Clinical Trial Protocol

Protocol Title:	A Multi-Center, Double-Masked Evaluation of the Efficacy and Safety of CSF-1 in the Treatment of Presbyopia
Protocol Number:	18-150-0006
Study Phase:	2b
Investigational Product Name:	CSF-1 (pilocarpine hydrochloride 0.2% or 0.4% and diclofenac sodium 0.006%) Ophthalmic Solution
IND	131464
Indication:	Presbyopia
Investigators:	TBD
Sponsor:	Orasis Pharmaceuticals, Ltd 12 Maskit St., P.O.B 12929 Herzliya 4673312, Israel +972 9 8877745
Contract Research Organization:	[redacted]
IRB/IEC:	[redacted]

	Date
Original Protocol:	15 November 2018
Amendment 1:	08 February 2019
Amendment 2:	05 June 2019

Confidentiality Statement

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MEDICAL MONITOR

Medical Monitor:	[redacted]

[redacted] PERSONNEL

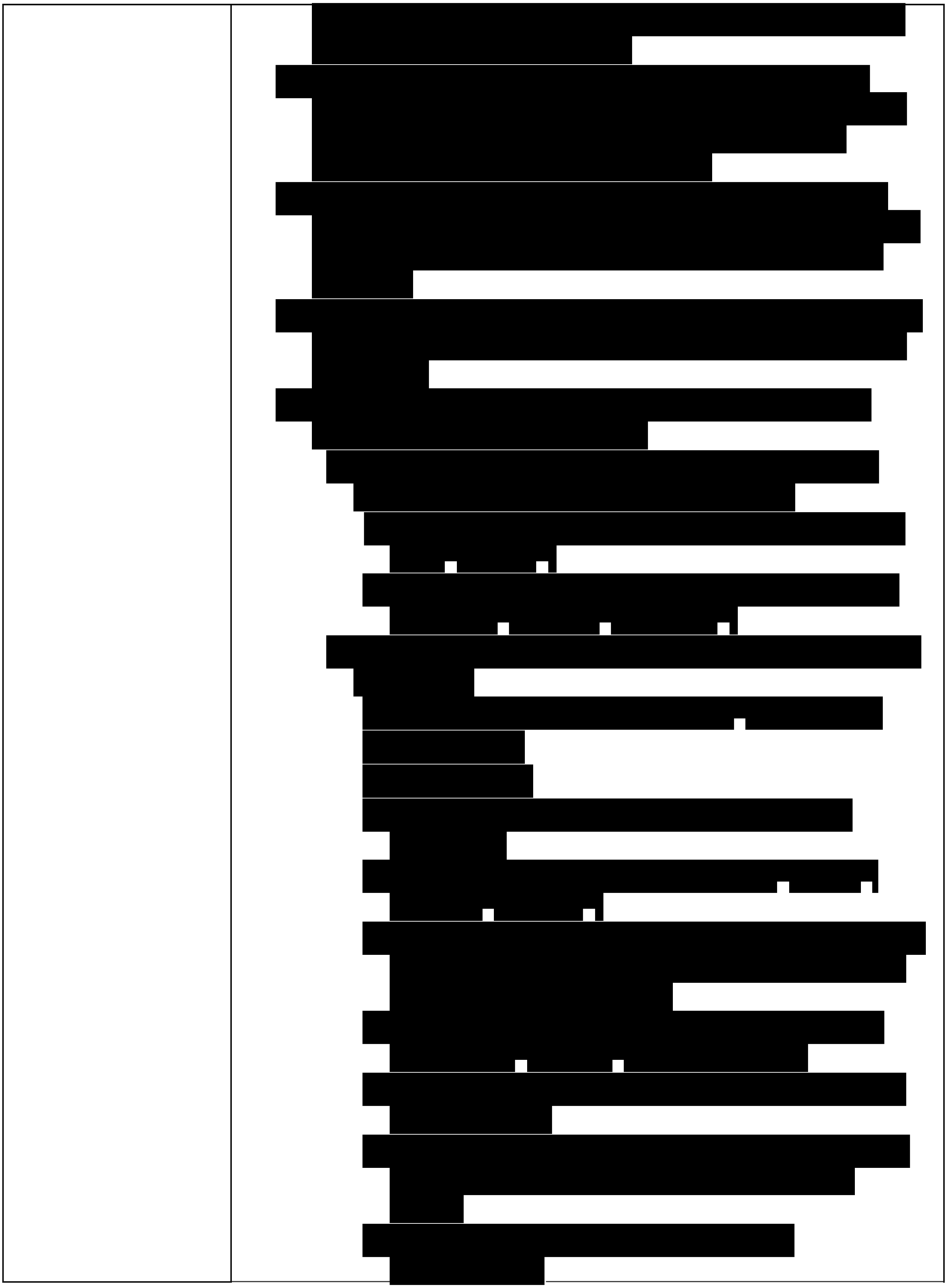
Department Sr. Vice President:	[redacted]
Project Manager:	[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked Evaluation of the Efficacy and Safety of CSF-1 in the Treatment of Presbyopia
Protocol Number:	18-150-0006
Investigational Products:	• CSF-1: pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose]) and diclofenac sodium (0.006%) • Pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose]) • Diclofenac sodium (0.006%)
Study Phase:	2b
Primary Objective:	• To evaluate the efficacy of CSF-1 for the treatment of presbyopia
Secondary Objectives:	• To evaluate the safety, tolerability, and efficacy of CSF-1 versus the individual components for the treatment of presbyopia • To evaluate the safety, tolerability, and efficacy (onset and duration) of 2 concentrations of CSF-1 ([0.2%/0.006%] and [0.4%/0.006%]) for the treatment of presbyopia
Overall Study Design:	
Structure:	Multi-center, randomized, double-masked, parallel-group, safety, and efficacy study
Duration:	Approximately 2 to 4 weeks (4 study visits)
Controls:	Individual components of the combination therapy (pilocarpine hydrochloride alone and diclofenac sodium alone)
Treatment plan:	Visit 1: Qualified subjects will receive 1 drop of Refresh Classic® (placebo) instilled to each eye. Visit 2: Following the pre-treatment assessments, qualified subjects will be randomized 1:1:1 to 1 of the following treatment arms: CSF-1 (pilocarpine hydrochloride [0.2%]/diclofenac sodium [0.006%]), pilocarpine (0.2%) alone, or diclofenac sodium (0.006%) alone. All subjects will dose twice daily [redacted] in both eyes with a single drop for approximately 1 week. Visit 3: Following the visit 3 assessments, subjects will continue BID dosing [redacted] in both eyes for approximately 1 week. Subjects initially randomized to the CSF-1 arm will now receive pilocarpine hydrochloride (0.4%)/diclofenac sodium (0.006%); subjects randomized to the pilocarpine hydrochloride (0.2%) alone arm will now receive pilocarpine hydrochloride (0.4%) alone; and subjects randomized to the diclofenac sodium alone arm will continue dosing with diclofenac sodium (0.006%) alone.

Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.
Study Population Characteristics:	
Number of Subjects:	Approximately 150 subjects (3 arms; 50 subjects per treatment arm) will be enrolled.
Condition/Disease:	Healthy adult subjects ages 45 to 64 years who have presbyopia
Inclusion Criteria:	Subjects must: 1. [redacted] 4. Have best corrected visual acuity (BCVA) at 40 cm ≥ 0.40 and ≤ 0.90 logarithm of the minimum angle of resolution (LogMAR, approximately between 20/50 and 20/160 Snellen) in at least 1 eye at visit 1 prior to placebo dosing and in the same eye at visit 2 (pre-treatment); 5. [redacted]

	9. [redacted]
Exclusion Criteria:	Subjects must <u>not</u>: 1. [redacted] 2. Have known contraindications or a sensitivity to the use of any of the IPs or their components; 3. [redacted]



	[redacted] 19. Have a condition or a situation that in the investigator's opinion may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.
Study Treatments	• CSF-1: Pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose]) and diclofenac (0.006%) • Pilocarpine hydrochloride (0.2% [low dose])/(0.4% [high dose]) • Diclofenac sodium (0.006%) All patients will dose BID [redacted] in both eyes with a single drop of IP.
Evaluation Criteria:	
Primary Efficacy Endpoint	Percentage of subjects with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment at visit 3 and visit 4
Secondary Efficacy Endpoints	• [redacted] • Percentage of subjects with a ≥ 2-line (10 letter) gain in BCVA at 40 cm at each time point at visit 3 and visit 4 • [redacted]
Safety Endpoints	[redacted] • Adverse events (AEs) (reported, elicited, and observed)

General Statistical Methods and Types of Analyses

Analysis Sets:

- Intent-to-Treat Analysis Set – The Intent-to-Treat analysis set (ITT) will include all randomized subjects. Subjects in the ITT will be analyzed as randomized.
- Per Protocol Set – The per-protocol (PP) set will include subjects in the ITT who do not have significant protocol deviations that affect the primary endpoint. Protocol deviations

will be assessed prior to database lock and unmasking. Subjects in the PP set will be analyzed as treated.

- [redacted]
- Safety Set – The safety set will include all subjects who have received at least one dose of the IP. Subjects in the safety population will be analyzed as treated.

Unit of Analysis:

The study eye will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The study eye will be defined as the eye that meets all enrollment criteria. If both eyes meet all enrollment criteria, then the eye with the worse Visit 2 (Day 1) BCVA at 40 cm will be the study eye. If both eyes have the same BCVA at 40 cm, the right eye will be the study eye.

General Considerations:

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

[redacted]

Safety analyses will be conducted in the safety population.

Hypothesis:

H_{01}: The difference, between study eyes treated with CSF-1 (0.4%/0.006%) and study eyes treated with diclofenac sodium (0.006%), in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment = 0.

H_{11}: The difference, between study eyes treated with CSF-1 (0.4%/0.006%) and study eyes treated with diclofenac sodium (0.006%), in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment ≠ 0.

H_{02}: The difference, between study eyes treated with Pilocarpine (0.4%) and study eyes treated with diclofenac sodium 0.006%, in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40cm, 1-hour post-treatment = 0.

H_{12}: The difference, between study eyes treated with Pilocarpine (0.4%) and study eyes treated with diclofenac sodium 0.006%, in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40cm, 1-hour post-treatment ≠ 0.

The study will be considered a success if either of the null hypotheses, H_{01} or H_{02}, are rejected in favor of their corresponding alternative hypotheses, H_{11} or H_{12}. The overall Type I error of the 2-sided alpha = 0.10 will be preserved through the use of Bonferroni correction procedures testing each hypothesis at a 2-sided alpha = 0.05.

If H_{01} is rejected and CSF-1 (0.4%/0.006%) is considered a success, then CSF-1 (0.2%/0.006%) will be tested against diclofenac sodium (0.006%) at a 2-sided alpha = 0.05. Similarly, if H_{02} is rejected and Pilocarpine (0.4%) is considered a success, then Pilocarpine (0.2%) will be tested against diclofenac sodium (0.006%) at a 2-sided alpha = 0.05. Within these hierarchical frameworks, these hypotheses can be tested at a 2-sided alpha = 0.05 while still preserving an overall Type I error of alpha = 0.10.

[redacted]

H_{14}: The difference, between study eyes treated with Pilocarpine (0.2%) and study eyes [redacted]

Sample Size:

Fifty subjects per each of the 3 treatment arms (150 total), yields an 85% power to establish superiority of CSF-1 (0.4%/0.006%) and Pilocarpine (0.4%) to diclofenac sodium 0.006% alone in the percentage of study eyes demonstrating a ≥ 3-line (15-letter) gain in BCVA at 40 cm, 1-hour post-treatment from the baseline measurement using a Pearson chi-squared test at a 2-sided alpha = 0.05 assuming that the diclofenac sodium 0.006% alone response is 5% and the CSF-1 response is 27%, resulting in an overall 2-sided alpha = 0.10 that accounts for the 2 tests of hypotheses utilizing Bonferroni correction procedures.

