Clinical Study Protocol

NCT Number: NCT04687137

Title: Open-arm, Japan Expanded Access Program with Lanadelumab (TAK-743) for Japanese Patients with Hereditary Angioedema

Study Number: TAK-743-5007

Document Version and Date: Amendment 01 / 09-Feb-2021

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

TAKEDA PHARMACEUTICALS

PROTOCOL

Title

Open-arm, Japan Expanded Access Program with Lanadelumab (TAK-743) for Japanese Patients with Hereditary Angioedema

Short Title

Open-arm, Japan Expanded Access Program with Lanadelumab for Japanese Patients with Hereditary Angioedema

Sponsor: Takeda Pharmaceutical Company Limited

Study Number: TAK-743-5007

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: Lanadelumab (TAK-743, formerly SHP643; DX-2930)

Date: 09 February 2021 **Amendment Number:** 01

Amendment History:

Date	Amendment Number	Region
06 October 2020	Initial version	Global
09 February 2021	01	Global

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the annexes

1.2 Principles of Clinical Studies

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.
- In Japan, these following ordinances must be complied for this study.
  - March 27, 1997, MHLW Ordinance No. 28. "The Ordinance on Good Clinical Practice".
  - "The Ordinance for Partial Revision of the Ordinance on Good Clinical Practice".
  - Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Pharmaceutical and Medical Device Act).

After obtaining the marketing authorization of this drug in Japan, this clinical trial will continue as a post-marketing clinical trial, and will comply with the GCP Ministerial Ordinance and the Ministerial Ordinance on the criteria for conducting post-marketing surveillance and testing of pharmaceuticals. After the transition to post-marketing clinical trials, the term “clinical trial” in the “clinical trial protocol” will be replaced with “post-marketing clinical trial”.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories) can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

[redacted] Date [redacted] Date

1.3 Protocol Amendment 01 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 01.

The primary purpose of this amendment is to update the protocol regarding the list of clinical laboratory tests and errata of original protocol. Other minor changes in procedures are proposed. Minor editorial changes are included for clarification purposes only. Full details on changes of text are given in Protocol Annex 4, including detailed rationale. The following is a summary of the changes made in the amendment:

- Correction of contraception procedure and duration, and relevant inclusion criterion.

  Justification: Inconsistencies within the original protocol is corrected according to acceptable contraception in Japan. Also, the contraception duration for female subjects is the same as Study SHP643-202.

- Change of allowable duration of the short or long-term prophylactic therapy for hereditary angioedema (HAE), eg, C1 inhibitor (C1-INH), attenuated androgens or anti-fibrinolytics after starting the treatment period.

  Justification: The allowable duration of therapy for HAE is extended like Study DX-2930-04.

- Correction of number of prefilled syringe (PFS) supplied to subjects.

  Justification: Considering the next visit, the required amount of study drug will be supplied to the subject who self-administer study drug.

- Medication history information of LTP will be recorded from 90 days prior to signing of informed consent.

  Justification: Medication history information will be recorded as with Study SHP643-302.

- Addition of the action taken of study drug for adverse event (AE).

  Justification: The action taken of study drug for AE includes dose reduced and dose increased.

- Addition of the list of clinical laboratory tests.

  Justification: Clarification of the parameters of clinical laboratory tests.

- Correction of the start date of the treatment duration.
- Addition of the rationale for the study due to new approval of berotralstat.
- Clarification of the informed consent of subjects aged 12 to 19.
- Clarification of the prohibited duration of angiotensin-converting enzyme (ACE) inhibitors in the excluded medication.
- Correction of the items the site representative records on the label of the study drug.

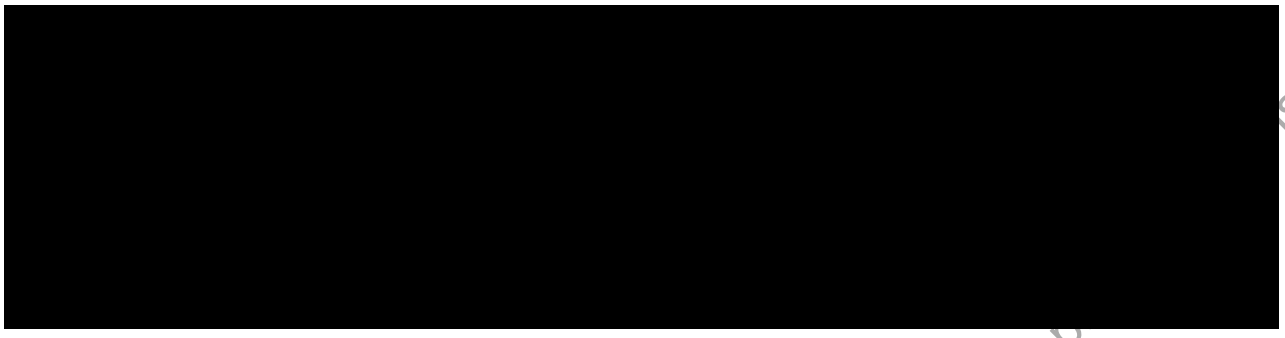
- Correction of how to return the used and unused PFS to study site.
- Correction of the person rollover subjects inform about an accidental overdose.
- Correction of the contents assigned by Interactive Response Technology (IRT).
- Clarification of the study procedure of rollover subjects and non-rollover subjects.
- Clarification of the timepoint when subjects can self-administer the study drug.
- Addition of the study visit of Study Day 266.
- Clarification of the reporting of ongoing AE and concomitant medication from the previous study.
- Clarification of the study visit when clinical laboratory testing is not performed.
- Correction of the study visits which can be done at local site or remotely (via phone or video) at investigator's discretion if approved by institutional review board (IRB).
- Clarification of the study day on telephone visits after Study Visit 14 (Day 182).
- Correction of the body temperature range on Grade 1 for fever oral in SYSTEMIC of National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity (Appendix E)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

[redacted]



2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** Lanadelumab (TAK-743)	
Title of Protocol: Open-arm, Japan Expanded Access Program with Lanadelumab (TAK-743) for Japanese Patients with Hereditary Angioedema.	**IND No.:** Not applicable	**EudraCT No.:** Not Applicable
Study Number: TAK-743-5007	**Phase:** Not applicable	

Study Design:

Study TAK-743-5007 is an open-arm, Japan Expanded Access Program with Lanadelumab (TAK-743) for Japanese patients with Type I or II hereditary angioedema (HAE). Two types of subjects will be enrolled into this study:

- Subjects who rollover from Study SHP643-302.
- Subjects who are non-rollovers (ie, were not participants in Study SHP643-302).

Subjects who discontinue from Study SHP643-302 after providing informed consent are not eligible to enroll in Study TAK-743-5007.

Rollover subjects

There is no screening period for rollover subjects. The first study visit for rollover subjects (Day 0) is to occur on the same day as the Study SHP643-302 Day 378 study visit. Rollover subjects will complete all Study SHP643-302 final study assessments (Day 378) at which time they will be discharged from that study. Results of the final SHP643-302 assessments on Day 378 will be used as the predose results for Day 0 of Study TAK-743-5007.

Following informed consent and predose assessments, rollover subjects will continue with an open-label dose of 300 mg lanadelumab administered subcutaneously (SC) on Day 0. Rollover subjects will receive SC administration of lanadelumab 300 mg every 2 weeks (q2w) or every 4 weeks (q4w) at the discretion of the Investigator, with optional consultation with the sponsor, if they have been well-controlled (eg, attack free for 26 weeks).

Non-rollover subjects

Subjects with historical baseline HAE attack of at least 1 attack per 4 weeks in the recent 1 year who have not participated in Study SHP643-302 (non-rollovers) are permitted to enroll if they meet the eligibility requirements for expanded access.

Screening of some subjects is allowed following discussion with the sponsor: ie, subjects who screen failed out of the run-in period for Study SHP643-302 when enrollment for that study closed.

Once all screening assessments are completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following predose assessments, will receive an open-label dose of 300 mg lanadelumab administered SC on Day 0. Non-rollover subjects will receive SC administration lanadelumab 300 mg q2w or q4w if they have been well-controlled (eg, attack free for 26 weeks) and at the discretion of the Investigator with optional consultation with the sponsor.

All doses are to fall within the accepted ±4 day window around study visits. From Day 0 to Day 182, visits will occur q2w. After Day 182, study visits will occur every 12 weeks, and site personnel are to call subjects q2w to collect adverse events (AEs), concomitant medications, and to ensure all attacks have been appropriately documented.

The treatment period is to last up to lanadelumab manufacturing and sale, development discontinued or withdraw of new drug application.

Self-administration:

All subjects who are considered suitable candidates will be allowed to self-administer treatment throughout the study. Subjects are required to complete appropriate training by the Investigator or designee and have their understanding of the procedures confirmed by the Investigator or designee. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of lanadelumab at the study site.

Adolescent subjects self-administering lanadelumab are to be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer the study drug to an adolescent without study site personnel supervision.

Primary Objectives:

To ensure access to lanadelumab in Japanese subjects with HAE who meet the criteria for expanded access.

Secondary Objectives:

- To evaluate the long-term safety of repeated SC administration of lanadelumab.
- To evaluate the long-term efficacy of lanadelumab in preventing HAE attacks.

Subject Population: Japanese male/female HAE (Type I or II) subjects who are 12 years of age or older at the time of screening.

Number of Subjects:	**Number of Sites:**
Not applicable	Approximately 15 sites in Japan
Dose Level(s): Lanadelumab 300 mg q2w Lanadelumab 300 mg q4w at the discretion of the Investigator, with optional consultation with the sponsor, if well-controlled (eg, attack free for 26 weeks)	**Route of Administration:** Subcutaneous
Duration of Treatment: First patient in: February 2021 to last patient last visit: November 2021 or until lanadelumab manufacturing and sale, development discontinued or withdraw of new drug application	**Period of Evaluation:** Not applicable

Main Criteria for Inclusion:

Each subject has to meet the following criteria to be eligible for the study:

1. Be of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
2. Male and female HAE subjects who are 12 years of age or older at the time of screening.
3. Documented diagnosis of disease HAE (Type I or II) based on all of the following:
   - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening (or a prior lanadelumab study) that confirm HAE Type I or II: C1 inhibitor (C1-INH) functional level <40% of the normal level. Subjects with functional C1-INH level 40% to 50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by long-term prophylaxis (LTP) use. It is understood that C1-INH

therapy may alter the lab results of C1-INH assessments; therefore, the Investigator's discretion in collaboration with sponsor is advised for proper documentation of eligibility.

- At least one of the following: Age at reported onset of first angioedema symptoms ≤ 30 years, a family history consistent with HAE Type I or II, or C1q within normal range.

4. Non-rollover subjects only: A historical baseline HAE attack rate of at least 1 attack per 4 weeks in the recent 1 year.
5. Rollover subjects only: Subjects from Study SHP643-302 are permitted to rollover and enroll into this study if:
   - They completed the treatment period of Study SHP643-302; and
   - They consented to enter Study TAK-743-5007 on or before Day 350 of the SHP643-302 study (since Day 378 of Study SHP643-302 is also Day 0 of Study TAK-743-5007, informed consent may be completed on Day 364 or this visit, if not already provided).

Criteria for Exclusion:

Patients who meet any of the following criteria are excluded from the study:

1. If rolling over from Study SHP643-302, presence of important safety concerns that would preclude participation in this study.
2. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema, HAE with normal C1-INH (also known as HAE Type III/normal C1-INH), idiopathic angioedema, or recurrent angioedema associated with urticaria.
3. Dosing with an investigational drug (not including lanadelumab or other HAE therapies) or exposure to an investigational device within 4 weeks prior to screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
5. Unwilling to discontinue short or long-term prophylactic therapy for HAE, eg, C1-INH, attenuated androgens or anti-fibrinolytics within 3 weeks after starting the treatment period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or antifibrinolytic used to avoid angioedema complications from medically indicated procedures.
6. Any of the following liver function test abnormalities: alanine aminotransferase >3 × upper limit of normal (ULN), or aspartate aminotransferase >3 × ULN, or total bilirubin >2 × ULN (unless the bilirubin elevation is a result of Gilbert's syndrome).
7. Pregnancy or breast feeding.
8. Have any uncontrolled underlying medical condition which would require treatment adjustment during the study treatment period, that, in the opinion of the Investigator or sponsor, may confound the results of the safety assessments or may place the subject at risk. Subjects with stable treatment for at least 3 months prior to screening and NOT expecting any change to their treatment regimen for 6 months during the study treatment period, will not be excluded.
9. Subject has a known hypersensitivity to the study drug or its components.

Criteria for Evaluation and Analyses:

Safety measures:

- Number and percentage of subjects with treatment -emergent adverse events (TEAEs) including serious adverse events (SAEs) and adverse event of special interest (AESI).
- Number of subjects with clinically significant abnormal clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis).
- Number of subjects with clinically significant vital signs including blood pressure, heart rate, body temperature, and respiratory rate.

Efficacy measure:

- Non-rollover Subjects: Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182.

Statistical Considerations:

The Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of lanadelumab in this study. All safety and efficacy analyses will be based on the FAS.

Interim summary may be produced during the study to support regulatory reporting if requested by the authority.

Safety Analysis

Adverse events are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. No inferential statistics are planned.

Adverse event of special interests for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events).

The number and percentage of subjects with TEAEs will be displayed by system organ class and preferred term (PT) using MedDRA®.

All AEs will be provided in subject listings. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and Investigator-reported AESIs will be produced.

Efficacy Analysis

No statistical hypothesis testing will be performed. Time to the first Investigator-confirmed HAE attack will be analyzed using the Non-rollover subjects in FAS.

Time to first Investigator-confirmed HAE attack is to be calculated from the time of first dose of lanadelumab in this study to the start time of the first Investigator-confirmed HAE attack. If a subject does not have an attack, the subject will be censored from the time of first dose of lanadelumab to the earlier of the early discontinuation date or end of treatment period date. The time to the first Investigator-confirmed HAE attack (days) will be summarized using Kaplan-Meier methods.

Sample Size Justification: This study is designed to expand access of lanadelumab and evaluate the safety of open-label treatment with lanadelumab in subjects with HAE who participated in SHP643-302 (rollover subjects) and individuals who are not otherwise able to participate in SHP643-302 (non-rollover subjects). Therefore, no formal sample size calculation was performed.

3.0 LIST OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
B2	bradykinin type 2
CRF	case report form
eCRF	electronic case report form
C1-INH	C1-inhibitor
DMID	Division of Microbiology and Infectious Diseases
EDC	electronic data capture
ECG	electrocardiogram
EOS	End of Study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HAARP	hereditary angioedema attack assessment and reporting procedures
HAE	hereditary angioedema
hCG	human chorionic gonadotropin
HR	heart rate
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IgG1	immunoglobulin G subclass 1
IP	investigational product
IRB	institutional review board
IRT	Interactive Response Technology
IV	intravenous
KM	Kaplan-Meier
LTP	long-term prophylaxis
MedDRA	Medical Dictionary for Regulatory Activities
PFS	prefilled syringe
PK	pharmacokinetic
pKal	active plasma kallikrein
PT	preferred term
q2w	every 2 weeks
q4w	every 4 weeks

RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Assessments
SC	subcutaneous
SMQ	Standardized MedDRA Queries
SUSAR	suspected unexpected serious adverse reactions
TDC	Takeda Development Center
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

3.1 Corporate Identification

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

4.0 INTRODUCTION

Lanadelumab (TAK-743), is a recombinant Chinese hamster ovary cell expressed, fully human immunoglobulin G subclass 1 (IgG1), kappa light chain, monoclonal antibody. Lanadelumab is a potent and specific inhibitor of the proteolytic activity of active plasma kallikrein (pKal). The drug is approved for prevention of angioedema attacks in patients with Type I or II hereditary angioedema (HAE), which is a rare and life-threatening disease.

4.1 Background

Hereditary angioedema is a long-term, debilitating, and life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. Hereditary angioedema manifests clinically as unpredictable, intermittent attacks of subcutaneous (SC) or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia (Zuraw, 2008). Swelling may last up to 5 days; most patients suffer multiple attacks per year. The exact prevalence of HAE is unknown; however, current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50000 as likely the closest estimate (Bygum, A. 2009; Goring et al., 1998; Lei et al., 2011; Lumry, 2013; Nordenfelt et al., 2014; Roche et al., 2005). Obstruction of airways due to swelling in larynx could result in death due to asphyxiation (Bork et al., 2000; Bork et al., 2012). Approximately 50% of all HAE patients will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack (Bork et al., 2003; Bork et al., 2006). The incidence of death due to untreated laryngeal attacks is 30% to 40% and the risk of death is 3-fold greater in undiagnosed versus diagnosed patients (Bork et al., 2000; Bork et al., 2012; Bork et al., 2016). Abdominal attacks are often associated with nausea, vomiting, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Agostoni and Cicardi, 1992; Zuraw, 2008).

Approximately 85% of patients have Type I HAE, characterized by very low production of functionally normal C1-INH protein, while the remaining approximately 15% of patients have Type II HAE and produce normal or elevated levels of a functionally impaired C1-INH (Zuraw, 2008). Clinical suspicion of Type I and II HAE can be confirmed by available blood tests. In addition to abnormalities in C1-INH level and function, plasma C4 levels are markedly reduced at all times in blood from most patients. Acute treatments include purified, plasma-derived C1-INH, recombinant C1-INH, a pKal inhibitor (ecallantide), and a bradykinin type 2 (B2) receptor antagonist (icatibant). While acute treatments are effective at resolving the symptoms of acute attacks, they do not prevent attacks and thus leave patients at risk of developing debilitating and potentially life-threatening attacks.

4.1.1 Indication and Current Treatment Options

Hereditary angioedema International Treatment Guidelines state that the goal of prophylactic treatment is to reduce the frequency and severity of attacks and thus to increase patients' quality of life (Cicardi et al., 2012; Craig et al., 2012). These guidelines recommend C1-INH or attenuated androgens as the standard of care over anti-fibrinolytic agents (Cicardi et al., 2012; Craig et al., 2012). The most recent World Allergy Organization /European Academy of Allergy and Clinical Immunology guidelines (2017 revision and update) recommend C1-INH as first-line long-term prophylactic therapy (androgens as second-line). Anti-fibrinolytics are not recommended due to the lack of efficacy in long-term prophylaxis (LTP) (Maurer et al., 2018). A patient with HAE, regardless of age, is a candidate for a prophylactic regimen if a number of criteria are met which may include: events in life that are associated with increased disease activity, attack frequency or severity, history of laryngeal attacks, impact on quality of life including work and school performance, proximity to emergency care, physiological or psychological stress, etc. (Craig et al., 2009; Maurer et al., 2018).

Currently, there are no approved therapies in Japan that are safe and effective for the long-term prevention of angioedema attacks in patients with Types I or II HAE. The only currently approved HAE therapies in Japan are Berinert, a human plasma-derived C1-INH concentrate for intravenous (IV) administration indicated for the treatment of acute attack and peri-procedural (short-term) prevention of acute attacks and, more recently, Firazyr, a SC B2-receptor antagonist indicated for the treatment of acute attacks. The Japan HAE guidelines recommend LTP in patients with a history of laryngeal edema and/or a high frequency of attacks (ie, symptoms at least once per month and/or more than 5 days/month) (Horiuchi et al., 2012). As there are no approved therapies in Japan for the long-term prevention of angioedema attacks in patients with Types I or II HAE, the Japan HAE guidelines currently recommend off-label use of attenuated androgens (eg, danazol) and the anti-fibrinolytic tranexamic acid as first-line long-term prevention strategies.

Lanadelumab is expected to fulfill an unmet medical need in Japan for a long-term safe, effective and convenient intervention to prevent HAE attacks. Lanadelumab may provide significant benefit to Japanese HAE patients, given the demonstrated efficacy in preventing HAE attacks in an overseas population and the similarity in genetic characteristics, pathophysiology, and clinical presentation of HAE between the overseas population and Japanese HAE patients. The targeted indication of lanadelumab (SHP643, DX-2930) is for prophylaxis to prevent attacks of HAE in patients aged 12 years and older.

