Title: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part

NCT Number: NCT04984889

Protocol Approve Date: 08-Sep-2022

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

TAKEDA PHARMACEUTICALS

PROTOCOL:	**TAK-662-1501**
Title:	An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part
Short Title:	A Phase 1/2 Single-Dose Study of TAK-662 in Japanese Patients with Congenital Protein C Deficiency Followed by an Extension Part
Study Phase:	Phase 1/2
Drug:	TAK-662
IND Number:	Non-IND
EUDRACT Number:	Non-EUDRACT
Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka Japan
Principal / Coordinating Investigator:	Not applicable
Protocol History:	Protocol Amendment 3.0, Version Date: 08 September 2022 ***Replaces:*** Protocol Amendment 2.0, Version Date: 02 September 2021 Protocol Amendment 1.0, Version Date: 13 April 2021 Original Protocol, Version Date: 09 March 2021

PROTOCOL SIGNATURE PAGE

[redacted]

[redacted]

Investigator's Acknowledgement

I have read this protocol for Study TAK-662-1501.

Title: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part.

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: _____

_____

_____

Signature: _____ *Date:* _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

The primary purpose of this amendment is to add clinical data obtained from the Extension part into the interim analysis to support the Japanese New Drug Application (JNDA). The following is a summary of the changes made in the amendment:

- The description of "Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee" of statistical analysis in Section 1.1 and Section 9.2 was changed to use the safety and efficacy data of the Extension part for the first interim analysis.
- The supporting description on the procedure of on-demand treatment at home after the first infusion for the second and subsequent acute episode was added in the footnote (f) of Table 3 in Section 1.3 and in Section 8.1.2.3.1.
- Editorial correction of the protocol amendment 2.0.

See [redacted] for protocol history, including all amendments.

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 (see Protocol Annex) within 1 business day of the SAE occurrence, along with any relevant information. The investigator should submit the detailed SAE form to the sponsor/the Emergency Reception Center for Safety Information 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(s)
- 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 study participation.

Reporting of serious pretreatment events (PTEs) will follow the procedure described for SAEs.

PRODUCT QUALITY COMPLAINTS

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

A product quality complaint includes any instances where there is an allegation or report relating to Takeda licensed or IPs, 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 IP quality complaints include, but are not limited to, the following:

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

Please report the product quality complaint using the "Clinical Trial Material Complaint Form" provided with the pharmacy manual via the email address: [redacted]

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: TAK-662-1501	**Drug:** TAK-662
Title of the study: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part	
Short title: A Phase 1/2 Single-Dose Study of TAK-662 in Japanese Patients with Congenital Protein C Deficiency Followed by an Extension Part	
Study phase: Phase 1/2	
Number of subjects (total and per treatment arm): The study is planned to enroll more than 3 subjects in Japan.	
Investigator(s): Multicenter study.	
Site(s) and Region(s): The study will be conducted in approximately 5 study sites in Japan.	
Study period (planned): PK part: Aug 2021 to Dec 2021 Extension part (only for subjects who have completed PK part): until the commercial protein C concentrate is available at each study site or study termination in the extension part.	**Clinical phase:** 1/2
Objectives: **Primary:** To measure the pharmacokinetic (PK) parameters of TAK-662 in asymptomatic subjects with homozygous or double heterozygous congenital protein C deficiency in Japanese subjects. **Secondary:** To assess safety profile of TAK-662. To assess efficacy of TAK-662 in following 1) for on-demand treatment such as purpura fulminans (PF), coumarin-induced skin necrosis (CISN)/ warfarin-induced skin necrosis (WISN), and other vascular thromboembolic events; 2) for short-term thromboembolic prophylaxis during surgical procedures; and 3) for long-term prophylactic treatment of acute thrombotic episodes (Extension part).	
Rationale: The PK part of this Japanese study design will be identical with the overseas PK study design (Study IMAG-098) as much as possible for the purpose of comparing with the results of Study IMAG-098. Since obtaining PK parameters is the primary objective, an open-label design is chosen for this study. No control group is used in this study. An extension part (on-demand therapy, short-term prophylaxis, and long-term prophylaxis) will be conducted in the subjects who have completed PK part until the commercial protein C concentrate is available at each study site or study termination. Even under currently-available treatment options, high mortality and poor clinical course of protein C deficiency has been reported in Japan. The extension part will provide subjects with protein C deficiency opportunities to experience TAK-662 administration as a new treatment option.	

Investigational product, dose, and mode of administration:

The investigational product (IP) is TAK-662, which will be provided in vial form. TAK-662 is Protein C Concentrate, which is a lyophilized, sterile concentrate of human protein C. The protein C content is indicated in international unit (IU) on the label of each vial.

PK part:

All subjects will receive a single 80 IU/kg dose of TAK-662, infused over 15 minutes for the measurement of PK parameters, at Day 1. TAK-662 should be administered at a maximum injection rate of 2 mL/min except for children with a body weight of < 10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/min.

Extension part:

Dose will be decided according to an extension treatment that the subject will be enrolled at the time of treatment. TAK-662 should be administered at a maximum injection rate of 2 mL/min except for children with a body weight of < 10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/min.

Methodology:

This is a phase 1/2 open-label, non-randomized, non-controlled, single-dose, multicenter study to evaluate PK, safety, and tolerability of TAK-662 in Japanese subjects with congenital protein C deficiency followed by an extension part.

PK part:

The subject who has the prophylactic treatment of anticoagulants is allowed to be enrolled. The last prophylactic treatment including protein C ingredient must occur by at least 36 hours before the administration of TAK-662 on Day 1. Other prophylactic treatment such as oral anticoagulants can be administered without any restrictions on period.

The subject will receive a single 80 IU/kg dose of TAK 662 intravenously on Day 1. Prior to the IP administration, the subject will be admitted to the study site on Day −1. The prophylactic treatment will be given according to the subject's established treatment regimen and at the discretion of the investigator. For the subject with prophylactic treatment including protein C ingredient, the IP for PK will be administered at least after 36 hours of the prophylactic treatment.

From Day 1 to Day 3, the subject will stay in the study site and be followed up for PK and safety before and after the IP administration. The blood sampling for PK will be done immediately prior to infusion and at 30 minutes, and 1, 2, 4, 8, 12, 24, and 36 hours postinfusion; a sampling for the 36 hours postinfusion is allowed to be customized by age, especially for feasibility in children. After 7 days from the IP administration (Day 7), the subject will have the follow-up visit for safety assessment. For the subject who has the prophylactic treatment including protein C ingredient before the administration of the IP for PK, the blood sampling will be additionally done immediately prior to the prophylactic treatment and at 1, 17, and 25 hours post-treatment.

The analysis will be performed for PK and safety after all subjects have completed the Day 7 visit. It is planned to compare PK parameter of Japanese and non-Japanese subjects, by calculating PK parameter of each Japanese subject, then confirming whether it is within the range of (or not substantially different from) PK parameter of each non-Japanese subject in Study IMAG-098.

Extension part:

In the extension part of the current study, sponsor provides 3 different treatment options; on-demand treatment, short-term prophylaxis, and long-term prophylaxis. Based on investigator's careful evaluation on subject's medical condition, subject who completed PK part can continue the administration of TAK-662 until the commercial protein C concentrate is available at each study site or study termination. The 3 different treatment options provide different ways of protein C supplementation. Subject can participate in each of 3 options and can transfer from one to another at the investigator's discretion.

For on-demand treatment, subjects with PF, CISN/WISN, and/or other acute thromboembolic episode will be enrolled. For short-term prophylaxis, subjects requiring short-term prophylaxis with protein C concentrate/ TAK-662 for surgical procedures will be enrolled. For long-term prophylaxis, subjects requiring long-term prophylaxis with protein C concentrate/TAK-662 will be enrolled.

On-demand treatment and short-term prophylaxis may be carried out more than once depending on the subject's situation. In this case, after the completion of follow-up period, the subject will be re-enrolled and re-start the procedures from pre-dose/pre-surgery period. In addition, subject may transfer to the other treatment (eg, If a subjects who enrolled in long-term prophylaxis requires a surgery, he/she transfers to short-term prophylaxis. Once anticoagulation is initiated and the investigator determines that adequate anticoagulation is achieved, he/she will transfer back to long-term prophylaxis.).

Inclusion and Exclusion Criteria:

Inclusion Criteria:

PK part:

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

1. An understanding, ability, and willingness to fully comply with study procedures and requirements. If the subject is <20 years of age or informed consent cannot be obtained from the subject, a parent or legally authorized representative should perform this role.
2. Ability to voluntarily provide written, signed, and dated (personally, or via a parent or legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject) informed consent, and assent as applicable (only when informed consent can be obtained from the subject), to participate in the study.
3. Male and female subjects with Japanese nationality.
4. A diagnosis of congenital protein C deficiency (homozygous or compound heterozygous).
5. Asymptomatic subject.
6. Oral anticoagulants allowed to be received.
7. Male, or non-pregnant or non-lactating female who is sexually active and who agrees to comply with the applicable contraceptive requirements of this protocol, or females of non-childbearing potential. A negative pregnancy test at the Screening has to be documented.

Extension part:

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

1. Subjects who participated in the PK part of this study (TAK-662-1501).
2. An understanding, ability, and willingness to fully comply with study procedures and requirements. If the subject is <20 years of age or informed consent cannot be obtained from the subject, a parent or legally authorized representative should perform this role.
3. Ability to voluntarily provide written, signed, and dated (personally, or via a parent or legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject) informed consent, and assent as applicable (only when informed consent can be obtained from the subject), to participate in the extension part of this study
4. Subject who are;
   a. Diagnosed with PF, CISN/WISN, and/or other acute thromboembolic episode for on-demand treatment only.
   b. Requiring treatment with TAK-662 for short-term prophylaxis for surgical procedures.
   c. Requiring treatment with TAK-662 for long-term prophylaxis.

Exclusion Criteria:

PK part:

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

1. Current or recurrent disease that could affect the action, or disposition of the IP, or clinical or laboratory assessments.
2. A body weight less than 8 kg.
3. Serious liver dysfunction, judged by the investigator.
4. Any thrombosis within 2 weeks prior to administration of the IP.
5. Other investigational product than TAK-662 received within 60 days prior to the administration of the IP.
6. Current or relevant history of physical or psychiatric illness, or any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the IP or procedures.
7. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) that could affect (improve or worsen) the condition being studied, or could affect the action or disposition of the IP, or clinical or laboratory assessment.
8. Known or suspected intolerance or hypersensitivity to the IP, closely-related compounds, or any of the stated ingredients.
9. Known history of alcohol or other substance abuse within the last year.
10. Within 30 days prior to the first dose of IP, a subject has been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this sponsored study.

Extension part:

The subject who participated in the PK part will be excluded from the extension part of the study if any of the following exclusion criteria are met.

1. New serious medical conditions which could affect patient’s safety or treatment were observed during participation in the PK part of this study (TAK-662-1501).
2. Planning to participate in clinical trials of other investigational drugs or medical devices.
3. Females of childbearing potential who do not agree to use acceptable contraception.

Maximum duration of subject participation in the study:

PK part:

The study period is composed of Screening period, Treatment period, and Follow-up period.

- Screening period: 2 weeks (Day −14 to Day −1)
- Treatment period: 3 days (Day 1 to Day 3)
- Follow-up period: 4 days (Day 4 to Day 7)

Extension part:

In the extension part, sponsor provides 3 different treatment options; on-demand treatment, short-term prophylaxis, and long-term prophylaxis. The extension part will continue until the commercial protein C concentrate is available at each study site or study termination. The duration of subject participation is determined depending on which study part to be enrolled. On-demand treatment is composed of pre-dose period, treatment period, and follow-up period. Short-term prophylaxis is composed of pre-surgery period, treatment period, and follow-up period. Long-term prophylaxis is composed of pre-dose period, treatment period, and follow-up period.

Statistical analysis:

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

Interim analyses of study data will be undertaken as described below. No adaptive design or data monitoring committee (DMC) is planned for this study. One formal interim data analyses to support the Japanese New Drug Application (JNDA) submission will be completed. It will summarize PK, safety and efficacy of treatment with TAK-662 in Japanese subjects with homozygous or double heterozygous congenital protein C deficiency. The first interim analysis will be conducted after all enrolled subjects have reached last visit of the PK part and at least 3 treatments (any of either on-demand treatment, short-term prophylaxis or long-term prophylaxis) have been provided to any subjects in the Extension part. The target data is all data obtained at this point in the PK part and Extension part. An interim clinical study report summarizing data of the first interim analysis will be prepared. The clinical data cut-off date will be stated in the Statistical Analysis Plan. As applicable, additional interim analysis will be conducted after the first interim analysis.

- Sample Size and Power Considerations

The number of patients with severe congenital protein C deficiency is very low. And the target number of patients is set to 3 or more in consideration of feasibility and inclusion/exclusion criteria in this study based on the opinions of specialists in Japan.

- Statistical Analysis Set(s)

The safety population will include all enrolled subjects in the study who take at least 1 dose of TAK-662.
A subject will be considered enrolled in the study once the informed consent/assent has been obtained and the subject meets all of the study inclusion criteria. The safety population will be used for safety analyses.

The pharmacokinetic population will include all study participants who take at least 1 dose of TAK-662 and have enough number of quantifiable blood levels for TAK-662 collected post-dose without important protocol deviations/violations or events thought to substantially affect the PK. The PK population will be used for PK analyses.

The efficacy population will include all study participants who take at least 1 dose of TAK-662 in the extension part. The efficacy population will be used for efficacy analyses.

- Efficacy Analyses

1.On demand therapy

The treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events will be rated as "*effective*", "*effective with complications*", or "*not effective*" according to the efficacy rating scale. The rating of treatment effect will be listed and summarized using descriptive statistics.

2.Short-term prophylaxis

Percentage of surgical episodes for which TAK-662 will be utilized as short-term prophylaxis, that is free of presentations of PF or thromboembolic complications will be calculated. PF or thromboembolic complications will be listed and summarized using descriptive statistics.

3.Long-term prophylaxis

Number of episodes of PF and/or thrombotic episodes while receiving long-term prophylaxis and rate of episodes of PF and/or thrombotic episodes per month will be calculated. Episodes of PF and/or thrombotic episodes will be listed and summarized using descriptive statistics.

- Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment emergent adverse events (TEAEs) will be calculated overall, by system organ class (SOC), by preferred term. Treatment emergent adverse events will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, serious adverse events (SAEs), and deaths will be similarly summarized/listed.

Clinical laboratory tests and vital signs will be summarized by visit. Potentially clinically important findings will also be summarized or listed.

- Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed using the observed Protein C activity in plasma of the pharmacokinetic population. Pharmacokinetic parameters including but not limited to terminal half-life ($t_{1/2}$), incremental recovery (IR), in-vivo recovery (IVR), area under the curve (AUC), maximum concentration (C_{max}), and minimum time to reach maximum concentration (t_{max}) will be computed using noncompartmental methods. Pharmacokinetic parameters will be listed and summarized using descriptive statistics. Data will be presented graphically if appropriate.

1.2 Schedule of Activities (Pharmacokinetic Part)

Table 1. Schedule of Activities (Pharmacokinetic Part)

	Screening period	Treatment period				Day 7 (±3 day) / Follow-up [a]	Extension part
Procedure	**Days –14 to –2**	**Day –1**	**Day 1**	**Day 2**	**Day 3**		
Informed consent [b]	X						On-demand treatment; refer to Table 2, Table 3 Short-term prophylaxis; refer to Table 4 Long-term prophylaxis; refer to Table 5
Inclusion/exclusion criteria	X	X					
Demographics and medical history	X						
Medication history	X						
Physical exam	X						
Vital signs [c]	X	X	X	X			
Height, weight, and BMI [d]	X						
Concomitant medications	X	X	X	X	X	X	
12-lead ECG	X						
Clinical laboratory evaluations	X		X [e]	X		X	
Serum pregnancy test (β-hCG) [f]	X						
FSH [f]	X						
Hospitalization		X [g]	X	X	X		
Study drug dosing [h]			X				
PK blood collection [i]			X	X	X		
PTE/AE assessment	X	X	X	X	X	X [j]	

Table 1. Schedule of Activities (Pharmacokinetic Part)

	Screening period	Treatment period				Day 7 (±3 day) / Follow-up [a]	Extension part
Procedure	**Days –14 to –2**	**Day –1**	**Day 1**	**Day 2**	**Day 3**		

[a] If a subject is early terminated, regardless of the reason, the evaluations listed for the Day 7 visit will be performed as completely as possible.

[b] 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 legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject.

[c] Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be assessed prior to and 1 hour after administration of the prophylactic treatment including protein C ingredient (in subjects participating in the pre-pharmacokinetic wash-out segment), and prior to and 30 minutes, 2 hours, 4 hours, and 24 hours after administration of the investigational product (IP) for pharmacokinetics (PK).

[d] Body mass index (BMI) will be calculated by the Sponsor.

[e] Blood sample for clinical laboratory evaluations at Day 1 will be drawn before administration of the IP.

[f] A serum β-hCG pregnancy test and FSH test will only be performed on females of child-bearing potential.

[g] A subject is allowed to stay in a hospital from one day before Day −1 (ie, Day −2), if applicable.

[h] All subjects will receive a single 80 IU/kg dose of TAK-662 at Day 1 for the measurement of PK parameters. All subjects will be closely monitored throughout the course of the study. Subjects on prophylactic treatment including protein C ingredient will receive an intravenous infusion by 36 hours prior to administration of the IP. Should a subject experience a thrombotic event during the 36-hour washout period, that subject will not participate in the study.

[i] PK samples will be collected at pre-dose and at 0.5 hours, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours (Day 2), and 36 hours [*](Day 3) after completing administration of the test dose of the IP ([*] the feasibility of PK collection at 36 hours after administration needs to be assessed). For the subject who has the prophylactic treatment including protein C ingredient before the administration of the IP for PK, the blood sampling will be additionally done immediately prior to the prophylactic treatment and at 1, 17, and 25 hours post-treatment.

[j] All AEs and serious AEs that are not resolved at the time of this contact will be followed to closure ([redacted]).

Abbreviations. AE=adverse event, β-hCG= beta human chorionic gonadotropin, BMI=body mass index, ECG=electrocardiogram, FSH=follicle-stimulating hormone, IP=investigational product, PK=pharmacokinetics, PTE=pretreatment event.