[redacted]

Primary Efficacy Analysis:

[redacted]

Descriptive statistics will be presented for each time point by treatment group. Testing of the percentage of subjects with a ≥ 3-line (15-letter) improvement from baseline will be completed accounting for the correlations between treatments and periods within a subject using a logistic (binomial error and logit link) model estimated by generalized estimating equation (GEE) methods. Aspects of the model include:

- Response measure: indicator of whether the subject had a ≥ 3-line (15-letter) improvement from baseline in the assessment of BCVA at 40 cm in the study eye
- Covariate: baseline BCVA at 40 cm in the study eye
- Fixed effect explanatory measures: treatment

- Random effect measure: subject, to account for the correlation between treatments within a subject
- Repeated measures correlation: estimated with an unstructured covariance matrix in the GEE model

Standard errors and confidence intervals (CIs, 90% and 95%) will also be presented for each treatment group and the difference between treatment groups. [redacted]

Secondary Efficacy Analysis:

[redacted]

[redacted]

Safety Analysis:

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. Treatment emergent AEs, those that occur after the first dose of IP, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Similar summaries will also be presented for treatment-emergent AEs (TEAEs) related to IP and by severity. When reporting the incidence of AEs, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT within the specific treatment period. AEs will be reported separately by period.

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
BID	twice daily
BCVA	best corrected visual acuity
cd/m^2	candela per square meter
CFR	Code of Federal Regulations
CI	confidence interval
eCRF	electronic case report form
D	diopter
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GEE	generalized estimating equation
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug application
IOL	intraocular lens
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
HIPAA	Health Information Portability and Accountability Act
LASEK	laser-assisted epithelial keratomileusis
LASIK	laser-assisted in-situ keratomileusis
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	millimeters of mercury
mPP	modified per protocol
NSAID	non-steroidal anti-inflammatory drug
OTC	over-the-counter
PP	per protocol
PRK	photorefractive keratectomy
PT	preferred term
RGP	rigid gas permeable
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
VA	visual acuity

1 INTRODUCTION

Most individuals will develop symptoms of presbyopia by age 50 (Truscott 2009), and approximately 50% of the population with presbyopia does not have adequate corrective lenses, resulting in some level of disability when performing tasks requiring near visual acuity (VA) (Holden et al 2008). This resulted in a global burden of presbyopia exceeding 1.8 billion people in 2015 (Holden et al 2008), and prevalence is increasing. The primary symptom of this condition is a progressive blurring of vision when performing near tasks such as reading, sewing, working at a computer, and using a tablet or cellular phone. Other symptoms include headaches and visual fatigue, which impair one's quality of life (Truscott 2009).

The underlying cause of presbyopia is an inability to change optical power (accommodation) (Donders 1864). Accommodation is facilitated by the contraction of the ciliary muscle fibers, which change the shape and location of the crystalline lens of the eye. In response to near vision, the crystalline lens becomes thicker and more rounded in response to the actions of the ciliary muscle fibers (Garner and Yap 1997, Croft et al 2001, Glasser 2006). As an individual ages, the lens becomes stiffer and less amenable to changing shape in response to ciliary muscle activity and this culminates in the symptoms of presbyopia.

The neural mechanism of accommodation is the adjustment of the size of the pupil. Pupil size is determined by the dimensions of sphincter and dilator muscle spindles of the iris. The pupil becomes smaller when the eye accommodates. This reduction in the size of the pupil (termed miosis) improves the resolution of the retinal image by preventing diverging light rays hitting the periphery of the cornea and lens from reaching the retina. Miosis further increases the depth of field of the eye. A relatively small pupil offers increased depth of field in a way similar to that achieved by reducing the aperture of a camera.

Current presbyopia treatment strategies include: corrective lenses with single vision or bifocal/multifocal lenses, corneal refractive surgery, corneal inlay procedures, and intra-ocular lens surgery. Monovision correction improves the near vision of one eye (through the use of lenses, contacts, or surgery) while allowing the other eye to be used for distance vision. This approach has had variable results and may cause disturbances in depth-perception (Fernandez et al 2013). Glasses consisting of a pinhole to block out peripheral rays of light have also been used to improve vision in presbyopia (Emsley 1946, Borish 1975). Pinhole glasses severely restrict the wearer's peripheral vision placing the patient at risk while driving or performing other similar tasks. Lastly, surgical correction of vision in presbyopia includes conductive keratoplasty, laser-assisted in-situ keratomileusis (LASIK), laser-assisted epithelial keratomileusis (LASEK), photorefractive keratectomy (PRK), corneal inlays, and accommodative or multifocal intraocular lenses (IOLs). The results of these procedures are variable, at times inconsistent, and contraindicated in some patient groups (Moussa et al 2017). The inconsistencies regarding the success of some of these procedures of presbyopia treatment indicate a need for alternative strategies.

The treatment proposed here repurposes a muscarinic receptor agonist to stimulate effects on iris and ciliary contractility via stimulation of Muscarinic acetylcholine receptor M3. Pilocarpine, a muscarinic agonist, has been successful in treating cases of dilated pupil following ocular surgery (Patel et al 2002) and a broad spectrum of systemic conditions including botulism (Monaco et al 1998), leprosy (Lana-Peixoto et al 2014), sarcoidosis (Bowie and Givre 2003), and Ross syndrome (Weller et al 1992, Chemmanam et al 2007). Low dose pilocarpine

hydrochloride induced miosis also improves Adie's pupil (a neurological disorder affecting the pupil size) in adults, children (Younge and Buski 1976, Flach and Dolan 1985, Soylev et al 1997, Jacobson and Vierkant 1998, Bartlett and Jaanus 2002), dogs (Gerding et al 1986), and cases of pharmacologically-induced anisocoria (Jacobson and Olson 1993).

Muscarinic receptor agonists are known to induce inflammation (Verbout and Jacoby 2012). Thus, combining a non-steroidal anti-inflammatory drug (NSAID) with pilocarpine hydrochloride may reduce the inflammatory response associated with pilocarpine hydrochloride. Diclofenac sodium is a safe and effective NSAID prescribed for the management of pain following corneal refractive surgery (Narvaez et al 2004, Colin and Paquette 2006, Parker et al 2011), inflammation post-cataract extraction (Flach et al 1998, Kocak et al 1998, Flach and Dolan 2000), and allergic conjunctivitis (Laibovitz et al 1995).

CSF-1 Ophthalmic Solution (CSF-1) was well tolerated and resulted in noticeable miosis after topical application in an investigator-initiated feasibility study. Two additional clinical studies (Phase 2a) demonstrated favorable safety and preliminary efficacy and thus support the continued development of CSF-1 as an ophthalmic solution to treat presbyopia. This is a factorial study to determine the importance of each active ingredient and the impact of increasing pilocarpine hydrochloride concentrations (0.2% versus 0.4%) on the efficacy of CSF-1 for the treatment of presbyopia.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of CSF-1 for the treatment of presbyopia.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety, tolerability, and efficacy of CSF-1 versus the individual components for the treatment of presbyopia
- [redacted]

3 CLINICAL HYPOTHESES

The clinical hypothesis of this study is that CSF-1 (the combination of pilocarpine hydrochloride and diclofenac sodium) is superior and/or safer/better tolerated compared with pilocarpine hydrochloride alone and diclofenac sodium alone (0.006%) in improving near vision in subjects with presbyopia.

4 OVERALL STUDY DESIGN

This is a 4-visit randomized, double-masked, multi-center, parallel-group study evaluating the safety and efficacy of CSF-1 compared with pilocarpine hydrochloride alone and diclofenac

sodium (0.006%) alone in approximately 150 subjects with presbyopia. Study design is summarized in Figure 1.

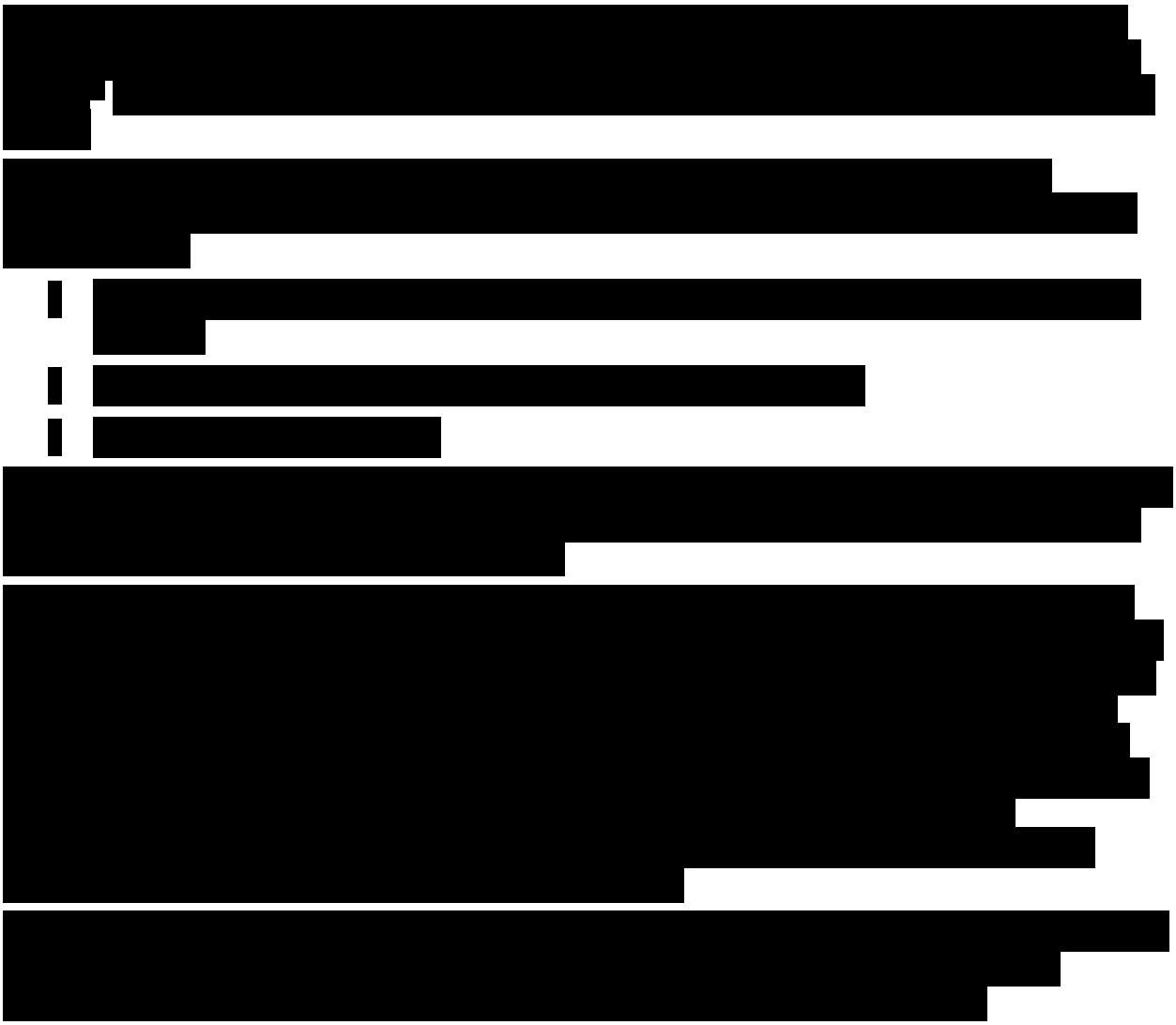
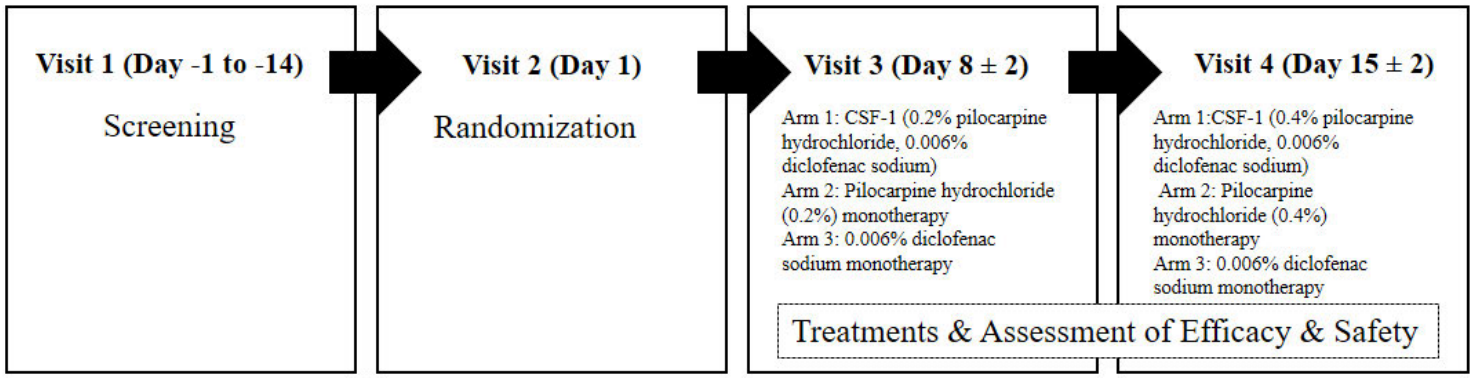