4.1.2 Non-clinical studies with Lanadelumab

The nonclinical program conducted to date indicated no safety signal or toxicity with SC administered lanadelumab at doses of up to and including the highest tested dose (50 mg/kg, once weekly) for 6 months in cynomolgus monkeys. Collectively, the nonclinical studies demonstrate that lanadelumab did not have adverse effects on vital functions or produce adverse target organ pathologies in rats or cynomolgus monkeys and support the safe use in patients with HAE as a prophylactic treatment by SC injection.

4.1.3 Clinical studies with Lanadelumab

To date, the worldwide applications for marketing authorization of lanadelumab have been supported by 5 clinical studies. Results for all 5 clinical studies and summary of results in adolescent patients with HAE (in Studies DX-2930-03 and DX-2930-04) are briefly summarized below:

- Clinical study DX-2930-01 evaluated the safety, tolerability, and pharmacokinetic (PK) of a single dose of lanadelumab (0.1, 0.3, 1.0, or 3.0 mg/kg) in healthy subjects. The data demonstrated that lanadelumab was well tolerated by healthy subjects up to doses of 3.0 mg/kg without evidence of dose-limiting toxicity. The PK profile demonstrated linear, dose-dependent exposure with a mean half-life of approximately 17 to 21 days across dose groups. The exposure was dose proportional and the half-life was consistent across the dose groups.
- Clinical study DX-2930-02 evaluated the safety, tolerability, and PK of 2 doses of lanadelumab (30, 100, 300, or 400 mg) separated by 14 days in HAE subjects and demonstrated that lanadelumab was well tolerated following 2 doses up to 400 mg. There were no deaths, serious adverse events (SAEs), discontinuations due to an adverse event (AE), or safety signals following lanadelumab treatment. In a prespecified efficacy analysis, a statistically significant finding of HAE attack prevention by lanadelumab was observed. Specifically, in comparison to placebo, attack rate was reduced by 100% and 88% in the 300 mg and 400 mg lanadelumab treatment groups, respectively.
- Study DX-2930-03 (HELP Study™) was a multicenter, randomized, double-blind, placebo-controlled, parallel group efficacy and safety study to evaluate lanadelumab for LTP against acute attacks of HAE. The primary objective of the study was to evaluate the efficacy of lanadelumab in preventing HAE attacks.

  Over the 26-week treatment period, all 3 lanadelumab dose regimens, 150 mg every 4 weeks (q4w), 300 mg q4w, and 300 mg every 2 weeks (q2w), resulted in a highly statistically significant percentage reduction in the least squares mean Investigator-confirmed HAE attack rate compared with placebo of 76%, 73%, and 87% (adjusted $p<0.001$), respectively, for the primary endpoint. Furthermore, all 3 lanadelumab regimens demonstrated highly statistically significant attack rate reductions compared with placebo for all secondary efficacy analyses. Notably, the magnitude of the treatment effect was consistently the largest across all endpoints in the lanadelumab 300 mg q2w treatment arm compared with the lanadelumab q4w arms. The evidence of prevention of HAE attacks was indicated by sustained decreased frequency of attacks, decreased severity of attacks, reduced need for rescue medication (acute treatment), and improved health-related quality of life (HRQoL). Lanadelumab was generally well tolerated over the 26-week treatment period; no treatment-related SAEs or deaths were reported.
- Study DX-2930-04 (HELP Study Extension™) is an open-label, long-term safety and efficacy extension study of DX-2930-03 to evaluate the study drug, lanadelumab, in preventing acute angioedema attacks in patients with Type I or II HAE. At the time of the

interim analysis based on the data cutoff date of 31 August 2018, the safety profile in this study was consistent with the pivotal Study DX-2930-03 and previous interim analysis (data cutoff date of 01 September 2017) for the global marketing license or authorization applications for lanadelumab. No treatment-related SAEs or deaths were reported. Treatment-emergent AEs (TEAEs) for most subjects were mild or moderate in severity with few reported severe events considered related to lanadelumab treatment. Lanadelumab 300 mg q2w remained highly effective during this extension study for rollover and non-rollover subjects. Efficacy was maintained and shown to be durable with over 12 months of lanadelumab exposure across Study DX-2930-03 and Study DX-2930-04 for rollover subjects. Improved HRQoL based on adverse event-quality of life scores were observed for rollover and non-rollover subjects.

- Study SHP643-101 was a Phase 1, open-label, matched-control, single dose, single-center study. Its primary objective was to evaluate the PK properties of lanadelumab administered as a single SC dose of 300 mg in healthy adult male and female volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy volunteer subjects. All 32 subjects completed the study. Following single SC administration of 300 mg lanadelumab in healthy Japanese subjects, peak and overall systemic exposure to lanadelumab (C_{max}, area under the concentration-time curve from time zero to the last measurable concentration [$AUC_{0\text{-last}}$] and area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{0\text{-}\infty}$]) was similar to that observed in healthy Caucasian subjects, as determined from the 90% confidence intervals.

Adolescent clinical trial experience

The Phase 3 clinical studies for lanadelumab, pivotal Study DX-2930-03 and open-label extension Study DX-2930-04 (ongoing), evaluated the adult and adolescent population; inclusion of adolescents in these studies was justified based on the similarity of the pathophysiology and clinical presentation of HAE in adults and adolescents, as well as by the lack of any safety signal identified in nonclinical and clinical studies to date. In the 23 unique adolescent subjects who participated across Phase 3 Studies DX-2930-03, no safety signals were identified in terms of clinical laboratory hematology or coagulation, laboratory test abnormalities, vital signs, physical examination, or electrocardiograms (ECGs). Overall, the safety and tolerability of lanadelumab were similar in the pediatric population (12 to <18 years old) and adults (≥18 years old).

Based on analyses of PK parameters for adolescents and adults in Phase 3 studies, no influence of age was apparent on clearance of lanadelumab after correcting for body weight. Based on the evaluation of PK, efficacy and safety, no dosing regimen adjustment has been recommended for adolescents (12 to <18 years).

4.2 Rationale for the Proposed Study

Lanadelumab was approved in the year 2018 in the United States, Canada, and the European Union, followed by multiple countries in 2019 for routine prophylaxis to prevent attacks of angioedema in HAE patients 12 years and older. Lanadelumab marketing licensing and

authorization packages are currently being reviewed in many other countries. Lanadelumab is a highly potent and specific inhibitor of pKal (Ki = 125 pM). As lanadelumab has a long half-life (approximately 14 days in HAE subjects), it was hypothesized that treatment with lanadelumab every 2 or 4 weeks would provide persistent suppression of pKal and thus prevention of HAE attacks. Lanadelumab is now approved for SC administration at the recommended dose 300 mg q2w. A dosing interval of 300 mg q4w may be considered in patients who are stable and attack free on treatment.

There are no drugs that have been approved in Japan for LTP of HAE Type I and II at the time the study was planned. There is strong scientific rationale and high unmet medical need to expand the use of lanadelumab as a prophylactic therapy. In Japan, the sponsor is planning to file a marketing approval application based on the results of a Japanese Phase 3 study in Japanese HAE patients that is currently underway (study SHP643-302). By expanding access to subjects who rolled over from SHP643-302, and those who were not enrolled, the probability of benefit to the subjects with HAE will increase. The present study is an expanded access program that aims to provide access to lanadelumab in Japanese subjects with HAE and monitor the safety of SC lanadelumab administered every 2 or 4 weeks.

4.3 Benefit/Risk Profile

Lanadelumab, a first-in-class monoclonal antibody against active pKal, represents a therapeutic innovation that will address the unmet medical needs within the HAE community and thus is expected to be of major public health interest. It is a fully human IgG1 monoclonal antibody inhibitor of active pKal with a long half-life, which allows for convenient, infrequent SC self-administration (eg, q2w).

In the pivotal Phase 3 study, lanadelumab demonstrated highly statistically significant and clinically meaningful reductions in HAE attacks over the 26-week treatment period compared with placebo across primary and all secondary efficacy analyses. Evidence for prevention and control of HAE symptoms was indicated by sustained decreased frequency and severity of attacks, high proportion of attack-free subjects (eg, 77% attack free at steady state in lanadelumab 300 mg q2w), reduced number of high morbidity attacks, reduced need for rescue medication (acute treatment), and improved HRQoL (81% subjects achieving responder definition in lanadelumab 300 mg q2w treatment). The efficacy results observed with lanadelumab (particularly at the dose of 300 mg q2w) confirmed the expected significant benefit based on superior efficacy over existing treatments.

From a benefit/risk perspective, lanadelumab is generally well tolerated and has not shown safety limitations (as compared with C1-INH or androgens) and thus provides significant improvement on the benefit/risk profile. In addition, importantly for patients, lanadelumab's unique mechanism of action and properties allow reduced dosing frequency (eg, q2w) with SC self-administration (10 to 60 seconds), which significantly reduces the burden of treatment as compared with a daily oral or twice weekly IV or SC treatment experienced by patients; therefore, lanadelumab offers a more effective and convenient therapy for patients suffering from HAE.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to ensure access to lanadelumab in Japanese subjects with HAE who meet the criteria for expanded access.

5.1.2 Secondary Objectives

- To evaluate the long-term safety of repeated SC administration of lanadelumab.
- To evaluate the long-term efficacy of lanadelumab in preventing HAE attacks.

5.2 Endpoints

5.2.1 Safety Endpoints

The following safety endpoints are to be evaluated:

- Number and percentage of subjects with TEAEs, including SAEs and adverse events of special interest (AESIs).
- Number of subjects with clinically significant abnormal laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis).
- Number of subjects with clinically significant vital signs including blood pressure (BP), heart rate (HR), body temperature, and respiratory rate (RR).

5.2.2 Efficacy Endpoints

The following efficacy endpoint is to be evaluated:

- Non-rollover Subjects: Time to first HAE attack after Day 0 for the efficacy evaluation period of Day 0 through Day 182.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, Japan Expanded Access Program with lanadelumab (TAK-743) for Japanese patients with Type I or II HAE. Two types of subjects will be enrolled into this study:

- Subjects who rollover from Study SHP643-302.
- Subjects who are non-rollovers (ie, were not participants in Study SHP643-302).

Rollovers from Study SHP643-302

Subjects from Study SHP643-302 are permitted to rollover and enroll into this study if:

1. They have completed the treatment period of Study SHP643-302; and
2. They have consented to enter Study TAK-743-5007 on or before Day 350 of the SHP643-302 study (since Day 378 of Study SHP643-302 is also Day 0 of Study TAK-743-5007, informed consent may be completed on Day 364 or this visit, if not already provided).

Subjects who discontinue from Study SHP643-302 after providing informed consent are not eligible to enroll in Study TAK-743-5007.

There is no screening period for rollover subjects. The first study visit for rollover subjects (Day 0) is to occur on the same day as the Study SHP643-302 Day 378 study visit. Rollover subjects will complete all Study SHP643-302 final study assessments (Day 378) at which time they will be discharged from that study. Results of the final SHP643-302 assessments on Day 378 will be used as the predose results for Day 0 of Study TAK-743-5007.

Following informed consent and predose assessments, rollover subjects will continue with an open-label dose of 300 mg lanadelumab administered SC on Day 0. Rollover subjects will receive SC administration of lanadelumab 300 mg q2w or q4w at the discretion of the Investigator, with optional consultation with the sponsor, if they have been well-controlled (eg, attack free for 26 weeks). Rollovers from Study SHP643-302 who have been self-administering the study drug at the time of screening will be permitted to continue self-administration of lanadelumab.

Non-rollover subjects

Subjects with historical baseline HAE attack of at least 1 attack per 4 weeks in the recent year who have not participated in Study SHP643-302 (non-rollovers) are permitted to enroll if they meet the eligibility requirements for expanded access.

Screening of some subjects is allowed following discussion with the sponsor: ie, subjects who screen failed out of the run-in period for Study SHP643-302 when enrollment for that study closed.

Once all screening assessments are completed and eligibility confirmed, non-rollover subjects will arrive at the study site and, following predose assessments, will receive an open-label dose of 300 mg lanadelumab administered SC on Day 0. Non-rollover subjects will receive SC administration lanadelumab 300 mg q2w or q4w if they have been well-controlled (eg, attack free for 26 weeks) and at the discretion of the Investigator with optional consultation with the sponsor.

All doses are to fall within the accepted ± 4 days window around study visits. From Day 0 to Day 182, visits will occur q2w. After Day 182, study visits will occur every 12 weeks, and site personnel are to call subjects q2w to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.

All subjects who are considered suitable candidates will be allowed to self-administer treatment throughout the study. Subjects are required to complete appropriate training by the Investigator or designee and have their understanding of the procedures confirmed by the Investigator or designee (refer Section 9.1.13.1 for more details).

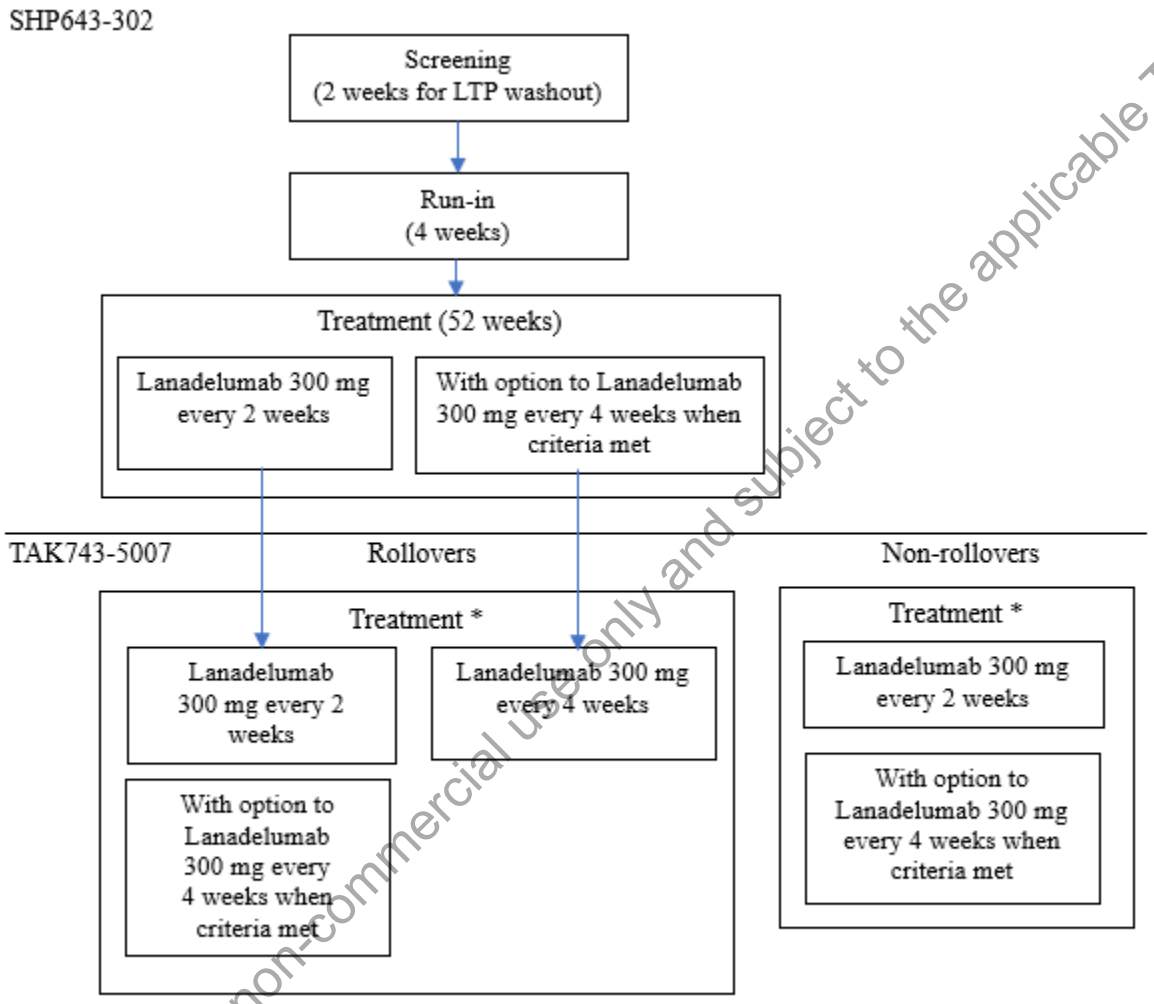
The treatment period is to last up to lanadelumab manufacturing and sale, discontinued development, or withdrawal of new drug application.

If a subject experiences an acute angioedema attack at any time during the study that in the opinion of the Investigator requires medical intervention, standard of care therapy is to be provided based on subject's medical history and per locally approved product information.

Administration of lanadelumab and study procedures is to continue without alteration to [redacted] even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

An overview of the study design scheme is provided in Figure 6.a. All study procedures are detailed in the schedule of assessments [redacted]

Figure 6.a Schematic of Study Design



*Until moment of lanadelumab manufacturing and sale, development discontinued, or withdraw of new drug application

LTP = long-term prophylaxis

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Scientific rationale for study design

The current study is designed in view of Japan HA regulations and intends to ensure access to lanadelumab in Japanese subjects with HAE who meet the criteria for expanded access.

An open-label design selected to ensure maximum and expanded access to the patients as it is the primary objective of the study and norm for expanded access programs.

The eligibility criteria are identical to those in Study SHP643-302 with respect to subject age, diagnosis, and clinical presentation of HAE at study entry.

Non-rollover, they need to have historical baseline HAE attack of at least 1 attack per 4 weeks.

No separate screening procedures for rollover patients to lessen the patient burden.

6.2.2 Justification for dose

In all the countries where lanadelumab have been approved, the recommended dose regimen is 300 mg q2w. A dosing interval of 300 mg q4w may be considered in patients who are stably attack free on treatment.

Based on the totality of efficacy, PK and pharmacodynamic, and safety data from the pivotal overseas study in adolescent and adult subjects with HAE (Study DX-2930-03), the 300 mg q2w dose regimen was considered the recommended dose as it consistently demonstrated the greatest treatment effect compared with placebo and had an optimal benefit-risk profile during the 26 weeks of treatment period. Lanadelumab treatment resulted in a high proportion of subjects being attack free on all dosing regimens evaluated (300 mg q2w, 300 mg q4w, and 150 mg q4w), with the 300 mg q2w dosing regimen having the highest percentage of subjects (44%) who were attack free for the entire 26-week treatment period, and approximately 77% of subjects attack free after achieving steady state.

The ongoing open-label Phase 3 HELP Study Extension™ (Study DX-2930-04) in adolescent and adult subjects with HAE demonstrated that the prevention of HAE attacks for lanadelumab 300 mg q2w was consistent with a substantially longer treatment duration. The safety profile in this study was consistent with the pivotal Study DX-2930-03. No treatment-related SAEs or deaths were reported. Treatment-emergent AEs for most subjects were mild or moderate in severity with few severe events were considered related to lanadelumab treatment.

Lanadelumab 300 mg q2w provides exposure approximately above the maximal inhibitory concentration (IC90) of cHMWK, EAUC90 for clinical response in the majority of subjects across a large range of body weight (46.8 to 150 kg), and the safety profile supports lanadelumab 300 mg q2w as the recommended fixed-dose regimen, including adolescent population. Meanwhile, understanding the need for clinicians to individualize therapy, including an opportunity for flexible dosing regimen, and thus, extending the dosing interval beyond q2w to q4w represents a substantial quality of life benefit for patients and could be considered if the subjects are well-controlled (eg, attack free for 26 weeks) on the recommended dose.

A Phase 1 clinical study (Study SHP643-101), the data indicated that the peak and systemic exposure to lanadelumab (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$) in healthy Japanese subjects was similar to that observed in healthy Caucasian subjects. Lanadelumab was generally safe and well tolerated by both ethnic groups.