1.3 Schedule of Activities (Extension part: On-Demand Treatment)

Table 2. Schedule of Activities (On-Demand Treatment): First Acute Episode

	Pre-dose	Treatment period					At the end of treatment [a]	Follow-up (7 days after the last dose of IP)
		Day E1				On and After Day E2		
		0 hour	6 hours after the first dose of IP	12 hours after the first dose of IP	18 hours after the first dose of IP	Every 6 or 12 hours		
Eligibility check [b]	X							
Diagnosis of acute episode (PF, CISN/WISN, and thrombotic event) [c]	X							
Concomitant medications	←	—	—	—	—	—	—	→
Lesion assessment / Photography [d]		X / X	X / X*	X / X*	X / X*	X / X*	X / X	
Hematology [e]	X							X
Protein C Activity [f]	(X)		(X)	(X)		(X)	(X)	
Vital signs	X							X
Study drug dosing [g]		X	(X)**	(X) **	(X) **	(X) **		
AE assessment		←	—	—	—	—	—	→

[a] Treatment with TAK-662 will be ended when the investigator determines that the acute episode have recovered or tend to improve (eg, purpura area reduction or fading).
[b] Pregnancy urine test will be performed at the site within 3 days of first dose.
[c] The investigators will diagnose purpura fulminans (PF), coumarin-induced skin necrosis (CISN)/ warfarin-induced skin necrosis (WISN), and thrombosis.
[d] Lesion assessment will be performed by the investigators at each point before administrating of investigational product (IP). Images of the lesion site will be taken before the first infusion on Day E1 and at the end of treatment when investigators determine that the acute episode have recovered or tend to improve. Image of the lesion site can be taken between the 2 points if applicable.
*In principle, it is carried out in the hospital, but the subject can return home after infusion if the investigator allows it. In this case, subject may take a picture of the lesion site at home and send it to the investigator (refer to the manual for data handling of imaging data). If a next infusion is required based on the investigator's decision, the subject will have to visit the site.
[e] Hematological tests will be performed at a central laboratory.
[f] Protein C activity measurement may be performed at the discretion of the investigator. If protein C activity will be measured, the time point of measurement is also at the discretion of the investigator.

Table 2. Schedule of Activities (On-Demand Treatment): First Acute Episode

	Pre-dose	Treatment period					At the end of treatment [a]	Follow-up (7 days after the last dose of IP)
		Day E1				On and After Day E2		
		0 hour	6 hours after the first dose of IP	12 hours after the first dose of IP	18 hours after the first dose of IP	Every 6 or 12 hours		

[g] Upon presentation with an acute event, the subject will be infused with a dose of 100-120 IU/kg. The subsequent 3 infusions will be administered every 6 hours at a dose of 60-80 IU/kg. Subsequent infusions (45-60 IU/kg) are also continued every 6 or 12 hours until resolution of all non-necrotic lesions and/or stabilization of thrombi (in the case of a thrombotic episode).
** When the acute episode is not recovered or improved after the first dose, further infusions are continued.

Abbreviations. AE=adverse event, CISN= coumarin-induced skin necrosis, IP=investigational product, PF= purpura fulminans, WISN=warfarin-induced skin necrosis.

Table 3. Schedule of Activities (On-Demand Treatment): Second and Subsequent Acute Episodes (Home Infusion)

	Pre-dose	Treatment period					At the end of treatment [a]	Follow-up (7 days after the last dose of IP)
		Day E1				On and After Day E2		
		0 hour	6 hours after the first dose of IP	12 hours after the first dose of IP	18 hours after the first dose of IP	Every 6 or 12 hours		
Diagnosis of acute episode (PF, CISN/WISN, and thrombotic event) [b]	X							
Concomitant medications	←	—	—	—	—	—	→	
Lesion assessment / Photography [c]			X / X*	X / X*	X / X*	X / X*	X / X	
Hematology [d]								X
Protein C Activity [e]			(X)	(X)		(X)	(X)	
Vital signs								X
Study drug dosing [f]		X	(X)**	(X)**	(X)**	(X)**		
Subject Diaries [g]		X						
AE assessment		←	—	—	—	—	—	→

[a] Treatment with TAK-662 will be ended when the investigator determines that the acute episode have recovered or tend to improve (eg, purpura area reduction or fading).

[b] The investigators will diagnose purpura fulminans (PF), coumarin-induced skin necrosis (CISN)/ warfarin-induced skin necrosis (WISN), and thrombosis. Subject will have to take a picture of the lesion site at home upon presentation with an acute event. It is allowed for the investigators to confirm it later.

[c] A picture of the lesion site will be taken at each point before administrating of investigational product (IP). Images of the lesion site will be taken before the first infusion at pre-dose by subject (at the time of diagnosis of acute episode) and at the end of treatment when investigators determine that the acute episode have recovered or tend to improve. Image of the lesion site can be taken between the 2 points if applicable.
*After visiting the site and received a subsequent infusion at the site, the subject can return home if the investigator allows it. In this case, subject may take a picture of the lesion site at home and send it to the investigator so that the investigator will perform lesion assessment (refer to the manual for data handling of imaging data). If a next infusion is required based on the investigator's decision, the subject will have to visit the site.

[d] Hematological tests will be performed at a central laboratory.

[e] Protein C activity measurement may be performed at the discretion of the investigator. If protein C activity will be measured, the time point of measurement is also at the discretion of the investigator.

Table 3. Schedule of Activities (On-Demand Treatment): Second and Subsequent Acute Episodes (Home Infusion)

	Pre-dose	Treatment period					At the end of treatment [a]	Follow-up (7 days after the last dose of IP)
		Day E1				On and After Day E2		
		0 hour	6 hours after the first dose of IP	12 hours after the first dose of IP	18 hours after the first dose of IP	Every 6 or 12 hours		

[f] The dose regimen of IP is the same as that of treatment for the first acute episode. The first infusion of IP will be possible at home. If the first infusion is done at home, subject will have to visit the site (however, if the investigator determines the recovery or improvement of the acute episode by assessing the picture of the lesion site, which is taken by the subject at home after the first infusion and is sent to the investigator, the timing of this investigator's decision is considered as the end of treatment and the subject will not have to visit the site. If a next infusion is required based on the investigator's decision, the subject will have to visit the site). If the first infusion is done at the site, follow the procedures for first acute episode (Table 2)
** When the acute episode is not recovered or improved after the first dose, further infusions are continued.

[g] The dosing information at home will be recorded on a subject diary. Subject will have to bring the subject diary to the site when he/she visits the site.

Note: the schedule of activities for on-demand treatment differs depending on episodes which a subject has, ie, first acute episode OR second and subsequent acute episodes. Refer to Section 8.1.2.1 for details.

Abbreviations. AE=adverse event, CISN= coumarin-induced skin necrosis, IP=investigational product, PF= purpura fulminans, WISN=warfarin-induced skin necrosis.

1.4 Schedule of Activities (Extension part: Short-Term Prophylaxis)

Table 4. Schedule of Activities (Short-Term Prophylaxis)

	Pre-surgery [a]	Treatment period			At the end of treatment [b]	Follow-up (7 days after the last dose of IP)
		Day E1 (day of surgery)	Day E2	On and After Day E3		
Eligibility check [c]	X					
Physical exam	X				X	
Concomitant medications	←	—	—	—	—	→
Hematology [d]	X				X	
Protein C Activity [e]	(X)	(X)	(X)	(X)	(X)	
Vital signs	X		X		X	
Study drug dosing	X	X [f]	X [f]	X [f]		
AE assessment	←	—	—	—	—	→

[a] For subjects on anticoagulation therapy who required elective surgery (non-emergency), treatment with TAK-662 will be initiated at a dose of 100-120 IU/kg once daily until anticoagulation therapy is successfully switched to TAK-662 prior to surgery. For subjects on anticoagulation therapy who required emergency surgery, vitamin K dosage can reverse anti-coagulation due to warfarin, and TAK-622 treatment (100-120 IU/kg) should be started.

[b] Treatment with TAK-662 will be ended when the investigator determines that adequate anticoagulation is achieved.

[c] Pregnancy urine test will be performed at the site within 3 days of first dose.

[d] Hematological tests will be performed at a central laboratory. Baseline hematologic tests will be performed within 7 days prior to first dose.

[e] Protein C activity measurement may be performed at the discretion of the investigator. If protein C activity will be measured, the time point of measurement is also at the discretion of the investigator.

[f] Fifteen minutes prior to surgery, a dose of 60-80 IU/kg will be administered. The same dose will be continued once every 6 hours for the first 24 hours after surgery began. The frequency of infusions is reduced to 3 times daily at a dose of 45-60 IU/kg between 24 and 48 hours, and twice daily after 48 hours at the same dose (45-60 IU/kg).

Abbreviations. AE=adverse event, IP=investigational product.

1.5 Schedule of Activities (Extension part: Long-Term Prophylaxis)

Table 5. Schedule of Activities (Long-Term Prophylaxis)

	Pre-dose	Treatment period			End of study [a]/ Follow-up (7 days after the last dose of IP)
		1st 3 prophy. infusions	Following of 1st 3 prophy. infusions	Every 1 M±2 wks	
Eligibility check [b]	X				
Concomitant medications	←	—	—	—	→
Hematology [c]	X			X	
Protein C Activity [d]			X	X	
Hospitalization [e]	←	—	→		
Study drug dosing [f]		←	—	—	→
Subject Diaries [g]				←	— →
AE assessment		←	—	—	→

[a] End of study is defined as the time TAK-662 becomes available at the site.
[b] Pregnancy urine test will be performed at the site within 3 days of first dose.
[c] Hematological tests will be performed at a central laboratory. Baseline hematologic tests will be performed within 7 days prior to first dose. Hematologic tests every 1 month (±2 weeks) will be performed at pre-infusion, and may be skipped at the discretion of the investigator.
[d] Protein C activity will be performed before infusion of IP. Protein C activity every 1 month (±2 weeks) may be skipped at the discretion of the investigator.
[e] Subject is allowed to discharge at the investigator's discretion after the measurement of protein C activity following of 1st 3 prophylaxis infusions.
[f] A dose of 45-60 IU/kg will be administered upon initiation of long-term prophylaxis twice daily. The first 3 doses will be administered at the site. The dose will be adjusted by referring to the latest Protein C activity at the investigator's discretion.
[g] Subject diary will be completed throughout home treatment times after discharge. Subject will have to bring the subject diary to the site when he/she visits the site.
Abbreviations. AE=adverse event, IP=investigational product, M=month, prophy.= prophylaxis, wks=weeks.

2. INTRODUCTION

Protein C Concentrate (human) (TAK-662) is approved as Ceprotin® in European countries and the United States. TAK-662 is a double virus-inactivated, lyophilized concentrate for intravenous use, manufactured from pooled human plasma.

2.1 Indication and Current Treatment Options

Protein C, a vitamin K-dependent plasma protein, is an important component of the coagulation system. Protein C exerts anticoagulant effects via a chemical cascade in which protein C is activated to activated protein C, a serine protease, by binding to thrombomodulin-bound thrombin. The activated protein C inactivates Factor Va and Factor VIIIa, thereby resulting in the inhibition of tenase and prothrombinase activities and ultimately creating an anticoagulant effect.

The pathophysiological role of protein C came to be understood through descriptions of congenital deficiency with lesions characteristic of hereditary thromboembolic diseases such as extensive necrotic skin lesions (purpura fulminans [PF]), thrombotic events in the central nervous system and thrombosis of the retinal vessels.

One of the most common symptoms of protein C deficiency, PF, is a life-threatening complication that frequently appears during the first several days of life in infants congenitally deficient in protein C (Marlar et al., 1989). The clinical symptoms of PF consist of ecchymotic skin lesions which rapidly develop into hemorrhagic bullae with subsequent gangrenous necrosis sometimes extending to the fascia and leading to autoamputation. In addition, cerebral thrombotic complications can occur in utero or after birth and are responsible for hydrocephalus, mental retardation, delayed development and seizures. Retinal thrombosis can cause partial or complete blindness.

Severe protein C deficiency (homozygous or compound heterozygous forms) is extremely rare (1 in 500,000 to 1 in 750,000 births), but partial deficiencies (heterozygous forms) are much more frequent (1 in 200 to 1 in 500) (Goldenberg and Manco-Johnson, 2008, Kottke-Marchant and Comp, 2002). The low prevalence of patients with severe genetic protein C deficiency may be explained by fetal demise and prenatal deaths before diagnosis. The incidence of protein C deficiency in persons who present with clinical symptoms has been estimated at 1 in 20,000 (Dahlbäck, 1995). In Japan, the number of the patients of congenital protein C deficiency is estimated to be less than 1,000 as in the latest patient survey 2017 by the category of "Other hereditary coagulation factor deficiency" (Ministry of Health Labour and Welfare [MHLW], 2017). A survey for patients with cardiovascular disorder from 1986 to 1996 in Japan reported that 43 patients with protein C deficiency were screened from approximately 26,800 patients, and the observed prevalence of protein C deficiency was 1 per 620 (Sakata et al., 1999). This prevalence is in agreement with that of foreign countries.

In overseas countries, according to guideline in American College of Chest Physicians (ACCP), for acute symptoms in newborn with homozygous protein C deficiency, replacement therapy with fresh frozen plasma and/or protein C is recommended. For long-term prophylaxis treatment in those patients after stabilization of acute symptoms, protein C replacement and vitamin K antagonists, low molecular heparin and liver transplantation are recommended (ACCP 9th; (Guyatt et al., 2012). In addition, according to guideline in American Society of Hematology (ASH), for PF in infants with homozygous protein C deficiency, anticoagulant therapy and protein C replacement are recommended (Schünemann et al., 2018). The ASH guideline panel also suggests using protein C replacement rather than anticoagulation, or using anticoagulation plus protein C replacement rather than anticoagulation alone, in pediatric patients with congenital PF due to homozygous protein C deficiency (Monagle et al., 2018).

In Japan, for thrombosis in children, anticoagulant therapy and/or thrombolytic therapy are recommended based on severity. For long-term prophylaxis treatment in those patients, anticoagulant therapy is recommended, and replacement therapy is used, if needed. Currently, in Japan, human activated protein C, freeze-dried concentrated (activated protein C) is available for treatment of deep venous thrombosis (DVT), acute pulmonary thromboembolism, and PF caused by congenital protein C deficiency.

2.2 Product Background and Clinical Information

TAK-662 is considered to be a safe, well-tolerated and efficacious product for the treatment of PF and coumarin-induced skin necrosis (CISN)/ warfarin-induced skin necrosis (WISN) in patients with severe protein C deficiency and for short-term prophylaxis in patients with severe congenital protein C deficiency (e.g. prior to and during surgery or invasive therapy, in the initial phase of oral anticoagulation therapy, or in case of failure of oral anticoagulation therapy). Treatment with TAK-662 then may be life-saving and play a substantial role in preventing major thrombotic complications and irreversible organ damage. In addition, in March 2007, Food and Drug Administration (FDA) approved Ceprotin® for “pediatric and adult patients with severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans” (Food and Drug Administration [FDA], 2018). There were no adverse events (AEs), no literature reports on thrombotic events, and no protein C inhibitor formation during the time of long-term prophylaxis.

The information of Protein C Concentrate/TAK-662 from non-clinical and clinical studies is summarized below.

Non-clinical safety

The Protein C Concentrate did not produce adverse effects in a series of safety pharmacology studies. The doses in these studies are 200 to 500 international unit (IU)/kg, which is greater than the anticipated maximum clinical dose of 120 IU/kg.

The No Observed Adverse Effect Level (NOAEL) of single dose toxicity studies in mice and rats were 1,500 and 2,000 IU/kg, respectively, which was the highest dose tested. Both results indicated a sufficiently large safety margin between the anticipated maximum human dose (120 IU/kg) and NOAEL. No concerns were raised by the in vitro studies on mutagenicity. Investigation of local tolerance in rabbits indicated that the product was well tolerated after intravenous, intraarterial, and paravenous injection. In addition, as a result of an exploratory study on antigenicity in a rabbit, no changes-neither formation of neoantigens nor disappearance of antigens were detected.

Clinical pharmacology

Pharmacokinetic (PK) properties of Protein C Concentrate/TAK-662 were investigated in 2 studies in asymptomatic subjects (Studies IMAG-098 and 400101) as well as in symptomatic subjects (retrospective data collection [RDC] of the use of Protein C Concentrate for treatment of protein C deficiency [Studies IMAG-039, IMAG-041, and compassionate use]). The list of the studies is shown below.

The analysis of the PK parameters showed considerable inter-subject variation. Half-life ($t_{1/2}$) is shorter and clearance (CL) of protein C is higher in children than in older subjects. Therefore, neonates and very young children require higher doses than adults, especially when they are in the acute phase of the disease.

Considering these variations, no general recommendations for a dosage regimen can be made. Consequently, careful monitoring throughout the treatment is necessary in order to ensure that adequate protein C activity are maintained. The amount of Protein C Concentrate administered, the frequency of administration and the duration of treatment should be based on the patient's protein C plasma activity and on the clinical condition of the patient.

Clinical efficacy and safety

The efficacy and safety of Protein C Concentrate/TAK-662 in subjects with severe congenital protein C deficiency were investigated in the following clinical studies:

- RDC: Clinical Studies IMAG-039 and IMAG-041 and Compassionate Use
  - Study IMAG-039: An Open-Label Study of the Efficacy and Safety of Protein C Concentrate (Human) Vapor Heated in the Treatment of Severe Congenital Protein C Deficiency With or Without Purpura Fulminans
  - Study IMAG-041: An Open-Label Study of the Efficacy and Safety of Protein C Concentrate (Human) Vapor Heated in the Treatment of Warfarin (Coumarin)-Induced Skin Necrosis
- Study IMAG-098: A Clinical Study on the Pharmacokinetics of Protein C Concentrate (Human) Vapor Heated in Asymptomatic Subjects with Homozygous or Double Heterozygous Congenital Protein C Deficiency
- Study 400101: A Phase 2/3 Clinical Study for the Determination of the Efficacy and Safety of Protein C Concentrate in Subjects with Severe Congenital Protein C Deficiency
- Study 400501: A Retrospective Study to Capture Dosing and Treatment Outcome Data in Subjects With Severe Congenital Protein C Deficiency Who Were Treated With Protein C Concentrate Under an Emergency Investigational New Drug (IND)

In addition, following registry study was conducted in the United States (US) and European Union (EU) after the above clinical studies.

- Study 400701: A prospective, international, multi-center, open-label, noninterventional, observational, post-authorization registry of subjects prescribed and treated with CEPROTIN (Protein C Concentrate [Human])

Efficacy:

In RDC of Study IMAG-039, Study IMAG-041, and compassionate use study, a large increase in protein C value from baseline was observed after the first dose of TAK-662 based on all the treatments in available data. The initial dose was 20 U/kg to 70 U/kg twice a day (BID). TAK-662 was effective in the treatment of protein C deficiency in patients with severe congenital protein C deficiency and in patients with simple heterozygous, acquired, other/unknown protein C deficiency.

The results of a prospective study, Study 400101, showed that TAK-662 is effective in the acute phase of treatment of PF, CISN/WISN, and other vascular thromboembolic events in patients with severe congenital protein C deficiency. In patients with severe congenital protein C deficiency, TAK-662 has been shown to be effective in both short-term replenishment (during surgery and at the initiation of oral or parenteral anticoagulant therapy) and long-term replenishment for thromboprophylaxis. In a retrospective study 400501, TAK-662 was shown to be effective in the treatment of acute thrombotic episodes in patients with severe congenital protein C deficiency. In addition, it was suggested that short-term and long-term replenishment with TAK-662 is effective for thromboprophylaxis.

A post-marketing registry study in 25 patients with severe congenital or acquired protein C deficiency (Study 400701) provided efficacy and safety for surgical/invasive procedures or acute episodes in patients with severe congenital or acquired protein C deficiency. Furthermore, it also provided an evidence to support a favorable benefit-risk profile of TAK-662 in long-term replacement in 19 patients.