Figure 1 Study Design



5 STUDY POPULATION

Approximately, 150 healthy adult subjects between 45 and 64 years of age with presbyopia who do not have any conditions, in the investigator's opinion, that may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

5.1 Inclusion Criteria

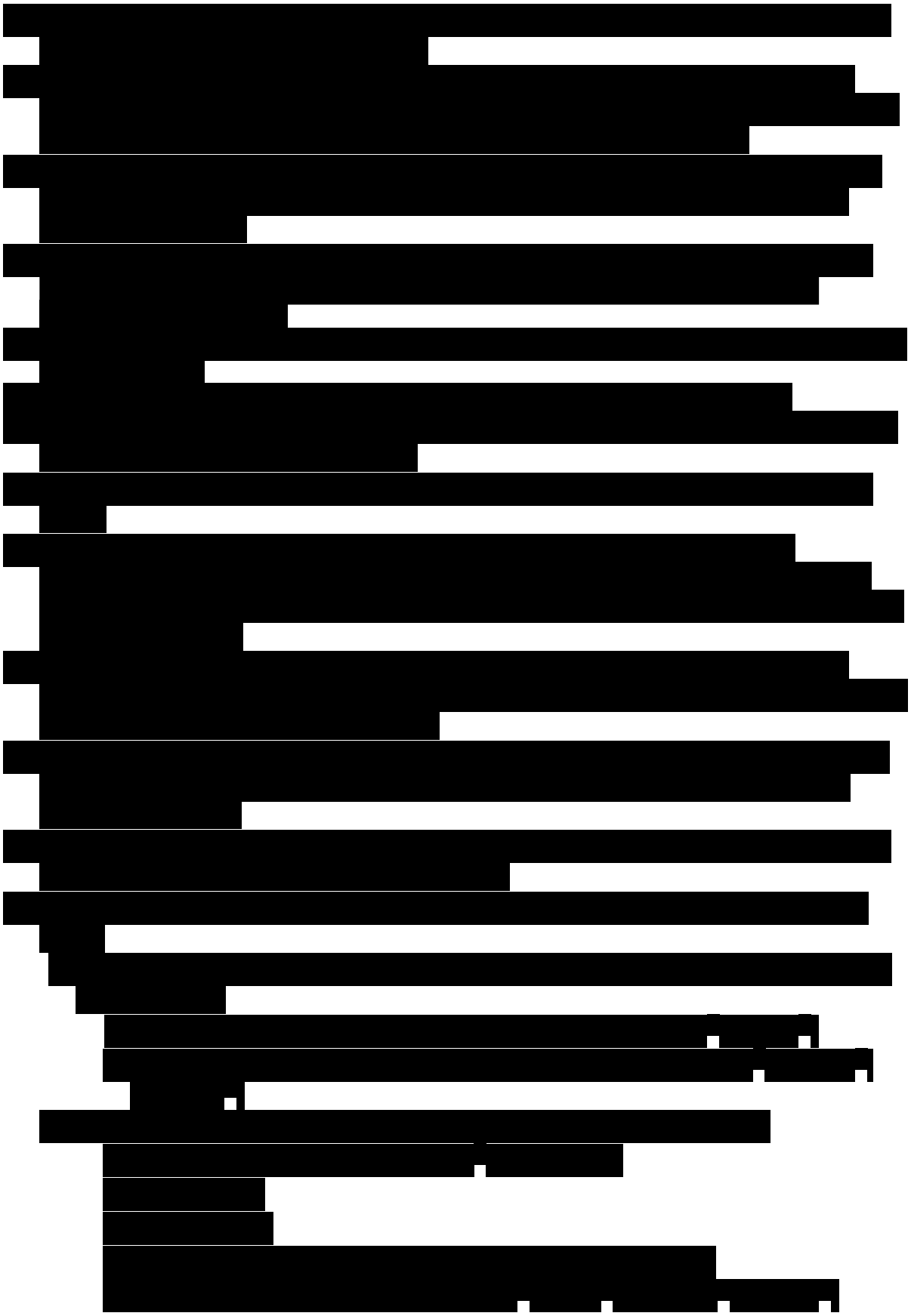
Subjects must:

1. [redacted]
4. Have BCVA at 40 cm ≥ 0.40 and ≤ 0.90 logarithm of the minimum angle of resolution (LogMAR, approximately between 20/50 and 20/160 Snellen) in at least 1 eye at visit 1 prior to placebo dosing and in the same eye at visit 2 (pre-treatment);
5. Have between -4.50 to +2.00 diopter (D) of sphere in each eye determined by manifest [redacted]

5.2 Exclusion Criteria

Subjects must not:

1. [redacted]



[redacted]

19. Have a condition or a situation that in the investigator's opinion may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation, including but not limited to unstable cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease.

5.3 Withdrawal Criteria

Subjects will be withdrawn from the study if any of the following criteria are met:

- Be a female of childbearing potential who is currently pregnant, nursing, or planning a pregnancy; tests positive to a urine pregnancy test at visit 4; or refuses to use an adequate method of contraception for the duration of the study;
- Have an active ocular infection (bacterial, viral, or fungal), active ocular inflammation (e.g. moderate to severe blepharitis, allergic conjunctivitis, peripheral ulcerative keratitis, scleritis, uveitis) at visit 2, visit 3, or visit 4 in either eye.
- Subjects may also be withdrawn from the study for the following reasons:
    - Adverse event (AE)
    - Lost to follow-up
    - Withdrawal of consent by subject
    - investigator discretion
    - Death
    - Subject not adequately following required study procedures
    - Study terminated by the Sponsor
    - Other

Subject withdrawals will be documented on the subject's source document.

6 STUDY PARAMETERS

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoints

- Percentage of subjects with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment at visit 3 and visit 4

6.1.2 Secondary Efficacy Endpoints

[redacted]

- Percentage of subjects with a ≥ 2-line (10 letter) BCVA at 40 cm gain at each time point at visit 3 and visit 4

[redacted]

6.1.3 Criteria for Effectiveness

Changes in BCVA at 40 cm distance will be calculated as the difference, in logMAR units, between the post-treatment monocular (study eye) minus baseline monocular (study eye). A 3-line improvement in VA is considered clinically meaningful.

6.2 Safety Endpoints

- BCVA
- Best-corrected low luminance distance VA
- Slit lamp biomicroscopy
- Conjunctival redness grading
- IP drop comfort assessment
- IOP
- AEs (reported, elicited, and observed)

7 STUDY MATERIALS

7.1 Study Treatments

7.1.1 Investigational Product

The IP is CSF-1, a topical eye drop solution for [redacted] presbyopia, which works by reducing the natural pupil size and increasing the depth of field. The formulation developed by Orasis Pharmaceuticals Ltd. is a viscous eye drop containing the active ingredients pilocarpine hydrochloride and diclofenac sodium with the addition of excipients, [redacted]. The inclusion of an NSAID (diclofenac sodium) may reduce the inflammatory response induced by pilocarpine hydrochloride. Pilocarpine hydrochloride alone will be evaluated for comparison at both 0.2% and 0.4%, with the same formulation tabulated in Table 1, except for the removal of diclofenac sodium. Similarly, a control of diclofenac sodium 0.006% alone will be evaluated for comparison, likewise, with the same formulation tabulated in Table 1, except for the removal of pilocarpine hydrochloride.

Table 1 CSF-1 formulation

Ingredient	Concentration [mg/mL]	Concentration [%w/v]	Purpose
Pilocarpine Hydrochloride	2 or 4	0.2 or 0.4	Active ingredient
Diclofenac Sodium	0.06	0.006	Active ingredient
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

7.1.2 Instructions for Use and Administration

All study treatments are topical ophthalmic solutions that should be administered bilaterally. A single drop should be instilled in each eye, BID, in the morning and afternoon [redacted]. Subjects will be instructed to close their eyes for 30 seconds after instillation.

7.1.3 Subject Instructions

[redacted]

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Section 5.2 and Section 5.3 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e. changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF) and other written documentation in accordance with local privacy requirements (where applicable). Additional information can be found in Section 11.1.1.

8.1.3 Washout Intervals

Per exclusion criteria #17, subjects must abstain from the use of the following systemic medications during the timeframe noted below:

i. The day of the study visit or within 12 hours prior to a study visit (chronic, daily use is not allowed):
   a. nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. Advil®, Motrin®)
   b. narcotic (opiate class) pain medication (e.g. codeine, OxyContin®, Vicodin®, Tramadol®)

ii. Two (2) weeks (14 days) prior to visit 1 or for the duration of the study:
   c. bladder medication (e.g. Urecholine®, bethanechol)
   d. antipsychotics
   e. antidepressants
   f. ADHD medications
   g. alpha-blockers (e.g. tamsulosin [Flomax®], Jayln®, Uroxatral®, Rapaflo®)
   h. anticholinergics (e.g. atropine, belladonna, benztropine, dicyclomine, donepezil, hyoscyamine, propantheline, scopolamine, trihexphenidyl)
   i. muscarinic receptor agonists or cholinergic agonists (e.g. Salagen®, Evoxac®) other than the IP
   j. OTC or prescription antihistamines or decongestants
   k. any ophthalmic medications (other than artificial tears or lubricant eye ointment [see exclusion criteria 8 and 9])
   l. any other medication affecting the pupil or accommodation
   m. recreational drug use (e.g. marijuana, methadone, heroin, cocaine).

8.1.4 Procedures for Final Study Entry

Subjects must satisfy all inclusion and none of the exclusion criteria in order to be entered into the study.

8.1.5 Pregnancy

Females must have a negative urine pregnancy test at visit 1, if female of childbearing potential (those who have experienced menarche and who are not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

In the event a female has a positive urine pregnancy test at visit 4, the subject will be withdrawn from the study and the investigator will notify [redacted] and the sponsor within 24 hours of knowledge of the positive pregnancy test.

8.1.6 Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a subject number (a five-digit number starting with the 2-digit site number followed by a sequential three-digit number starting with 001). Once a subject meets all qualification criteria at visit 2, he/she will be randomized in a 1:1:1 ratio via an interactive response technology system to 1 of 3 treatment groups: 1: CSF-1, 2: pilocarpine hydrochloride alone, 3: diclofenac sodium alone, and stratified by iris color (brown versus light [i.e. blue, green, gray, and hazel]) and by baseline manifest refraction spherical equivalent (-4.5 D to <-0.5 D, -0.5 D to +0.75 D, and >+0.75 D to +2.0 D); randomization will not be stratified by site.

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g. iris color and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-masked treatment will be used to reduce the potential of bias during data collection and the evaluation of clinical endpoints.

8.2 Concurrent Therapies and Medical History

The use of any concurrent medication, prescription, or OTC taken within 30 days of Visit 1, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

All significant current and prior ocular medical and surgical history is to be recorded on the subject's source document and corresponding eCRF. All current and prior significant general medical and surgical history is to be recorded on the subject's source document and corresponding eCRF.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

Prohibited Medications/Treatments

Washout intervals as described in Section 8.1.2 should be followed for all prohibited medications. Soft contact lenses must be removed at least 7 days prior to study visit 1 and during the study, and RGP contact lenses must be removed at least 14 days prior to study visit 1 and during the study.