The present study is an expanded access program that aims to provide access to lanadelumab in Japanese subjects with HAE and monitor the safety of SC lanadelumab administered every 2 or 4 weeks.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-743, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Each subject has to meet the following criteria to be eligible for the study:

1. In the opinion of the Investigator, the subject is capable of understanding and complying with protocol requirements.
2. Be of Japanese descent, defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
3. Male and female HAE subjects who are 12 years of age or older at the time of screening.
4. Documented diagnosis of disease HAE (Type I or II) based on all of the following:
   - Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).
   - Diagnostic testing results obtained during screening (or a prior lanadelumab study) that confirm HAE Type I or II: C1-INH functional level <40% of the normal level. Subjects with functional C1-INH level 40% to 50% of the normal level may be enrolled if they also have a C4 level below the normal range. Subjects may be retested if results are incongruent with clinical history or believed by the Investigator to be confounded by LTP use. It is understood that C1-INH therapy may alter the lab results of C1-INH assessments; therefore, the Investigator's discretion in collaboration with sponsor is advised for proper documentation of eligibility.
   - At least one of the following: Age at reported onset of first angioedema symptoms ≤30 years, a family history consistent with HAE Type I or II, or C1q within normal range.
5. Non-rollover subjects only: A historical baseline HAE attack rate of at least 1 attack per 4 weeks in the recent 1 year.
6. Rollover subjects only: Subjects from Study SHP643-302 are permitted to rollover and enroll into this study if:
   - They completed the treatment period of Study SHP643-302; and
   - They consented to enter Study TAK-743-5007 on or before Day 350 of the SHP643-302 study (since Day 378 of Study SHP643-302 is also Day 0 of Study TAK-743-5007, informed consent may be completed on Day 364 or this visit, if not already provided).
7. Adult subjects and caregivers of subjects under the age of 20 are willing and able to read, understand, and sign an informed consent form. Subjects aged 12 to 19, whose caregiver has provided informed consent, are willing and able to read, understand and sign an informed consent form (an assent form, if applicable) as much as possible.
8. Agree to adhere to the protocol-defined schedule of treatments, assessments, and procedures.

9. Males and females who are fertile and sexually active must adhere to contraception requirements for the duration of the study as follows:

    - Females* of childbearing potential must agree to be abstinent or it is recommended to use highly effective forms of contraception from the screening period through 70 days after the final study visit. Notes: 1) A female whose male partner has had a vasectomy must agree to use 1 additional form of medically acceptable contraception. 2) Use of a male condom with or without spermicide or cervical cap diaphragm or sponge with spermicide or a combination (double-barrier methods) are not considered highly effective.
    - Females of nonchildbearing potential, defined as surgically sterile (status post-hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for at least 12 months do not require contraception during the study.
    - Males, including males who are surgically sterile (post-vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 70 days after the final study visit.

*Note: Female rollover subjects (those who previously participated in Study SHP643-302) of childbearing potential may continue to use the birth control method used during Study TAK-743-5007.

7.2 Exclusion Criteria

Subjects who meet any of the following criteria are excluded from the study:

1. If rolling over from Study SHP643-302, presence of important safety concerns that would preclude participation in this study.
2. Concomitant diagnosis of another form of chronic, recurrent angioedema such as acquired angioedema, HAE with normal C1-INH (also known as HAE Type III/normal C1-INH), idiopathic angioedema, or recurrent angioedema associated with urticaria.
3. Dosing with an investigational drug (not including lanadelumab or other HAE therapies) or exposure to an investigational device within 4 weeks prior to screening.
4. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks prior to screening or any newly initiated or dose modification of estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) 3 months prior to the screening visit.
5. Unwilling to discontinue short or long-term prophylactic therapy for HAE, eg, C1-INH, attenuated androgens or anti-fibrinolytics within 3 weeks after starting the treatment period. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or antifibrinolytic used to avoid angioedema complications from medically indicated procedures.
6. Any of the following liver function test abnormalities: alanine aminotransferase (ALT) >3 × upper limit of normal (ULN), or aspartate aminotransferase (AST) >3 × ULN, or total bilirubin >2 × ULN (unless the bilirubin elevation is a result of Gilbert's syndrome).

7. Pregnancy or breast feeding.
8. Have any uncontrolled underlying medical condition which would require treatment adjustment during the study treatment period, that, in the opinion of the Investigator or sponsor, may confound the results of the safety assessments or may place the subject at risk. Subjects with stable treatment for at least 3 months prior to screening and NOT expecting any change to their treatment regimen for 6 months during the study treatment period, will not be excluded.
9. Subject has a known hypersensitivity to the study drug or its components.

7.3 Excluded Medications

Use of the following treatments will not be permitted during the study:

- LTP for HAE (eg, use of C1-INH for LTP, attenuated androgens, or antifibrinolytics) once LTP is discontinued (within 3 weeks following the first dose of lanadelumab).
- ACE inhibitors within 4 weeks prior to screening and during the study.
- Estrogen-containing medications with systemic absorption within 3 months prior to screening and during the study.
- Use of androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, and testosterone) for non-HAE related medical conditions or for HAE after discontinuation during the first 2 weeks during the treatment period.
- Any other investigational drug or device.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.12.

1. Adverse event. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
2. Significant protocol deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category [Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category]).

5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

7. Lack of efficacy. The Investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Death.
9. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit. Discontinued or withdrawn subjects will not be replaced.

7.5.1 Individual Stopping Rules

Dosing for any individual subject will be discontinued or interrupted if the subject experienced a lanadelumab-related SAE (or a lanadelumab-related, clinically significant non-serious AE) that, in the assessment of the Investigator, warranted discontinuation from further dosing for that subject's wellbeing. The Investigator has the ability to contact and consult with the sponsor on such matters. Subjects are to continue to be followed through the completion of all scheduled nondosing visits, unless they requested to be discontinued from the study.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug

The study drug is lanadelumab, which will be provided as a sterile, preservative free, ready-to-use solution at a concentration of 150 mg/mL. The study drug will be provided in a prefilled syringe (PFS) at a dosage strength of 300 mg (300 mg/2 mL). Prefilled syringe is filled to deliver a nominal volume of 2 mL of lanadelumab SC.

Labels containing study information and pack identification are applied to the study drug container.

All study drug is labeled with a minimum of the following: protocol number, MedID number, lot number, expiry date, dosage form, directions for use, storage conditions, the sponsor's name and address, and the statements "For clinical trial use only" and "Keep out of sight and reach of children". The label will comply with Japanese GCP.

Space is allocated on the label so that the site representative can record a subject number and Investigator name.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the study drug in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.

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

The open-label lanadelumab will be supplied by the sponsor and pre-packaged in a study kit for the study. Each study kit will contain 1 PFS of study drug. Both the PFS and carton (kit) will be appropriately labeled according to local regulations and bear the unique study drug kit number. The investigative site will provide ancillary supplies to the subjects. The site has the option of using needles of a different gauge to aid subject comfort with each SC injection.

Detailed instructions on preparation and administration of study drug will be provided to the clinical sites in a Pharmacy Manual.

Subjects (or parents/caregivers) who elect to self-administer study drug, where permitted per protocol (see Section 9.1.13.1) will be provided the following supplies as applicable:

- Required number of PFS.
- Ancillary supplies, and a container for sharps disposal.
- Subject accountability form to record study drug administration details.

All used and unused PFS should be returned to the study kit cartons/boxes for drug accountability. Written instructions on lanadelumab handling and self-administration procedures will be provided to trained subjects (and their parent/caregiver) prior to initiating self-administration. Refer to the Pharmacy Manual for additional details on lanadelumab and its administration.

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

8.1.1.2 Rescue Medication

Hereditary angioedema attacks occurring during the run-in period and study treatment periods will be treated according to the local standard of care. In case of insufficient response to the first dose, additional rescue medications will be allowed. Administration of lanadelumab and study procedures will continue without alteration to the protocol-specified study schedule, even if the subject has symptoms of an HAE attack on the day of lanadelumab administration and/or receives treatment for an HAE attack.

8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol includes the study drug (lanadelumab).

8.1.2 Storage

The Investigator has overall responsibility for ensuring that study drug 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. Study drug is distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the PFS labels as they are distributed.

Lanadelumab should be stored in a refrigerator at 2°C to 8°C. Prefilled syringes should be removed from refrigeration and allowed to get to room temperature before administration. Do not freeze. The PFS should be protected from light in the original carton. Refer to the latest version of the Investigator's Brochure for current stability data.

Before use, each PFS of study drug should be inspected for appearance. Any PFS containing visible particles or discoloration should not be used. Avoid shaking or vigorous agitation of the PFS.

Any unused contents of a PFS of study medication should be discarded in accordance with local requirements for investigational materials. Intact PFS of study medication that are not used during the course of the clinical study should be returned according to direction from the sponsor.

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

The sponsor should be notified immediately if there are any changes to the storage area of the study drug that could affect the integrity of the product(s), eg, fumigation of a storage room. Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and regimen

This is an open-label study. There are 2 sets of subjects-rollovers (from the previous study) and non-rollover subjects who will be enrolled to receive lanadelumab after fulfilling the inclusion criteria.

Lanadelumab will be administered by SC injection in the abdominal area, thigh, or upper arm. Rollovers from Study SHP643-302 who have been self-administering the study drug at the time of screening will be permitted to continue self-administration of lanadelumab. Upper arm location is not recommended for self-administration but rather an additional injection site when administered by a parent/caregiver or health care provider.

Subjects will receive SC administration of lanadelumab 300 mg q2w or q4w at the discretion of the Investigator, with optional consultation with the sponsor, if they have been well-controlled (eg, attack free for 26 weeks).

Dose Modification

- Dose modification may be considered for individual subjects based on benefit-risk assessment (See Section 4.3).
- Subjects may receive 300 mg q4w at the discretion of the Investigator, with optional consultation with the sponsor, if they have been well-controlled (eg, attack free for 26 weeks).

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on AE case report forms (CRFs) according to Section 10.0.

Serious adverse events associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In case of accidental overdose the rollover subjects (who self-administered the study drug) should inform it to site. In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

An Interactive Response Technology (IRT) vendor will be used for this study to manage packaged Investigational product (IP) supply, IP shipments, receipt of IP at clinical sites, randomization of IP to subjects, expiry tracking, IP returns, and IP accountability.

Subjects will receive treatment according to the study schedule. The Enrollment Number will be entered onto the eCRF.

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

The subject number represents a unique number corresponding to study drug allocated to the subject, once eligibility has been determined.

Subjects will be assigned to receive the next available medication ID number allocated to each study site. The medication ID number will be entered onto the eCRF.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

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

The Investigator has overall responsibility for administering and dispensing study drug (for dosing by site personnel and self-administration, respectively). The Investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the Investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

- Upon Continuously monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

Upon receipt of sponsor-supplied drug, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, Investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form/by recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file.

The Investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Self-administering subjects will either return their IP to site for accountability.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The Investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The Investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

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

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Assessments (SoA) is located in [redacted]

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent and assent forms must be approved for use by the reviewing IRB. Informed consent must be obtained prior to the subject entering into the study (or their parent/caregiver, as applicable), and before any protocol-directed procedures are performed. Assent will also be obtained from each subject, where required in accordance with IRB and local regulations, prior to performing any study-related activities. Subjects and their parent(s)/caregiver(s) may withdraw consent at any time. Participation in the study may be terminated at any time without the consent/assent of the subject (or their parent/caregiver, as applicable) as determined by the Investigator.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained, which will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

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

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

For rollover subjects, demography data from SHP643-302 will be re-entered for TAK-743-5007. However, medical history reported in the SHP643-302 study will not be re-entered into the eCRF for TAK-743-5007; only new medical history data will be entered.

For non-rollover subjects, medication history information to be obtained includes any medication relevant to eligibility criteria (efficacy/safety evaluation) stopped at or within 4 weeks prior to signing of informed consent. The information of LTP administration will be recorded from 90 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A complete physical examination will be performed by the Investigator or his/her qualified designee according to the SoA [redacted] The date and time of examination, and any findings, will be recorded on the source documents and eCRF.

Adverse events emerging from any physical examination will be recorded on the source document and eCRF.

The physical examination will be performed in accordance with standards at the site. The physical examination will include, at a minimum, assessments of the body systems listed below:

- General appearance.
- Ears, nose, and throat.
- Head and Neck.
- Ophthalmological.
- Respiratory.
- Cardiovascular.
- Abdomen.
- Neurological.
- Extremities.
- Dermatological.
- Lymphatic.

In addition, height and weight will be measured at the screening visit only in accordance with standards of the site.

9.1.4 Vital Sign Procedure

Vital signs will be assessed by the Investigator or his/her qualified designee according to the SoA [redacted] Vital signs will include body temperature, RR, BP (systolic and diastolic, resting more than 5 minutes), and HR (bpm). For HR measurement, it is acceptable to use sphygmomanometers to measure pulse rate instead of using ECG or stethoscope for HR. Vital signs will be obtained prior to dosing and 1 hour after dosing with a ±15 minutes window.

Routine vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest. Blood pressure should be determined using the same arm and the same equipment, and the same position for each assessment throughout the study.

During the study, additional vital signs measurements will be performed if clinically indicated.

Every effort should be made to measure and record vital signs prior to any blood sample collection.

The Investigator will assess whether a change from baseline (ie, the predose measurement at Visit 1/Day 0) in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE.

9.1.5 Efficacy Measurement

9.1.5.1 Collection of Hereditary Angioedema Attacks

Historical HAE attack information will be collected at screening for non-rollover subjects. Throughout the study (ie, from screening through follow-up), HAE attack information will be solicited by site personnel during scheduled study visits and site check-ins, as shown in SoA [redacted] In addition, study subjects (or parent/caregivers, in the event the subject is <18 years old or is incapacitated) will be instructed to report details of the HAE attack to the study site within 72 hours of the onset of the attack.

The collection, reporting and assessment of HAE attacks in this study will be done in accordance with the hereditary angioedema attack assessment and reporting procedures (HAARP) provided in [redacted] of this protocol. Site personnel will be trained on HAARP prior to screening subjects at their site.

9.1.5.2 Management of Acute Angioedema Attacks

Acute HAE attacks during the study are to be managed in accordance with the Investigator's usual care of their subjects, including use of acute attack therapies that the Investigator deemed medically appropriate. Use of C1-INH is permitted as an acute attack therapy but not as an LTP therapy. Administration of lanadelumab and study procedures is to continue without alteration to the protocol-specified study schedule, even if the subject had symptoms of an HAE attack the day of lanadelumab administration and/or received treatment for an HAE attack. The administration of lanadelumab can also be re-scheduled as long as the minimum and maximum timeframe between doses is met based on patient preference or physician discretion.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug including the rescue medications. These may be prescribed by a physician or obtained by the subject over-the-counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. For rollover subjects, any medications that are ongoing at the end of the previous study and that are still present at the time of enrollment into this study will be recorded in the eCRF for Study TAK-743-5007.

9.1.7 Documentation of Concurrent Medical Conditions

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

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with standard laboratory procedures using established and validated methods according to the SoA [redacted] Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the Investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

9.1.8.1 Laboratory testing and blood volume to be collected

Laboratory testing includes general safety parameters (hematology, serum chemistry, coagulation, and urinalysis), pregnancy tests, C1-INH functional assay, C4 assay, and C1q assay using established and validated methods. All laboratory tests will be performed using established and validated methods. Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Chemistry

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Blood urea nitrogen (BUN)
- Calcium
- Bicarbonate
- Chloride
- Creatinine
- Creatine phosphokinase (CPK)
- Glucose
- Phosphate
- Magnesium
- Potassium
- Sodium
- Total protein
- Uric acid

Hematology

- Hemoglobin
- Hematocrit

- Red blood cell (RBC) count
- White blood cell (WBC) count with differential
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Absolute platelet count

Coagulation

- Prothrombin time
- Activated partial thromboplastin time (aPTT)
- International Normalized Ratio (INR)

Urinalysis

- Bilirubin
- Glucose
- Ketones
- Blood
- Nitrite
- pH
- Protein
- Specific gravity
- Microscopy (if indicated by macroscopic findings)

Virology (at screening only for rollover subjects)

- Hepatitis B Surface Antigen (HbsAg)
- Hepatitis C Virus (HCV)
- Human Immunodeficiency Virus (HIV)

When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order of safety assessment (hematology, coagulation, and serum chemistry) and eligibility assessment (C1-INH functional assay, C4 assay, and C1q assay). Subjects will be seated in a supine position during blood collection.

The maximum volume of blood to be collected at any single visit and the approximate total volume of blood for the study will be specified in the Lab Manual. 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.

9.1.8.2 Blood Sample Collection, Storage and Shipping

Blood samples for laboratory assessments will be collected at the site by a trained site staff designated and/or approved by the study Investigator. Details for the collection, processing, storage, and shipment of samples for all laboratory determinations will be provided in the Laboratory Manual. Biological material will be stored and secured in a manner that assures that unauthorized access is prohibited, and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

9.1.9 Contraception and Pregnancy Avoidance Procedure

Lanadelumab has not been studied in pregnant women, and there are limited data from its use in pregnant women. However, a risk to the pregnant woman or developing fetus cannot be excluded. No evidence of testicular toxicity or adverse effects on male fertility or teratogenicity transferable to a fetus/embryo from animal studies were observed.

9.1.9.1 Male subjects and their Female Partners

Males, including males who are surgically sterile (post-vasectomy), with female partners of childbearing potential must agree to be abstinent or else use a medically acceptable form of contraception from screening through 70 days after the final study visit. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.9.2 Female subjects and their Male Partners

Females* of childbearing potential who are sexually active with a nonsterilized male partner must agree to be abstinent or it is recommended to use highly effective forms of contraception from the screening period through 70 days after the final study visit. 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 70 days following the last dose of IP.

- A female whose male partner, including males who have had a vasectomy, must agree to be abstinent or else use a medically acceptable form of contraception from screening through 70 days after the final study visit.
- Use of a male condom with or without spermicide or cervical cap diaphragm or sponge with spermicide or a combination (double-barrier methods) are not considered highly effective.

Females of nonchildbearing potential, defined as surgically sterile (status post-hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for at least 12 months do not require contraception during the study.

*Note: Female rollover subjects (those who previously participated in Study SHP643-302) of childbearing potential may continue to use the birth control method used during Study SHP643-302.

9.1.9.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, the acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - Intrauterine device.
        - Bilateral tubal occlusion.
    - Hormonal Methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral.
            - Intravaginal (eg, ring)*.
            - Transdermal*.
        - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;

- Oral*.
- Injectable*.
- Implantable*.

- Double-barrier method (contraceptive sponge, diaphragm or cervical cap* with spermicidal jellies* or creams* PLUS male condom).

2. Unacceptable methods of contraception includes:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides* only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap*/diaphragm/sponge without spermicide* and without condom.

   Note:*These contraception methods and pregnancy avoidance procedures are not approved in Japan.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular serum/urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a. Contraceptive requirements of the study.
   b. Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c. Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
      iv. Is there a chance you could be pregnant?
5. In addition to a negative urine hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no

delayed menses), a negative serum/urine hCG pregnancy test prior to receiving any dose of study medication.

9.1.9.4 General Guidance With Respect to the Avoidance of Pregnancy

From signing of informed consent and throughout the duration of the study and for 70 days after the last dose, female subjects of childbearing potential (ie, nonsterilized, premenopausal female subjects) who are sexually active must use acceptable methods of contraception. Also from signing of informed consent, throughout the duration of the study, and for 70 days after last dose, nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use contraception. Such subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study. During the course of the study, regular urine hCG pregnancy tests will be performed, and subjects will receive continued guidance with respect to avoiding pregnancy as part of the study procedures [redacted]

In addition to a negative urine hCG pregnancy test at screening, subjects also must have a negative serum/urine hCG pregnancy test on the day of the first dose of study drug (predose), prior to receiving any dose of study drug.

The contraceptive methods available in Japan are shown below.

Nonsterilized males with female partners of childbearing potential must use condoms (with or without spermicide). Females of childbearing potential with male partners who are participating in this study and female subjects of childbearing potential with nonsterilized male partners must use the following contraceptive methods.

- Intrauterine device (IUD).
- Bilateral tubal occlusion.
- Vasectomized partner* (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).

Note: *must agree to be abstinent or else use a medically acceptable form of contraception from screening through 70 days after the final study visit.

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation. (Not used for female subjects).