Safety:

The safety profile of TAK-662 is based on data in patients with severe congenital protein C deficiency in clinical trial(s) and in 79 patients from the compassionate use. The exposure period ranged from 1 day to 8 years. Hypersensitivity/allergic reaction (pruritus and rash) and mild headache were reported from 1 subject and were assessed by the investigator to be treatment-related.

As of 31 December 2020, the most frequent SAEs from company sponsored trials assessed as at least possibly related to study drug were pyrexia, vascular device infection, musculoskeletal chest pain, and seizure. Serious adverse events were reported predominantly from 4 studies (Studies 400101, IMAG-098, IMAG-103, and IMAG-112). Of all AEs reported in clinical trials regardless of seriousness, the adverse drug reactions assessed as probably related to TAK-662 identified were hypersensitivity (pruritus and rash) and dizziness.

No inhibitory anti-protein C antibodies were observed in 14 pediatric patients from long term prophylaxis part of Study 400101 were tested for antibody to protein C. None of patients were positive. Similarly, in Study IMAG-098, all 13 subjects were negative for inhibitory antibodies against protein C at baseline and the 12 subjects whose antibody titers were measured were negative at 3 months.

Adverse reactions observed post-marketing included hemothorax, hypotension, hyperhidrosis, pyrexia, and restlessness. The frequency of these adverse reactions was difficult to estimate because of spontaneous reports. No serious hypersensitivity reactions had been reported as of 31 December 2020.

2.3 Study Rationale

The PK part of Japanese clinical study design will be identical with the overseas PK study design (Study IMAG-098) as much as possible except that: 1) the target population is Japanese patients and 2) the planned sample size will be 3 or more. After the PK part, an extension part (on-demand therapy, short-term prophylaxis, and long-term prophylaxis) will be conducted in the subjects who have completed PK part.

In the PK part, study design of the Japanese clinical study is investigated for the purpose of comparing with the results of Study IMAG-098. The Sponsor has concluded that the design of the Japanese study will be appropriate based on PK similarity evaluation and consistency of demographic characteristics as follows.

Dose and administration, sampling points and PK parameters in the Japanese study are identical to that in Study IMAG-098, for the purpose of evaluation of PK in Japanese subjects and comparing with the results of Study IMAG-098. Considering that number of subjects is very limited in the Japanese study, the Sponsor plans to evaluate PK similarity between Japanese and non-Japanese, by confirming whether the PK of each Japanese subject is within the range of (or not significantly different from) non-Japanese subjects in Study IMAG-098. Of note, as a result of PK evaluation for non-Japanese subject with age ranging 1 to 39 years old in overseas clinical trials, $t_{1/2}$ was tended to be shorter and CL was tended to be higher in younger subjects. The Sponsor considers it is possible to evaluate PK similarity considering the effect of age, because age of the current Japanese patients with severe congenital protein C deficiency in a range of 3 years to twenties, which is within the range of non-Japanese subject in overseas clinical trials.

To ensure consistency of demographic characteristics between Study IMAG-098 and the Japanese study, the target patient is same for both studies. In addition, inclusion/exclusion criteria in the Japanese study design are identical with Study IMAG-098 as much as possible. For the patients with homozygous or double heterozygous protein C deficiency, the level of protein C activity is less than 1% (Goldenberg and Manco-Johnson, 2008, Ishimura M et al., 2018), which is significantly lower than that of heterozygous protein C deficiency (30% to 50%). To reduce the effect of endogenous protein C in patients with heterozygous protein C deficiency on evaluation for PK similarity, the Sponsor concludes target patient should be limited to severe congenital protein C deficiency, which is identical to Study IMAG-098.

The endpoints in the Japanese study are set identical to those in Study IMAG-098 as much as possible except that inhibitory antibodies against protein C (anti-protein C antibody) is not investigated in the Japanese study. No anti-protein C antibody development has been reported in both clinical development program of Protein C Concentrate and Periodic Benefit-Risk Evaluation Report. Furthermore, there is no laboratory institution to evaluate anti-protein C antibody over the world at the moment.

Taken together, it seems that the risk of anti-protein C antibody development is minimal, thus the Sponsor considers that measurement of inhibitory antibodies against protein C is not required.

If a subject wishes continuous administration of TAK-662 after the completion of the PK part, the subject can participate in the extension part based on the investigator's judgement. The study design, and dose and administration of TAK-662 for the extension part are referred to that of Study 400101; however, these are not identical to Study 400101 because the study purpose is different each other.

2.4 Benefit/Risk Assessment

Currently, in Japan, human activated protein C, freeze-dried concentrated (activated protein C) is available for treatment of DVT, acute pulmonary thromboembolism, and PF caused by congenital protein C deficiency. The activated protein C is generally used under hospitalization. Furthermore, a supply of this drug needs some time, and hence it cannot be used for long-term prophylaxis treatment due to too short $t_{1/2}$ (alpha phase: 8.8 min, beta phase: 71.5 min) of this drug (Goldenberg and Manco-Johnson, 2008, Yoshida M et al., 2018).

Overseas clinical studies and literature reports have confirmed the efficacy of TAK-662 in patients with congenital protein C deficiency of acute treatment for thrombotic diseases such as PF and CISN/WISN, perioperative management such as surgical operation, and short-term and long-term supplementation such as initiation of oral anticoagulants. TAK-662 is effective in the treatment of life-threatening serious thrombotic diseases in patients with congenital protein C deficiency. It is considered that TAK-662 contributes to the improvement of prognosis and quality-of-life (QoL) by preventing the progression to serious disease and its sequelae.

The safety of TAK-662 was demonstrated in both RDC ([Studies IMAG-039, IMAG-041, and compassionate use] and Study 400501), all 2 prospective clinical studies (Studies IMAG-098 and 400101), and the registry study (Study 400701). It then can be concluded that TAK-662 is a safe and well-tolerated product.

Thus, the overall assessment on the benefits and risks of TAK-662 concludes that the benefit of a single 80 IU/kg dose of TAK-662 for Japanese patients with congenial protein C deficiency in this Japanese study will outweigh the risks.

The extension part will be conducted to evaluate the safety and efficacy of on-demand therapy, short-term prophylaxis, and long-term prophylaxis. The study design of extension part will be identical with the overseas study design (Study 400101) as much as possible. The results of Study 400101 demonstrate that TAK-662 is effective in the treatment of acute episodes of PF, CISN/WISN, and other vascular thromboembolic events in subjects with severe congenital protein C deficiency.

The data also indicate that both short-term (during surgical procedures and the initiation of oral or parenteral anticoagulation) and long-term thrombotic prophylaxis with TAK-662 is effective in subjects with severe congenital protein C. In addition, the safety results also contributed supportive evidence that TAK-662 has acceptable safety and tolerability. No new safety signals were identified. Furthermore, the dosage and administration of TAK-662 for this study are the same as those described in the US package insert.

Always refer to the latest version of the TAK-662 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of TAK-662.

2.5 Compliance Statement

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

The responsibilities of the study sponsor and investigator(s) are described fully in [redacted]

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To measure the PK parameters of TAK-662 in asymptomatic subjects with homozygous or double heterozygous congenital protein C deficiency in Japanese subjects.

3.1.2 Secondary Objectives

- To assess safety profile of TAK-662.
- To assess efficacy of TAK-662 in following 1) for on-demand treatment such as PF, CISN/WISN, and other vascular thromboembolic events; 2) for short-term thromboembolic prophylaxis during surgical procedures; and 3) for long-term prophylactic treatment of acute thrombotic episodes (Extension part).

[redacted]

3.2 Study Endpoints

Table 6. Objectives and Endpoints

Objective		Endpoint(s)
Primary		
• To measure the pharmacokinetic (PK) parameters of TAK-662 in asymptomatic subjects with homozygous or double heterozygous congenital protein C deficiency in Japanese subjects.		• Protein C activity • PK parameters including but not limited to terminal half-life ($t_{1/2}$), incremental recovery (IR), in-vivo recovery (IVR), area under the curve (AUC), maximum concentration (C_{max}), and minimum time to reach maximum concentration (t_{max})
Secondary		
• To assess safety profile of TAK-662.		• The primary variable for safety assessment is the number of subjects with treatment-related adverse experiences. Other Safety Endpoint • Body temperature, blood pressure, and pulse rate are monitored before and after the investigational product administration, and the last prophylactic treatment (if applicable) prior to the test dose.
• To assess efficacy of TAK-662 (Extension part)	On-demand treatment	• The treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events are rated as *effective*, *effective with complications*, or *not effective* when it is determined that the next infusion is unnecessary according to the efficacy rating scale.
	Short-term prophylaxis	• Percentage of surgical episodes during short-term prophylaxis, for which TAK-662 is utilized as short-term prophylaxis, that is free of presentations of PF or thromboembolic complications.
	Long-term prophylaxis	• Number and rate of episodes of PF and/or thrombotic episodes during long-term prophylaxis.
[redacted]		
• [redacted]		• [redacted]

4. STUDY DESIGN

4.1 Overall Design

This is a phase 1/2 open-label, non-randomized, non-controlled, single-dose, multicenter study to evaluate PK, safety, and tolerability of TAK-662 in Japanese subjects with congenital protein C deficiency followed by an extension part.

PK part:

The study is planned to enroll more than 3 subjects in Japan. The subject who has the prophylactic treatment of anticoagulants is allowed to be enrolled. The last prophylactic treatment including protein C ingredient must occur by at least 36 hours before the administration of TAK-662 on Day 1. Other prophylactic treatment such as oral anticoagulants can be administered without any restrictions on period.

Once all screening assessments following informed consent (and assent where applicable) are completed and eligibility is confirmed, the subject will receive a single 80 IU/kg dose of TAK-662 intravenously on Day 1. Prior to the IP administration, the subject will be admitted to the study site on Day −1 (One day earlier hospitalization [Day −2] is allowed if applicable). The prophylactic treatment will be given according to the subject's established treatment regimen and at the discretion of the investigator. For the subject with prophylactic treatment including protein C ingredient, the IP for PK will be administered at least after 36 hours of the prophylactic treatment.

From Day 1 to Day 3, the subject will stay in the study site and be followed up for PK and safety before and after the IP administration. The blood sampling for PK will be done immediately prior to infusion and at 30 minutes, and 1, 2, 4, 8, 12, 24, and 36 hours postinfusion; a sampling for the 36 hours postinfusion is allowed to be customized by age, especially for feasibility in children. After 7 days from the IP administration (Day 7), the subject will have the follow-up visit for safety assessment. For the subject who has the prophylactic treatment including protein C ingredient before the administration of the IP for PK, the blood sampling will be additionally done immediately prior to the prophylactic treatment and at 1, 17, and 25 hours post-treatment.

The analysis will be performed for PK and safety after all subjects have completed the Day 7 visit. It is planned to compare PK parameter of Japanese and non-Japanese subjects, by calculating PK parameter of each Japanese subject, then confirming whether it is within the range of (or not substantially different from) PK parameter of each non-Japanese subject in Study IMAG-098. PK similarity will be made comprehensively considering all the PK parameters together.

Extension part:

In the extension part of the current study, sponsor provides 3 different treatment options; on-demand treatment, short-term prophylaxis, and long-term prophylaxis. Based on investigator's careful evaluation on subject's medical condition, subject who completed PK part can continue the administration of TAK-662 until the commercial protein C concentrate is available at each study site or study termination. The 3 different treatment options provide different ways of protein C supplementation. Refer to Section 8.1.2 for the assessments and procedures. Subject can participate in each of 3 options and can transfer from one to another at the investigator's discretion. Refer to Section 6.2.2 for the dosage regimen of each treatments.

For on-demand treatment, subjects with PF, CISN/WISN, and/or other acute thromboembolic episode will be enrolled. For short-term prophylaxis, subjects requiring short-term prophylaxis with protein C concentrate/TAK-662 for surgical procedures will be enrolled. For long-term prophylaxis, subjects requiring long-term prophylaxis with protein C concentrate/TAK-662 will be enrolled.

On-demand treatment and short-term prophylaxis may be carried out more than once depending on the subject's situation. In this case, after the completion of follow-up period, the subject will be re-enrolled and re-start the procedures from pre-dose/pre-surgery period. In addition, subject may transfer to the other treatment. (eg, If a subject who enrolled in long-term prophylaxis requires a surgery, he/she transfers to short-term prophylaxis. Once anticoagulation is initiated and the investigator determines that adequate anticoagulation is achieved, he/she will transfer back to long-term prophylaxis.)

4.2 Scientific Rationale for Study Design

PK part:

Since obtaining PK parameters is the primary objective, an open-label design is chosen for this study. No control group is used in this study.

Extension part:

Even under currently-available treatment options, high mortality and poor clinical course of protein C deficiency has been reported in Japan (Ohga et al., 2013). The extension part will provide subjects with protein C deficiency opportunities to experience TAK-662 administration as a new treatment option until the commercial protein C concentrate is available at each study site or study termination.

4.3 Justification for Dose

PK part:

The IP dose for PK measurements will be 80 IU/kg. The test dose was determined based on the dose used in clinical study IMAG-098 conducted in overseas countries.

In Study IMAG-098, this dose was used for evaluation of PK of protein C, and to compare the PK profile in Study IMAG-098, the same dose is chosen for this study.

The prophylactic treatment will be given according to the subject's established treatment regimen and at the discretion of the investigator.

Extension part:

In the extension part, dose of TAK-662 will be decided by the treatment part that the subject will be enrolled at the time of treatment. The IP dose of on-demand treatment, short-term prophylaxis, and long-term prophylaxis were determined based on the dose used in clinical study (Study 400101) and clinical dose in overseas countries.

Japanese PK data derived from precedent PK part will be provided by sponsor to the investigator, which might help their judgement on the dosing.

4.4 Duration of Subject Participation and Study Completion Definition

PK part:

The subject's maximum duration of participation is expected to be approximately 8 days including the Day −1 stay. The study will be completed in approximately 5 months.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 8.1.1.3 for the defined follow-up period for this protocol).

Extension part:

The extension part will continue until the commercial protein C concentrate is available at each study site or study termination. The duration of subject participation and study completion date are determined depending on which study part to be enrolled (refer to Section 6.2.2 for the IP dose for this protocol).

4.5 Sites and Regions

The study will be conducted in approximately 5 study sites in Japan.

5. STUDY POPULATION

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

5.1 Inclusion Criteria

PK part:

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

1. An understanding, ability, and willingness to fully comply with study procedures and requirements. If the subject is <20 years of age or informed consent cannot be obtained from the subject, a parent or legally authorized representative should perform this role.
2. Ability to voluntarily provide written, signed, and dated (personally, or via a parent or legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject) informed consent, and assent as applicable (only when informed consent can be obtained from the subject), to participate in the study.
3. Male and female subjects with Japanese nationality.
4. A diagnosis of congenital protein C deficiency (homozygous or compound heterozygous).
5. Asymptomatic subject.
6. Oral anticoagulants allowed to be received.
7. Male, or non-pregnant or non-lactating female who is sexually active and who agrees to comply with the applicable contraceptive requirements of this protocol, or females of non-childbearing potential. A negative pregnancy test at the Screening visit has to be documented. Definitions of the childbearing potential female and the applicable contraceptive requirements are defined in Section 5.4.

Extension part:

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

1. Subjects who participated in the PK part of this study (TAK-662-1501).
2. An understanding, ability, and willingness to fully comply with study procedures and requirements. If the subject is <20 years of age or informed consent cannot be obtained from the subject, a parent or legally authorized representative should perform this role.

3. Ability to voluntarily provide written, signed, and dated (personally, or via a parent or legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject) informed consent, and assent as applicable (only when informed consent can be obtained from the subject), to participate in the extension part of this study.
4. Subject who are;
    a. Diagnosed with PF, CISN/WISN, and/or other acute thromboembolic episode for on-demand treatment only.
    b. Requiring treatment with TAK-662 for short-term prophylaxis for surgical procedures.
    c. Requiring treatment with TAK-662 for long-term prophylaxis.

5.2 Exclusion Criteria

PK part:

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

1. Current or recurrent disease that could affect the action, or disposition of the IP, or clinical or laboratory assessments.
2. A body weight less than 8 kg.
3. Serious liver dysfunction, judged by the investigator.
4. Any thrombosis within 2 weeks prior to administration of the IP.
5. Other investigational product than TAK-662 received within 60 days prior to the administration of the IP.
6. Current or relevant history of physical or psychiatric illness, or any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the IP or procedures.
7. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) that could affect (improve or worsen) the condition being studied, or could affect the action or disposition of the IP, or clinical or laboratory assessment. See Section 6.6 (Prior and Concomitant Treatment) for a list of prohibited and restricted medications.
8. Known or suspected intolerance or hypersensitivity to the IP, closely-related compounds, or any of the stated ingredients.
9. Known history of alcohol or other substance abuse within the last year.

10. Within 30 days prior to the first dose of IP, a subject has been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this sponsored study.

Extension part:

The subject who participated in the PK part will be excluded from the extension part of the study if any of the following exclusion criteria are met.

1. New serious medical conditions which could affect patient's safety or treatment were observed during participation in the PK part of this study (TAK-662-1501).
2. Planning to participate in clinical trials of other investigational drugs or medical devices.
3. Females of childbearing potential who do not agree to use acceptable contraception.

5.3 Restrictions

PK part:

Subjects on prophylactic treatment who experienced a thrombotic complication during the last prophylactic treatment or the subsequent washout period were not to be entered into the study.

Extension part:

There are no restrictions for the extension part.

5.4 Reproductive Potential

5.4.1 Female Contraception

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

Female children and adolescent subjects should be either:

- Premenarchal and either Tanner stage 1 or less than age 9 years, or
- Females of childbearing potential with a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at the Screening visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Female adult subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Of childbearing potential with a negative serum β-hCG pregnancy test at the Screening visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

- Intrauterine device
- Bilateral tubal interruption / tubal ligation
- A male partner who is the only partner of the subject and was postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate
- Progestin/estrogen mixed preparation for inhibition of ovulation

5.4.2 Male Contraception

A male subject who is non-sterilized and sexually active with a female partner of childbearing potential must use male condom with or without spermicide.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

The investigational product is TAK-662, which will be provided in vial form.

TAK-662 is Protein C Concentrate, which is a lyophilized, sterile concentrate of human protein C. The protein C content is indicated in IU on the label of each vial. Two vial sizes are available: 500 IU for reconstitution in 5 mL Sterile Water for Injection or 1,000 IU for reconstitution in 10 mL Sterile Water for Injection. The pH of the reconstituted product is 6.7 to 7.3. The composition is described below:

Composition of TAK-662 After Reconstitution

	Vial Size	
Component	**500 IU**	**1,000 IU**
Human protein C activity[a]	500 IU	1,000 IU
Human albumin	40 mg	80 mg
Sodium chloride	44 mg	88 mg
Trisodium citrate.$2H_2O$	22 mg	44 mg

[a] Protein C amidolytic activity is determined in comparison with a reference preparation calibrated against the 1st International Standard for Protein C in Plasma, code 86/622.

Additional information is provided in the current TAK-662 IB.

6.1.2 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

6.2.1 Allocation of Subjects to Treatment

Not applicable.