8.3 Examination Procedures

Procedures to be performed at the Study Visit with Regard to Study Objective

The following procedures should be conducted at each study visit in the following order:

8.3.1 Visit 1 (Day -1 to -14)

[redacted]

8.3.2 Visit 2 (Day 1)

[redacted]

[redacted]

IP

8.3.3 Visit 3 (Day 8 ± 2)

[redacted]

9. Instillation of morning dose of IP

[redacted]

21. Collect IP/dosing diary

8.3.4 Visit 4 (Day 15 ± 2)

[redacted]

10. Instillation of morning dose of IP

[redacted]

23. Study exit

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visit

Refer to Appendix 1: [redacted] for a schedule of measurements at the visit.

8.4.2 Unscheduled Visits

In the case of an AE, an unscheduled visit may occur. The investigator may perform additional assessments at their discretion. All additional assessments will be documented in the subject's source document.

8.5 Compliance with Protocol

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s), such as Food and Drug Administration (FDA) GCP Regulations and Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312, as appropriate.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study and sucessfullly completes Visit 4.

8.6.2 Withdrawn Subjects

A subject may be withdrawn for meeting any of the withdrawal criteria as described in Section 5.3.

8.6.3 Discontinued Subjects

A discontinued subject is one who does not complete the 4 protocol-defined study visits. A subject may be discontinued at the discretion of the investigator, sponsor, and/or the institutional review board (IRB). Notification of early discontinuation from the study and the reason for discontinuation will be made to the sponsor and/or [redacted].

Prior to discontinuing a subject, every effort should be made to obtain as much follow-up data as possible, and to retrieve all study materials. AEs will be followed as described in Section 9.

8.7 Study Termination

The study may be terminated at any time by the investigator, the sponsor, and/or [redacted] with appropriate notification.

8.8 Study Duration

This study is comprised of 4 visits over a total duration of approximately 2 to 4 weeks.

8.9 Monitoring and Quality Assurance

During the course of the study an [redacted] monitor, or designee, will make routine site visits to review protocol compliance, assess IP accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, and [redacted] quality assurance and/or its designees may carry out on-site inspections and/or audits that may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g. off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the subject's source document and eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to IP, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

All AEs will be collected from the time a subject signs the ICF through the subject's study exit visit.

9.1.1 Severity

The severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.

- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2 Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the IP caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the IP caused the AE.

"Suspected adverse reaction" means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g. tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- *Unexpected*: an AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.
- *Not applicable:* an AE unrelated to the IP.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological (or other) properties of the product but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE. The medical monitor will review and determine the expectedness of any serious adverse event (SAE) following the investigator's assessment. The final classification of an AE is subject to the sponsor's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if < 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/Phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g. intra-ocular hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to [redacted], the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate subject source document and eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to [redacted] the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported by the investigator to [redacted] and the sponsor within 24 hours of becoming aware of the event. All information relevant to the SAE must be recorded on the appropriate source document, SAE Report Form, and eCRF. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the sponsor in addition to the information reported on the source document, SAE Report Form, and eCRF. All subjects experiencing a SAE must be followed-up with and the outcome reported.

In the event of a SAE, the investigator must notify [redacted] and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide [redacted] and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

Medical Monitor:	[redacted]
Project Manager:	[redacted]

9.4 Procedures for Unmasking (if applicable)

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. When possible (i.e. in non-emergent situations), [redacted] and/or the study sponsor should be notified before unmasking the IP.

9.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution, until the subject is lost to follow-up or until the AE is otherwise explained. Resolution means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the source document with the status noted.

If the investigator becomes aware of any new information regarding a SAE (i.e. resolution, change in condition, or new treatment), a new SAE Report Form must be completed and faxed/emailed to [redacted] and/or the study sponsor within 24 hours. The original SAE Report Form is not to be altered. The SAE Report Form should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 General Considerations

In general, quantitative/continuous data will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Qualitative/categorical data will be

summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

For all variables, baseline is defined as the pre-randomization measurement taken at Visit 2 (Day 1). If the measurement is not available from Visit 2 (Day 1), then the measurement from screening Visit 1 (Day -1 to -14) will be used as baseline for all treatments/visits. Change from baseline will be calculated as follow-up measure minus baseline measure.

The primary analyses of the primary and secondary endpoints will be conducted in the PP, include observed data only, and use statistical models, which adjust for the correlation between treatments within an eye and/or subject.

The secondary analyses of the primary and secondary endpoints will be conducted in the ITT, include observed data only, and use similar statistical models as the primary analyses. No subject data will be excluded from the ITT due to protocol violations/deviations.Sensitivity analysis on the primary efficacy variable will be performed on both the PP and ITT imputing missing data as failures; [redacted]

Safety analyses will be conducted in the safety population.

10.2 Hypotheses

H_{01}: The difference, between study eyes treated with CSF-1 (0.4%/0.006%) and study eyes treated with diclofenac sodium 0.006%, in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment = 0.

H_{11}: The difference, between study eyes treated with CSF-1 (0.4%/0.006%) and study eyes treated with diclofenac sodium 0.006%, in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment ≠ 0.

H_{02}: The difference, between study eyes treated with Pilocarpine (0.4%) and study eyes treated with diclofenac sodium 0.006%, in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment = 0.

H_{12}: The difference, between study eyes treated with Pilocarpine (0.4%) and study eyes treated with diclofenac sodium 0.006%, in the percentage of study eyes with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment ≠ 0.

The study will be considered a success if either of the null hypotheses, H_{01} or H_{02}, are rejected in favor of their corresponding alternative hypotheses, H_{11} or H_{12}. The overall Type I error of the 2-sided alpha = 0.10 will be preserved through the use of Bonferroni correction procedures testing each hypothesis at a 2-sided alpha = 0.05.

If H_{01} is rejected and CSF-1 (0.4%/0.006%) is considered a success, then CSF-1 (0.2%/0.006%) will be tested against diclofenac sodium (0.006%) at a 2-sided alpha = 0.05. Similarly, if H_{02} is rejected and Pilocarpine (0.4%) is considered a success, then Pilocarpine (0.2%) will be tested against diclofenac sodium (0.006%) at a 2-sided alpha = 0.05. Within these hierarchical

frameworks, these hypotheses can be tested at a 2-sided alpha = 0.05 while still preserving an overall Type I error of alpha = 0.10.

[redacted]

10.3 Study Populations

- Intent-to-Treat Analysis Set – The ITT will include all randomized subjects. Subjects in the ITT will be analyzed as randomized.
- Per Protocol Set – The PP set will include subjects in the ITT who do not have significant protocol deviations that affect the primary endpoint. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP set will be analyzed as treated.
- [redacted]
- Safety Set – The safety set will include all subjects who have received at least 1 dose of the IP. Subjects in the safety population will be analyzed as treated.

10.4 Unit of Analysis

The study eye will be used for all monocular analyses. The fellow eye will inherently be included in all binocular analyses. Both eyes will be displayed and analyzed for all ophthalmic safety variables.

The study eye will be defined as the eye that meets all enrollment criteria. If both eyes meet all enrollment criteria, then the eye with the worse Visit 2 (Day 1) BCVA at 40 cm will be the study eye. If both eyes have the same BCVA at 40 cm, the right eye will be the study eye.

10.5 Efficacy Endpoints

10.5.1 Primary Efficacy Endpoint

The percentage of subjects with a ≥ 3-line (15 letter) gain in BCVA at 40 cm, 1-hour post-treatment at visit 3 and visit 4 from the baseline measurement

10.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- [redacted]
- Percentage of subjects with a ≥ 2-line (10 letter) gain in BCVA at 40 cm [redacted] at visit 3 and visit 4
- [redacted]

10.6 Safety Endpoints

The safety endpoints are:

- BCVA
- Best-corrected low luminance distance VA
- Slit lamp biomicroscopy
- Conjunctival redness grading
- IP drop comfort assessment
- IOP
- AEs (reported, elicited, and observed)

10.7 Sample Size

Fifty subjects per each of the 3 treatment arms (150 total), yields an 85% power to establish superiority of CSF-1 (0.4%/0.006%) and Pilocarpine (0.4%) to diclofenac sodium 0.006% alone in the percentage of study eyes demonstrating a ≥ 3-line (15-letter) gain in BCVA at 40 cm, 1-hour post-treatment from the baseline measurement using a Pearson chi-squared test at a 2-sided alpha = 0.05 assuming that the diclofenac sodium 0.006% alone response is 5% and the CSF-1 response is 27%, resulting in an overall 2-sided alpha = 0.10 that accounts for the 2 tests of hypotheses utilizing Bonferroni correction procedures.

At least approximately 30% of subjects will have light (i.e. blue, green, gray, and hazel) iris and at least approximately 30% will have a brown iris. The actual percentages will vary based on enrollment.

10.8 Demographic and Baseline Characteristics

Subject demographics including age, gender, race, ethnicity, and iris color will be presented using summary statistics (mean, SD, minimum, maximum, and median).

10.9 Efficacy Analysis

10.9.1 Primary Efficacy Analyses

The primary efficacy variable in this study is the percentage of study eyes with a ≥ 3-line (15-letter) gain in BCVA at 40 cm, 1-hour post-treatment at visit 3 and/or visit 4 from the baseline measurement. The primary analysis will use the PP population on observed data only. The primary analyses will be completed using Bonferroni alpha adjustment to maintain the overall Type I error as detailed in the hypothesis section with statistical inference made on the comparisons between CSF-1 (0.4%/0.006%) versus diclofenac sodium 0.006% and between Pilocarpine (0.4%) versus diclofenac sodium 0.006% Again as detailed in the hypothesis section, only if the higher dose concentrations, for CSF-1 (0.4%/0.006%) and/or Pilocarpine (0.4%), respectively, are successful will the corresponding lower dose concentrations, for CSF-1 (0.2%/0.006%) and/or Pilocarpine (0.2%), respectively, have inference made on the statistical test.

10.9.2 Secondary Efficacy Analysis

[redacted]

10.10 Safety Analysis

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and be presented in a data listing. Treatment emergent AEs (TEAEs), those that occur after the first dose of IP within each period, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Similar summaries will also be presented for TEAEs related to the IP and by severity. When reporting the incidence of AEs, a subject will only be counted once if they ever experience an event within the SOC and ever experience the individual PT within the specific treatment period. AEs will be reported separately by period.

[redacted]

Full details of the safety analyses will be specified in the formal SAP.

10.11 Interim Analysis

An interim analysis may be provided when approximately 50% of the subjects have completed the study. If an interim analysis is completed, O'Brien-Fleming alpha spending function will be used to specify the interim boundaries for stopping for efficacy and for non-binding futility as well as adjusting the final 2-sided alpha level.

10.12 Missing Data

Sensitivity analysis on the primary efficacy variable will be performed on both the PP and ITT imputing missing data as failures; additional sensitivity analyses such as pattern mixture model multiple imputation methodologies and tipping point analyses may be performed and will be specified in the SAP.

10.13 Adjustment for Multiplicity

For the primary hypotheses, the study will be considered a success if either of the null hypotheses, H_{01} or H_{02}, are rejected in favor of their corresponding alternative hypotheses, H_{11} or H_{12}. The overall Type I error of the 2-sided alpha = 0.10 will be preserved through the use of Bonferroni correction procedures testing each hypothesis at a 2-sided alpha = 0.05.

Again as detailed in the hypothesis section, only if the higher dose concentrations, for CSF-1 (0.4%/0.006%) and/or Pilocarpine (0.4%), respectively, are successful will the corresponding lower dose concentrations, for CSF-1 (0.2%/0.006%) and/or Pilocarpine (0.2%), respectively, have inference made on the statistical test. Within these hierarchical frameworks, these hypotheses can be tested at a 2-sided alpha = 0.05 while still preserving an overall Type I error of alpha = 0.10.