9.1.10 Pregnancy

For all females, pregnancy testing will be performed at the time points specified in SoA [redacted] if pregnancy is suspected; or on withdrawal (early termination visit) of the subject from the study. Pregnancy testing at Day 0 will be urine-based. All other pregnancy testing in this study may be urine- or serum-based.

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied study drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 160 days after the last dose, should also be recorded following authorization from the subject's partner.

All pregnancies are reported from the time informed consent is signed until the defined follow-up period. The pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0/Annex 1.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the Investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All pregnancies, including female partners of male subjects, in subjects on study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 Electrocardiogram

A standard 12-lead ECG (single recording) will be performed at screening visit, final visit/ early termination, and when clinically indicated. The date and time of each ECG and its results will be documented in the source documents and eCRF.

9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. A screen failure is a subject who has given informed consent and failed to meet all inclusion criteria and/or has met at least 1 of the exclusion criteria and has not been administered study drug. Once a subject has been designated as a screen failure, the subject may be rescreened at the discretion of the Investigator and following discussion with the sponsor medical monitor.

If the subject is withdrawn at the screening visit, the Investigator should complete the eCRF.

Screening of some subjects is allowed to have following discussion with the sponsor: ie, subjects who screen fail out of the run-in period for Study SHP643-302 when enrollment for that study closed.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.

- Other.

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

9.1.13 Other Assessments

9.1.13.1 Self-administration of Lanadelumab

All subjects who are considered suitable candidates will be allowed to self-administer treatment throughout the study.

Self-administration will be permitted after a subject (and/or their parent/caregiver) has received appropriate training by the Investigator or designee and has demonstrated their understanding of self-administration. Subjects are allowed to initiate self-administration at the subject's home or other agreed upon location after receiving the first 2 doses of lanadelumab at the study site. Subjects can also self-administer lanadelumab for Dose 3 thereafter. The first dose of self-administration is required to be administered at the study site. Once initiated, subjects can self-administer subsequent doses of lanadelumab at the study site (when visits are scheduled study site visits) or the subject's home (or other agreed upon location, when the study permitted off-site dosing).

Rollover subjects from Study SHP643-302 who were self-administrating the study drug at the time of screening will be permitted to continue self-administrating.

Adolescent subjects self-administering lanadelumab are to be supervised by a parent/legal guardian/caregiver. Alternatively, a parent/legal guardian/caregiver, after completing appropriate training, will be allowed to administer the study drug to an adolescent without study site personnel supervision.

The Investigator or designee will train subjects (and/or parents/caregivers) who elect to self-administer lanadelumab on the following:

- The subject's (or parent/caregiver's) transportation of study drug using a sponsor-provided cooler, and the recommended storage conditions of study drug when stored at an off-site location.
- Maintenance of accurate records regarding each administration of study drug including supply identification (ie, lot/kit number), date and time of injection, injection site location, infusion time, and if applicable, any reason the self-administration could not be completed as instructed.
- Retention of all used and unused PFS of study drug for drug accountability purposes.
- Additional information, as provided in the Pharmacy Manual.

Site personnel are to call subjects within approximately 3 days after the planned off-site self-administrations to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented. Throughout the study, study site personnel are to document information in source documents (ie, the subject's

medical record) and eCRF regarding the subject's experience with self-administration and SC administration of lanadelumab.

9.1.13.2 Injection Report

An Injection Report will be completed by the subject (or parent/caregiver) following each dose of lanadelumab, according to the SoA [redacted] The Injection Report will collect information on the subject's experience with SC injection and self-administration of lanadelumab.

Study personnel will document the subject's responses in the subjects' medical record and eCRF.

9.1.13.3 Biomarkers (C1-INH, C1q, and C4)

For non-rollover subjects, one blood sample will be obtained at the screening visit for evaluation of C1-INH, C4, and C1q to confirm a diagnosis of HAE. Diagnostic testing will be performed by a sponsor-approved central laboratory. Results of a C1-INH functional assay are required for eligibility assessment in all subjects. Results of the C4 assay are required for eligibility in subjects with a C1-INH level of 40 to 50%, and results of C1q assay are required for eligibility in subjects without a documented family history consistent with HAE Type I or II. With prior sponsor approval, subjects may be retested for C1-INH or C4 if results are incongruent with clinical history or believed by the Investigator to be confounded by recent LTP use. Note: Because C1-INH therapy may alter the laboratory results of C1-INH functional assay, the Investigator's discretion in collaboration with the medical monitor is advised for proper documentation of eligibility. No blood sampling is needed for rollover subjects.

9.2 Monitoring Subject Treatment Compliance

Treatment compliance and the extent of exposure to study drug will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects that received at least 80% of planned doses, summarized for each analysis population. All supplies used to administer study drug to the subject will be recorded on the eCRFs.

9.3 Schedule of Assessments

The schedule for all study-related procedures for all evaluations is shown in SoA [redacted]

9.3.1 Screening

Rollover subjects: For subjects rolling over from the SHP643-302 study, no screening visit is required. The first study visit for rollover subjects (Day 0) is to occur on the same day as the Study SHP643-302 Day 378 study visit.

Non-rollover Subjects: For subjects not rolling over from Study SHP643-302, subjects are required to provide informed consent and have screening assessments completed within 28 days prior to firs dose administration. Screened non-rollover subjects (adults and adolescents) who are

on LTP therapy for HAE can continue their current LTP until 3 weeks following the first dose of lanadelumab. It is understood that C1-INH therapy can alter the laboratory results of C1-INH assessments; therefore, the Investigator's discretion in collaboration with sponsor is advised for proper documentation of eligibility.

Procedures to be completed at screening include:

- Informed consent for non-rollover subjects.
- Eligibility review.
- Long-term prophylactic therapy.
- Demographics, medical history, and medication history.
- Pregnancy test (for female subjects).
- Complete physical examination, including documentation of height and weight.
- Vital signs.
- Prior and concomitant therapy (including medications and procedures).
- Concurrent medical conditions.
- Screening clinical laboratory tests.
- 12-lead ECG.
- Collection of historical HAE attack data [redacted]
- Functional C1-INH, C4, and C1q testing.
- Adverse events.

9.3.2 Treatment Period

9.3.2.1 Study Visit 1, Study Day 0

Visit 1 on Day 0 will be a scheduled on-site visit. The following procedures and assessments are to be performed on Day 0 prior to the first dose administration.

- Informed consent after site check-in with rollover subjects
  Informed consent may be completed on Day 364 of Study SHP643-302 or this visit, if not already provided.
- Confirmation of eligibility.
- Long-term prophylactic therapy details (tapered) for non-rollover subjects.
- Pregnancy test (for female subjects).
- Vital signs including body temperature, HR (pulse), BP, and RR.

- All clinical laboratory testing including hematology, coagulation, serum chemistry, and urinalysis.
- Prior or concomitant therapy (including medications and procedures).
- HAE attack data [redacted]

The following post-treatment procedures and assessments will be performed:

- Lanadelumab injection report.
- Vital signs including body temperature, HR (pulse), BP, and RR at 1 hour post-dose.
- Concomitant therapy (including medications and procedures).
- Adverse events collection, including SAEs and AESIs.

For rollover subjects, study site personnel will contact the subjects approximately every 7 days following the first dose of open-label lanadelumab solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open-label dose.

9.3.2.2 Study Visit 2 (Study Day 14) to Study Visit 14 (Study Day 182)

The assessment and other procedures that will take place from Study Visit 2 (Study Day 14) to Study Visit 14 (Study Day 182) are:

- Concomitant therapy (including medications and procedures).
- Adverse events collection, including SAEs and AESIs.
- HAE attack data [redacted]
- Lanadelumab injection report.

As indicated in SoA, the following procedures will be performed on Study Visits 2, 3, 5, 8, 11, and 14 (Study Day 14, 28, 56, 98, 140, and 182 respectively) are:

- Long-term prophylactic therapy details at Visit 2 and Visit 3 for non-rollover subjects.
- Vital signs including body temperature, HR (pulse), BP, and RR (both prior and 1 hour post-dose).
- Pregnancy test.
- Clinical laboratory testing (not performed on Visit 2 for all subjects, and not performed on Visit 5 and Visit 11 for rollover subjects).

Self-administration:

Subjects can also self-administer lanadelumab for Dose 3 thereafter. The first dose of self-administration is required to be administered at the study site. Once initiated, subjects can self-administer subsequent doses of lanadelumab at the study site (when visits are scheduled study site visits) or the subject's home (or other agreed upon location, when the study permitted off-site dosing).

Vital signs, pregnancy test and clinical laboratory testing at Study Visits 3, 5, and 11 (Study Day 28, 56, and 140 respectively) can be done at local site at investigator's discretion if approved by IRB.

Prior and concomitant therapy, adverse events collection, including SAEs and AESIs, HAE attack data and lanadelumab injection report from Study Visit 3 (Study Day 28) to Study Visit 13 (Study Day 168) except for Visit 8 (Study Day 98) can be done remotely (via phone or video) at investigator's discretion if approved by IRB.

9.3.3 Study Visit post Visit 14 (Day 182)

After Study Day 182, study visits will occur every 12 weeks, and site personnel are to make telephone calls to each subject q2w after Study Day 182 (except for in-clinic visits every 12 weeks) to collect AEs, concomitant medications, and to ensure all HAE attacks have been appropriately documented.

The treatment period is to last up to lanadelumab manufacturing and sale, development discontinued, or withdraw of new drug application. Administration of lanadelumab and study procedures is to continue without alteration to SoA, even if a subject receives treatment for a breakthrough angioedema attack on the day of a scheduled dose of study drug (if self-administering) or scheduled study visit.

Vital sings, pregnancy test, and clinical laboratory testing can be done at local site at Investigator's discretion if approved by IRB.

Prior and concomitant therapy, adverse events collection, including SAEs and AESIs, HAE attack data, and lanadelumab injection report can be done remotely (via phone or video) at Investigator's discretion if approved by IRB.

For Study Day 266, subjects should visit the study site for dispensing and/or administering study drug.

9.3.4 Safety Follow-up Visit

After completion of the treatment period, all subjects are to undergo safety evaluations during a 4-week follow-up period.

At the end of the follow-up period there will be a scheduled on-site end of study (EOS) visit, at which the following assessments and procedures will be performed:

- Vital signs including body temperature, HR (pulse), BP, and RR.

- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis.
- Pregnancy test (for female subjects).
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP [redacted]
- Prior and concomitant therapy (including medications and procedures).
- Adverse events collection, including SAEs and AESIs. Note: All AEs and SAEs that are not resolved at the time of this contact will be followed to closure.

9.3.5 Final Visit or Early Termination

All procedures and assessments scheduled for the EOS visit will be followed for the early termination visit

- Vital signs including body temperature, HR (pulse), BP, and RR.
- Clinical laboratory testing, including hematology, serum chemistry, coagulation, and urinalysis.
- Pregnancy test (for female subjects).
- 12-Lead ECG.
- HAE attack data (Note: Subjects must report details of an HAE attack to the study site within 72 hours of onset of the attack, in accordance with HAARP [redacted]
- Prior and concomitant therapy (including medications and procedures).
- Adverse events collection, including SAEs and AESIs. Note: All AEs and SAEs that are not resolved at the time of this contact will be followed to closure.
- Discharge from study.

9.3.6 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent and administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

In addition, drug-device AEs related to product malfunctions will be collected.

10.1.2 Additional Points to Consider for Adverse Events

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Adverse events caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing

for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The Investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

10. Results in DEATH.

11. Is LIFE-THREATENING.

- The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

12. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.

13. Results in persistent or significant DISABILITY/INCAPACITY.

14. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

15. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant Adverse Event List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure (including seizure and epilepsy)	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis (including interstitial lung disease)
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion, stillbirth and fetal death
COVID-19 related disease	COVID-19 pneumonia

Note: Terms identified on the Medically Significant adverse event List represent the broad medical concepts to be considered as "Important Medical Events" satisfying serious adverse event reporting requirements.

10.1.4 Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the Investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for Investigators as to how and when they should be reported to Takeda.

Adverse events of special interest include hypersensitivity reactions and events of disordered coagulation (bleeding AESIs and hypercoagulable AESIs).

10.1.5 Intensity of Adverse Events

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of Adverse Events

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the Investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or Investigator.

AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the Investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the Investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

AE = adverse event

10.1.9 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose interval was extended due to the particular AE.
- Dose Increased – the dose interval was returned to the original setting due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.

- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.1.13 Product Malfunctions

Malfunction means the failure of a drug product and/or medical device (eg, prefilled syringe) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the product. The intended performance of a product refers to the intended use for which the product is labeled or marketed.

An Investigator who is made aware of or identifies a potential product malfunctions should immediately report the event to the sponsor. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from the sponsor.

10.2 Procedures

10.2.1 Collection and Reporting of Adverse Events

10.2.1.1 Adverse Event Collection Period

Collection of AEs will commence from the time the subject signs the informed consent to participate in the study. For rollover subject, ongoing AEs (including HAE attacks) at the end of the previous study is required to be followed-up in the study. Routine collection of AEs will continue until final visit/ early termination.

10.2.1.2 Adverse Events Reporting

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious AEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

In this study, HAE attacks are to be captured as AEs. All AEs, regardless of seriousness, severity, or causal relationship to lanadelumab, are to be recorded on the AE page of the eCRF (with the exception of HAE attacks as indicated below). Any AE reported to the site meeting criteria for a SAE is required to be reported to the sponsor using the SAE Reporting Form in the electronic data capture (EDC) system within 3 working days of becoming aware of the event.

- Non-HAE attack AEs will be reported on the AE page of the eCRF. The severity of these AEs will be assessed according to the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table [redacted] and the DMID Pediatric Toxicity Table [redacted]

- These HAE attack AEs will be reported on the designated angioedema attack page of the eCRF. Severity of the angioedema attack will be assessed in accordance with HAARP, which includes an assessment using HAARP criteria [redacted] and an assessment using DMID criteria.

For all AEs that are reported as HAE attacks, the Investigator or physician designee is to review the event within 3 days of initial notification and, in accordance with HAARP, evaluate if it represents a confirmed HAE attack. If necessary for the evaluation, the Investigator or designee can contact the subject to receive additional information. Any subject-reported attack not confirmed by the Investigator or physician designee is required to have an alternate AE diagnosis recorded.

Emergency department visits for HAE attacks and HAE attacks resulting in hospital admissions are to be captured.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

10.2.1.3 Adverse Events of Special Interest

If the AESI that occurs during the treatment period or the follow-up period is considered to be clinically significant based on the criteria below, it should be reported by the Investigator to the sponsor/the Emergency Reception Center for Safety Information (see Annex 1) immediately or within 24 hours of/after the first onset or subject's notification of the event. Reporting urgency depends on the level of emergency. An AESI Form or an SAE form should be completed,

signed, or signed and sealed by the Investigator and reported to the sponsor/the Emergency Reception Center for Safety Information (see Annex) within 10 calendar days.

The Investigator should submit the original copy of the AESI Form or the SAE form to the sponsor. Adverse events of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

The following describe the AESI and the criteria for reporting AESI.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours, only if the reactions are suspected to be related to study drug.

Events of Disordered Coagulation

Bleeding AESI

Although activated partial thromboplastin time (aPTT) prolongation due to pKal inhibition is an artifactual in vitro phenomenon, as a precautionary measure in evaluating the safety of lanadelumab, bleeding events will be reported as AESI for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a clinical event of bleeding. Coagulation testing (aPTT, prothrombin time, and international normalized ratio) should be performed when possible, and when temporally reasonable, with any reports of bleeding or for clinical conditions possibly indicative of bleeding.

Hypercoagulable AESI

Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with a thrombotic or embolic etiology.

10.2.2 Collection and Reporting of Serious Adverse Events

When an SAE occurs through the 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 annex 1) within 24 hours 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 annex 1) 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.

10.3 Follow-up of Serious Adverse Events

If information not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form copy or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, Institutional Review Boards and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 3 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 Case Report Forms (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

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

All corrections must be initialed and dated. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included. All new additions are to be made with the date and sign.

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

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

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

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

12.2 Record Retention

The Investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated informed consent forms, copies of all query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

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

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued).
2. The day 3 years after the date of early termination or completion of the study.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared prior to the first subject enrolled and finalized prior to database lock to preserve the integrity of the statistical analysis and study conclusions. The SAP will provide the statistical methods and definitions for the analysis of the clinical outcomes 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, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

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

13.1.1 Analysis Sets

Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of lanadelumab. All safety and efficacy analyses will be based on the FAS and each subset in FAS defined below. Unless otherwise specified, summary tabulations conducted using FAS will be presented by the each subset and overall.

- Rollover subjects in FAS: the subset of subjects who participated in Study SHP643-302 and received any study drug after entering Study TAK-743-5007.
- Non-rollover subjects in FAS: the subset of subjects who entered Study TAK-743-5007 directly and received any study drug after entering Study TAK-743-5007.

13.1.2 Subject disposition

The numbers of subjects treated with study drug, completed the study, and discontinued prematurely by reason will be summarized for FAS.

13.1.3 Analysis of Demographics and Other Baseline Characteristics

Baseline HAE characteristics and demographic variables will be summarized for FAS.

13.1.4 Medical History

Medical history will be coded using the MedDRA and summarized by system organ class and preferred term (PT) for FAS.

13.1.5 Treatment Exposure and Compliance

Treatment compliance and the extent of exposure to study drug will be described by the percentage of planned doses received by the subject, total number of doses received by the subject, and the number and percentage of subjects that received at least 80% of planned doses, summarized for FAS.

13.1.6 Prior and Concomitant Medications

Concomitant medications will be coded using the WHO-Drug Dictionary. The number and percentage of subjects with prior or concomitant medications will be summarized by therapeutic class and PT for FAS. A separate, similar table will be provided for the subset of concomitant medications classified as rescue medications.

13.1.7 Efficacy Analysis

No statistical hypothesis testing will be performed.

Time to the first Investigator-confirmed HAE attack will be analyzed using the Non-rollover subjects for FAS.

Time to first Investigator-confirmed HAE attack is to be calculated from the time of first dose of lanadelumab in this study to the start time of the first Investigator-confirmed HAE attack. If a subject does not have an attack, the subject will be censored from the time of first dose of lanadelumab to the earlier of the early discontinuation date or end of treatment period date. The time to the first Investigator-confirmed HAE attack (days) will be summarized using Kaplan-Meier (KM) methods. Summaries will include 25th, 50th (median), and 75th percentiles, if estimable, and the corresponding 95% confidence intervals. In addition, KM plots detailing each subject's contribution to the analysis will be provided.

All efficacy data, including derived data, will be presented in subject data listings.

13.1.8 Safety Analysis

13.1.8.1 Adverse events

Adverse events are to be coded using the MedDRA coding dictionary. No inferential statistics are planned.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to lanadelumab in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

The number and percentage of subjects with TEAEs will be displayed by system organ class and PT using MedDRA for FAS. This tabulation will be repeated for related AEs, SAEs, related SAEs, severe AEs, related severe AEs, and Investigator-reported AESIs.

All AEs will be provided in subject listings. In addition, subject listings of AEs causing discontinuation of study medication, AEs leading to death, SAEs, related AEs, severe AEs, and Investigator-reported AESIs will be produced.

Adverse events of special interests for this study are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events). Standardized MedDRA Queries

(SMQ) for each AESI will be performed using the study data. A listing detailing the PT within the SMQ will be provided.

Injection site reaction AEs will be identified by AEs with the PTs starting with "Injection site," "Application site," or "Administration site." A listing of injection site reaction AEs will be provided.

13.1.8.2 Clinical laboratory evaluation

Laboratory test results will be summarized for FAS. All laboratory test results will be listed.

Subjects with clinically significant abnormal laboratory test results will be listed. This listing will include all results of the laboratory parameter that was abnormal and determined to be clinically significant by the Investigator for a subject across study visit to identify any trends.

13.1.8.3 Vital signs

Vital signs will be summarized for FAS. All vital signs will be listed.

Subjects with clinically significant vital sign values will be listed. This listing will include all results of the vital sign parameters that were determined by the Investigator to be clinically significant for a subject across study time points to identify any trends.

