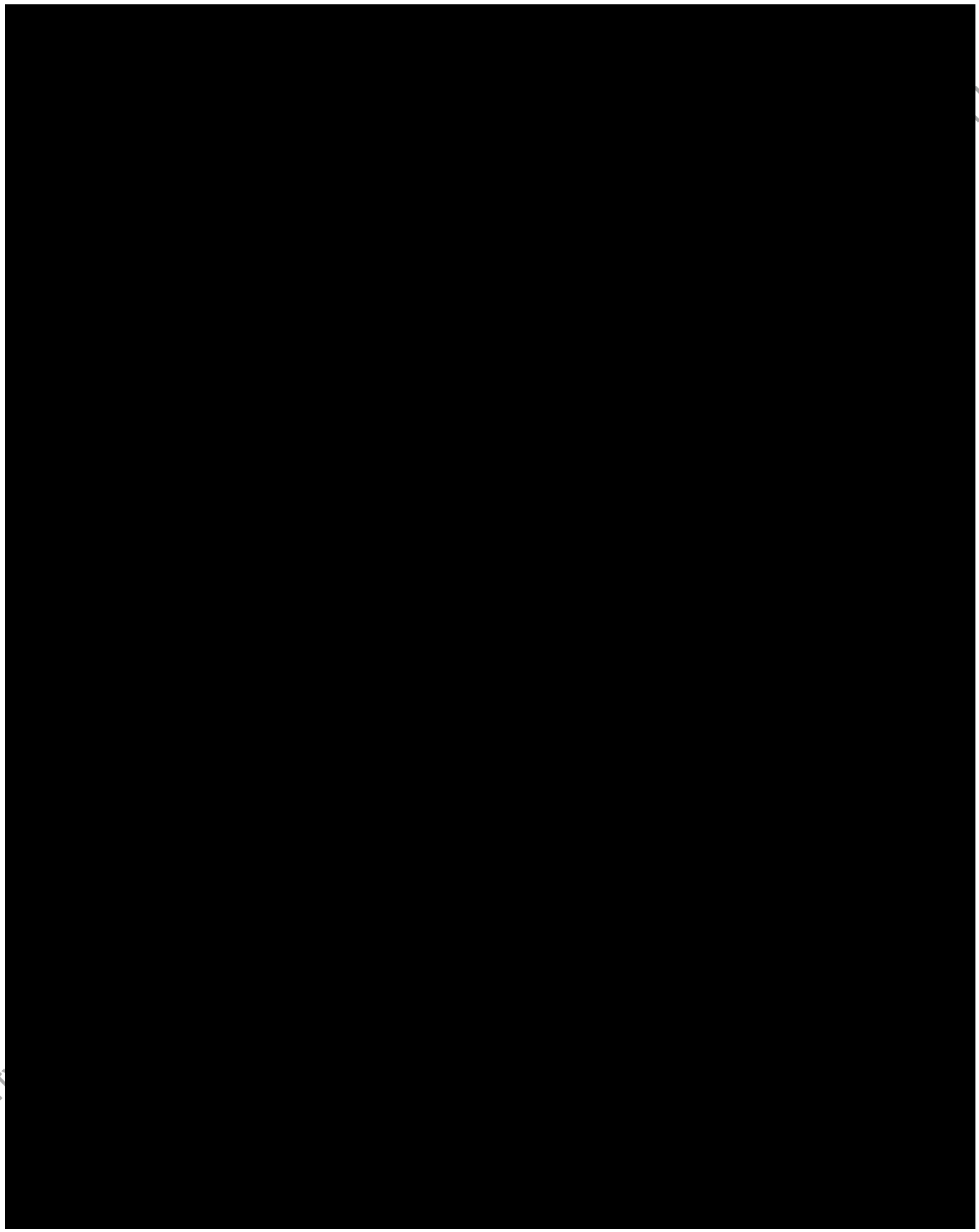




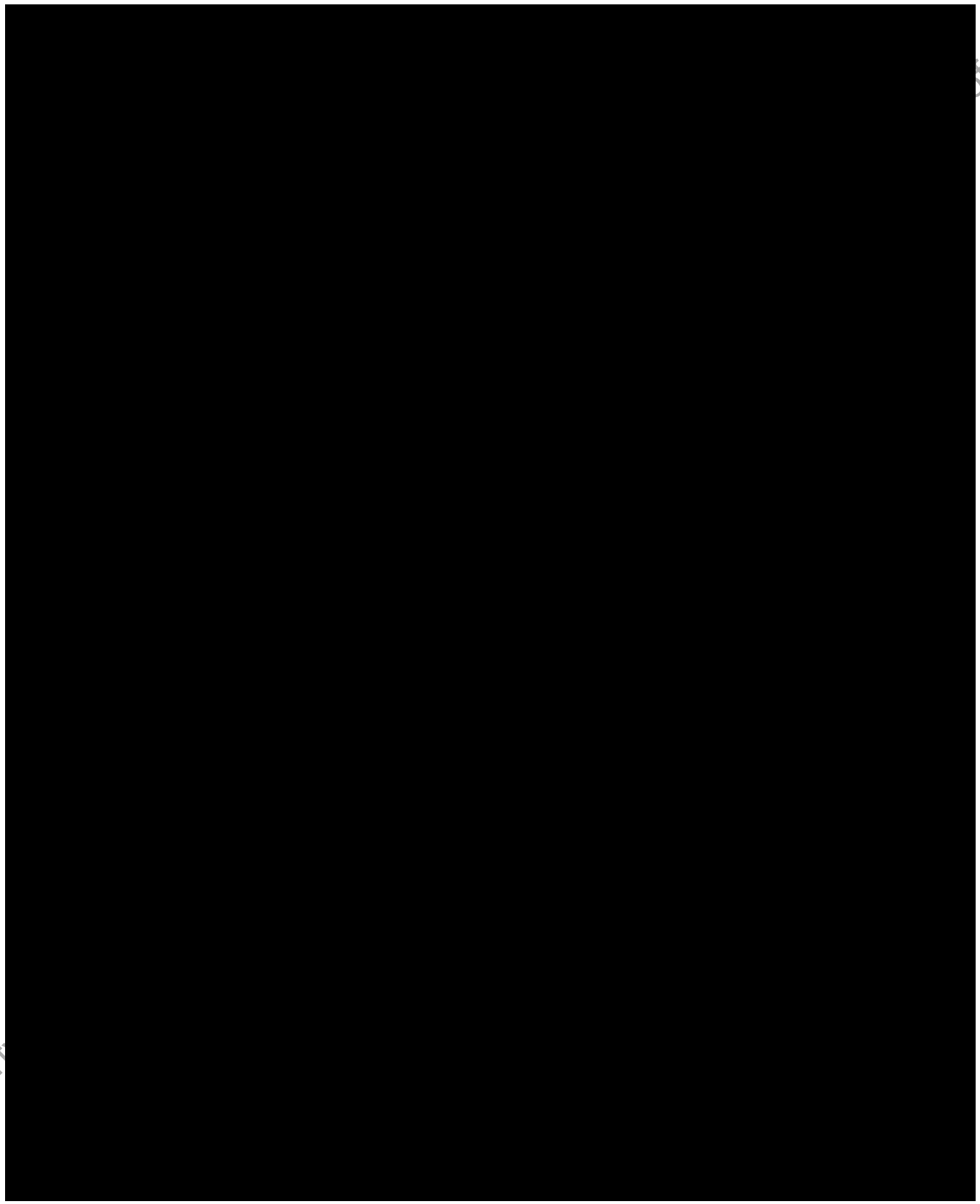