There will be no adjustment for multiplicity for testing of secondary endpoints.

[redacted]

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current GCPs, including the ICH Guidelines, and will, in general, be consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IPs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

All ICFs must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the ICF requires revision (e.g. due to a protocol amendment or

significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by [redacted] prior to submission to the governing IRB and that it is read, signed, and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by [redacted] and/or the sponsor and provided in writing by [redacted] and/or the sponsor prior to the consent process.

11.1.2 IRB Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB-approved version of the ICF will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [redacted] the sponsor, the IRB approving this study, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed in, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRFs serves as the investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study-related correspondence, patient records, consent forms, records of the distribution and use of all IPs, and copies of case report forms should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an

agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

11.5.1 Labeling/Packaging

[redacted]

The IP will be packaged and labeled into clinical kits. Each subject will be assigned a single master kit containing two smaller (inner) kits. Each master kit will be uniquely identified by the kit number; the 2 smaller kits inside will bear the same kit number with additional designation indicating the visit at which each is to be dispensed (i.e., visit 2 or visit 3). [redacted]

Clinical label texts for the packaging will meet applicable regulatory requirements and include the statement “Caution: New Drug-Limited by Federal Law to Investigational Use.”

11.5.2 Storage of Investigational Product

[redacted]

11.5.3 Accountability of Investigational Product

For in-office dosing, the IP is to be administered by study site personnel, and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP administered to subjects and the amount returned or disposed throughout the course of the study. A detailed inventory must be completed for the IP.

11.5.4 Return or Disposal of Investigational Product

All IPs will be returned to the sponsor or their designee or destroyed. The return or disposal of IP will be specified in writing. Any remaining IP will be collected from subjects at visit 3 and visit 4 before study exit.

11.5.5 IP Manual

Further details on labeling, packaging, storage, accountability, and return or disposal of investigational product can be found in the study IP Manual.

11.6 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's source document, eCRF, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g. by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when by adding to the correction his/her initials as well as the date of the correction.

11.7 Handling of Biological Specimens

Not applicable

11.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. [redacted] and the study sponsor will have the final decision regarding the manuscript and publication.

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13 APPENDICES

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APPENDIX 3: PROTOCOL AMENDMENT SUMMARY
AMENDMENT 1

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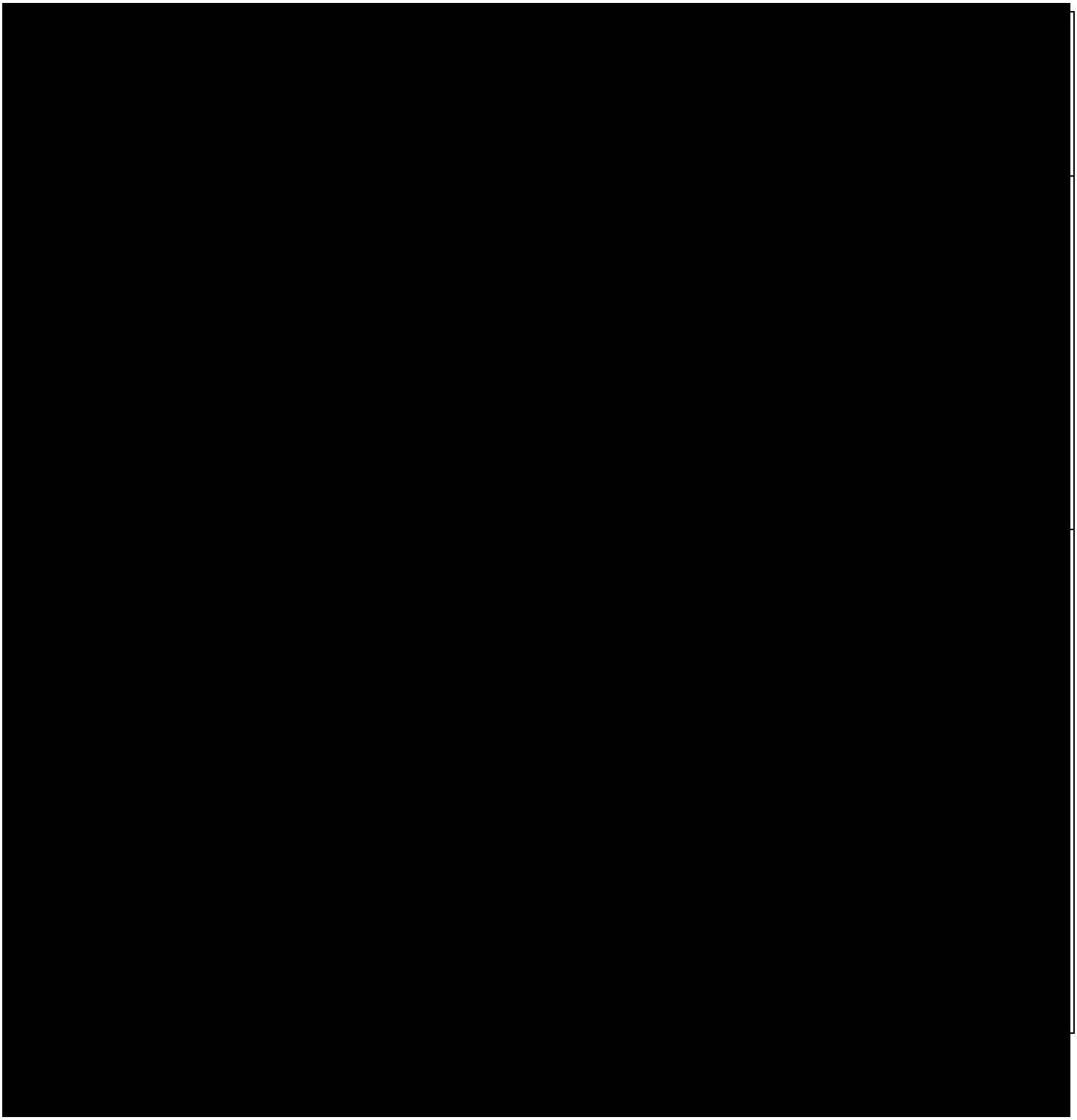