13.2 Interim Analysis and Criteria for Early Termination

Interim summary may be produced during the study to support regulatory reporting if requested by the authority.

13.3 Determination of Sample Size

This study is designed to expand access of lanadelumab and evaluate the safety of open-label treatment with lanadelumab in subjects with HAE who participated in SHP643-302 (rollover subjects) and individuals who are not otherwise able to participate in SHP643-302 (non-rollover subjects). Therefore, no formal sample size calculation was performed.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

The Investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The Investigator and study site/head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 Institutional Review Board Approval

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

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

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

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

15.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the Investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

Agostoni, A. and Cicardi, M. 1992. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine (Baltimore), 71, 206-15.

Bork, K., Siedlecki, K., Bosch, S., Schopf, R. E.and Kreuz, W. C. 2000. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clinic proceedings. Mayo Clinic, 75, 349-54.

Bork, K., Hardt, J., Schicketanz, K. H.and Ressel, N. 2003. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Intern Med, 163, 1229-35.

Bork, K., Meng, G., Staubach, P.and Hardt, J. 2006. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med, 119, 267-74.

Bork, K., Hardt, J.and Witzke, G. 2012. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol, 130, 692-7.

Bork, K., Bernstein, J. A., Machnig, T.and Craig, T. J. 2016. Efficacy of Different Medical Therapies for the Treatment of Acute Laryngeal Attacks of Hereditary Angioedema due to C1-esterase Inhibitor Deficiency. J Emerg Med, 50, 567-80.e1.

Bygum, A. 2009. Hereditary angio-oedema in Denmark: a nationwide survey. The British journal of dermatology, 161, 1153-8.

Cicardi, M., Bork, K., Caballero, T., Craig, T., Li, H. H., Longhurst, H., Reshef, A. and Zuraw, B. 2012. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy, 67, 147-57.

Craig, T. J., Levy, R. J., Wasserman, R. L., Bewtra, A. K., Hurewitz, D., Obtulowicz, K., Reshef, A., Ritchie, B., Moldovan, D., Shirov, T., Grivcheva-Panovska, V., Kiessling, P. C., Keinecke, H. O. and Bernst. 2009. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. Journal of Allergy and Clinical Immunology, The, 124, 801-808.

Craig, T., Pursun, E. A., Bork, K., Bowen, T., Boysen, H., Farkas, H., Grumach, A., Katelaris, C. H., Lockey, R., Longhurst, H., Lumry, W., Magerl, M., Martinez-Saguer, I., Ritchie, B., Nast, A., Pawankar, R., Zuraw, B. and Maurer, M. 2012. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J, 5, 182-199.

Goring, H. D., Bork, K., Spath, P. J., Bauer, R., Ziemer, A., Hintner, H. and Wuthrich, B. 1998. Hereditary angioedema in the German-speaking region. Hautarzt, 49, 114-22.

Horiuchi, T., Ohi, H., Ohsawa, I., Fujita, T., Matsushita, M., Okada, N., Seya, T., Yamamoto, T., Endo, Y., Hatanaka, M., Wakamiya, N., Mizuno, M., Nakao, M., Okada, H., Tsukamoto, H., Matsumoto, M., Inoue, N., Nonaka, M. and Kinoshita, T. 2012. Guideline for hereditary angioedema (HAE) 2010 by the Japanese Association for Complement Research - secondary

publication. Allergology international : official journal of the Japanese Society of Allergology, 61, 559-62.

Lei, W. T., Shyur, S. D., Huang, L. H., Kao, Y. H. and Lo, C. Y. 2011. Type I hereditary angioedema in Taiwan -- clinical, biological features and genetic study. Asian Pac J Allergy Immunol, 29, 327-31.

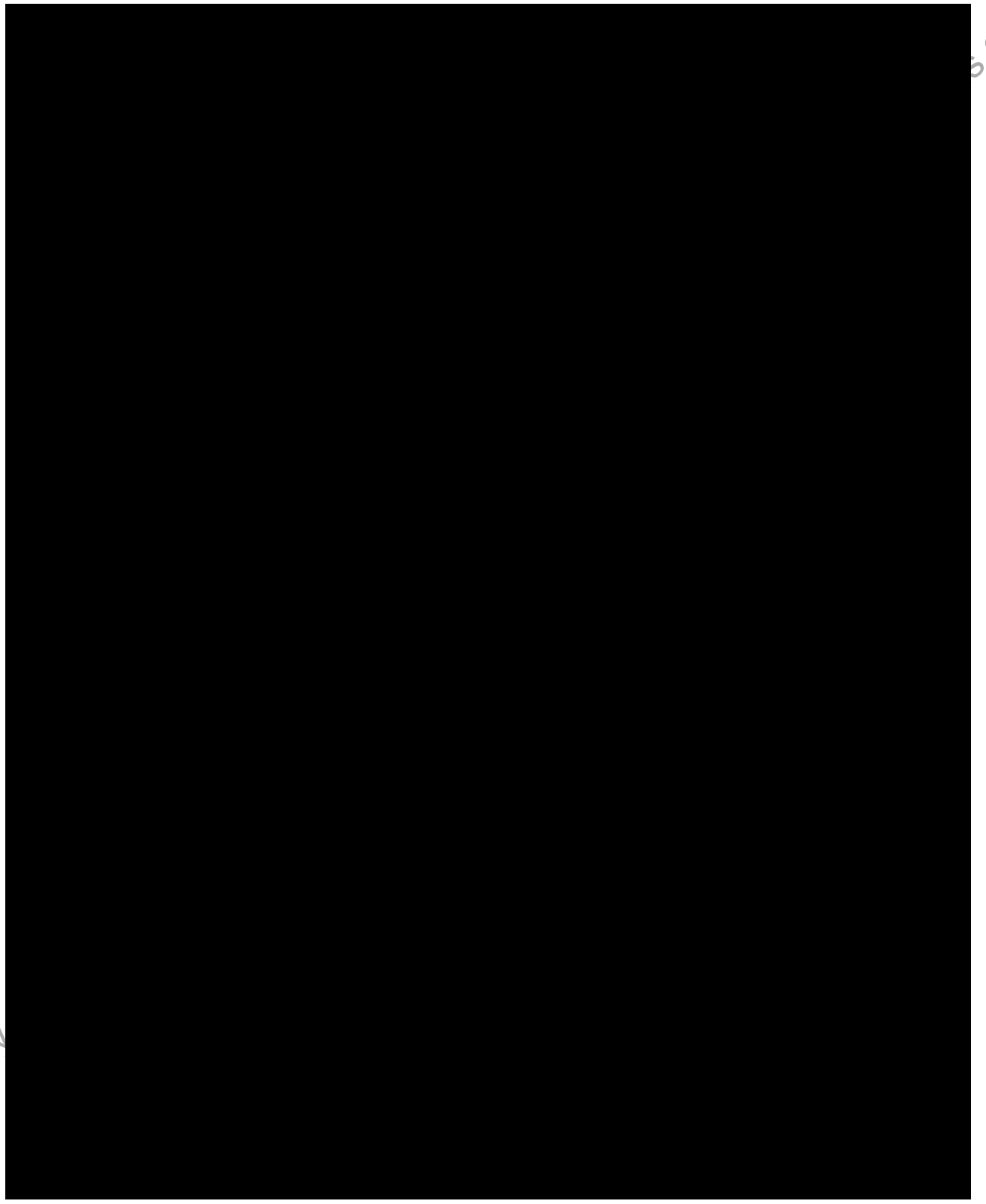
Lumry, W. R. 2013. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. American journal of managed care,19, s103-10.

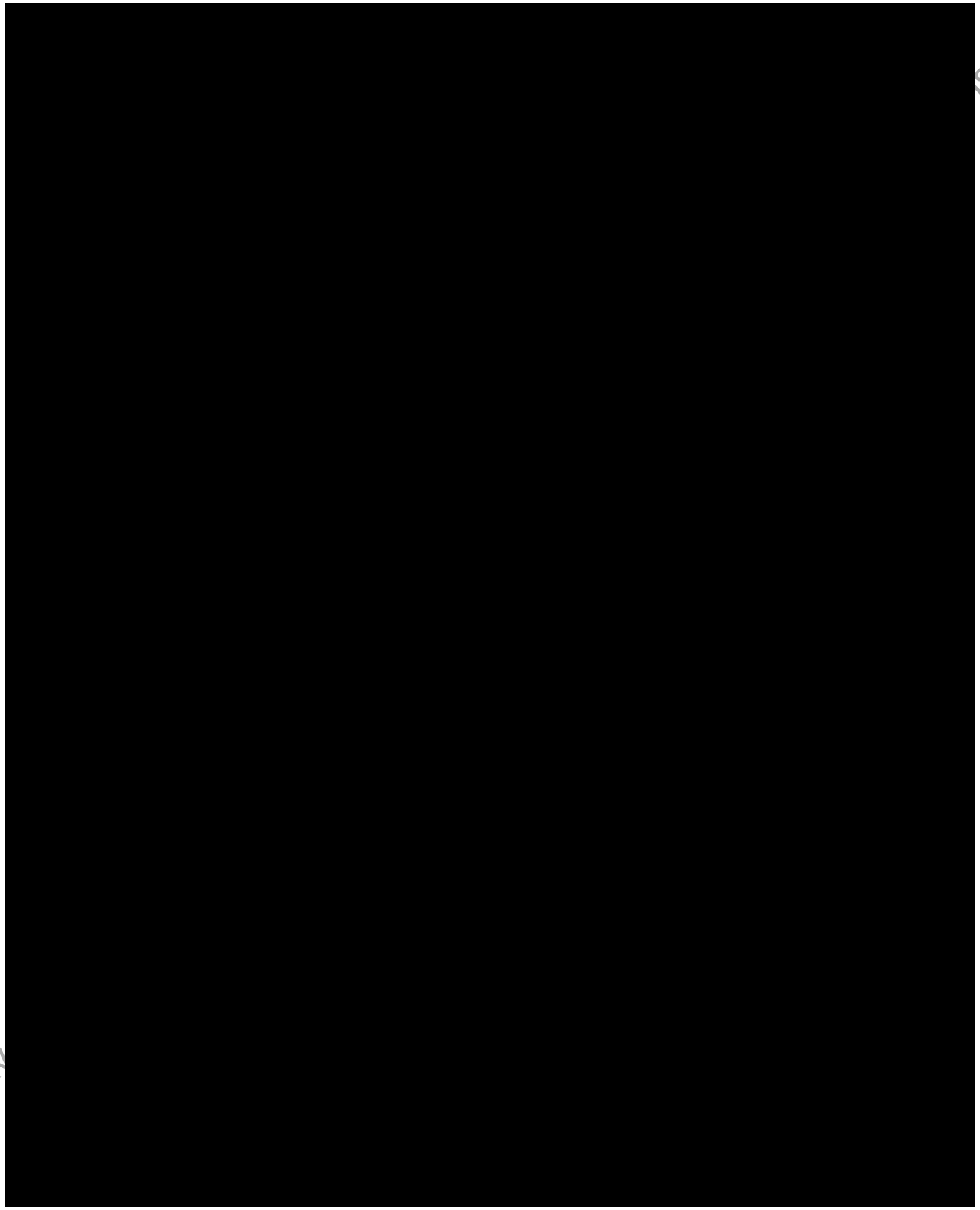
Maurer, M., Magerl, M., Ansotegui, I., Aygoren Pursun, E., Betschel, S., Bork, K., Bowen, T., Balle Boysen, H., Farkas, H., Grumach, A., Hide, M., Katelaris, C., Lockey, R., Longhurst, H., Lumry, W., Martinez-Saguer, I., Moldovan, D., Nast, A., Pawankar, R., Potter, P., Riedl, M., Ritchie, B., Rosenwasser, L., Sanchez-Borges, M., Zhi, Y., Zuraw, B. and Craig, T. 2018. The international WAO/EAACI guideline for the management of hereditary angioedema - the 2017 revision and update. Allergy.

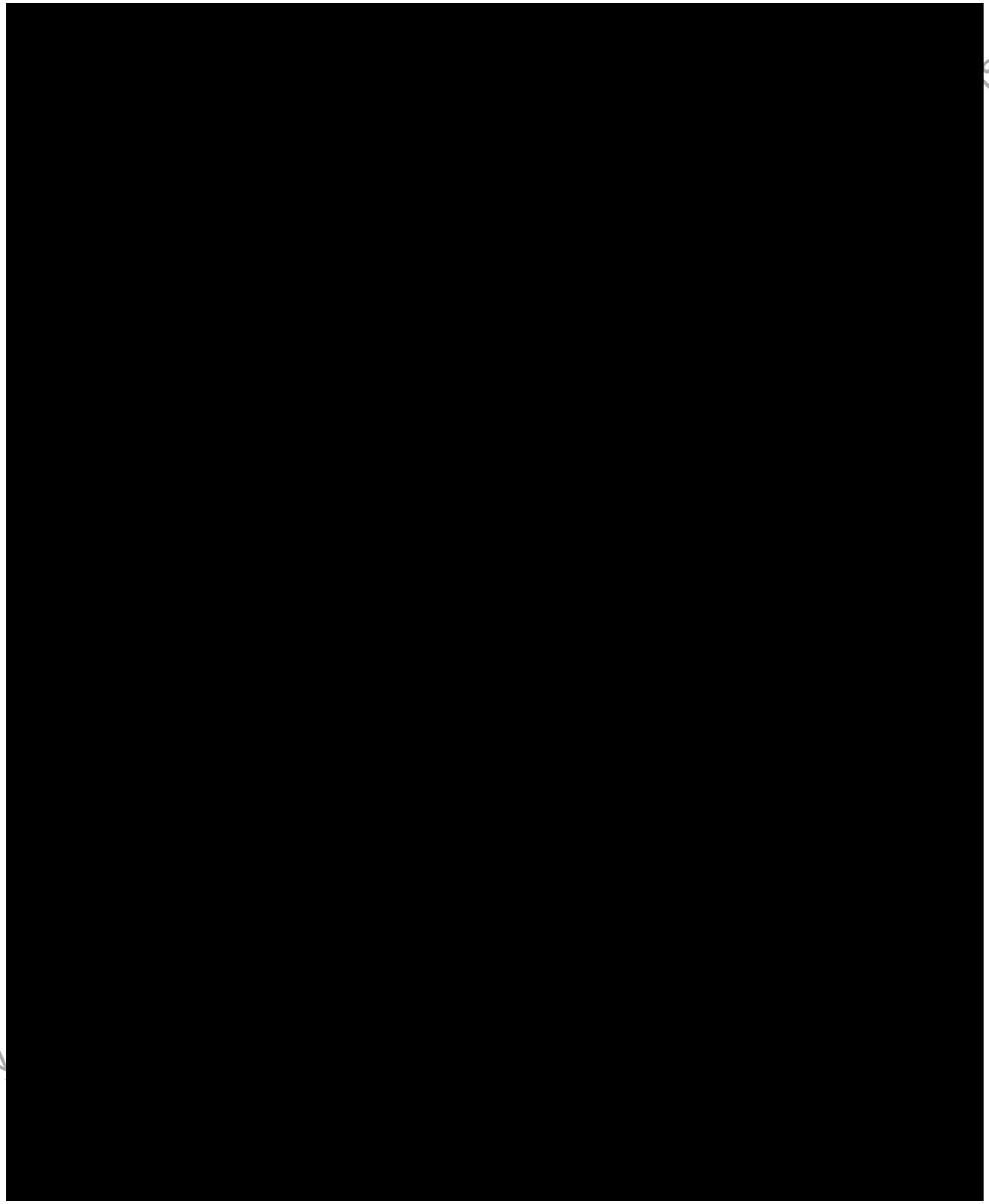
Nordenfelt, P., Dawson, S., Wahlgren, C. F., Lindfors, A., Mallbris, L. and Bjorkander, J. 2014. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc, 35, 185-90.

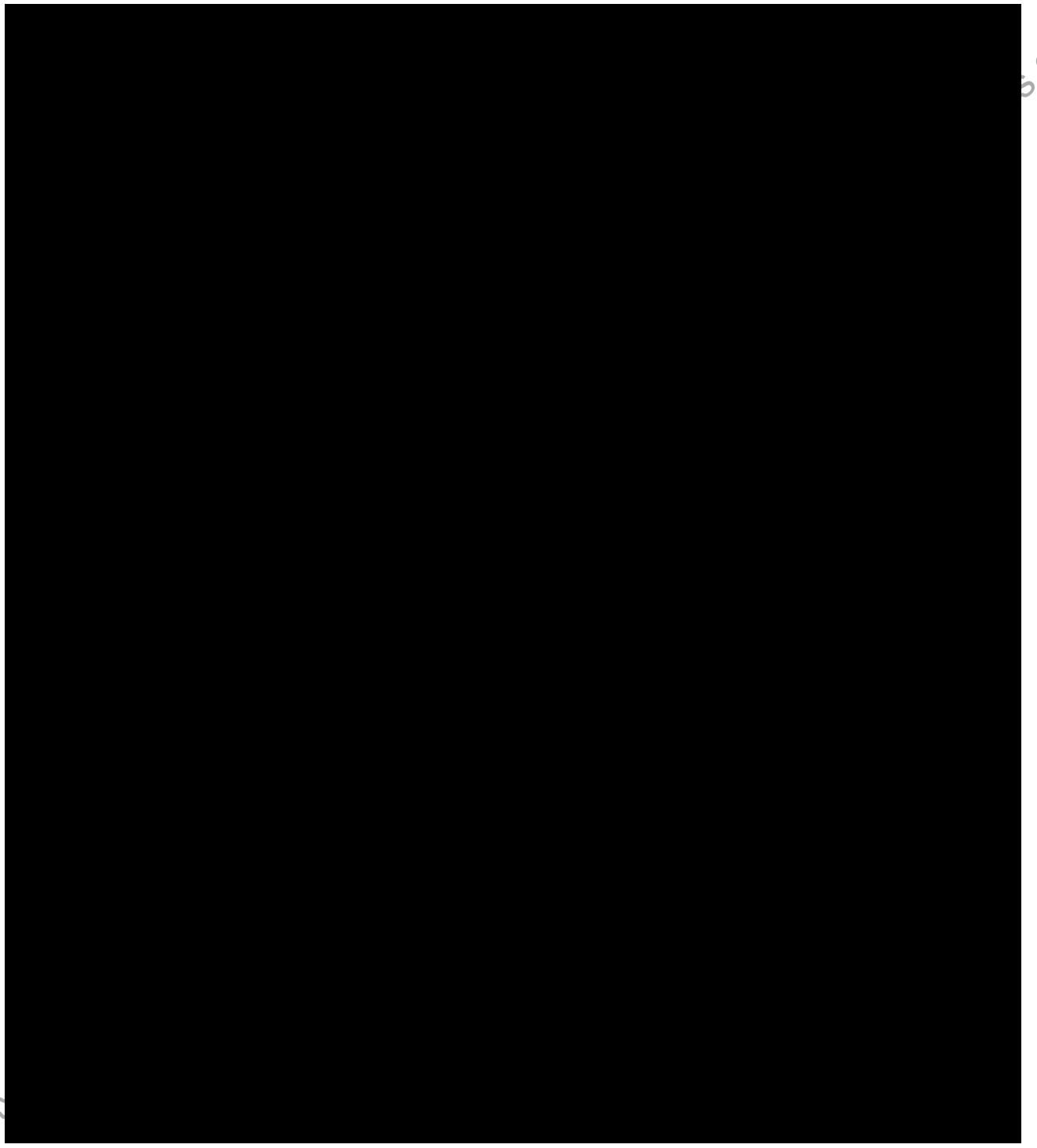
Roche, O., Blanch, A., Caballero, T., Sastre, N., Callejo, D. and Lopez-Trascasa, M. 2005. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol, 94, 498-503.