6.2.2 Dosing

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

PK part:

All subjects will receive a single 80 IU/kg dose of TAK-662, infused over 15 minutes for the measurement of PK parameters, at Day 1. TAK-662 should be administered at a maximum injection rate of 2 mL/min except for children with a body weight of < 10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/min. For administration by infusion, a disposable infusion set with adequate filter must be used. All subjects will be closely monitored throughout the course of the study including, the 36-hour washout period, IP dose administration and PK and the follow-up period.

Extension part:

Dose will be decided according to an extension treatment that the subject will be enrolled at the time of treatment. The on-demand treatment, short-term prophylaxis, and long-term prophylaxis will be given at the discretion of the investigator with reference to below. TAK-662 should be administered at a maximum injection rate of 2 mL/min except for children with a body weight of < 10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/min.

1) On-demand treatment

Upon presentation with an acute event, the subject will be infused with a dose of 100-120 IU/kg. The subsequent 3 infusions will be administered every 6 hours at a dose of 60-80 IU/kg. Subsequent infusions (45-60 IU/kg) are also continued every 6 or 12 hours until resolution of all non-necrotic lesions and/or stabilization of thrombi (in the case of a thrombotic episode). The treatment can terminate when an acute episode tends to improve.

If the subject, a parent or legally authorized representative wants to have the first infusion of TAK-662 at home for the second and subsequent acute episodes, the subject or caregiver should be trained to reconstitute and administer the study doses correctly. The subject or caregiver will be observed in performing these tasks by the investigator or trained study staff to verify adequate training. Then, the infusions of IP will be possible at home (refer to the training manual for self-injection). The dosing information at home will be recorded on a subject diary.

2) Short-term prophylaxis

Specific treatment regimens will apply for short-term prophylaxis of acute thrombotic episodes during surgery. For subjects on anticoagulation therapy who required elective surgery (non-emergency), treatment with TAK-662 will be initiated at a dose of 100-120 IU/kg once daily until anticoagulation therapy is successfully switched to TAK-662 prior to surgery. For subjects on anticoagulation therapy who required emergency surgery, vitamin K dosage can reverse anti-coagulation due to warfarin, and TAK-622 treatment (100-120 IU/kg) should be started. Fifteen minutes prior to surgery, a dose of 60-80 IU/kg will be administered.

The same dose will be continued once every 6 hours for the first 24 hours after surgery began. The frequency of infusions is reduced to 3 times daily between 24 and 48 hours, and twice daily after 48 hours at the same dose (45-60 IU/kg). Treatment with TAK-662 continues twice daily until anticoagulation therapy is initiated (if applicable) and the investigator determines that adequate level of the anticoagulation is achieved.

3) Long-term prophylaxis

A dose of 45-60 IU/kg will be administered upon initiation of long-term prophylaxis twice daily. The first 3 doses will be administered at the site. The dose will be adjusted by referring to the latest protein C activity at the investigator's discretion.

If the subject, a parent or legally authorized representative wants to have infusion of TAK-662 at home, the subject or caregiver should be trained to reconstitute and administer the study doses correctly. The subject or caregiver will be observed in performing these tasks by the investigator or trained study staff to verify adequate training. Then, the infusions of IP will be possible at home (refer to the training manual for self-injection). Each dosing information at home will be recorded on a subject diary.

The prophylactic treatment will be given according to the subject's established treatment regimen and at the discretion of the investigator in both of PK part and extension part.

6.2.3 Unblinding the Treatment Assignment

Not applicable.

6.2.4 Dose Modification

Not applicable in PK part. In the extension part, dose of TAK-662 will be modified per subjects.

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

6.3.1 Labeling

Labels containing study information and pack identification, compliant with local laws and regulations, are applied to the IP container.

Refer to the pharmacy manual for detail. Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

TAK-662 will be supplied lyophilized in vials containing target values of 500 IU or 1,000 IU protein C. Each vial will be accompanied by a suitable volume of Sterile Water for Injection.

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

6.3.3 Storage

TAK-662 is stable up to 3 years when stored at 2°C - 8°C. Do not use after the date of expiration provided by the sponsor. The vials must not be reused once subject information is filled out on their labels.

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

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

If subject will have infusion of TAK-662 at home, refer to the manual for self-injection.

6.3.4 Special Handling

TAK-662 is stored lyophilized and must be reconstituted immediately prior to application as follows:

1. Warm the unopened bottle containing the solvent to room temperature (maximum 37°C).
2. Remove the protective caps from the concentrate and solvent bottles and disinfect the rubber stoppers of both bottles.
3. The enclosed double-ended transfer needle is protected by two plastic caps sealed by a weld mark. Break the seal by twisting the cap. Remove one cap and insert the exposed needle into the rubber stopper of the solvent bottle. Remove the other cap from the double ended transfer needle taking care not to touch the exposed end.
4. Invert the solvent bottle over the concentrate bottle and insert the free end of the double-ended needle into the rubber stopper of the concentrate bottle to half its length. The solvent will be drawn into the concentrate bottle which is under a vacuum.
5. Disconnect the two bottles by removing the needle from the concentrate bottle. Agitate or rotate the concentrate bottle to accelerate dissolution.
6. Remove and discard the filter needle, attach a suitable needle and administer intravenously.

The reconstituted solution should be used within 3 hours.

For handling of test kits such as blood collection tubes and needles, refer to the pharmacy manual.

If subject will have infusion of TAK-662 at home, refer to the manual for self-injection.

6.4 Drug Accountability

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

The investigator has overall responsibility for administering/dispensing IP. 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 administer the IP only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the IP carrying his/her treatment assignment. All administered medication will be documented in the subject's source and/or other IP record.

No IP stock or returned inventory from a 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, and national laws must be adhered to for the transfer.

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

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

At the end of the study all empty/used IP packaging may be destroyed at the site or a local facility. Destruction of IP must be in accordance with local, and national laws.

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

The on-site pharmacist (site designee) will receive the pharmacy manual created by the Sponsor, according to which the site designee will appropriately manage the Sponsor-supplied drug.

The Investigator will also receive those procedures from the Sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management and dispensation of the Sponsor-supplied drug as well as return of them to the Sponsor or destruction of them. The on-site pharmacist (site designee) will immediately return unused IP to the Sponsor after the study is closed at the study site.

If subject will have infusion of TAK-662 at home, refer to the manual for self-injection.

6.5 Subject Compliance

Drug accountability must be assessed at the container/packaging level for unused IP or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.6 Prior and Concomitant Therapy

All non-study treatment including but not limited to herbal treatments and vitamins received within 30 days prior to the Screening visit and through the follow-up period must be recorded in the subject's source document.

6.6.1 Prior Treatment

Prior treatment includes all treatment (but not limited to herbal treatments and vitamins) received within 30 days prior to the Screening visit. Prior treatment information must be recorded in the subject's source document.

6.6.2 Concomitant Treatment

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

PK part:

The last prophylactic treatment including protein C ingredient must occur by at least 36 hours before the administration of TAK-662 on Day 1. The IP administration should be discontinued if the prophylactic treatment including protein C ingredient is administered in 36 hours prior to the IP administration. Other prophylactic treatment such as oral anticoagulants can be administered without any restrictions on period.

Extension part:

For 3 different treatments options, any type of anticoagulant therapy is allowed to continue during treatment with TAK-662. For short-term prophylaxis, the anticoagulant therapy should be terminated before the surgery.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT EARLY TERMINATION/WITHDRAWAL

7.1 Early Termination of Study Treatment

PK part:

If a subject is early terminated, regardless of the reason, the evaluations listed for the Day 7 visit will be performed as completely as possible. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for early termination, date of early termination of the IP must be recorded in the source documents.

Extension part:

If a subject is terminated during each schedule of on-demand treatment, short-term prophylaxis, and long-term prophylaxis, the assessment of end of treatment/study will be performed.

7.2 Reasons for Early Termination

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

Reasons for early termination include, but are not limited to:

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

No predetermined reasons for early termination specifically defined to the study are established.

7.3 Withdrawal from the Study

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

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

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (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.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Periods

Refer to Table 1, Table 2, Table 3, Table 4, and Table 5 for the schedule of treatment activities. Study assessments are detailed in Section 8.2.

8.1.1 PK Part

8.1.1.1 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 legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject. The nature and purpose of the study will be explained and the known adverse experiences with TAK-662 will be described to the subject or to the subject's parent or legally authorized representative. If the subject agrees to participate, or the subject's parent(s) or legally authorized representative agrees to permit participation in the study, they will be required to sign and date the consent form (and assent where applicable).

8.1.1.1.1 Screening Visit (Day −14 to Day −2)

At the Screening visit, the information/data of the subject in Table 1 will be collected by interview and appropriate tests, including but not limited to below:

- Subject history
  - date protein C deficiency diagnosed and protein C activity at diagnosis
  - underlying diagnosis
  - current regimen for prophylactic treatment with Protein C Concentrate or including protein C ingredient (if applicable)
  - medical history including surgeries
  - thrombotic events and skin necroses
  - previous treatment with blood products
- Physical examination

A general physical examination is carried out including age and sex, weight (kg), height (cm), pulse rate, blood pressure, respiration rate and body temperature.

Any subject who met all eligibility criteria will be assigned a unique identification number after receiving a signed informed consent. The study site is responsible for maintaining a current log of subject number assignments in order to avoid assignment errors.

The unique identification number must be entered on all study documentation (ie. Case report forms [CRFs], sample containers, etc.).

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered IP. Subjects who fail to meet eligibility criteria may be re-screened.

8.1.1.1.2 Baseline Visit (Day −1)

Subjects will be admitted to the study site at one day before the administration of the IP (Day −1) and will have the necessary study assessment (Table 1). If applicable, subjects are allowed to stay in a hospital from one day before Day −1 (ie, Day −2).

8.1.1.2 Treatment Period (Day 1, Day 2 and Day 3)

Subjects will have the necessary study assessment (Table 1). Blood sample for clinical laboratory evaluations at Day 1 will be drawn before administration of the IP.

All subjects will receive a single 80 IU/kg dose of TAK-662, infused over 15 minutes for the measurement of PK parameters, at Day 1. TAK-662 should be administered at a maximum injection rate of 2 mL/min except for children with a body weight of < 10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/min. All subjects will be closely monitored throughout the course of the study including the 36-hour washout period, IP dose administration, PK blood sampling, and the follow-up period.

Subjects on prophylactic treatment including protein C ingredient will receive an intravenous infusion by 36 hours prior to administration of the IP. Should a subject experience a thrombotic event during the 36-hour washout period, that subject will not participate in the study.

8.1.1.2.1 Subjects on prophylactic treatment

The last prophylactic treatment including protein C ingredient must occur by at least 36 hours before the administration of the IP on Day 1. Other prophylactic treatment such as oral anticoagulants can be administered without any restrictions on period. In subjects weighing more than 15 kg, additional 4 blood samples (7.2 mL, Table 7) will be drawn at the following intervals before and after administration:

- Immediately prior to prophylactic treatment including protein C ingredient, 1, 17, and 25 hours post-treatment.

At least 36 hours after the administration of prophylactic treatment including protein C ingredient, the IP for PK will be administered. Samples (Table 7) will be drawn at the following intervals before and after administration of the IP:

- Immediately prior to infusion, 30 minutes, and 1, 2, 4, 8, 12, 24, and 36 hours postinfusion; a sampling for the 36 hours postinfusion is allowed to be customized by age, especially for feasibility in children.

In order not to induce potential thrombotic events, those subjects who currently receive daily protein C replacement will not have blood drawn at the 36-hour time point.

After completing the PK blood collection, the subjects will be returned to their previously established prophylactic regimen.

8.1.1.2.2 Subjects on study treatment

The IP dose for PK will be administered and samples will be drawn at the following intervals before and after administration of the IP (Table 7):

- Immediately prior to infusion, 30 minutes, and 1, 2, 4, 8, 12, 24, and 36 hours postinfusion; a sampling for the 36 hours postinfusion is allowed to be customized by age, especially for feasibility in children.

8.1.1.3 Follow-up Period (Day 7)

The follow-up from IP administration in this protocol is for 7 days. If a subject is early terminated, regardless of the reason, the evaluations listed for the Day 7 visit will be performed as completely as possible.

At the end of this period there will be a follow-up visit to query for SAEs, AEs, concomitant treatments and clinical laboratory evaluations. AEs that are considered a causal relationship with IP and not resolved at the time of this contact will be followed to closure (see [redacted]).

8.1.2 Extension Part

8.1.2.1 Pre-dose/Pre-surgery

Based on investigator's careful evaluation on subject's medical condition, subject who completed PK part can continue the administration of TAK-662 until the commercial protein C concentrate is available at each study site or study termination. Prior to initiation of any study procedures, the informed consent (and assent where applicable) to participate in the extension part of the study must be obtained from a subject, or the subject's parent or legally authorized representative if the subject is <20 years of age or informed consent cannot be obtained from the subject. The nature and purpose of the study will be explained and the known adverse experiences with TAK-662 will be described to the subject or to the subject's parent or legally authorized representative. If the subject agrees to participate, or the subject's parent(s) or legally authorized representative agrees to permit participation in the study, they will be required to sign and date the consent form (and assent where applicable).

In the case a subject transfers from one treatment option to the other after entering the extension part (eg, If a subject who enrolled in long-term prophylaxis requires a surgery, he/she transfers to short-term prophylaxis. Once anticoagulation is initiated and the investigator determines that adequate anticoagulation is achieved, he/she will transfer back to long-term prophylaxis.), an additional informed consent (and assent where applicable) is unnecessary to be obtained.

At the pre-dose/pre-surgery visit, the information/data of the subject shown in Table 2, Table 3, Table 4, or Table 5 will be collected by interview and appropriate tests, including but not limited to below:

- Eligibility check (except for the second and subsequent acute episode of on-demand treatment)
- Physical exam (for short-term prophylaxis only)
- Diagnosis of acute episode (PF, CISN/WISN, and thrombotic event) (for on-demand treatment only)
- Concomitant medications
- Hematology (except for the second and subsequent acute episode of on-demand treatment)
- Protein C activity (for the first acute episode of on-demand treatment and short-term prophylaxis only. It is allowed to skip protein C activity at the discretion of the investigator.)
- Vital signs (for the first acute episode of on-demand treatment and short-term prophylaxis only)

On-demand treatment includes 2 patterns of procedures. One is procedures at the occurrence of the first acute episode. The assessment/procedure are shown in Table 2. The other is procedures at the occurrence of the second and subsequent acute episode which occurred after the end of treatment for the first episode. In the case of the second and subsequent acute episode, if a subject, a parent or legally authorized representative wants to have the first infusion of TAK-662 at home and is well trained, procedures and assessments shown in Table 3 will be performed. However, if the subject will have the first infusion at a site for the second and subsequent acute episode, procedures and assessments shown in Table 2 will be performed.

8.1.2.2 Treatment Period

8.1.2.2.1 On-Demand Treatment (Day E1, On and After Day E2)

Upon presentation with an acute event, the subject will be initially infused with TAK-662 at Day E1. The infusions will be continued until resolution of all non-necrotic lesions and/or stabilization of thrombi. Refer to Section 6.2.2 for dose and administration of TAK-662.

At the treatment period, the information/data of the subject shown in Table 2 (the first acute episode) and Table 3 (the second and subsequent acute episodes) will be collected by interview and appropriate tests, including but not limited to below:

- Concomitant medications
- Lesion Assessment / Photography*
- Protein C activity (6 and 12 hours after the first dose of IP at Day E1, every 6 or 12 hours on and after Day E2, and at the end of treatment. It is allowed to skip protein C activity at the discretion of the investigator.)
- Subject Diaries (if applicable)
- AE assessment

*: Lesion assessment will be performed by the investigators at each point before administrating of IP. Images of the lesion site will be taken before the first infusion on Day E1 (at the occurrence of the first acute episodes)/pre-dose (at the occurrence of the second and subsequent acute episodes) and at the end of treatment when investigators determine that the acute episode have recovered or tend to improve. Image of the lesion site can be taken between the 2 points if applicable. In principle, it is carried out in the hospital, but the subject can return home after infusion if the investigator allows it. In this case, subject may take a picture of the lesion site at home and send it to the investigator so that the investigator will perform lesion assessment (refer to the manual for data handling of imaging data). If a next infusion is required based on the investigator's decision, the subject will have to visit the site.

8.1.2.2.2 Short-Term Prophylaxis (Day E1, Day E2, On and After Day E3)

Specific treatment regimens will apply for short-term prophylaxis of acute thrombotic episodes during surgery. Subjects with elective surgery (non-emergency) and emergency surgery will be initially infused with TAK-662 at pre-surgery. The infusions will be continued until anticoagulation is initiated (if applicable) and the investigator determines that adequate level of anticoagulation is achieved. The items, contents, frequency of anticoagulation assessments will be determined by investigators. Refer to Section 6.2.2 for dose and administration of TAK-662.

At the treatment period, the information/data of the subject shown in Table 4 will be collected by interview and appropriate tests, including but not limited to below:

- Concomitant medications

- Protein C Activity (It is allowed to skip protein C activity at the discretion of the investigator.)
- Vital signs (Day E2 only)
- AE assessment

8.1.2.2.3 Long-Term Prophylaxis (First 3 Prophylaxis Infusions, Following of First 3 Prophylaxis Infusions, Every 1 Month)

Subjects with long-term prophylaxis will be infused according to the schedule (Table 5) and the infusions will be continued until TAK-662 became available at the site. Refer to Section 6.2.2 for dose and administration of TAK-662.

At the treatment period, the information/data of the subject shown in Table 5 will be collected by interview and appropriate tests, including but not limited to below:

- Concomitant medications
- Hematology (every 1 month only. It is allowed to skip this measurement at the discretion of the investigator)
- Protein C Activity (following of the first 3 prophylaxis infusions and every 1 month only. It is allowed to skip protein C activity every 1 month at the discretion of the investigator)
- Subject Diaries (during home treatment times)
- AE assessment

8.1.2.3 End of Treatment (On-Demand Treatment and Short-Term Prophylaxis)

8.1.2.3.1 On-Demand Treatment

The treatment can be ended when the investigators determine that the acute episode have recovered or tend to improve (e.g. purpura area reduction or fading).

At the end of treatment visit, the information/data of the subject shown in Table 2 (the first episode) and Table 3 (the second and subsequent acute episodes) will be collected by interview and appropriate tests, including but not limited to below. However, if the investigator determines the recovery or improvement of the acute episode by assessing the picture of the lesion site, which is taken by the subject at home after the first infusion for the second and subsequent acute episode and is sent to the investigator, the timing of this investigator's decision is considered as the end of treatment. In this case, the subject will not have to visit the site, and obtainable information/data below will be collected.

- Concomitant medications
- Lesion Assessment/Photography*
- Protein C activity (It is allowed to skip protein C activity at the discretion of the investigator.)
- AE assessment

*: It is allowed for him/her to take a picture of lesion site.

8.1.2.3.2 Short-Term Prophylaxis

Treatment will can be ended when anticoagulation is initiated (if applicable) and the investigator determines that adequate level of anticoagulation is achieved.