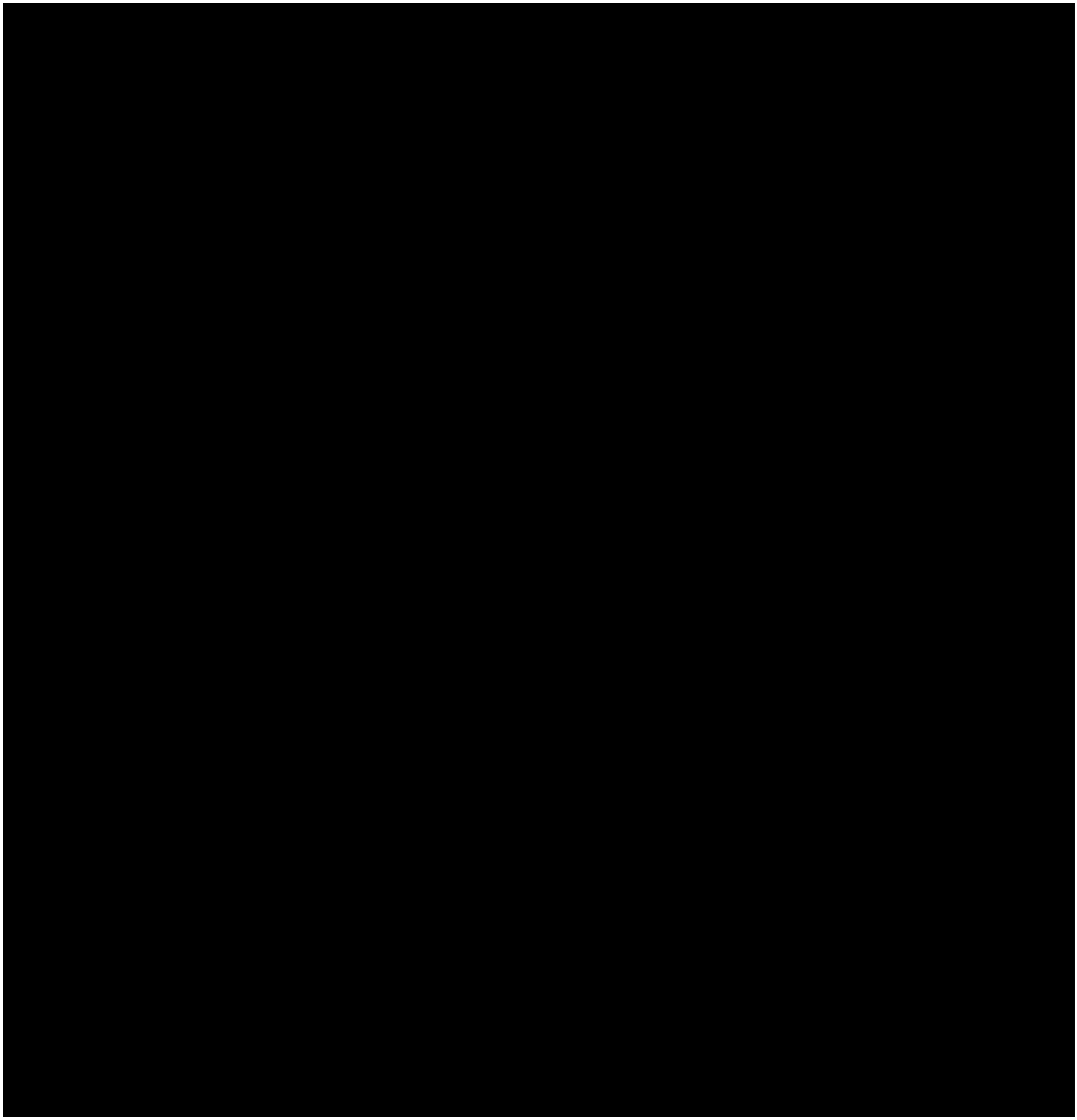

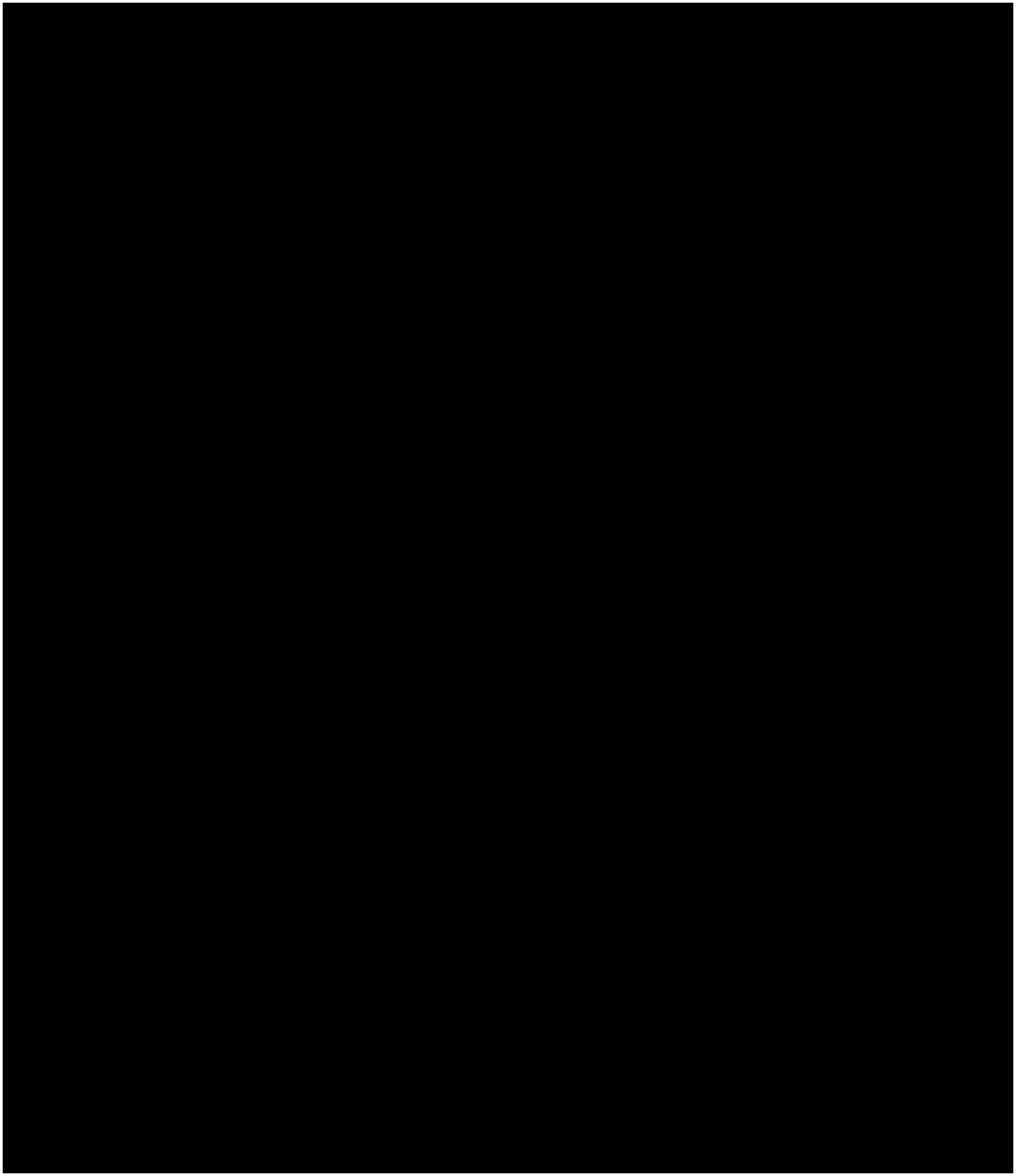

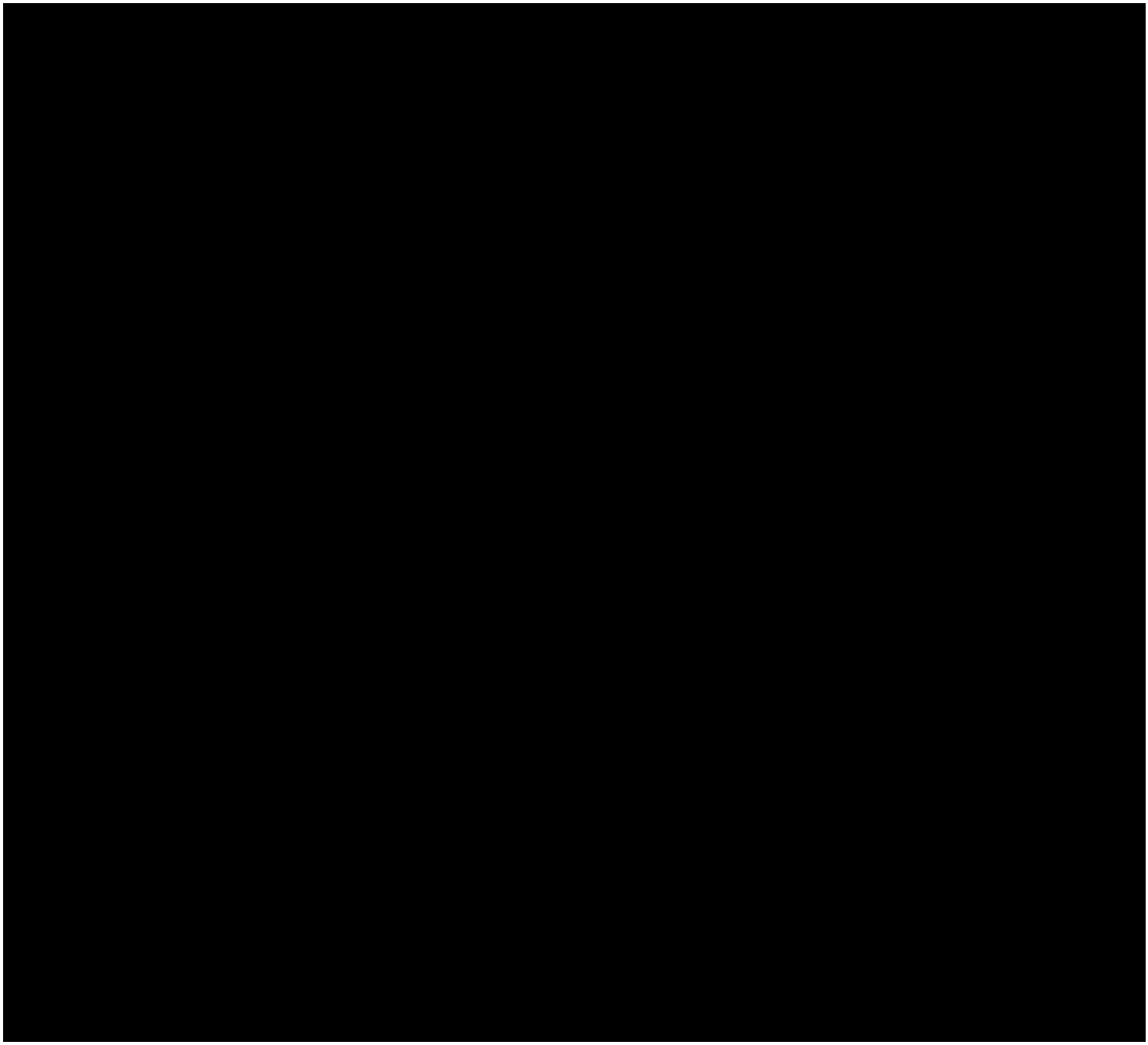

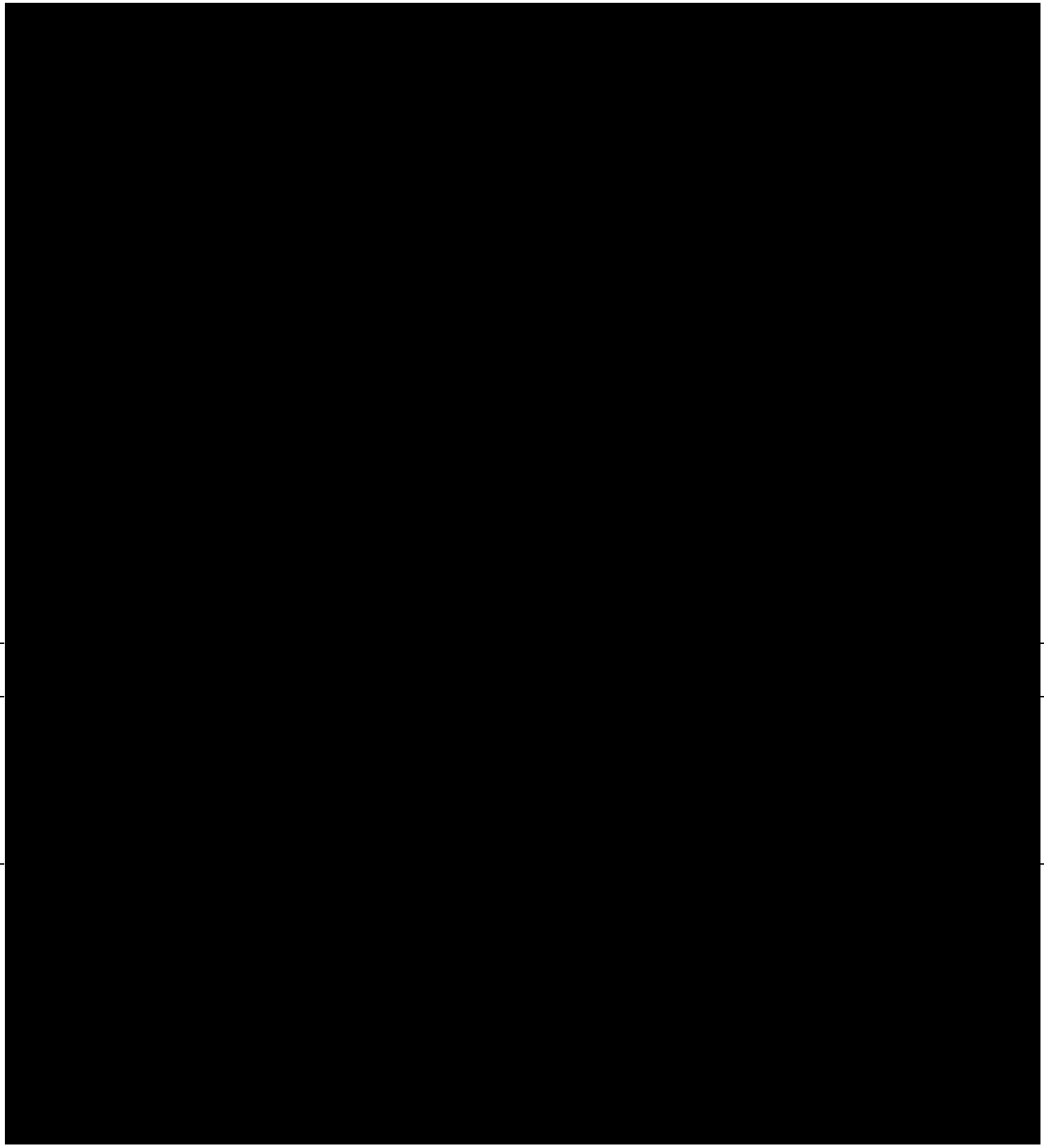

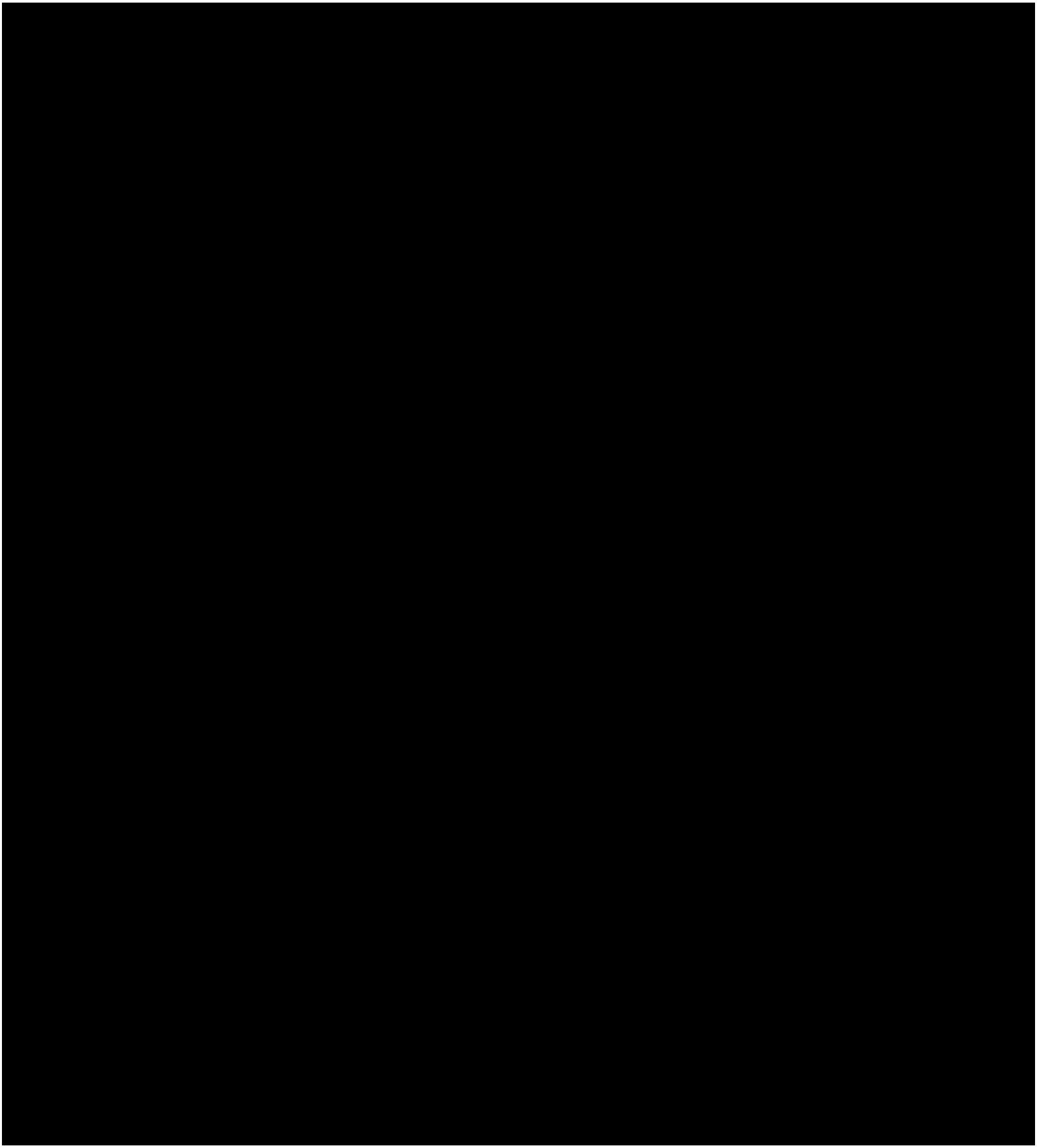