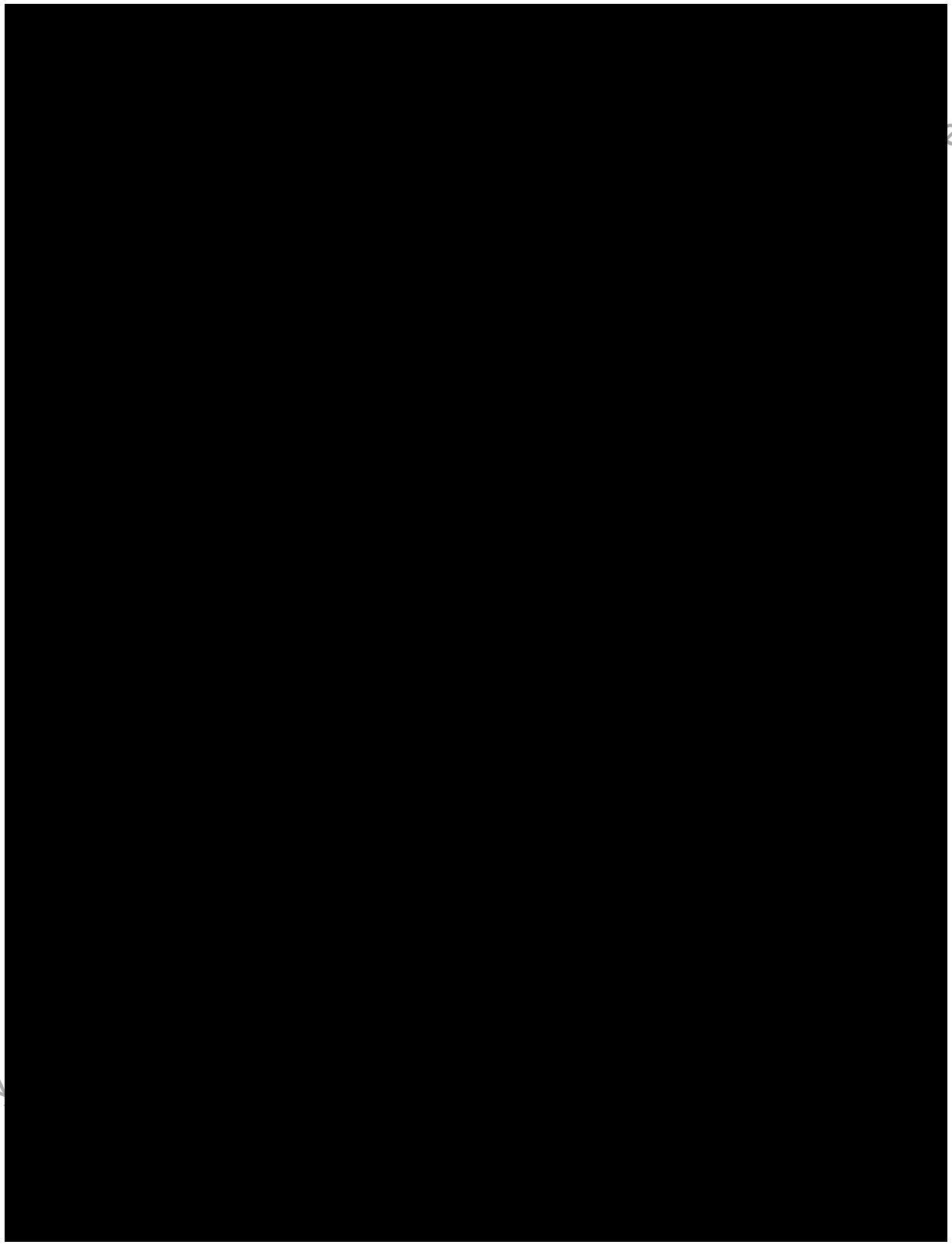
Zuraw, B. L. 2008. Clinical practice. Hereditary angioedema. N Engl J Med, 359, 1027-36.