At the end of treatment visit, the information/data of the subject shown in Table 4 will be collected by interview and appropriate tests, including but not limited to below:

- Physical exam
- Concomitant medications
- Hematology
- Protein C activity (It is allowed to skip protein C activity at the discretion of the investigator.)
- Vital signs
- AE assessment

8.1.2.4 End of Study/Follow-up (Long-Term prophylaxis)

Long-term prophylaxis will be ended when TAK-662 becomes available at the site. The subjects with long-term prophylaxis will be followed up for 7 days after the last dose of TAK-662.

At the end of study/follow-up visit, the information/data of the subject shown in Table 5 will be collected by interview and appropriate tests, including but not limited to below:

- Concomitant medications
- AE assessment (AEs that are considered a causal relationship with IP and not resolved at the time of this contact will be followed to closure. Refer to [redacted])

8.1.2.5 Follow-up (On-Demand Treatment and Short-Term Prophylaxis)

8.1.2.5.1 On-Demand Treatment

The subjects with on-demand treatment will be followed up for 7 days after the last dose of TAK-662.

At the follow-up visit, the information/data of the subject shown in Table 2 (the first acute episode) and Table 3 (the second and subsequent acute episodes) will be collected by interview and appropriate tests, including but not limited to below:

- Concomitant medications
- Hematology
- Vital signs
- AE assessment (AEs that are considered a causal relationship with IP and not resolved at the time of this contact will be followed to closure. Refer to [redacted])

8.1.2.5.2 Short-Term Prophylaxis

The subjects with short-term prophylaxis will be followed up for 7 days after last dose of TAK-662.

At the follow-up visit, the information/data of the subject shown in Table 4 will be collected by interview and appropriate tests, including but not limited to below:

- Concomitant medications
- AE assessment (AEs that are considered a causal relationship with IP and not resolved at the time of this contact will be followed to closure. Refer to [redacted])

8.2 Study Assessments

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The schedule of study procedures is located in Table 1, Table 2, Table 3, Table 4, and Table 5. All procedures must be performed by qualified and trained staff.

8.2.1 Demographic and Other Baseline Characteristics

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

8.2.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents. Body mass index (BMI) will be calculated by the Sponsor.

8.2.1.2 Medical and Medication History

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

8.2.1.3 Diagnosis of Acute Episode (PF, CISN/WISN, and Thrombotic Event) (On-Demand Treatment only)

Diagnosis of acute episode (PF, CISN/WISN, and thrombotic event) will be collected and recorded in the subject's source documents.

8.2.2 Efficacy

In the PK part, no efficacy of TAK-662 will be evaluated.

In the extension part, the efficacy assessments will be performed. For on-demand therapy, the treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events will be rated as *effective*, *effective with complications*, or *not effective* when it is determinate that the next infusion is unnecessary according to the efficacy rating scale. The procedures for lesion assessment / photography of on-demand treatment differs depending on the first acute episodes or the second and subsequent acute episodes. Refer to Section 8.1.2.2.1 for details.

For short-term prophylaxis, PF and/or thromboembolic complications during short-term prophylaxis, for which TAK-662 is utilized as short-term prophylaxis, will be recorded.

For long-term prophylaxis, the number of episodes of PF and/or thrombotic episodes while receiving long-term prophylaxis will be recorded.

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 cardiovascular, respiratory, gastrointestinal, and neurological systems.

Abnormalities identified at the Screening visit and at subsequent study visits will be recorded in the subject's source documents.

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. Refer to [redacted] for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.3.3 Vital Signs

PK part:

Vital signs (pulse rate, respiration rate, blood pressure, and temperature) will be assessed prior to and 1 hour after administration of the prophylactic treatment including protein C ingredient (in subjects participating in the pre-pharmacokinetic wash-out segment) and prior to and 30 minutes, 2 hours, 4 hours, and 24 hours after administration of the IP for PK. Measurement of vital signs is always performed prior to drawing the blood samples for PK.

The investigator will assess whether a change from baseline (Day −1) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

Extension part:

For on-demand treatment, vital signs will be measured at pre-dose (the first acute episode only) and follow-up. For short-term prophylaxis, vital signs will be measured at pre-surgery, Day E2, and the end of treatment.

8.2.3.4 Clinical Laboratory Tests

All clinical laboratory tests will be performed by a central laboratory at the time points, including baseline, specified in Table 1, Table 2, Table 3, Table 4, and Table 5. Reference ranges will be supplied by the central laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

A complete list of the clinical laboratory tests to be performed is provided in [redacted] Volume of blood samples for clinical laboratory tests is shown in Table 7 to Table 11.

8.2.3.5 Pregnancy Test

A serum β-hCG pregnancy test and follicle-stimulating hormone (FSH) test will be performed on all females of child-bearing potential at the Screening visit of PK part. A urine pregnancy test will be performed at pre-dose/pre-surgery of extension part.

8.2.3.6 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be evaluated at the Screening visit to assess the eligibility of the subject by the investigator (PK part only).

8.2.4 Other

8.2.4.1 Pharmacokinetics

8.2.4.1.1 Collection of Samples

Blood samples for the determination of the TAK-662 will be collected as detailed under schedule of assessments (Table 1 and Section 8.1.1.2).

Venous blood samples of approximately 1.8 mL will be collected for measurement of Protein C activity at times as specified in Table 1. Instructions for the collection and handling of biological samples will be provided by the Sponsor or designee. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood sample will be collected at each PK time point. The actual date and time (24-hour clock time) of each sample and the time and date of IP infusion start and stop, as well as start/stop of any infusion interruptions and restart of infusion will be recorded. Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

8.2.4.1.2 Determination of Drug Concentration

- Samples for the determination of protein C activity will be analyzed on behalf of the Sponsor using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.
- All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.
- Samples collected for analyses of protein C activity may also be used to evaluate safety aspects related to concerns arising during or after the study.

8.2.4.2 Pharmacodynamics

Not applicable.

8.2.4.3 Genetics

Not applicable.

8.2.4.4 Health-related Quality of Life (QoL)

Not applicable.

8.2.4.5 Healthcare Resource Utilization

Not applicable.

8.2.5 Volume of Blood to Be Drawn from Each Subject

PK part:

During the PK part of this study, it is expected that approximately 31 mL of blood will be drawn from all subjects (Table 7).

Table 7. Approximate Blood Volume (PK part)

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
		Screening	Day 1 [a]	Day 2 [a]	Day 3 [a]	Day 7	
Clinical laboratory tests	2 mL	1 (8 mL) [b]	1	1	0	1	14
PK blood collection	1.8 mL	0 [c]	9 [d]			0	16.2
		Total Approximate Blood Sampling Volume					30.2

[a] Depending on the start time of administration on Day 1, it is allowed to draw 36-hour blood sample on Day 3.
[b] Sample volume at screening is 8 mL including samples for pregnancy test and alanine aminotransferase measurement.
[c] Subjects receiving prophylaxis treatment including protein C ingredient should take an additional 4 blood draws (7.2 mL) at the final pre-trial administration: immediately prior to the prophylactic treatment, 1, 17, and 25 hours post-treatment. After completing the pharmacokinetic blood collection, the subjects will be returned to their previously established prophylactic regimen.
[d] PK samples will be collected at pre-dose and at 0.5 hours, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours (Day 2), and 36 hours (Day 3 a) after finishing administration of the test dose of the investigational product; a sampling for the 36 hours postinfusion is allowed to be customized by age, especially for feasibility in children.

Note: 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; however, the total volume drawn over the course of the study should be approximately 31 mL.

Extension part:

During the extension part of this study, total volume will be determined depending on which study part to be enrolled. The number of samples will be drawn at each time point in Table 8, Table 9, Table 10, and Table 11.

Table 8. Approximate Blood Volume (Extension Part: On-Demand Treatment): First Acute Episode

Sample Type	Sample Volume (mL)	Number of Samples				Total Volume (mL)
		Pre-dose	On and After Day E1	At the end of treatment	Follow-up (7 days after the termination of IP dose)	
Hematology	2 mL	1	0	0	1	4
Protein C activity	1.8 mL	Protein C activity measurement may be performed at the discretion of the investigator. If protein C activity will be measured, the time point of measurement is also at the discretion of the investigator.			0	-

Table 9. Approximate Blood Volume (Extension Part: On-Demand Treatment); Second and Subsequent Acute Episodes

Sample Type	Sample Volume (mL)	Number of Samples				Total Volume (mL)
		Pre-dose	On and After Day E1	At the end of treatment	Follow-up (7 days after the termination of IP dose)	
Hematology	2 mL	0	0	0	1	2
Protein C activity	1.8 mL	0	Protein C activity measurement may be performed at the discretion of the investigator. If protein C activity will be measured, the time point of measurement is also at the discretion of the investigator.		0	-

Table 10. Approximate Blood Volume (Extension Part: Short-Term Prophylaxis)

Sample Type	Sample Volume (mL)	Number of Samples			Total Volume (mL)
		Pre-surgery	On and After Day E1	At the end of treatment	
Hematology	2 mL	1 [a]	0	1	4
Protein C activity	1.8 mL	Protein C activity measurement may be performed at the discretion of the investigator. If protein C activity will be measured, the time point of measurement is also at the discretion of the investigator.			-

[a] Baseline hematologic test will have to be performed within 7 days prior to first dose.

Table 11. Approximate Blood Volume (Extension Part: Long-Term Prophylaxis)

Sample Type	Sample Volume (mL)	Number of Samples			
		Pre-dose	1st 3 prophy. infusions	Following of 1st 3 prophy. infusions	Every 1 M ±2 wks
Hematology	2 mL	1 [a]	0		1 [b]
Protein C activity	1.8 mL	0	0	1	1 [b]

[a] Hematologic tests will have to be performed within 7 days prior to first dose.

[b] Hematologic test and protein C activity every 1 month (±2 weeks) will be performed at pre-infusion, and may be skipped at the discretion of the investigator.

Note: Total volume will be determined depending on the time of termination.

Abbreviations. M=month, prophy.= prophylaxis, wks=weeks.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

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

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed. Computational details and methodology for the calculation of PK parameters for TAK-662 and other details will be described in the Clinical Pharmacology Analysis Plan (CPAP).

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 SAS® (North Carolina, US) Version 9.4 or higher.

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

Interim analyses of study data will be undertaken as described below. No adaptive design or data monitoring committee (DMC) is planned for this study. One formal interim data analyses to support the Japanese New Drug Application (JNDA) submission will be completed. It will summarize PK, safety and efficacy of treatment with TAK-662 in Japanese subjects with homozygous or double heterozygous congenital protein C deficiency. The first interim analysis will be conducted after all enrolled subjects have reached last visit of the PK part and at least 3 treatments (any of either on-demand treatment, short-term prophylaxis or long-term prophylaxis) have been provided to any subjects in the Extension part. The target data is all data obtained at this point in the PK part and Extension part. An interim clinical study report summarizing data of the first interim analysis will be prepared. The clinical data cut-off date will be stated in the SAP. As applicable, additional interim analysis will be conducted after the first interim analysis.

9.3 Sample Size and Power Considerations

The number of patients with severe congenital protein C deficiency is very low. And the target number of patients is set to 3 or more in consideration of feasibility and inclusion/exclusion criteria in this study based on the opinions of specialists in Japan.

9.4 Statistical Analysis Sets

The safety population will include all enrolled subjects in the study who take at least 1 dose of TAK-662. A subject will be considered enrolled in the study once the informed consent/assent has been obtained and the subject meets all of the study inclusion criteria. The safety population will be used for safety analyses.

The pharmacokinetic population will include all study participants who take at least 1 dose of TAK-662 and have enough number of quantifiable blood levels for TAK-662 collected post-dose without important protocol deviations/violations or events thought to substantially affect the PK. The PK population will be used for PK analyses.

The efficacy population will include all study participants who take at least 1 dose of TAK-662 in the extension part. The efficacy population will be used for efficacy analyses.

9.5 Efficacy Analyses

- On demand therapy

The treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events will be rated as "*effective*", "*effective with complications*", or "*not effective*" according to the efficacy rating scale. The rating of treatment effect will be listed and summarized using descriptive statistics.

- Short-term prophylaxis

Percentage of surgical episodes for which TAK-662 will be utilized as short-term prophylaxis, that is free of presentations of PF or thromboembolic complications will be calculated. PF or thromboembolic complications will be listed and summarized using descriptive statistics.

- Long-term prophylaxis

Number of episodes of PF and/or thrombotic episodes while receiving long-term prophylaxis and rate of episodes of PF and/or thrombotic episodes per month will be calculated. Episodes of PF and/or thrombotic episodes will be listed and summarized using descriptive statistics.

9.6 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent adverse events (TEAEs) will be calculated overall, by system organ class (SOC), by preferred term. Treatment-emergent adverse events will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests and vital signs will be summarized by visit. Potentially clinically important findings will also be summarized or listed.

9.7 Pharmacokinetic Analyses

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.3 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US). Computational details and methodology for the calculation of PK parameters for TAK-662 and other details will be described in the CPAP.

Pharmacokinetic parameters will be listed and summarized using descriptive statistics. Data will be presented graphically if appropriate.

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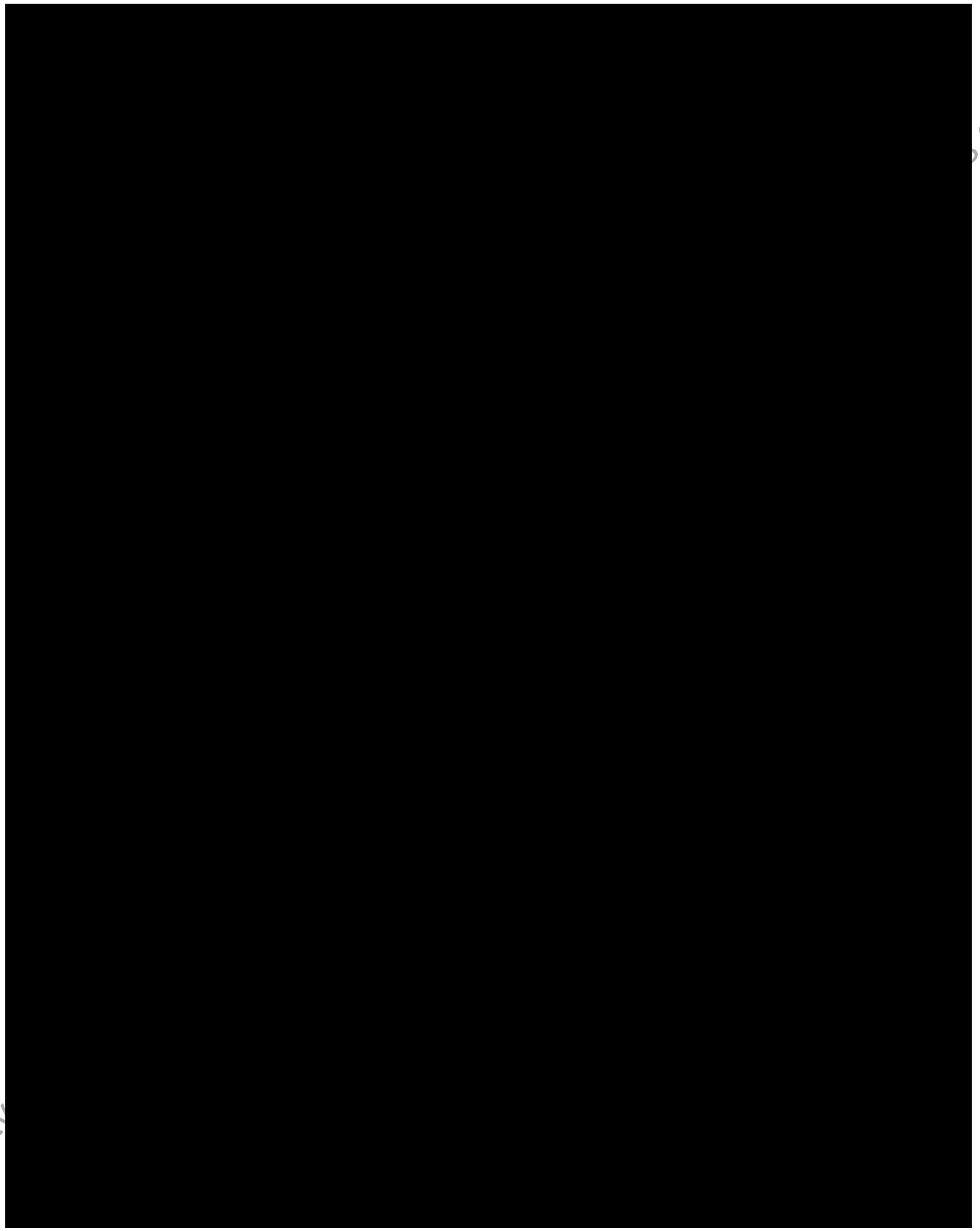