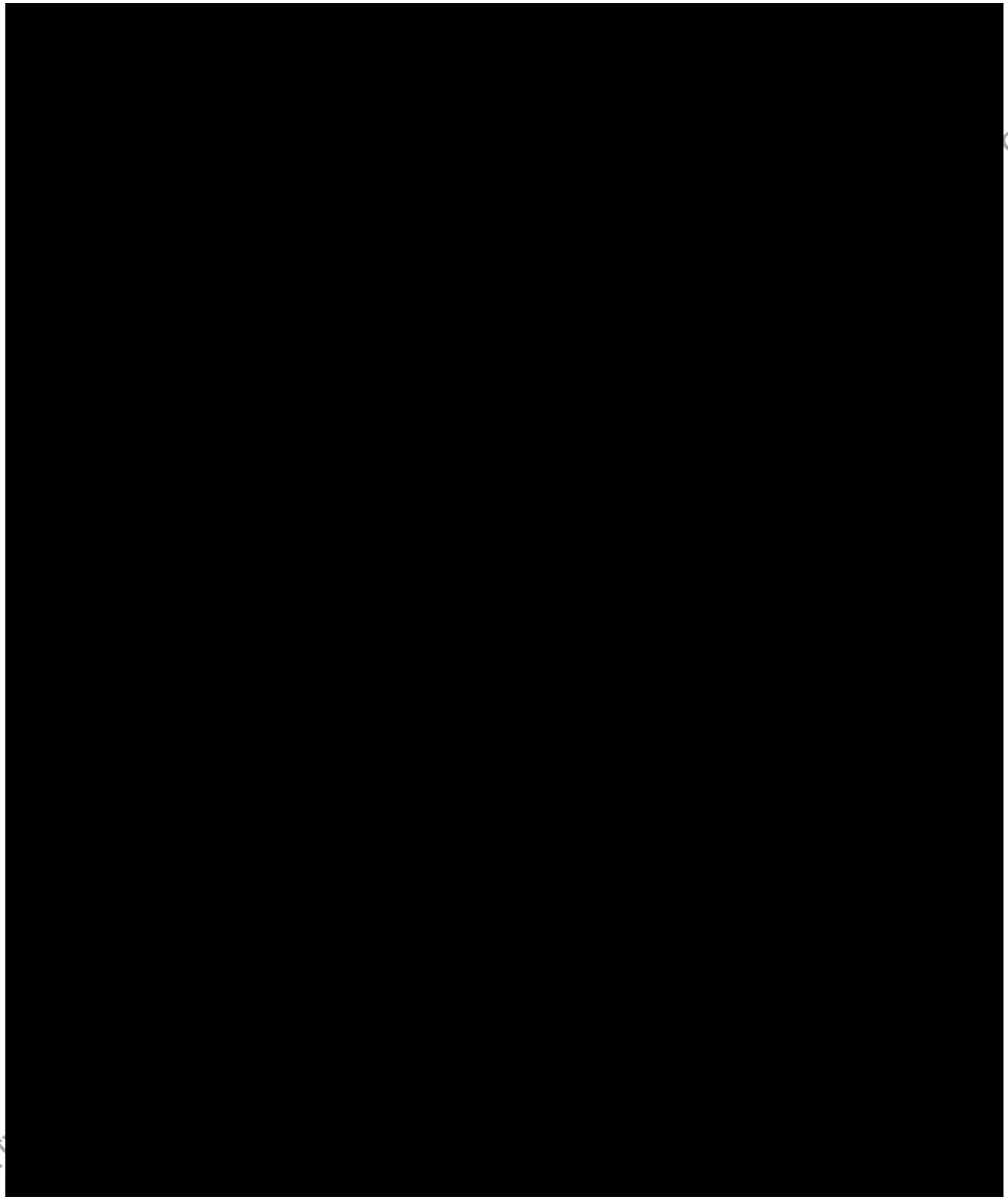