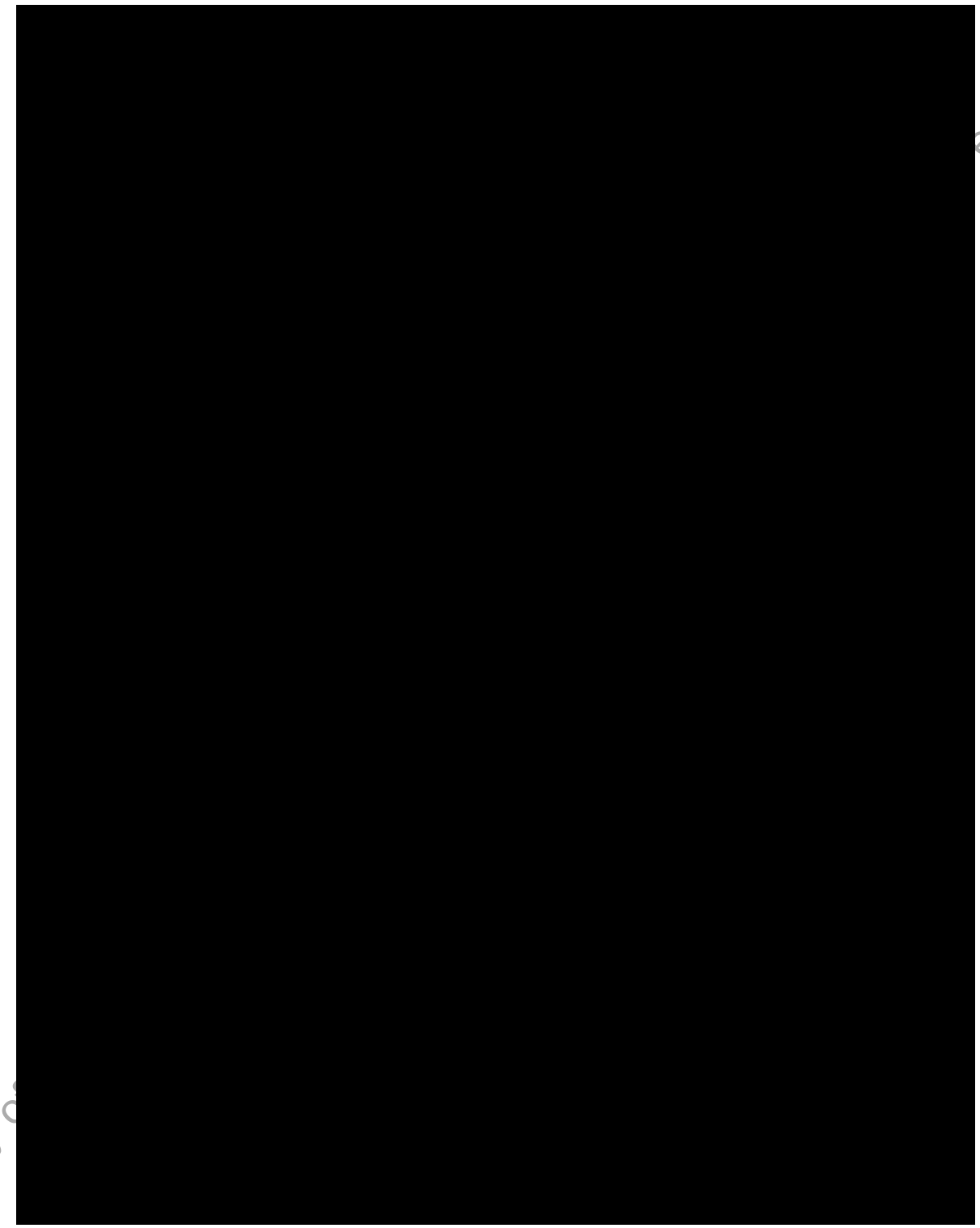


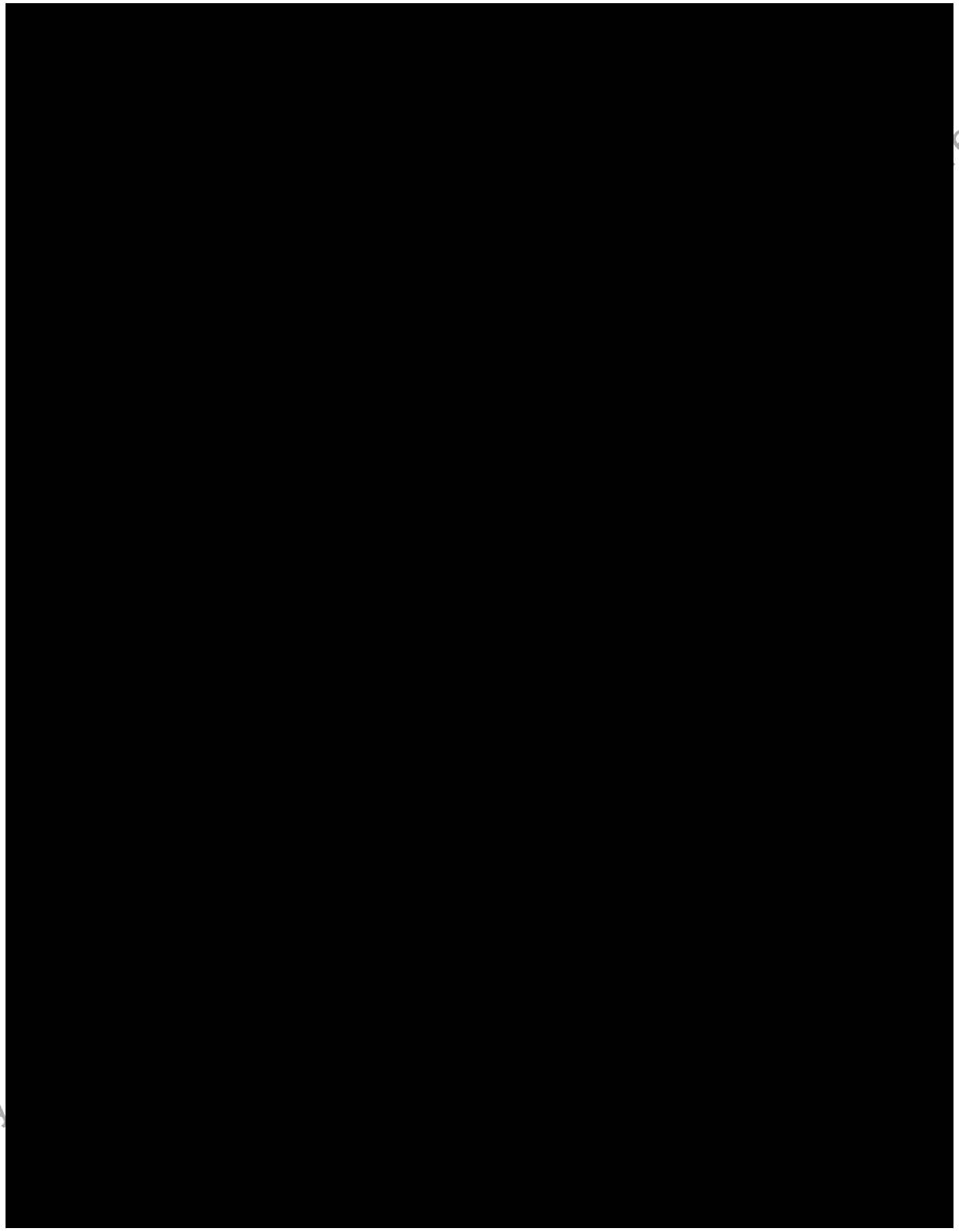


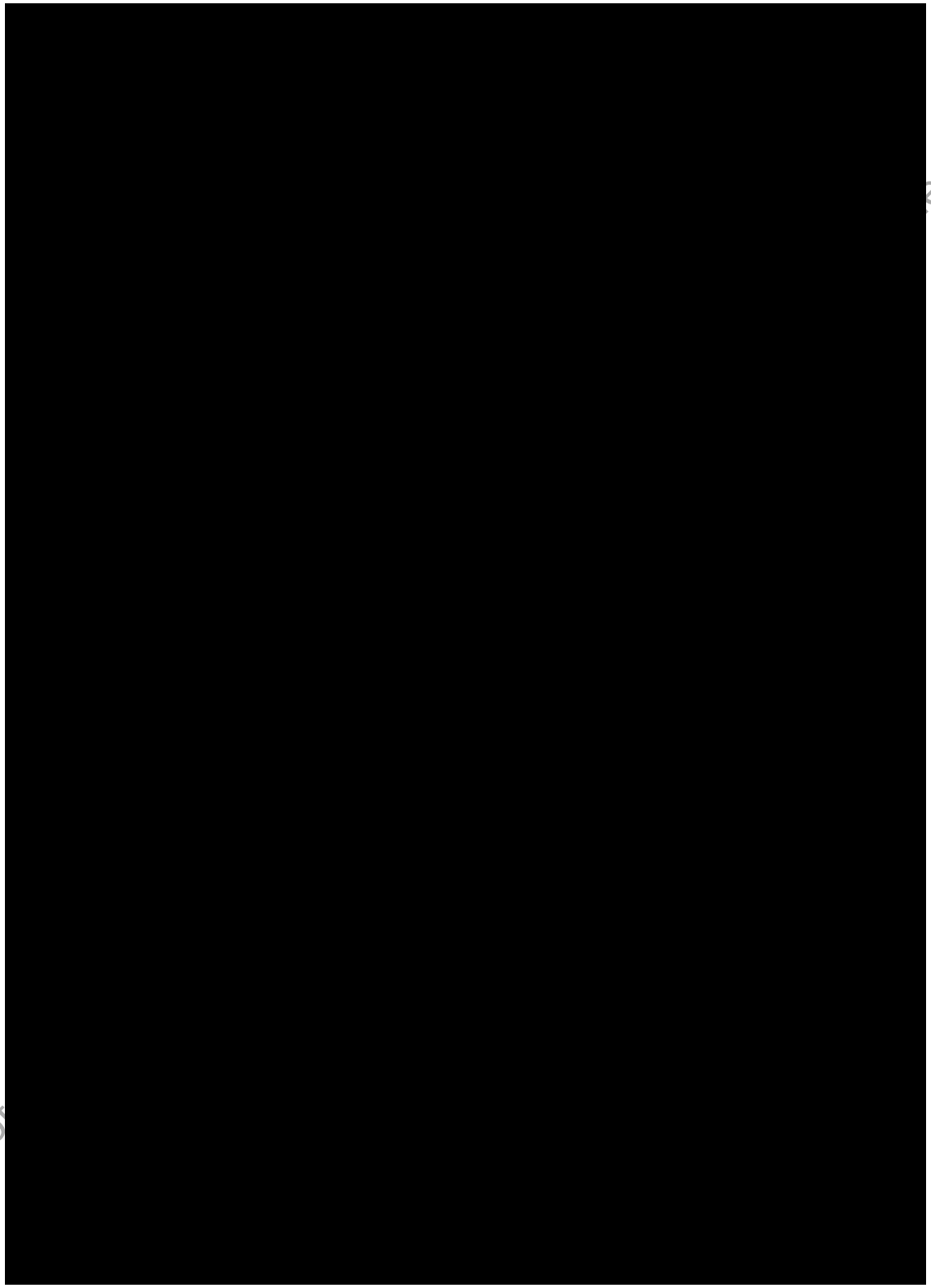


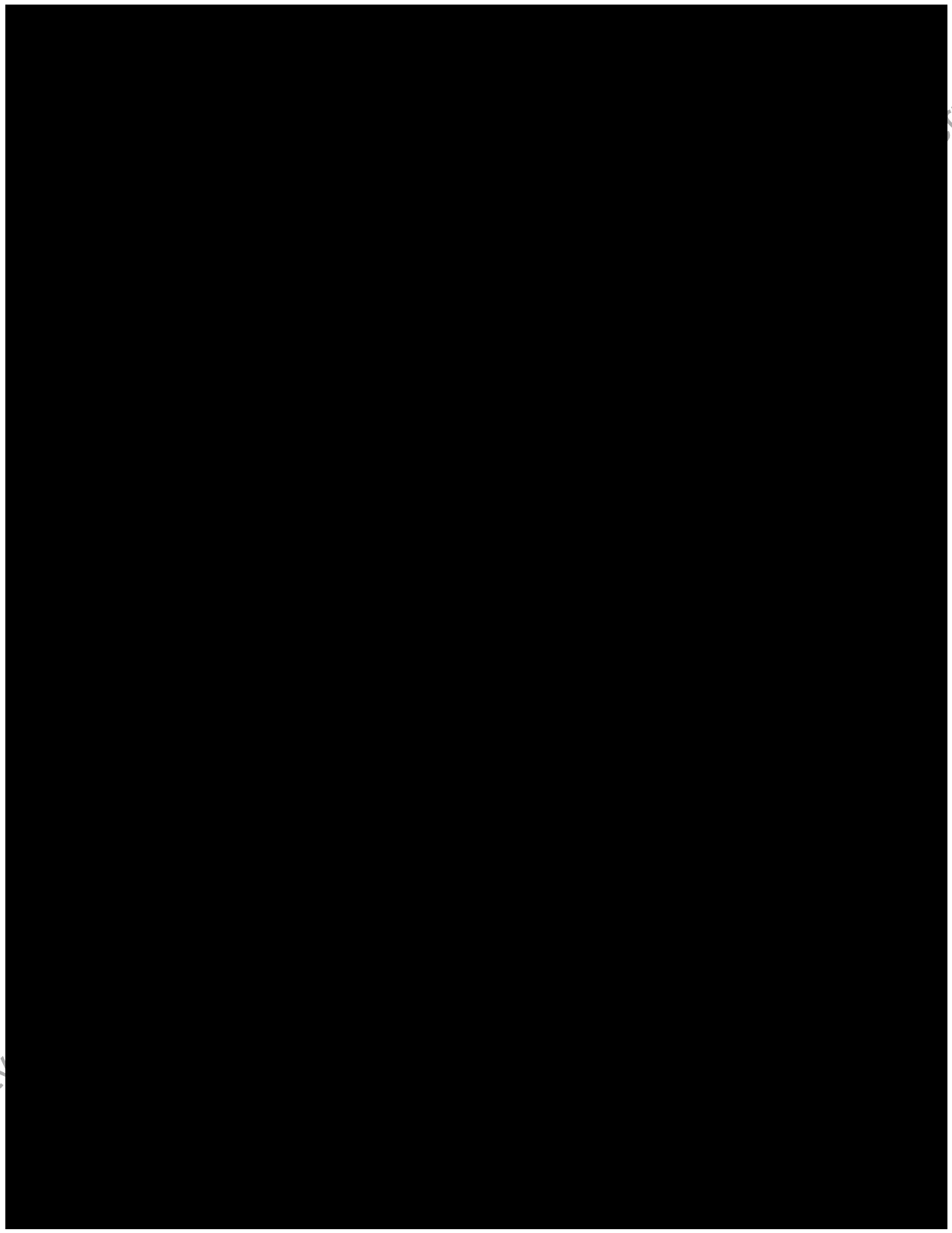




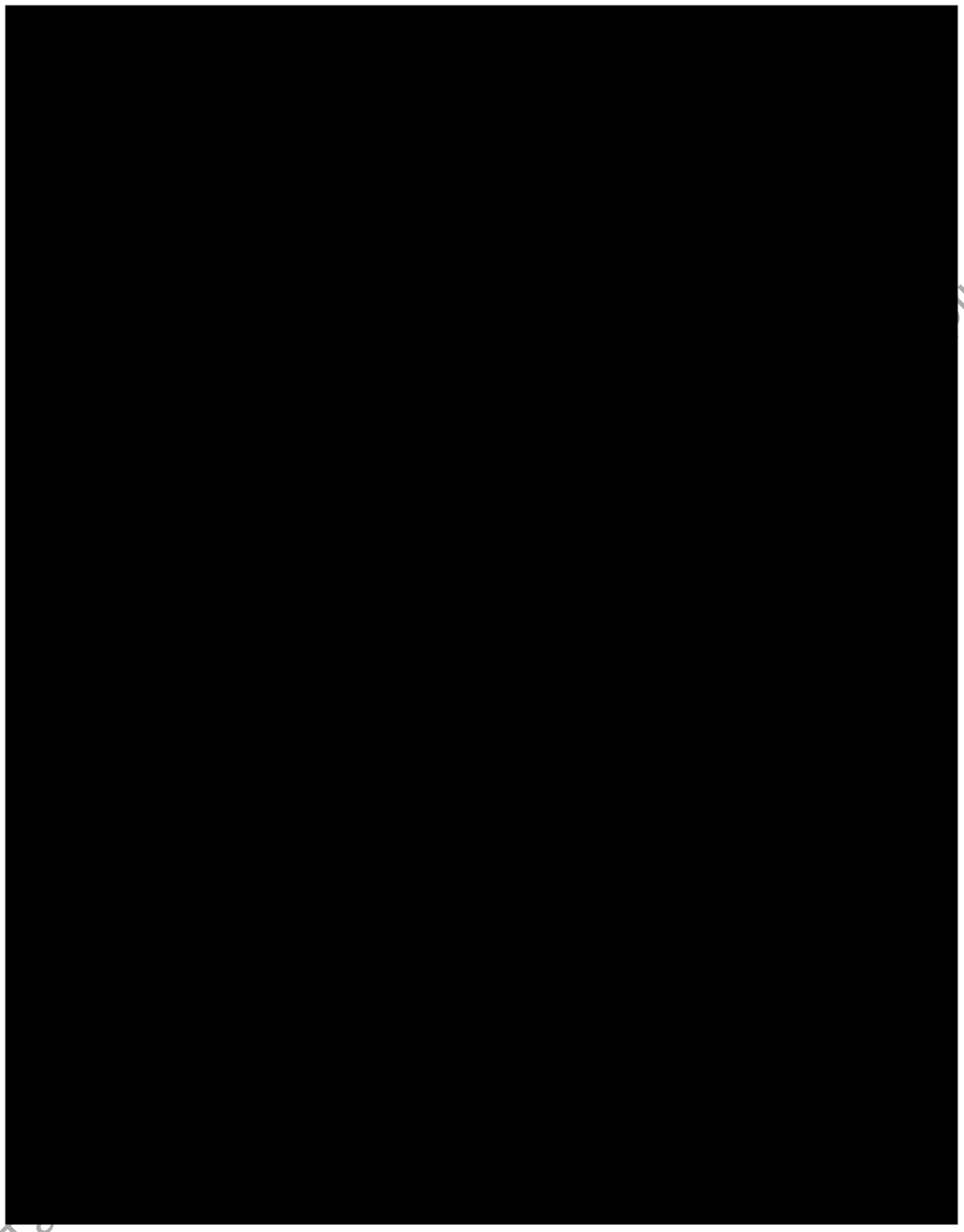


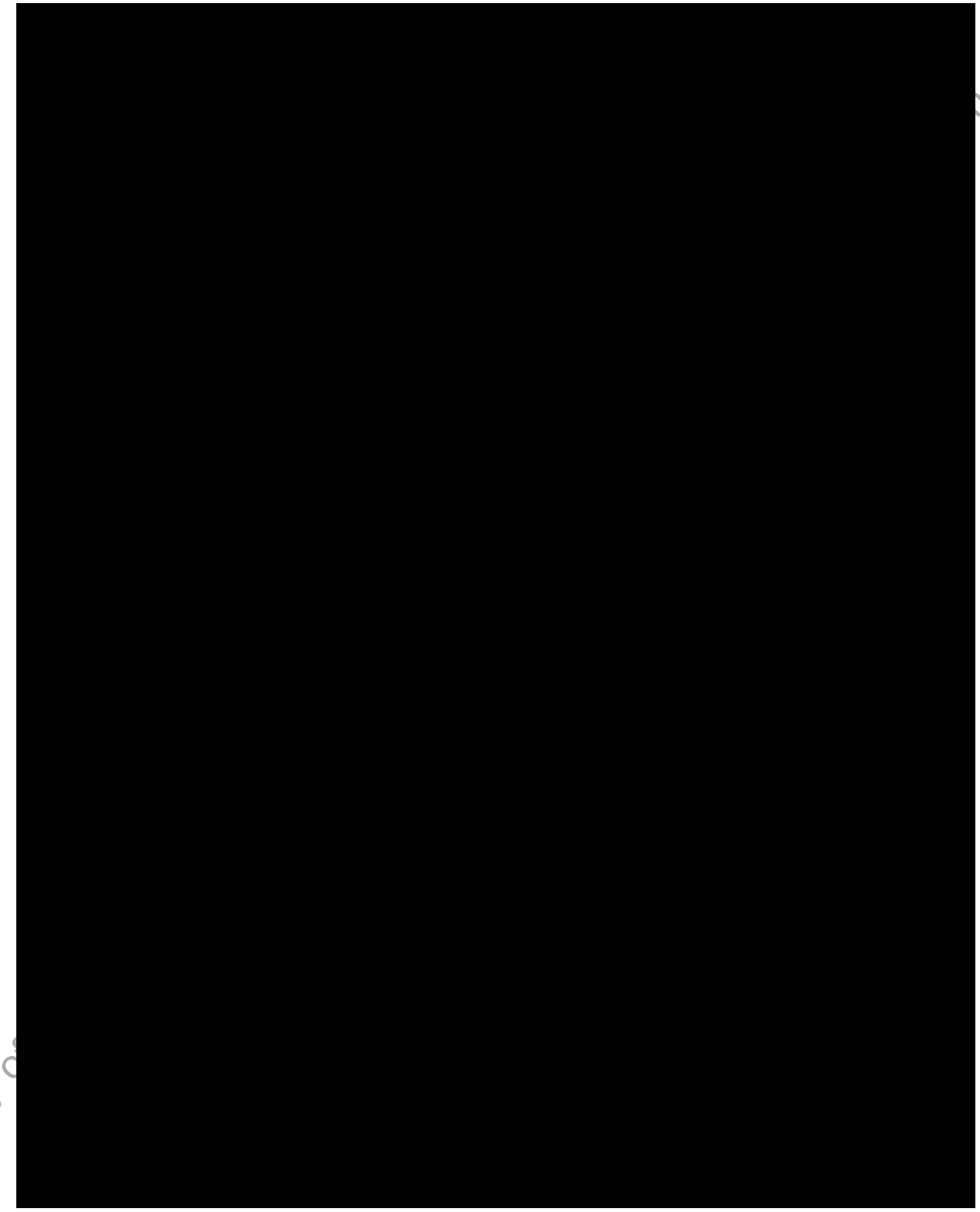


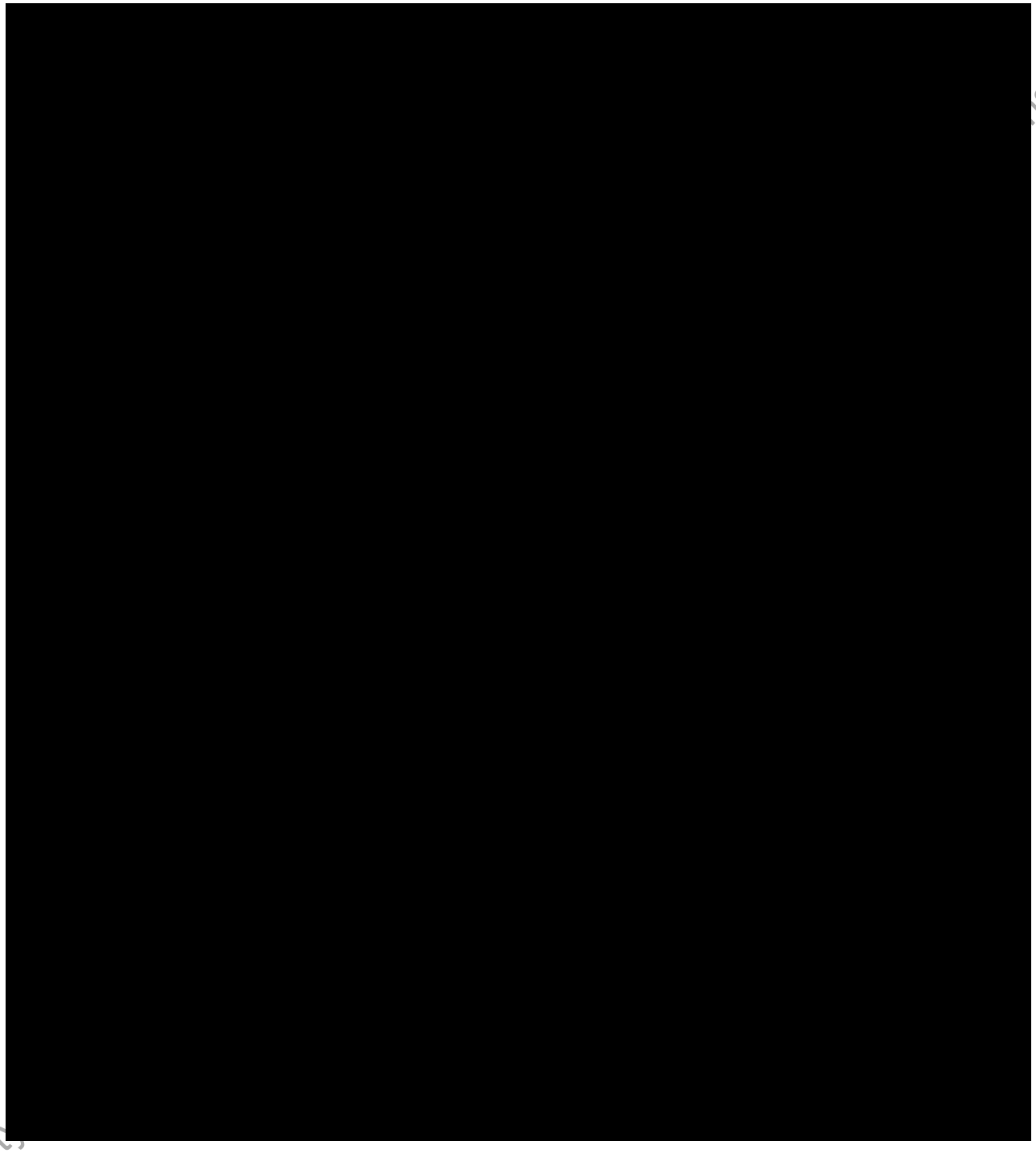


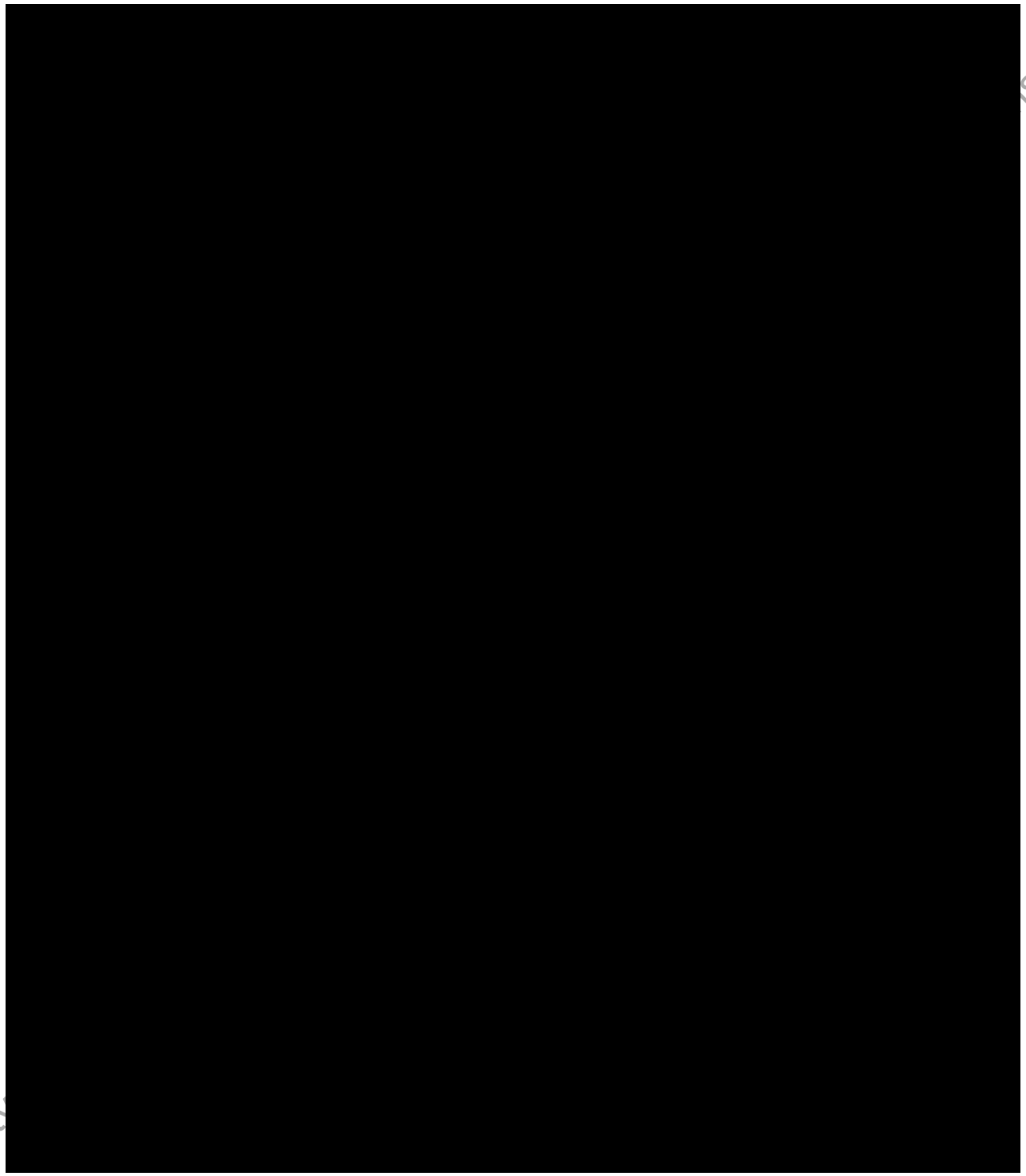


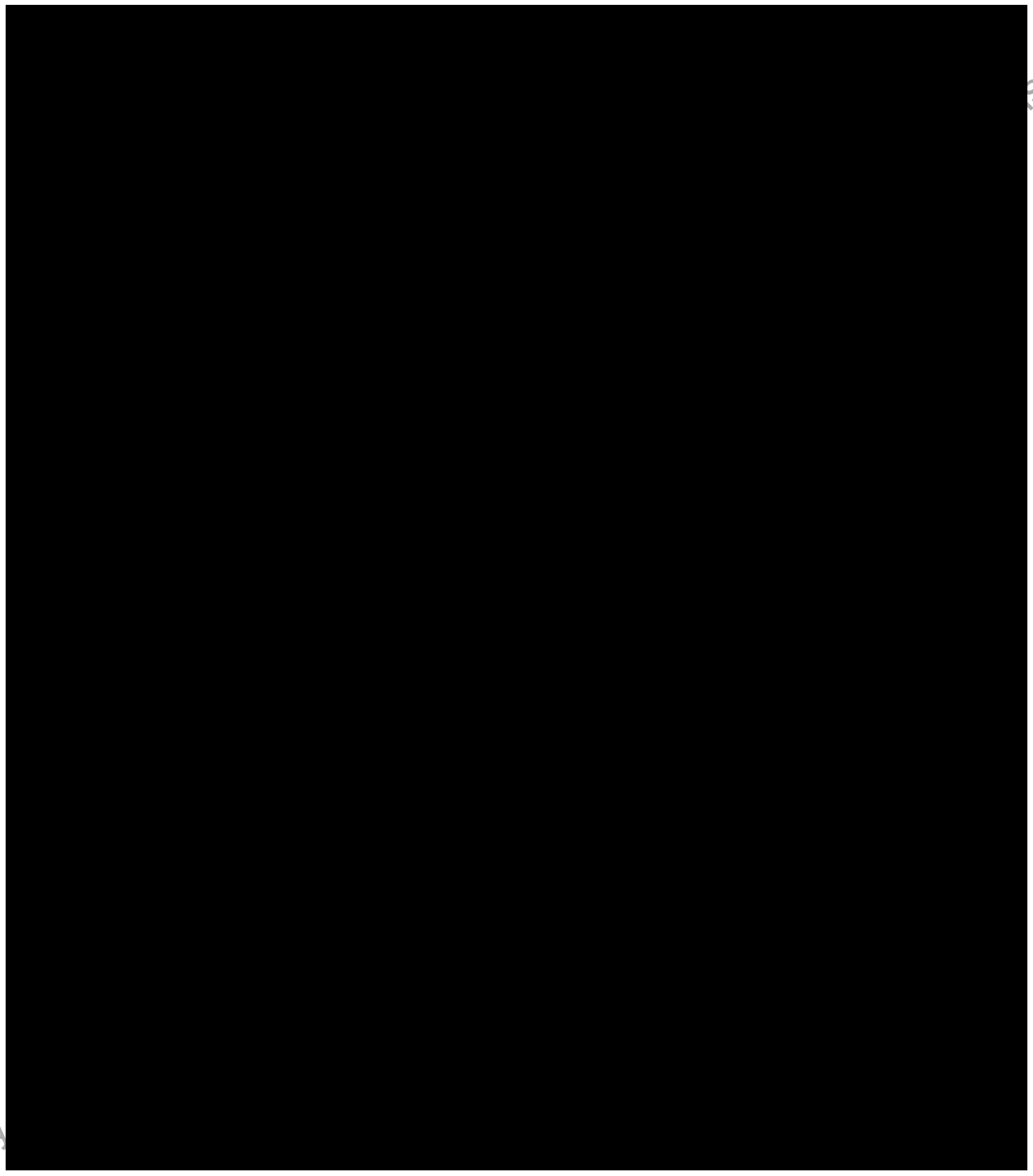
[redacted]