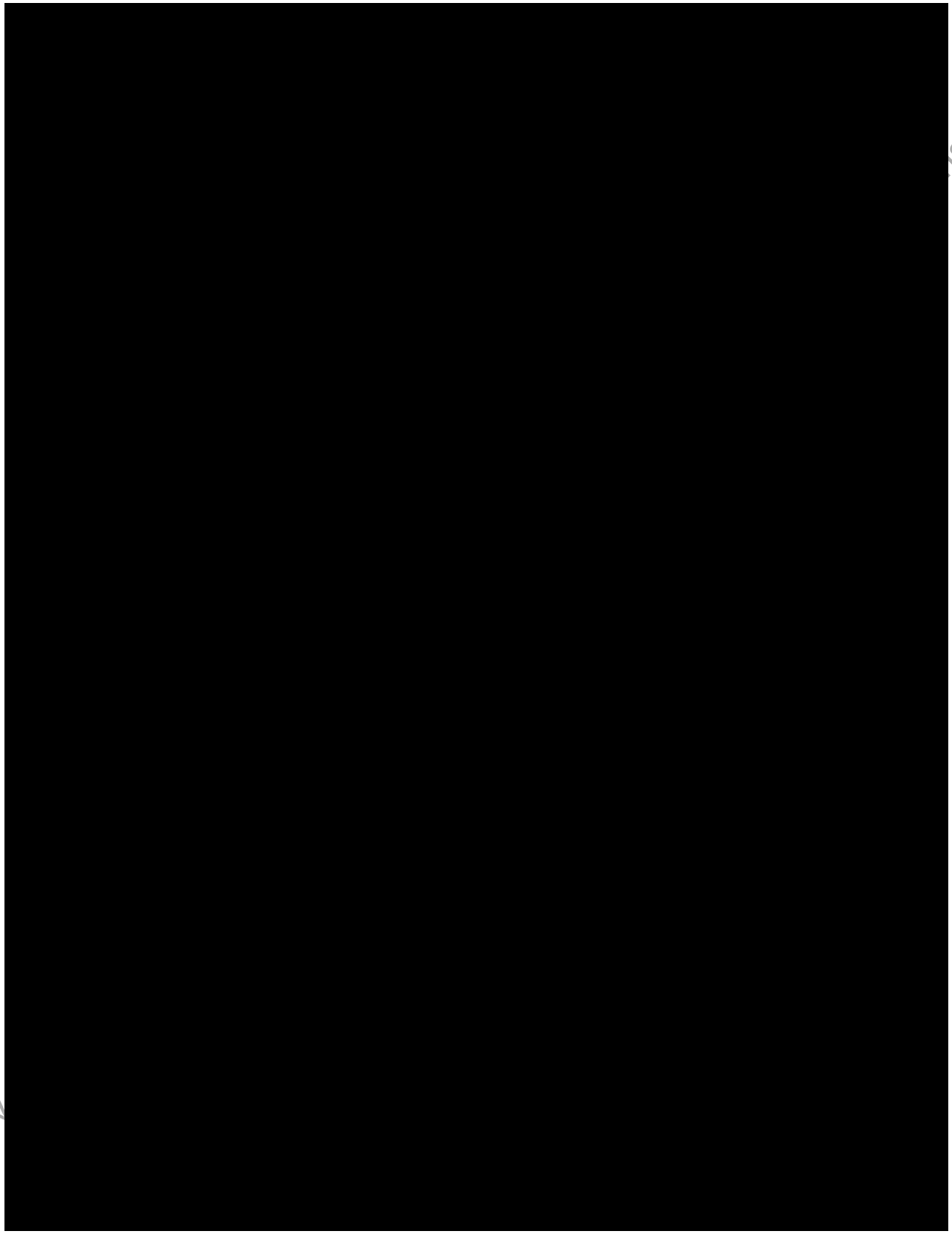

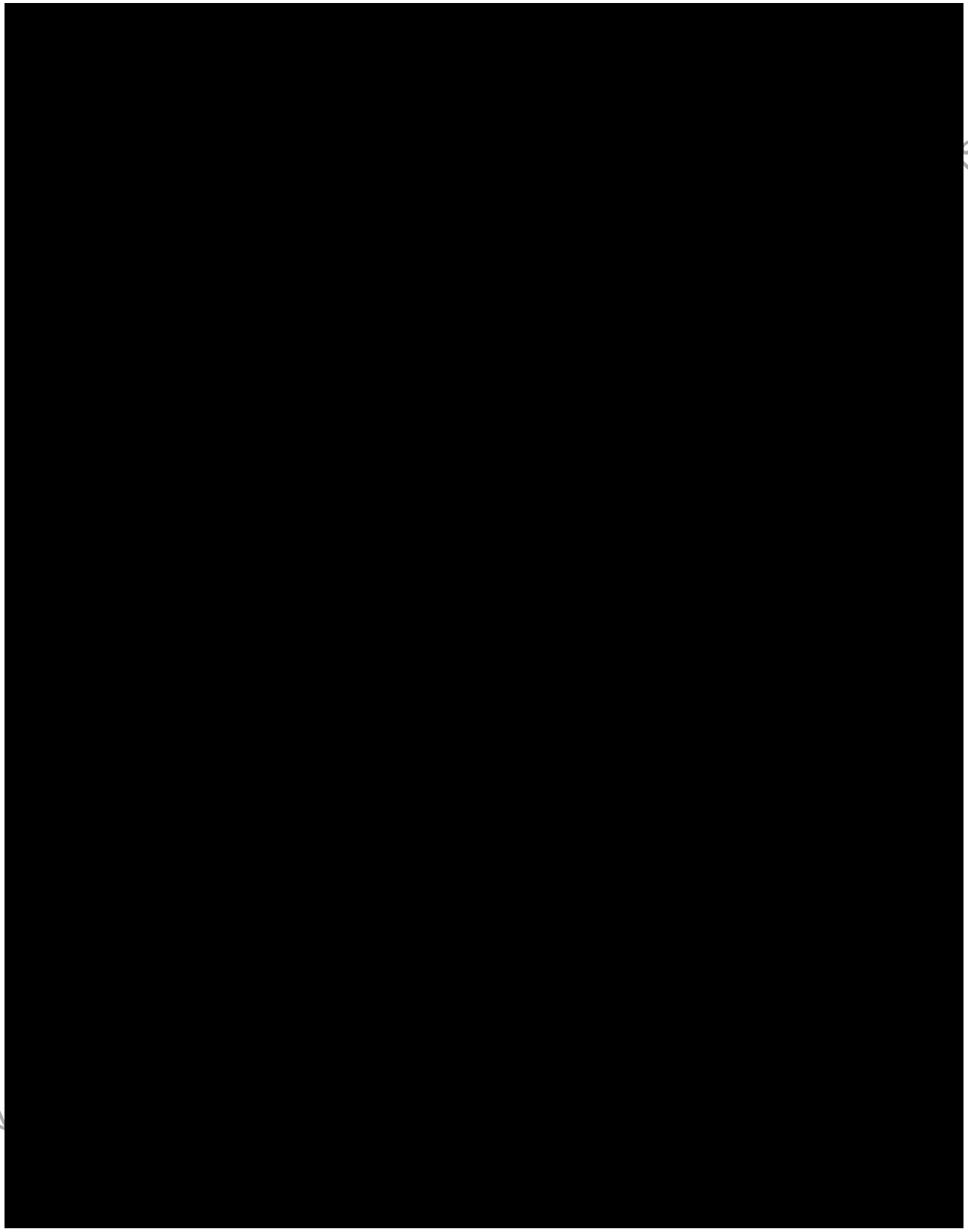

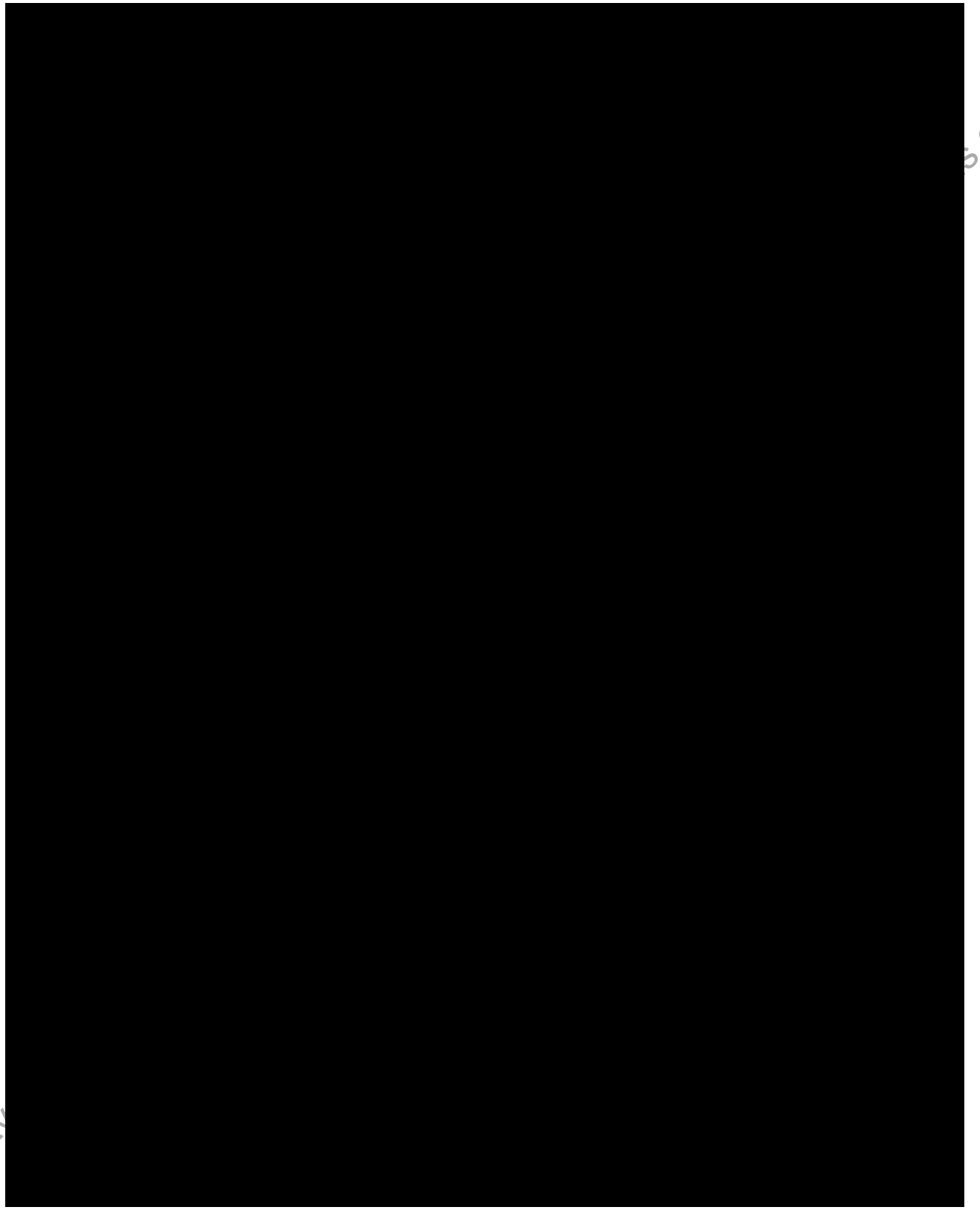

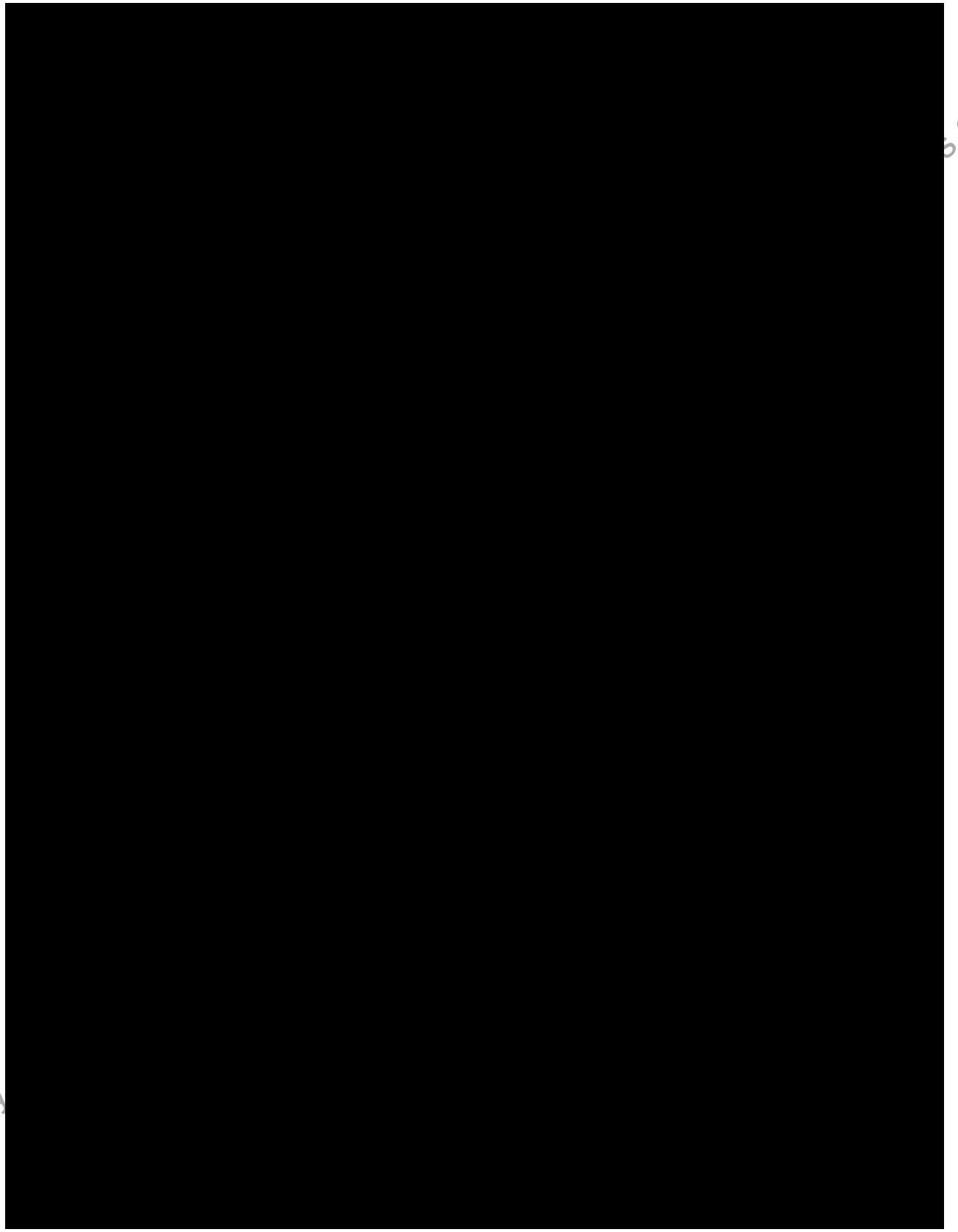

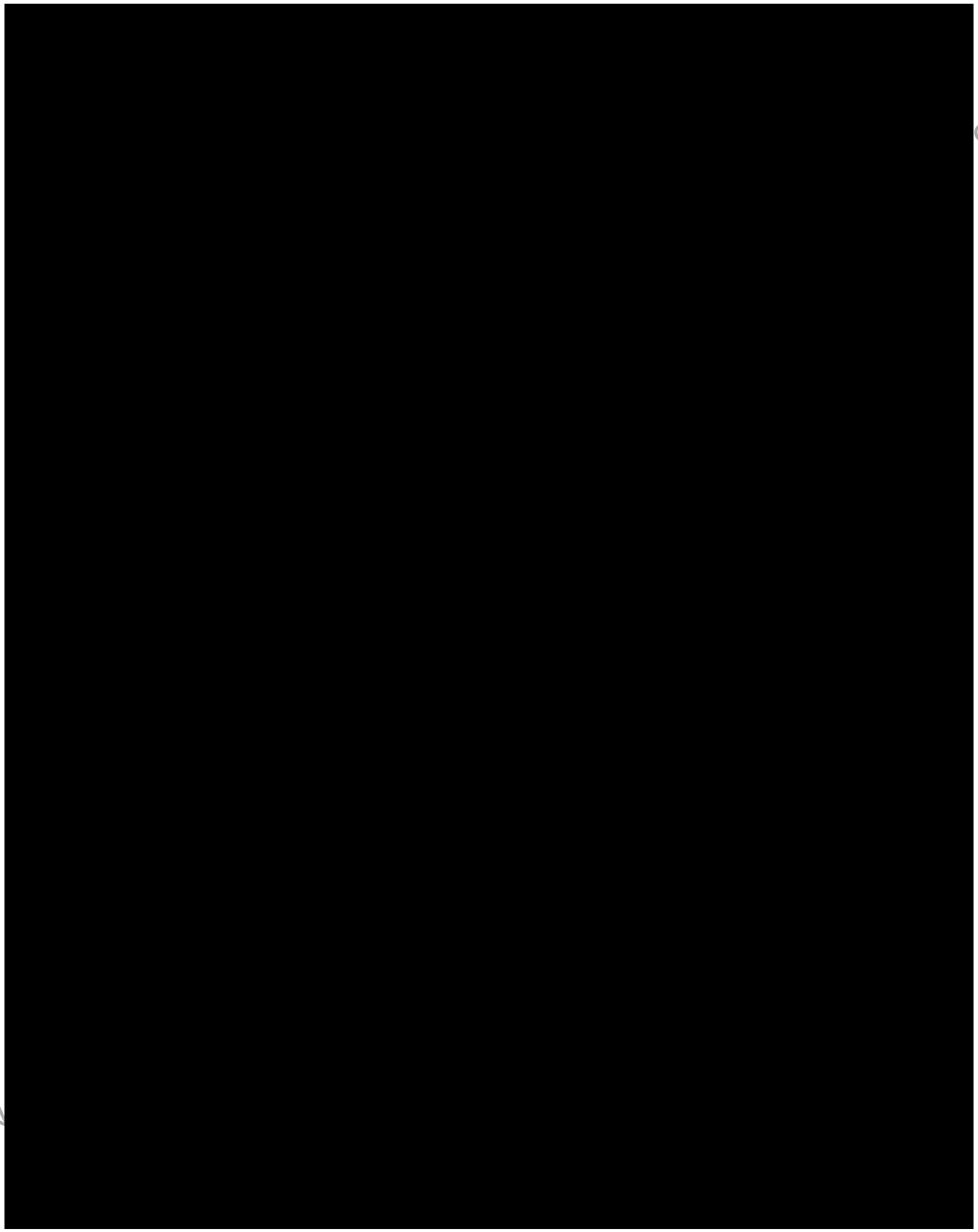

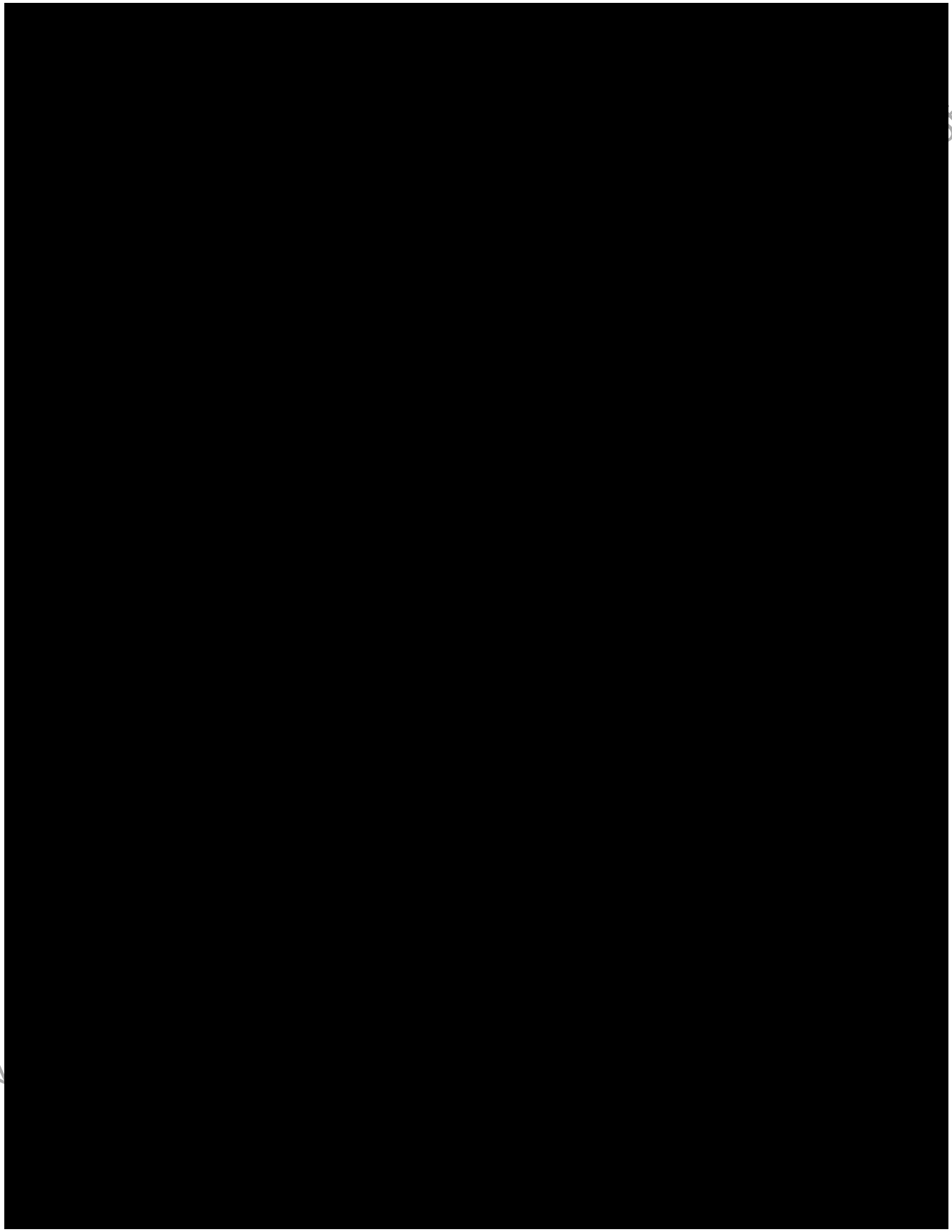