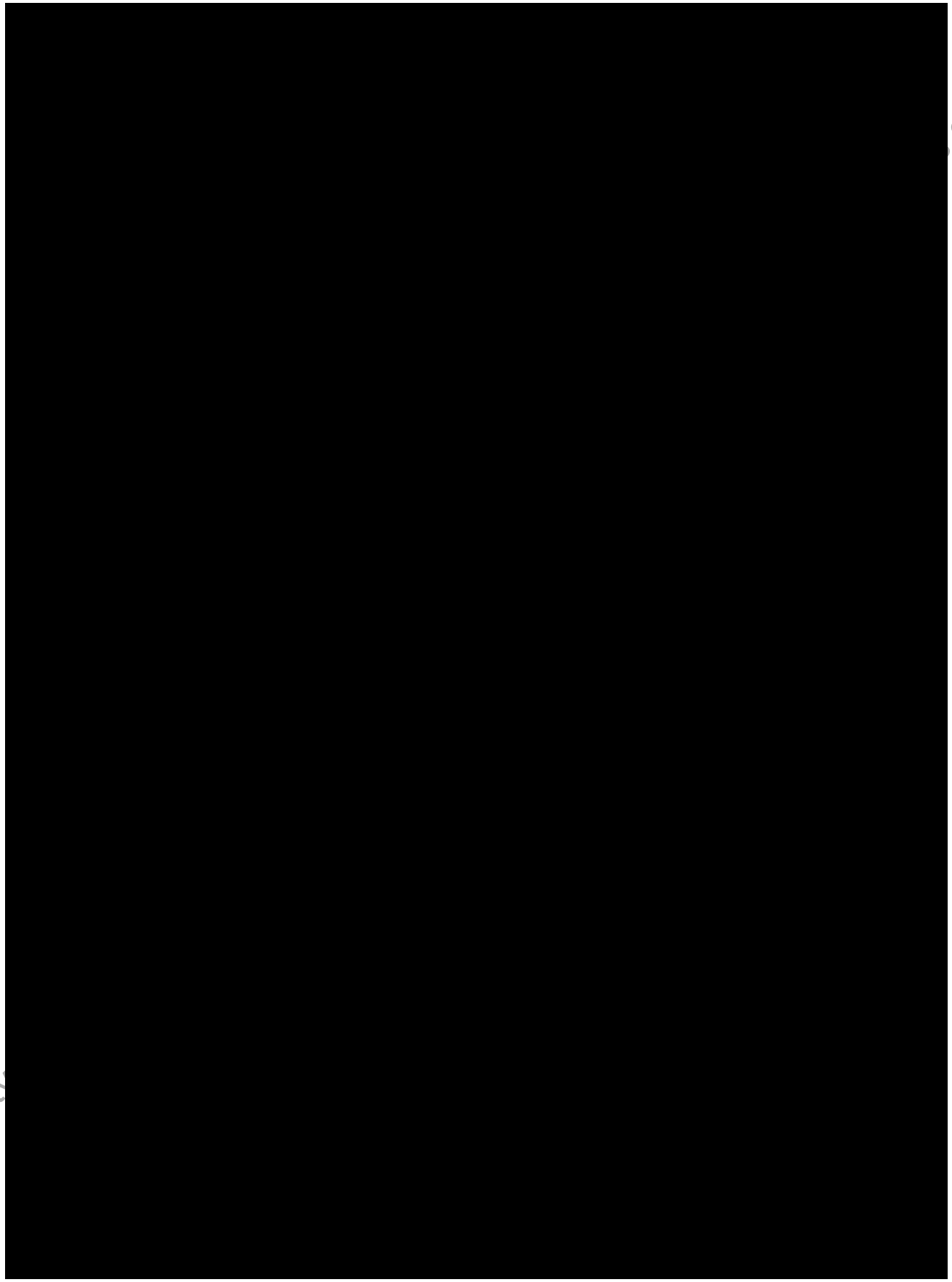


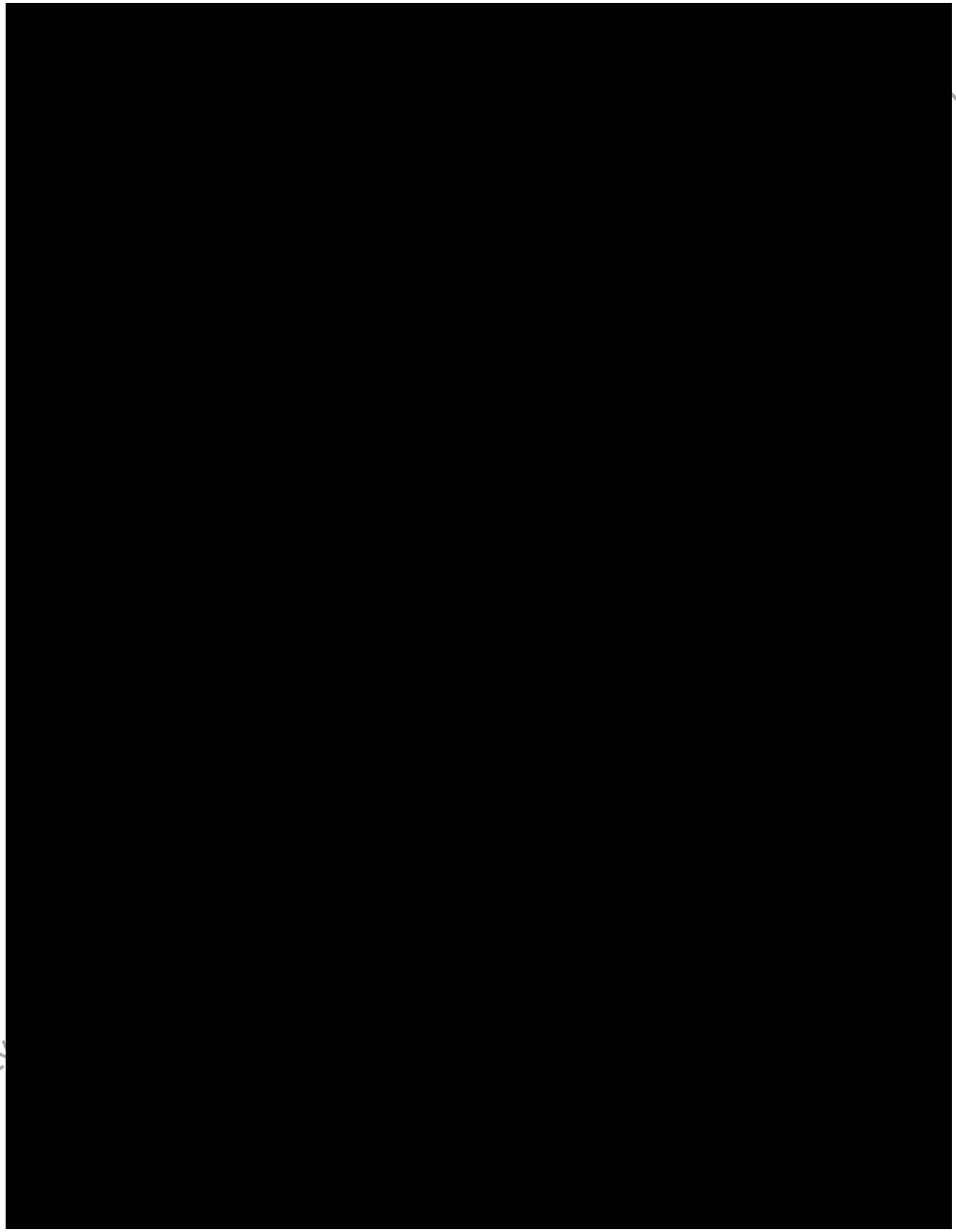