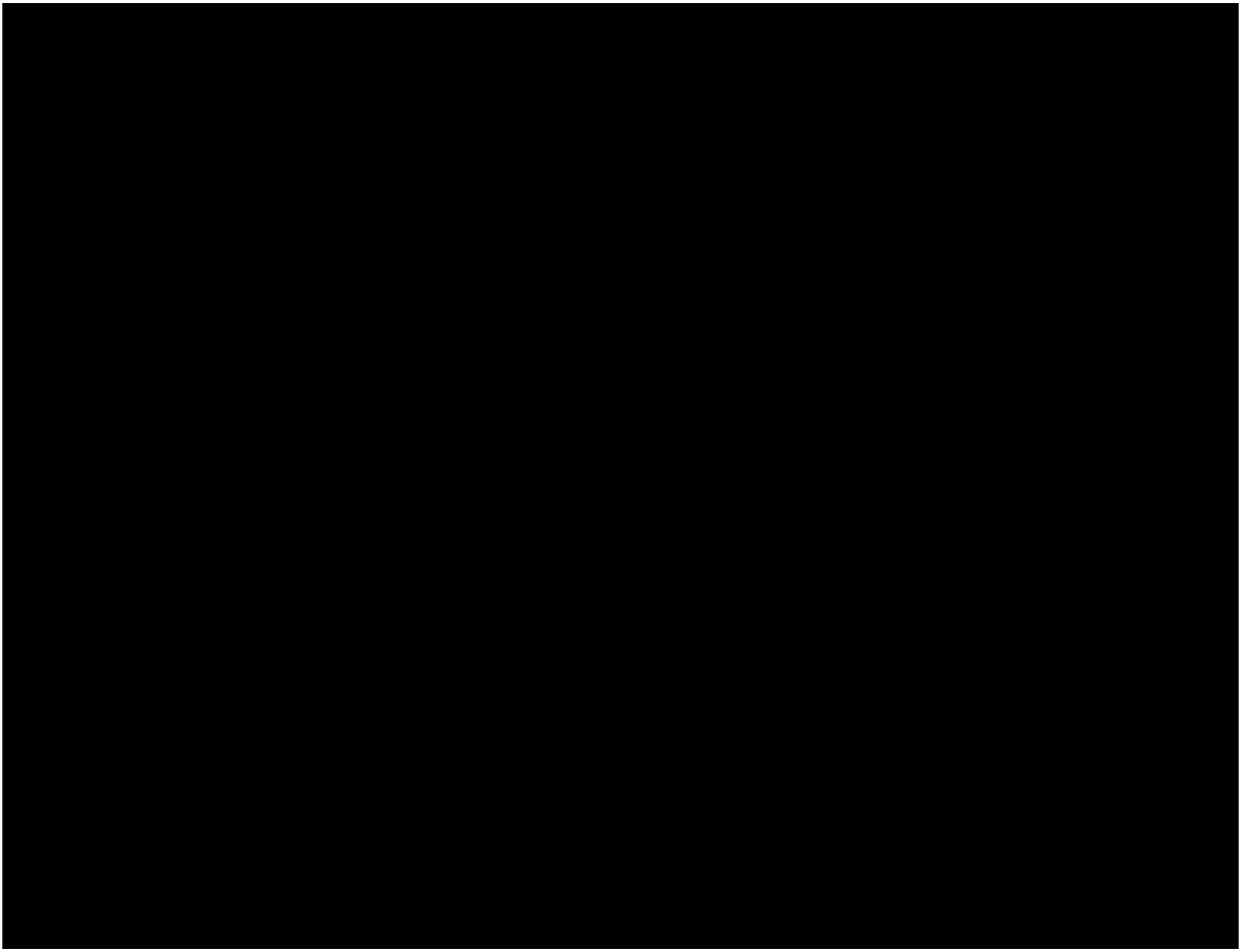

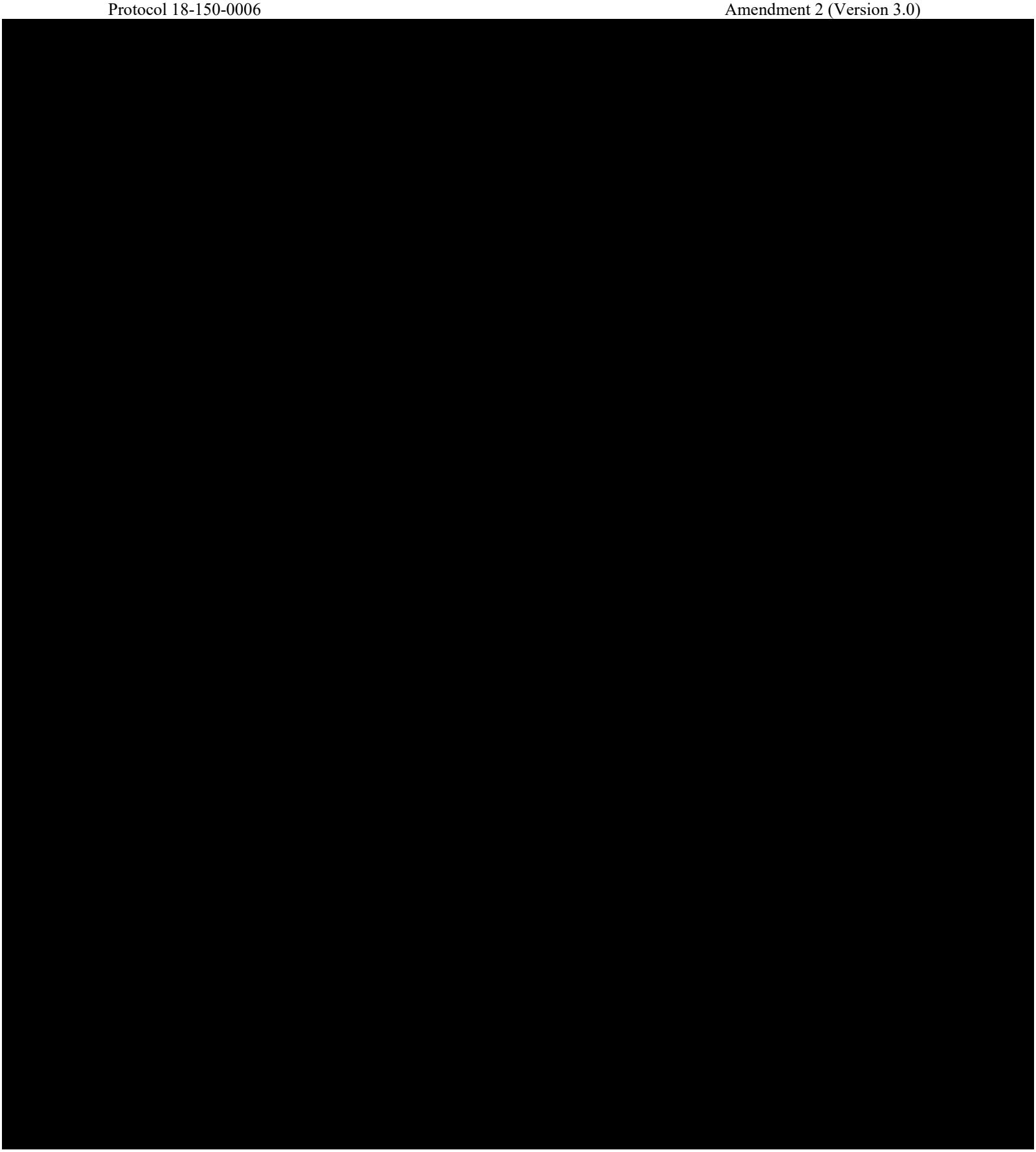

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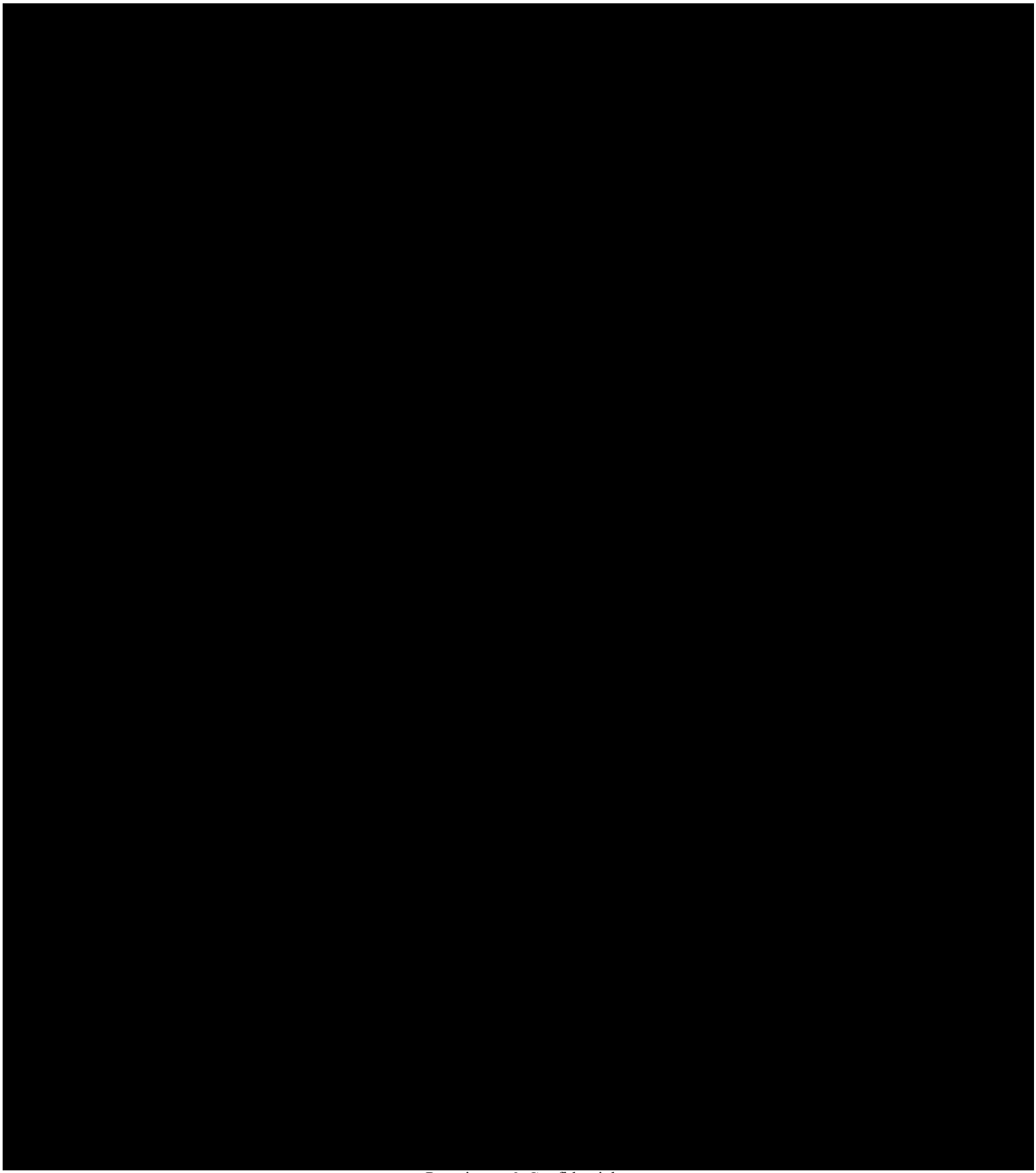