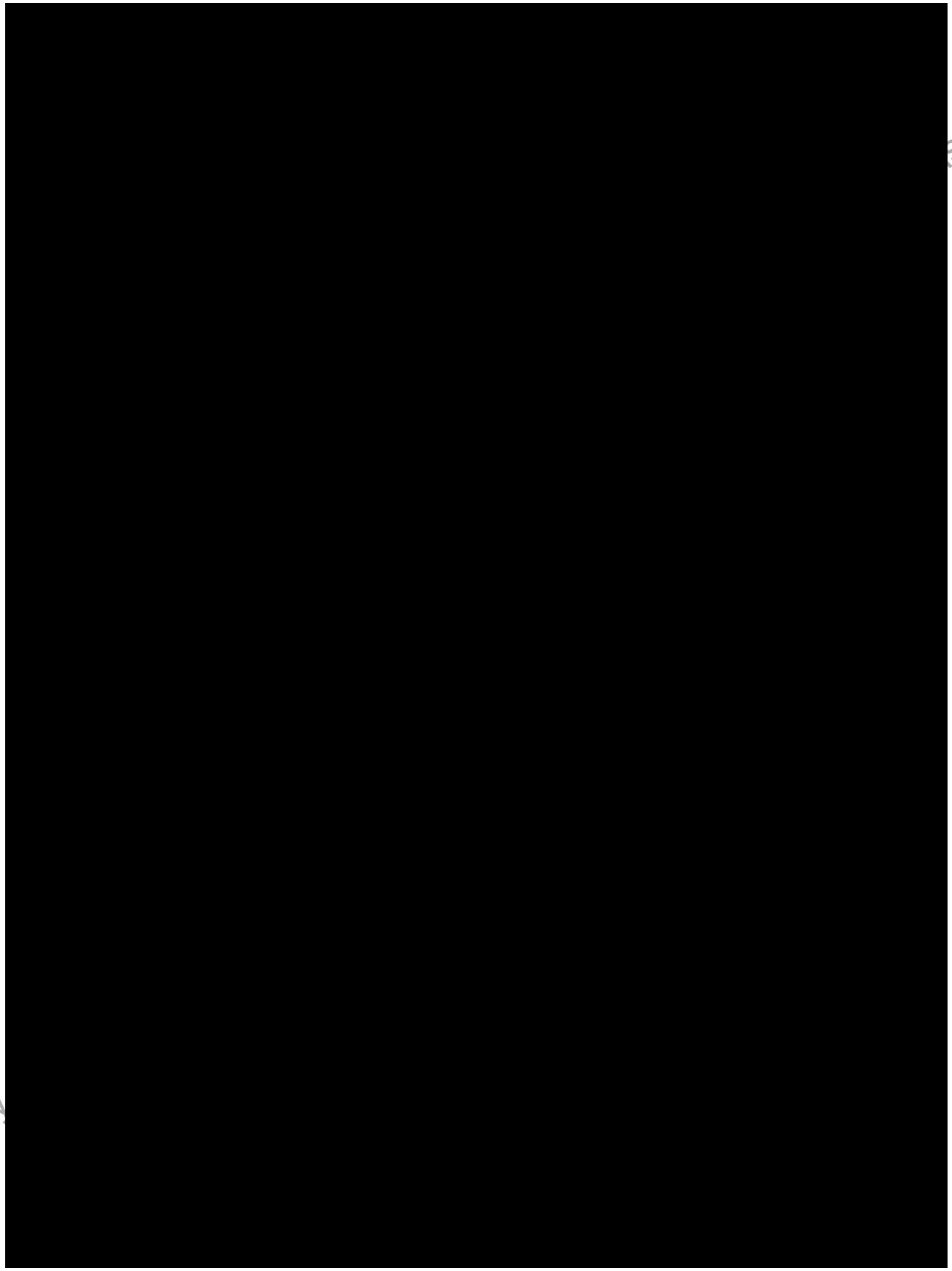

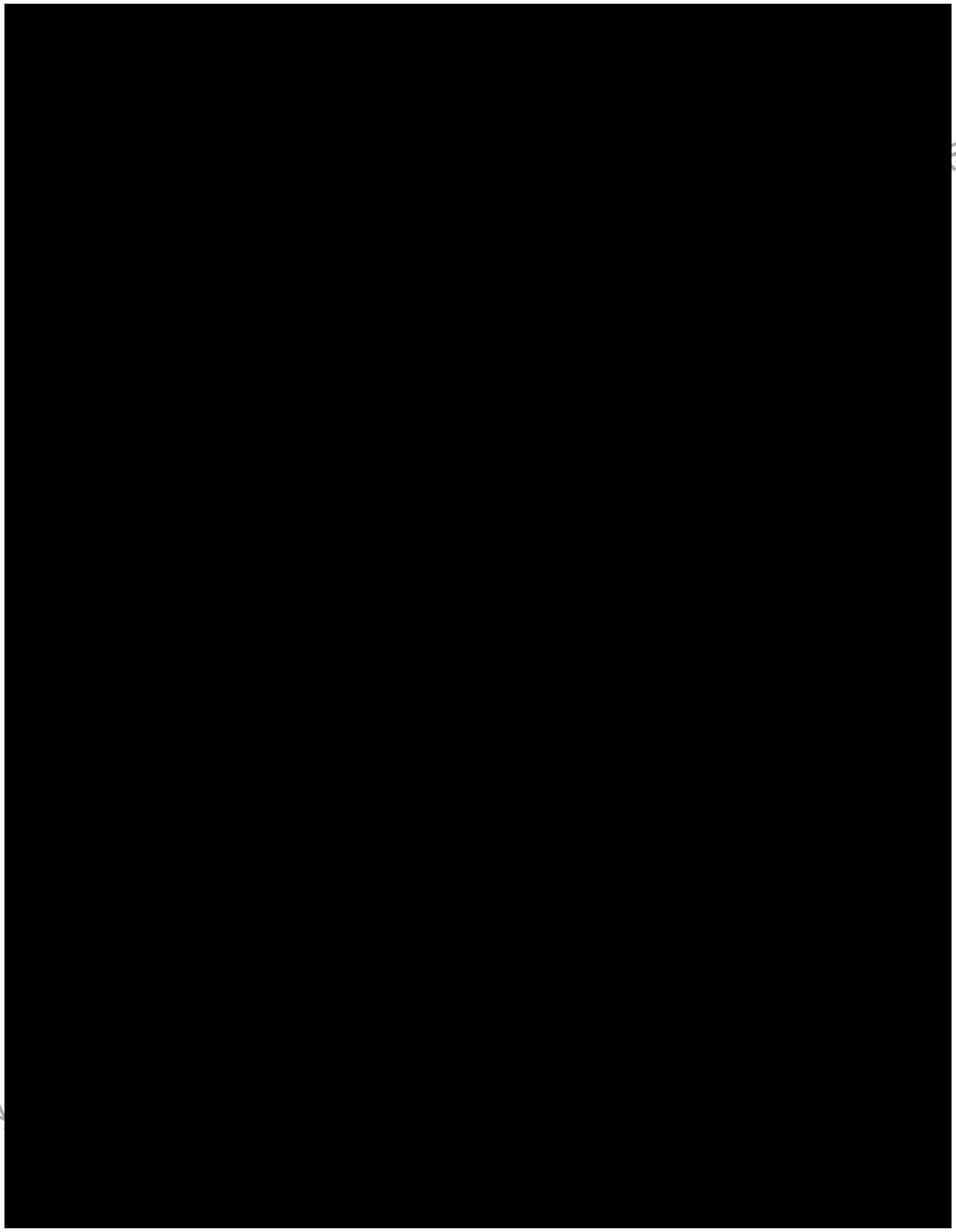

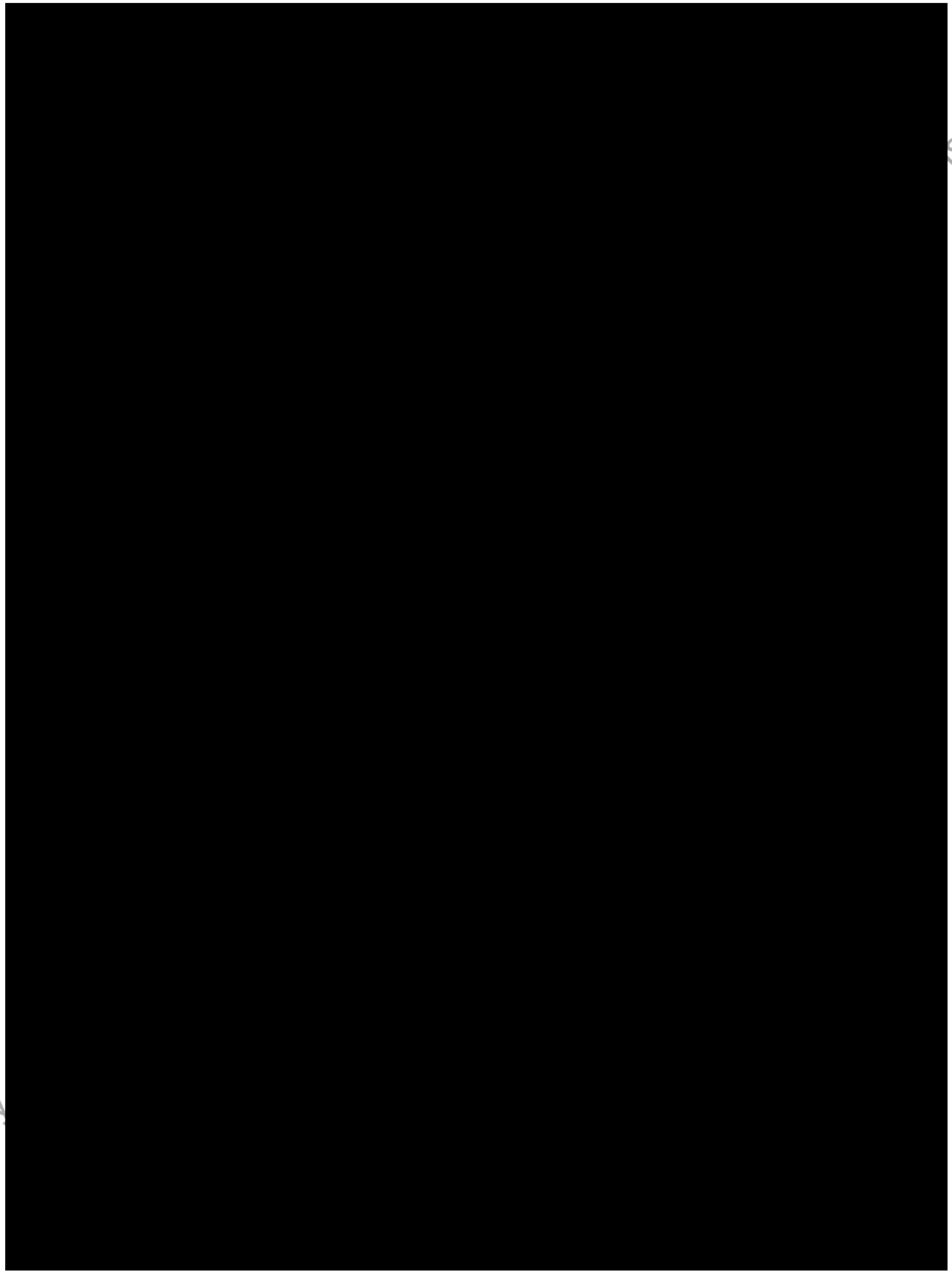

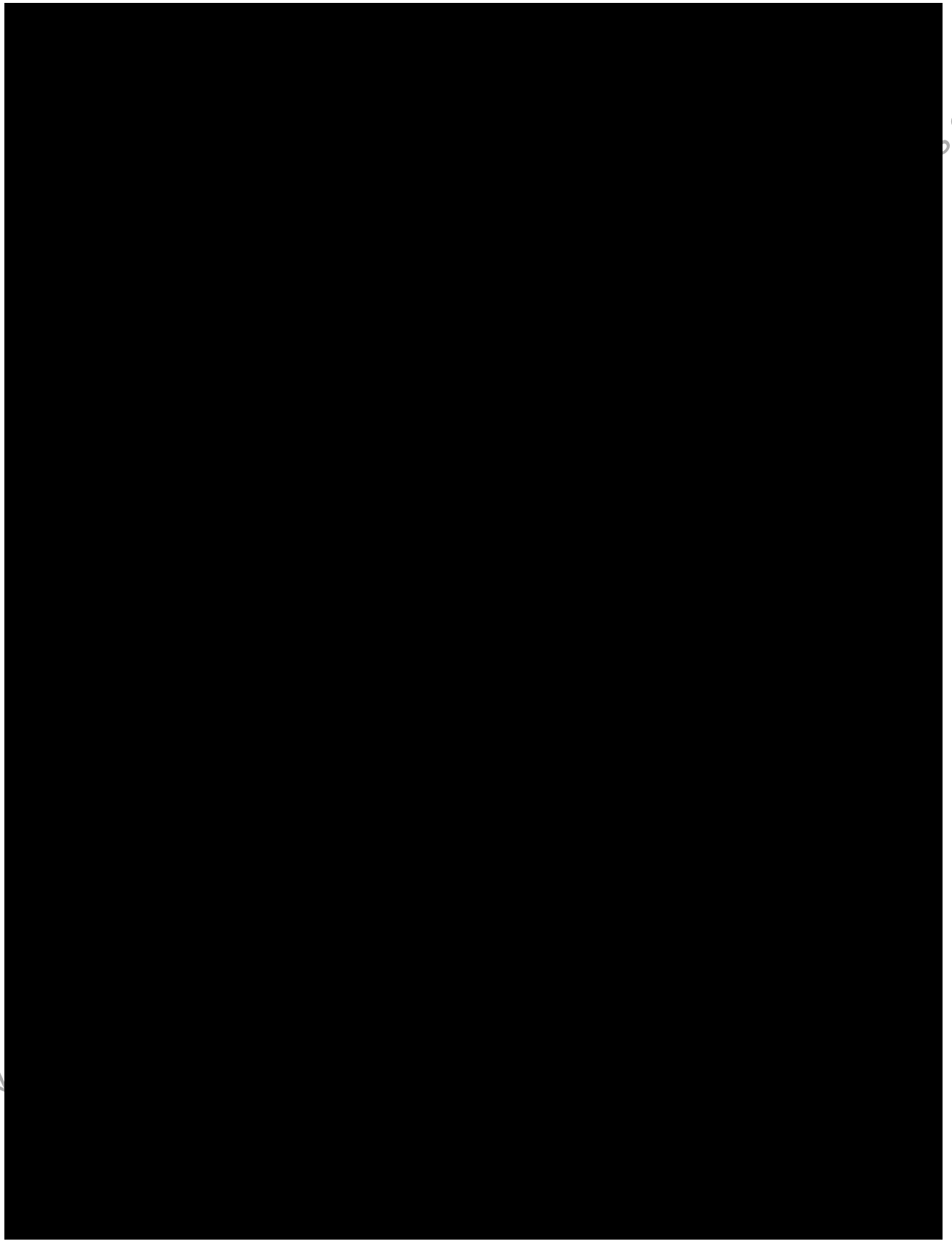

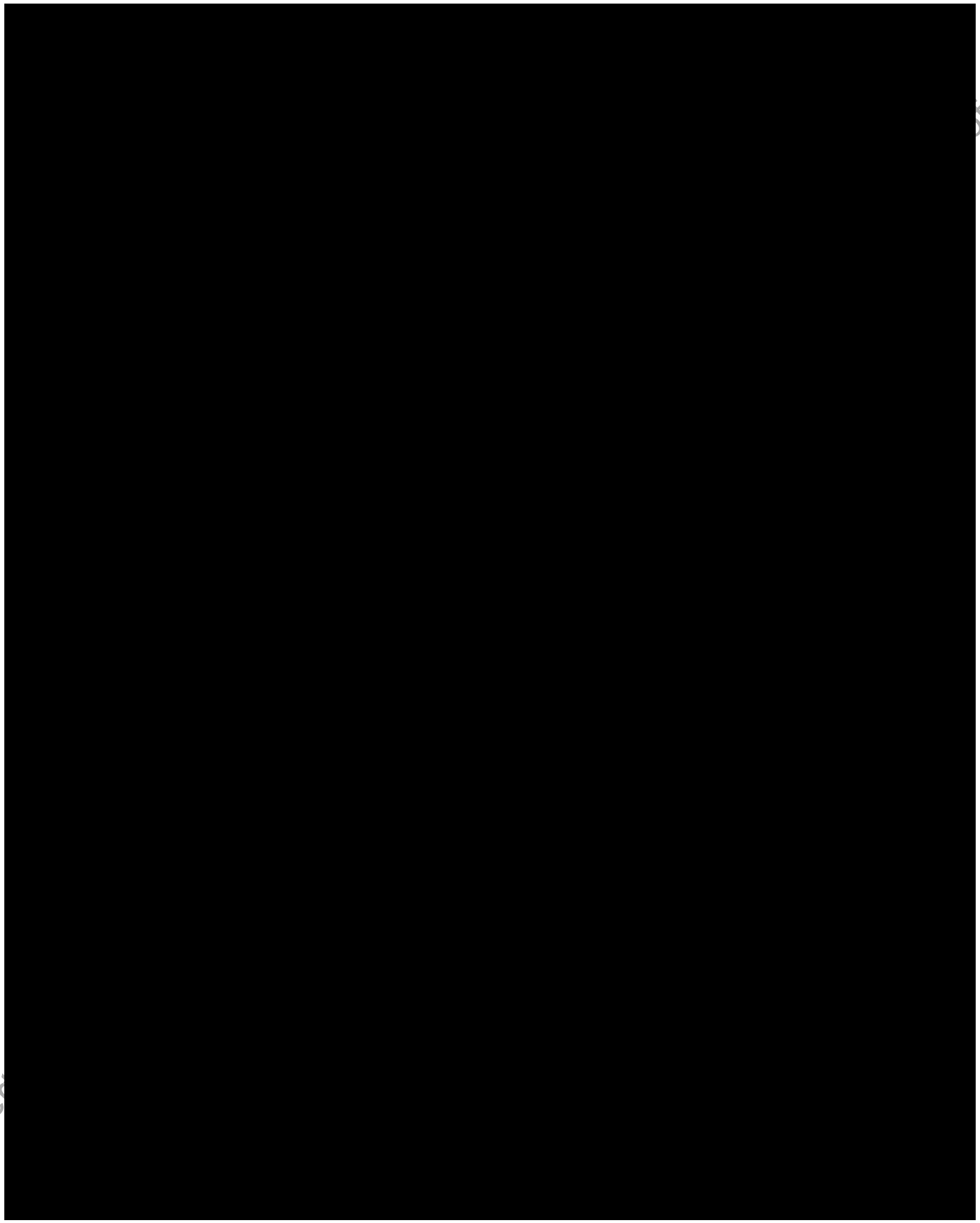

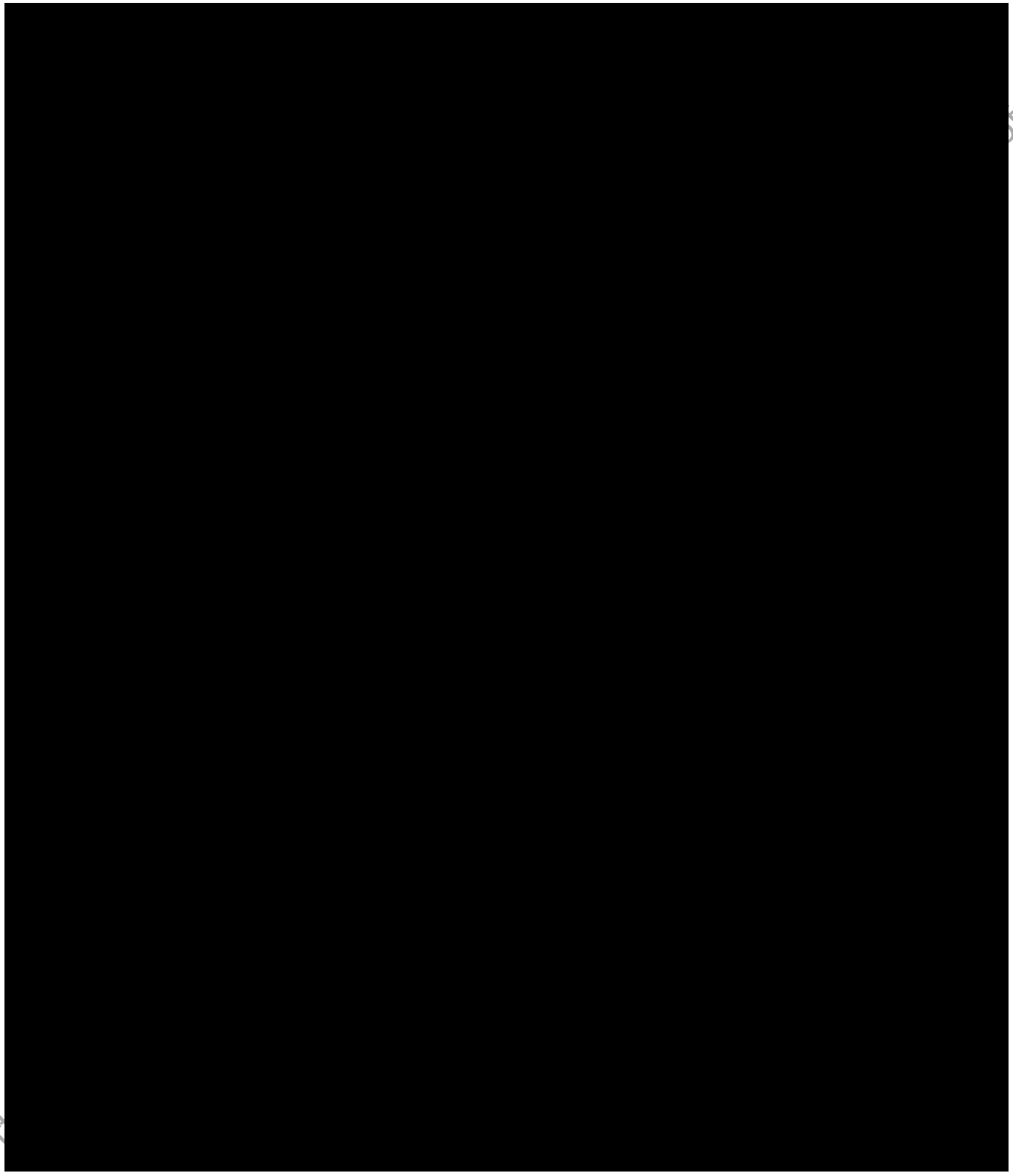