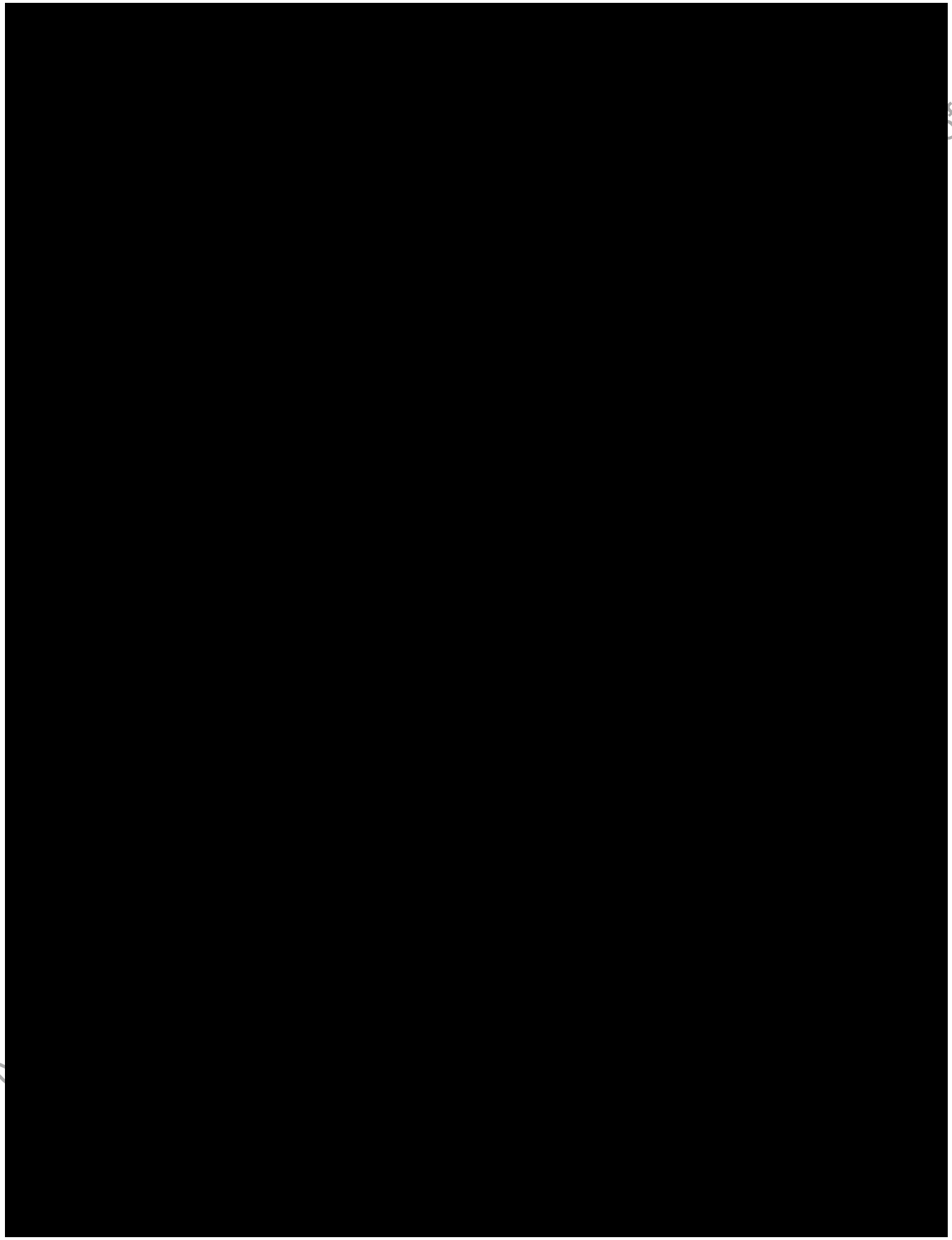
Appendix 10 