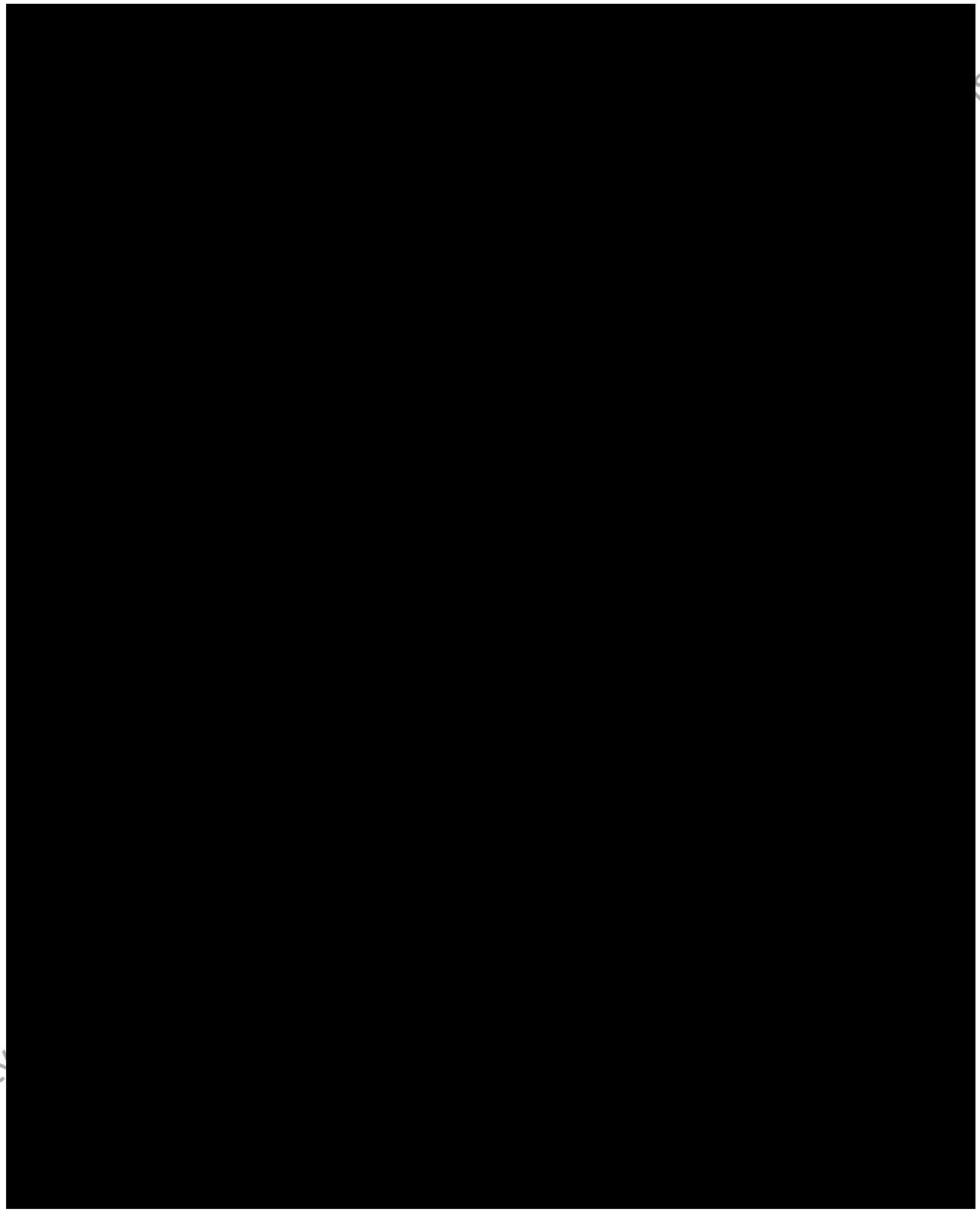




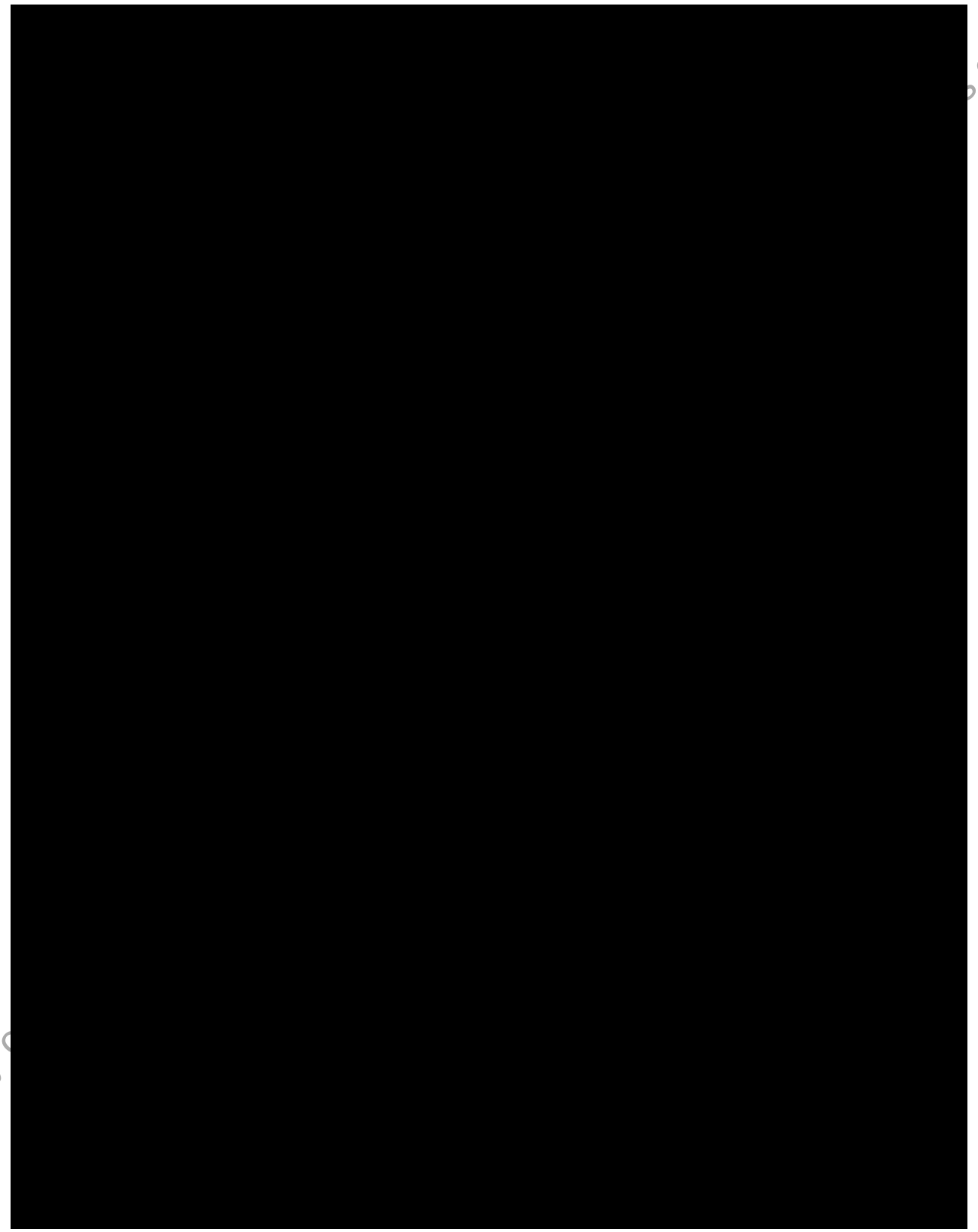


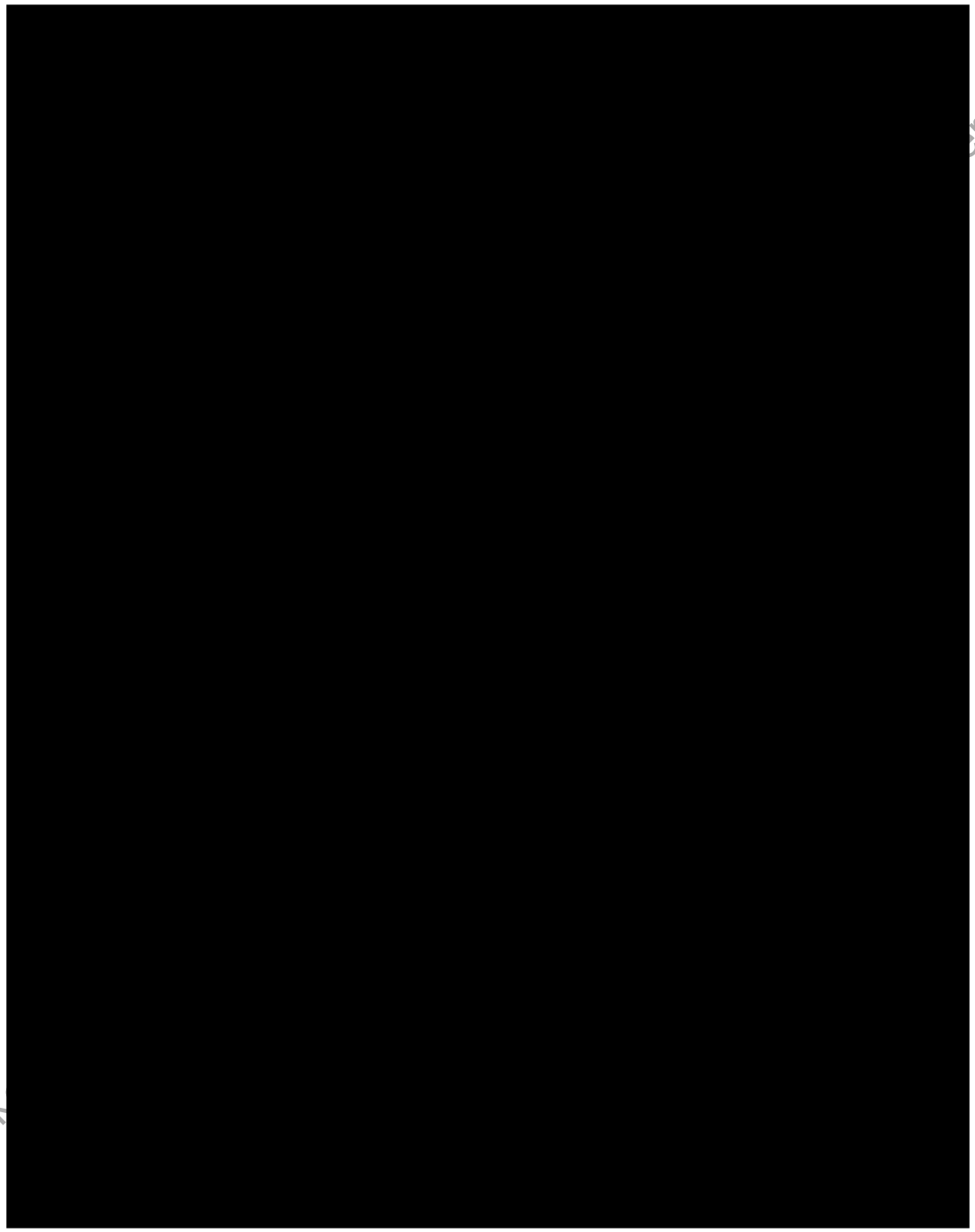


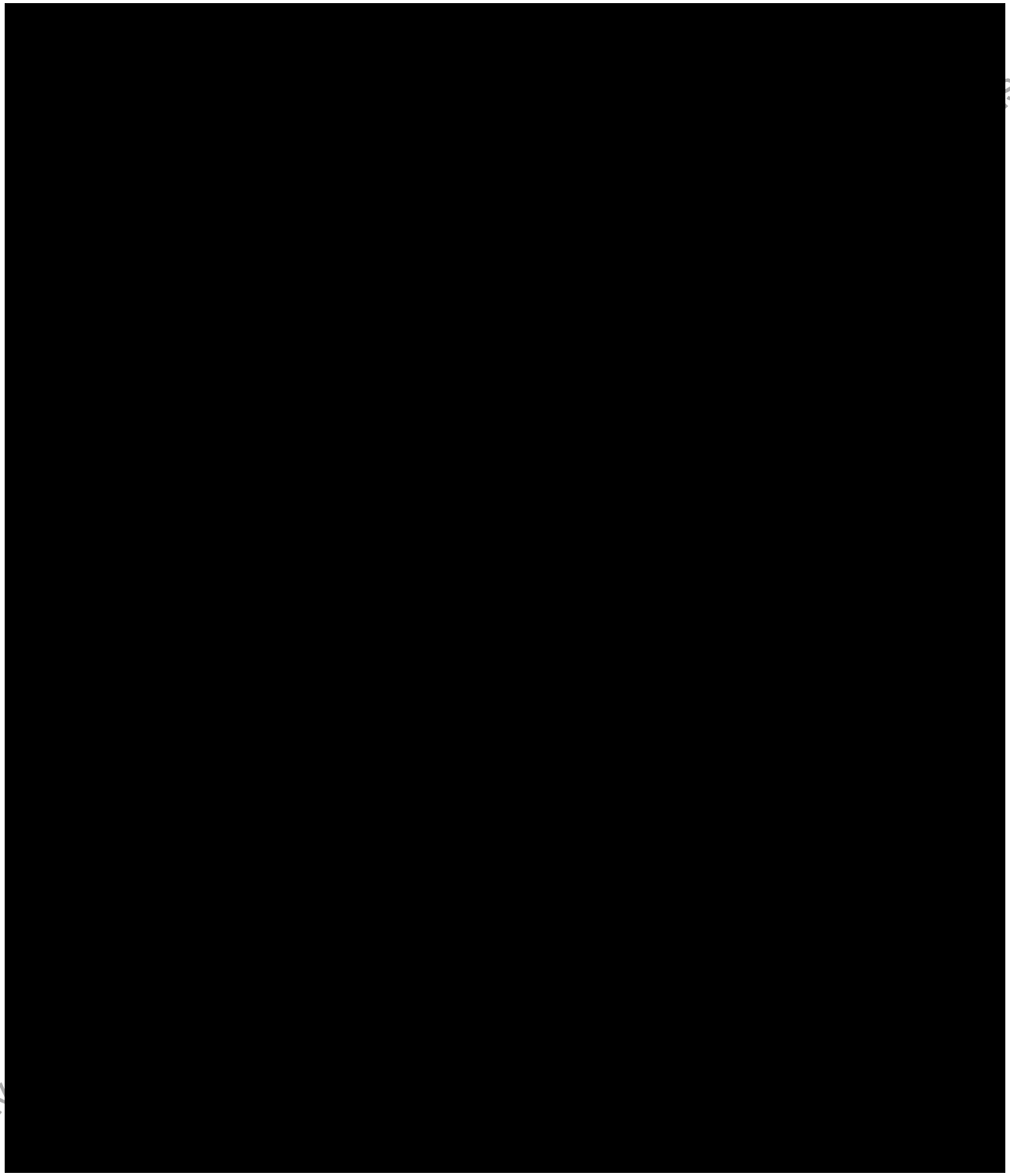


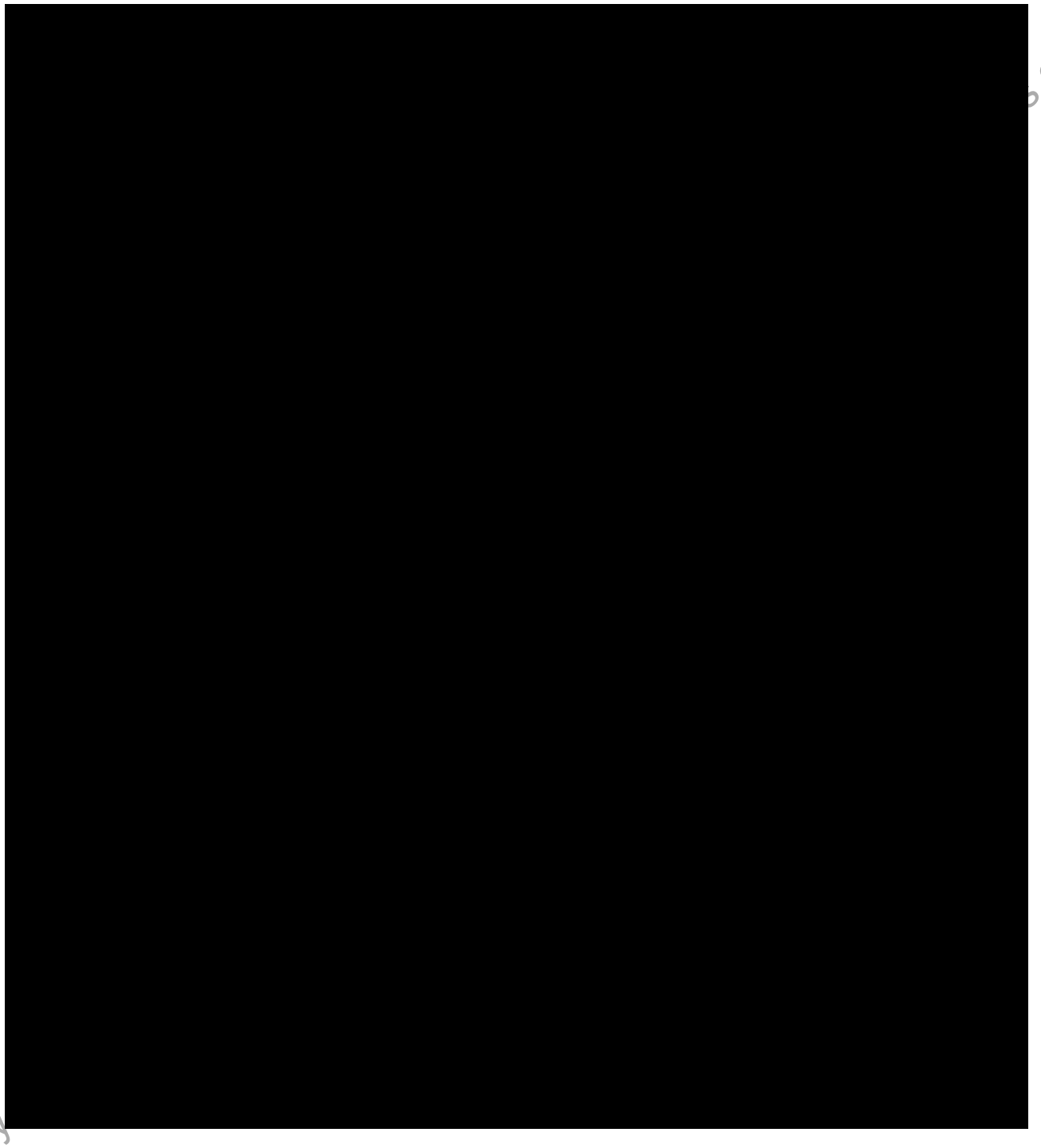


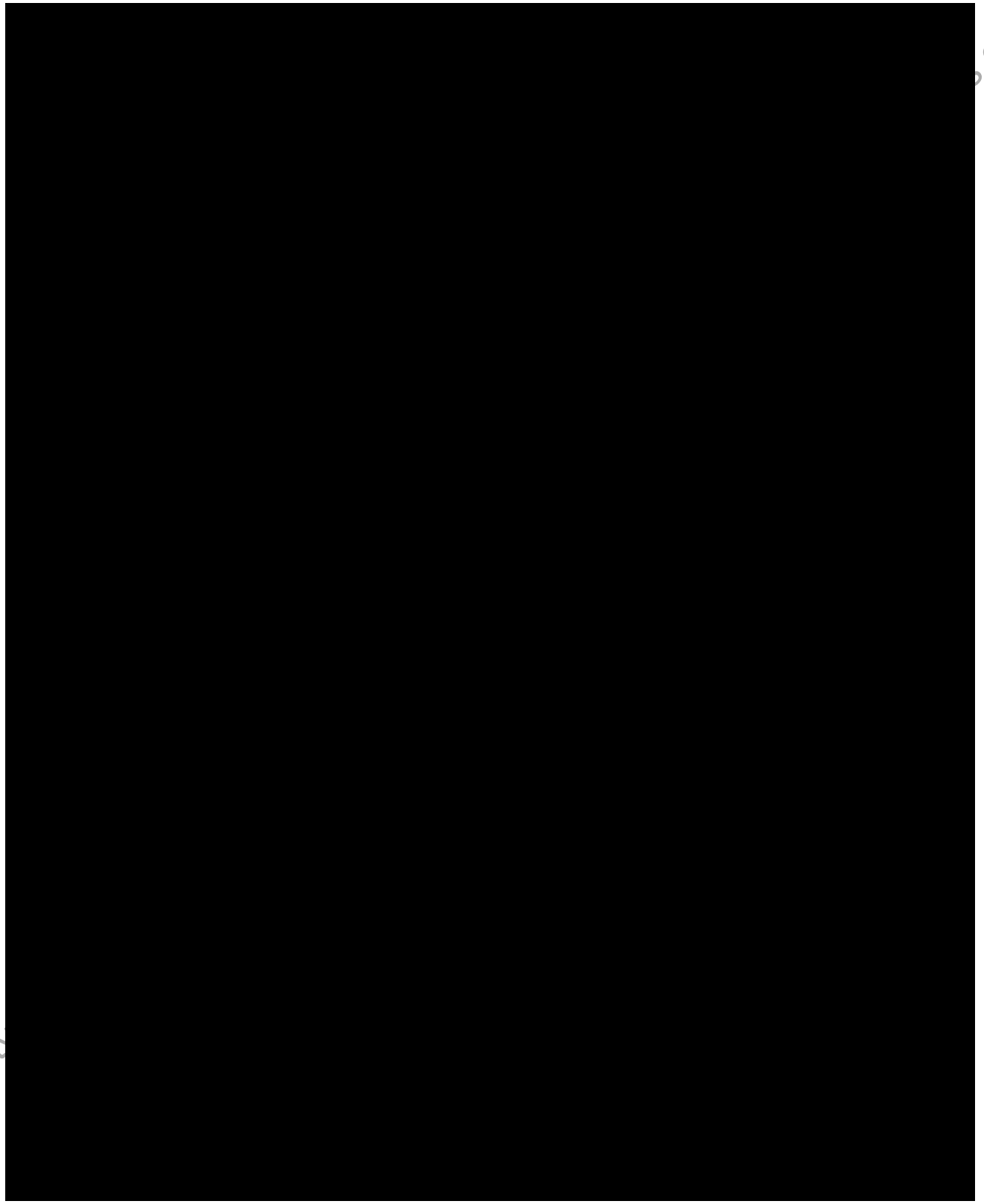
[redacted]











[redacted]