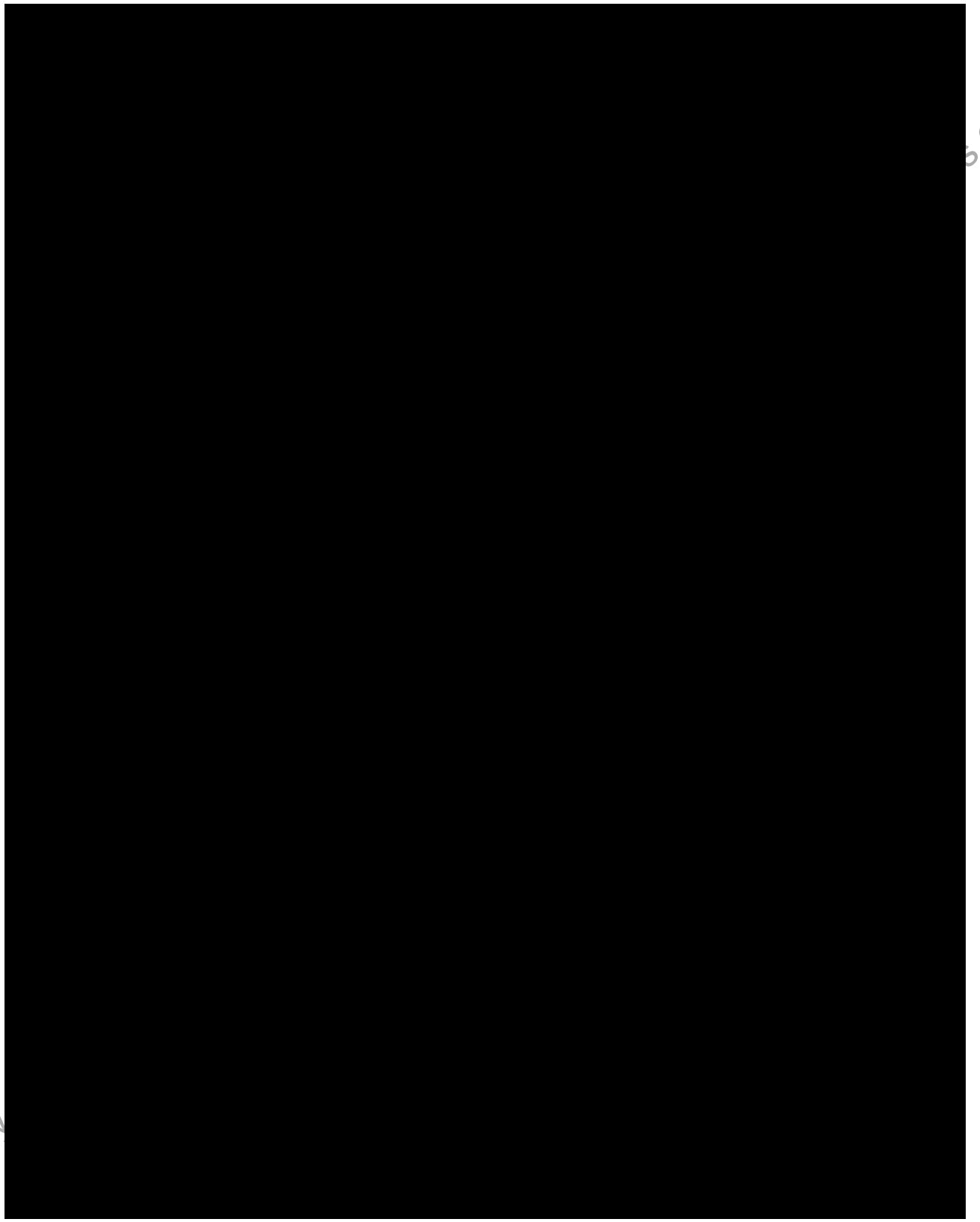

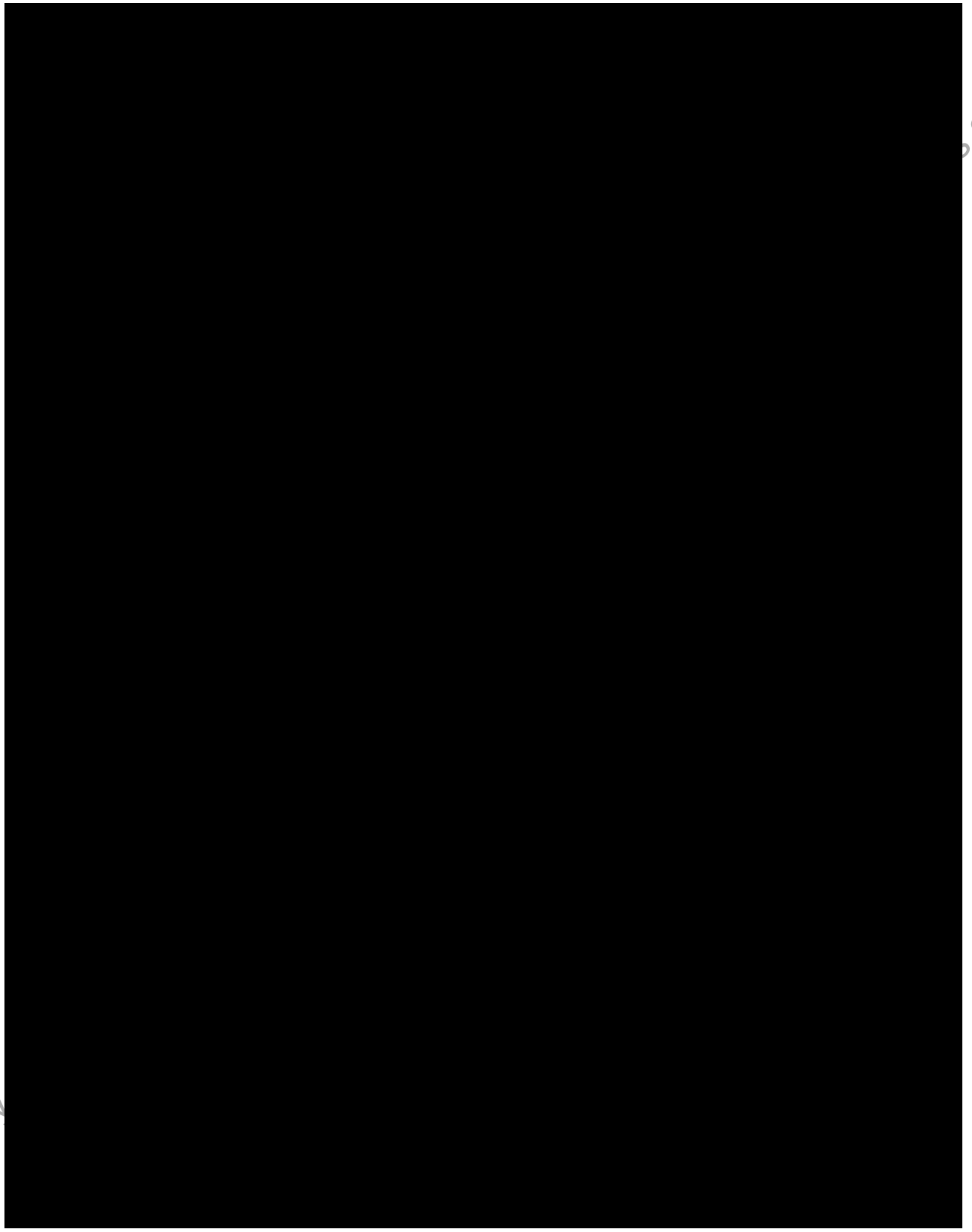

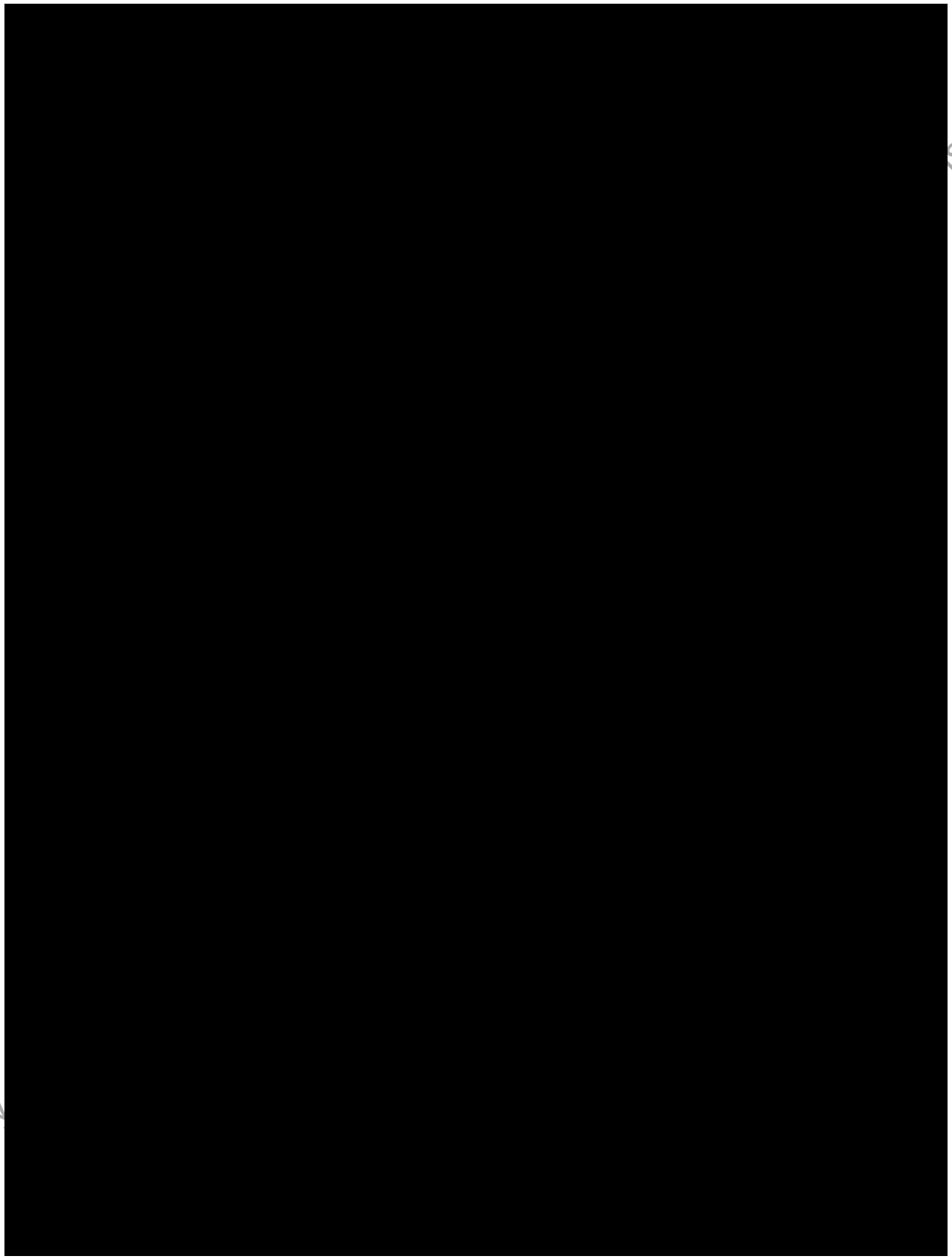

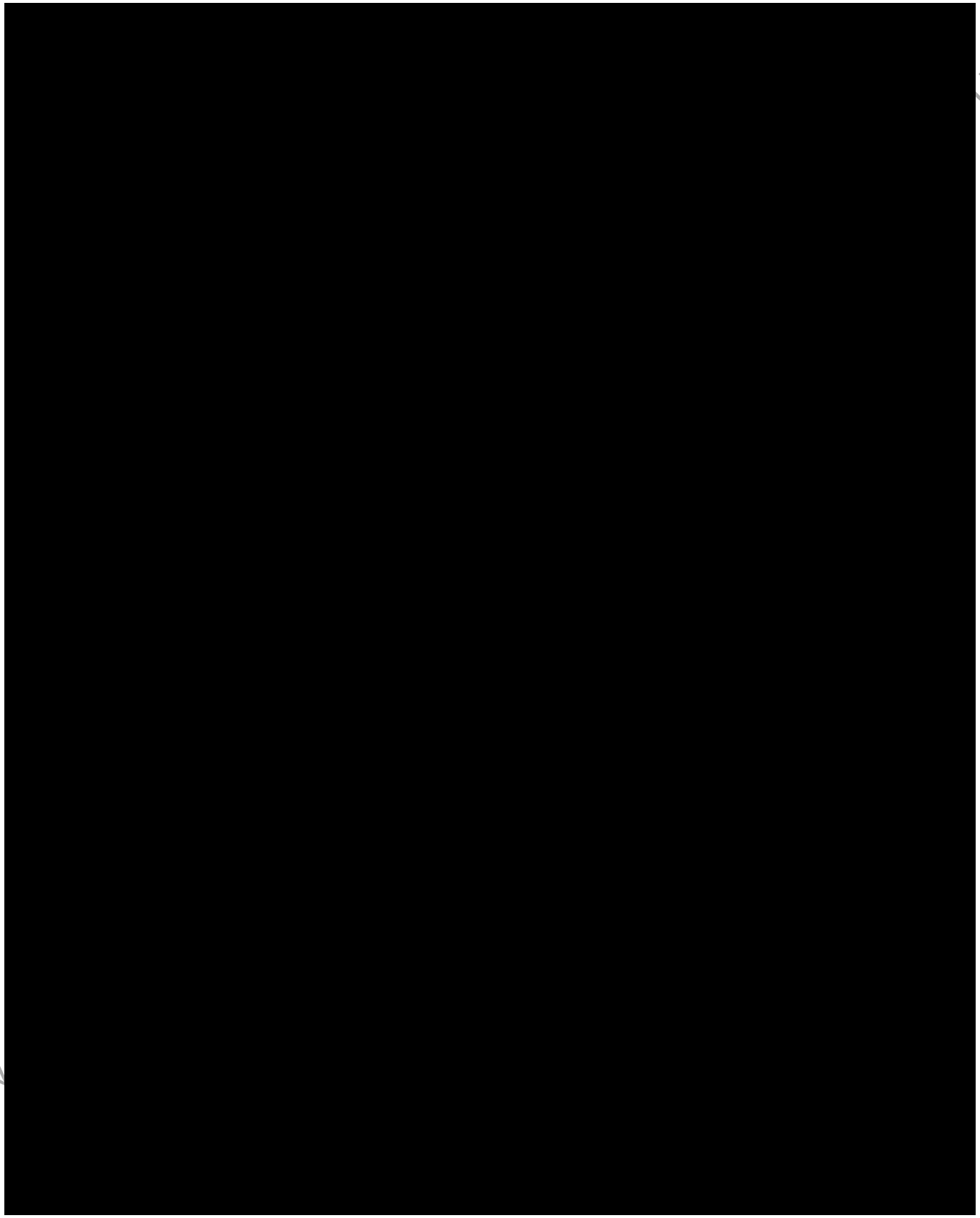

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