Diagnostic Criteria for Chronic GVHD

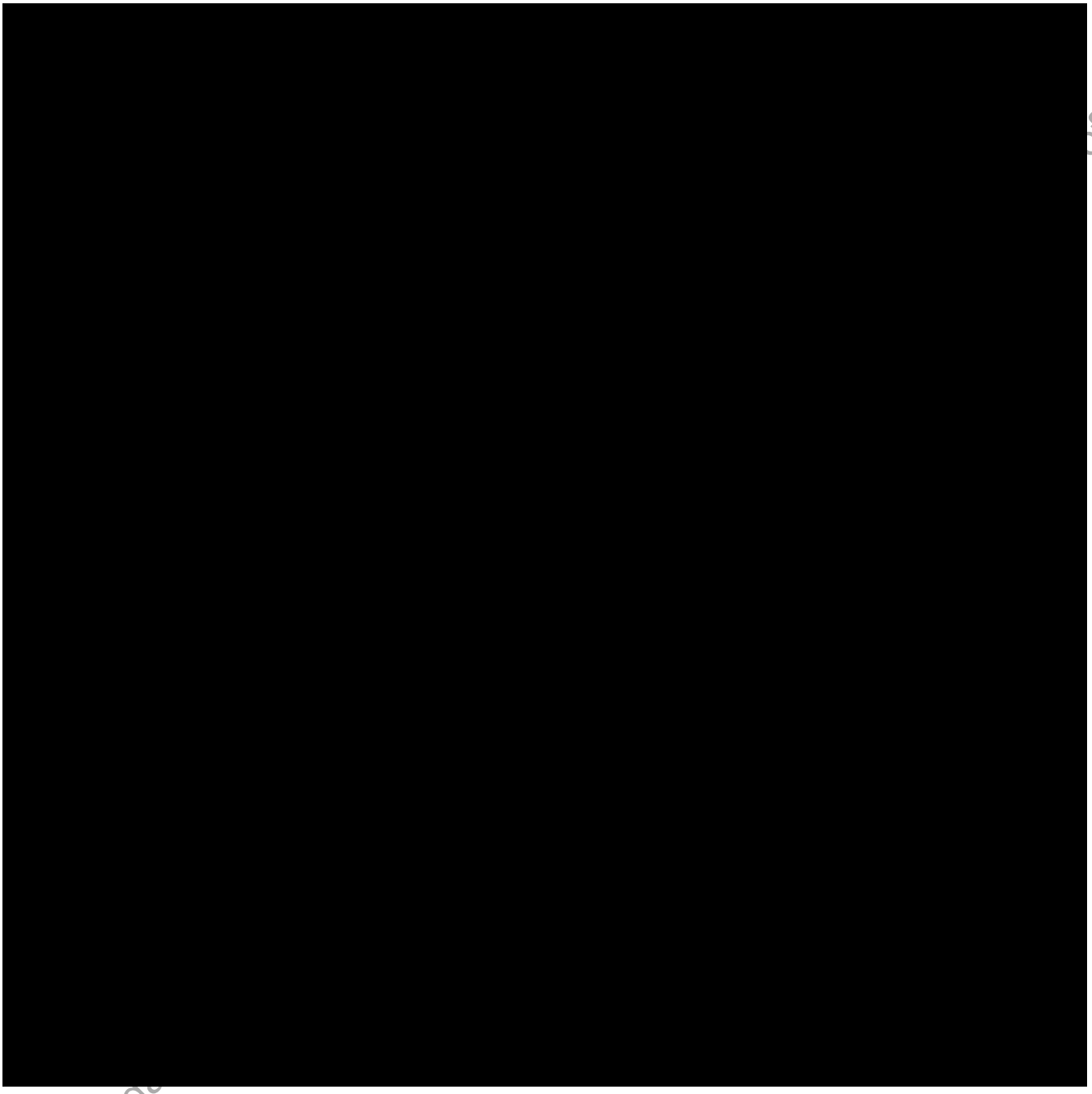












Appendix 13 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	26 Jul 2021	Japan
Amendment 1	28 Oct 2021	Japan