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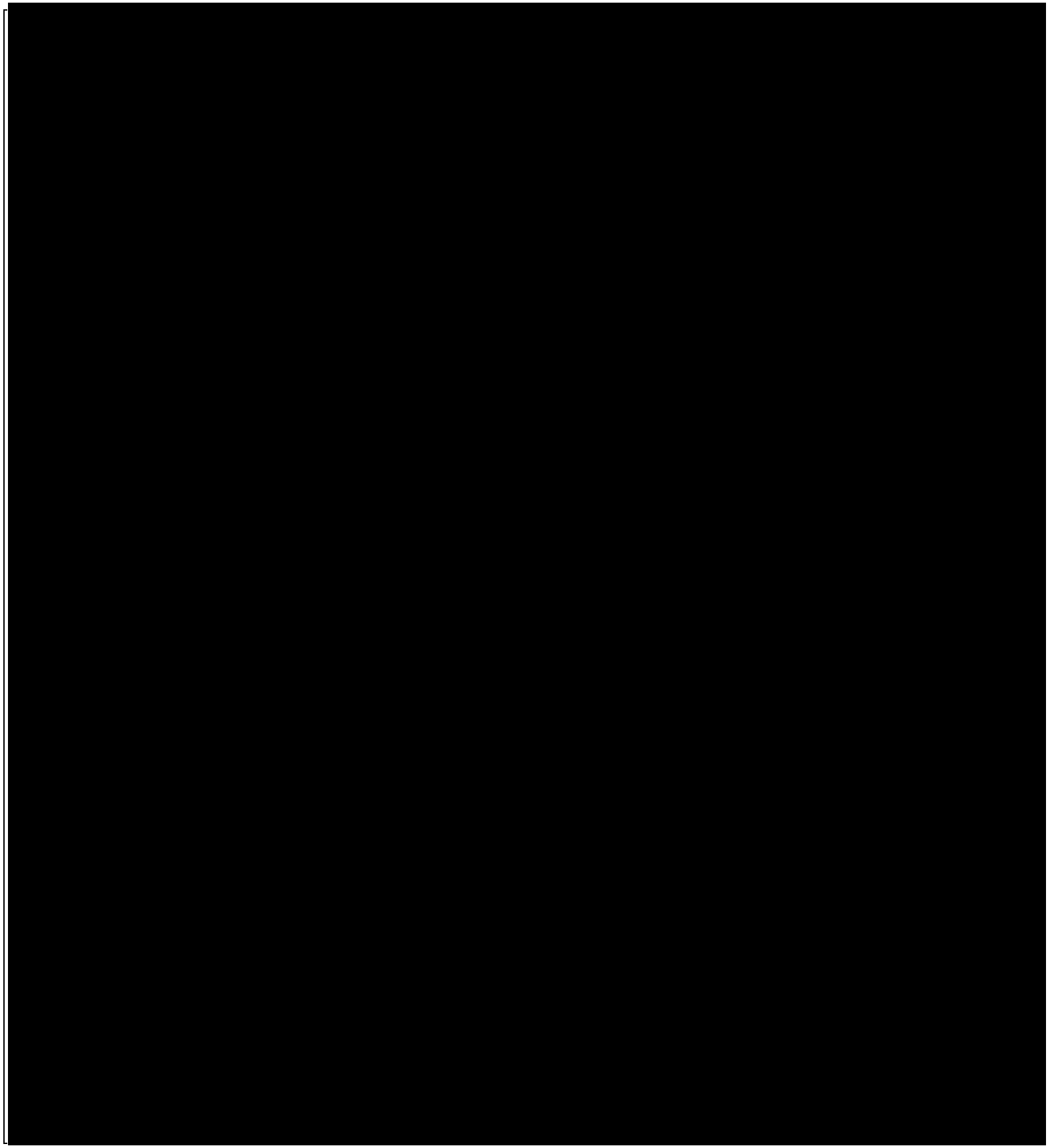

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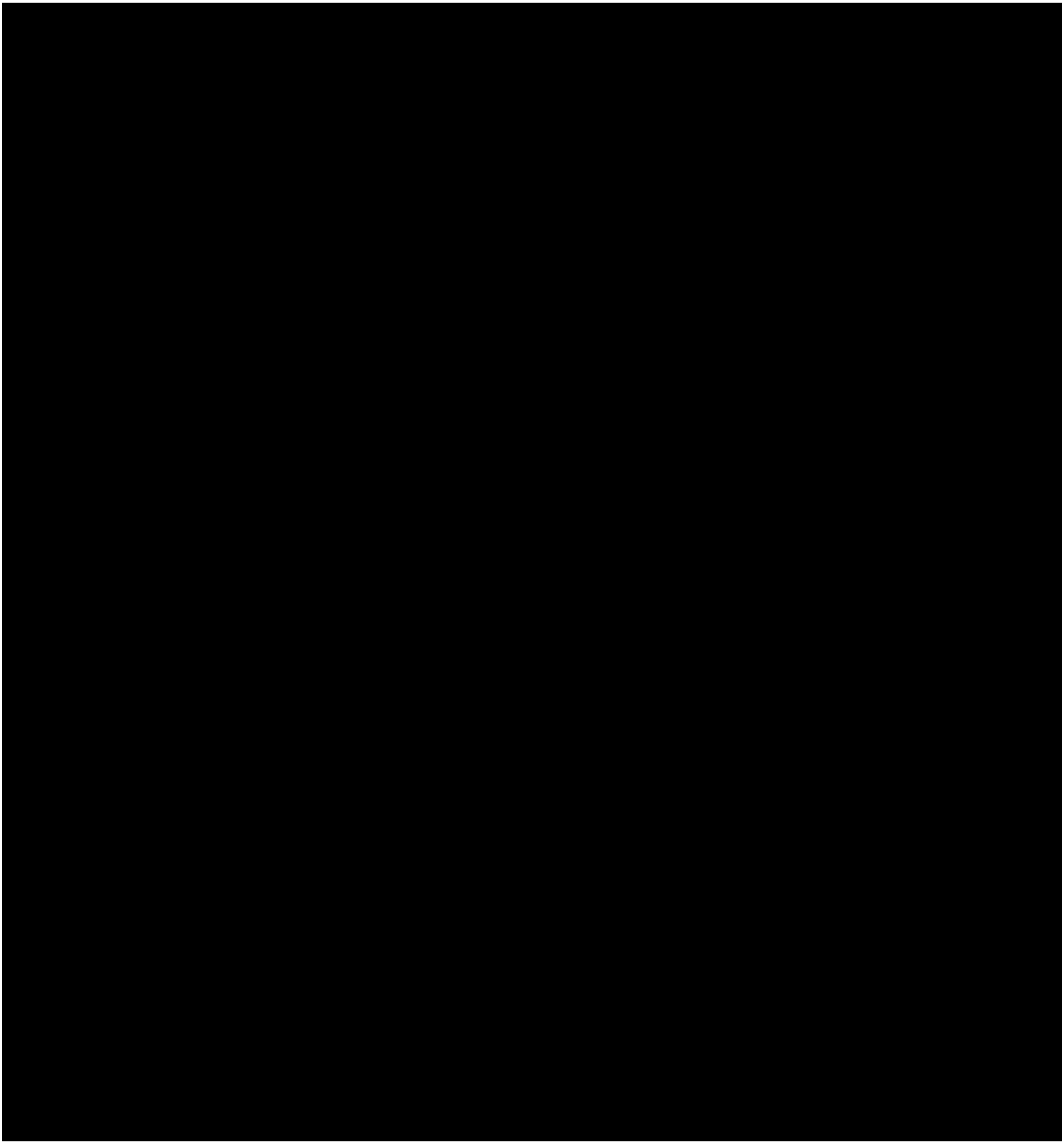

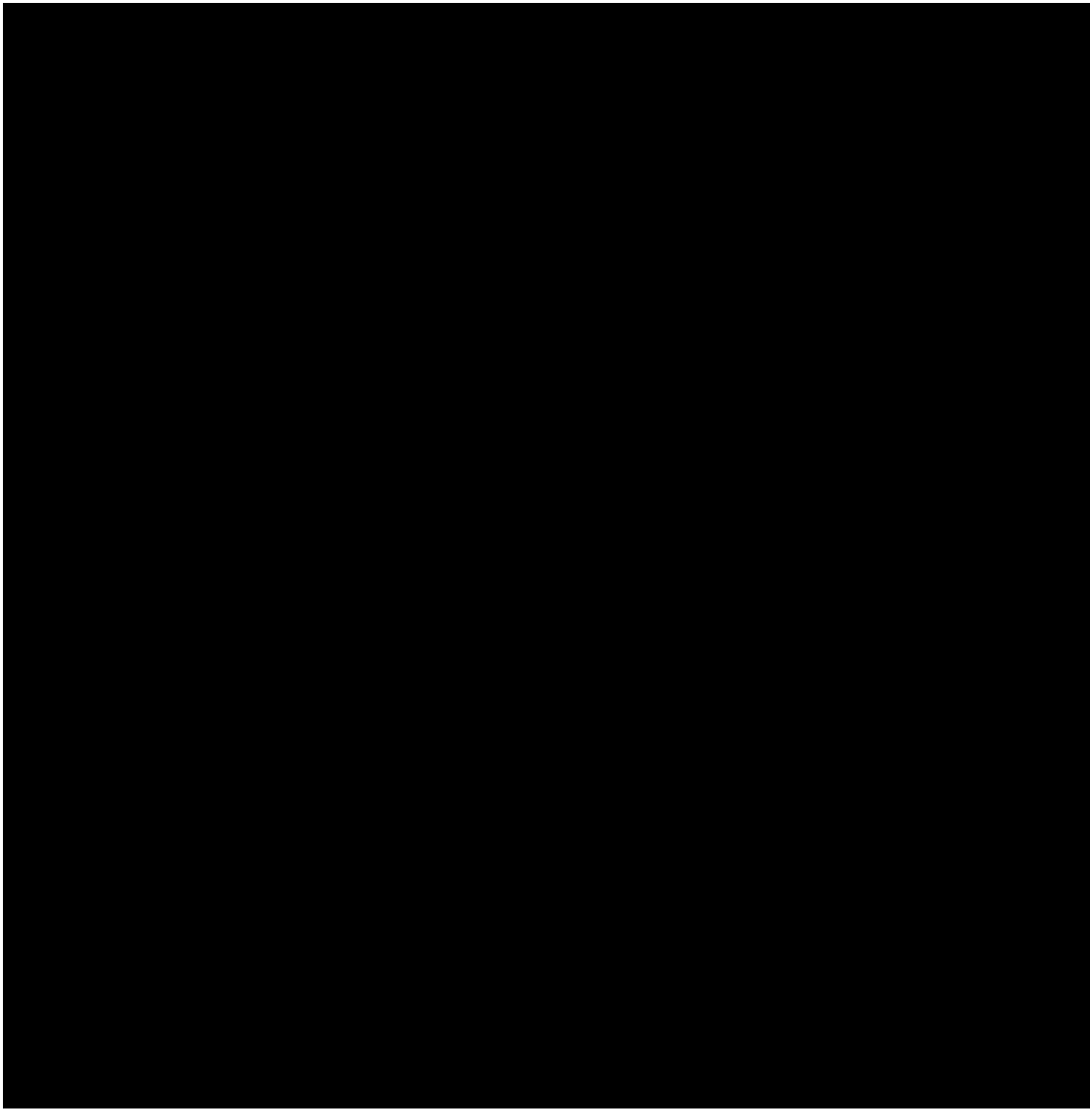

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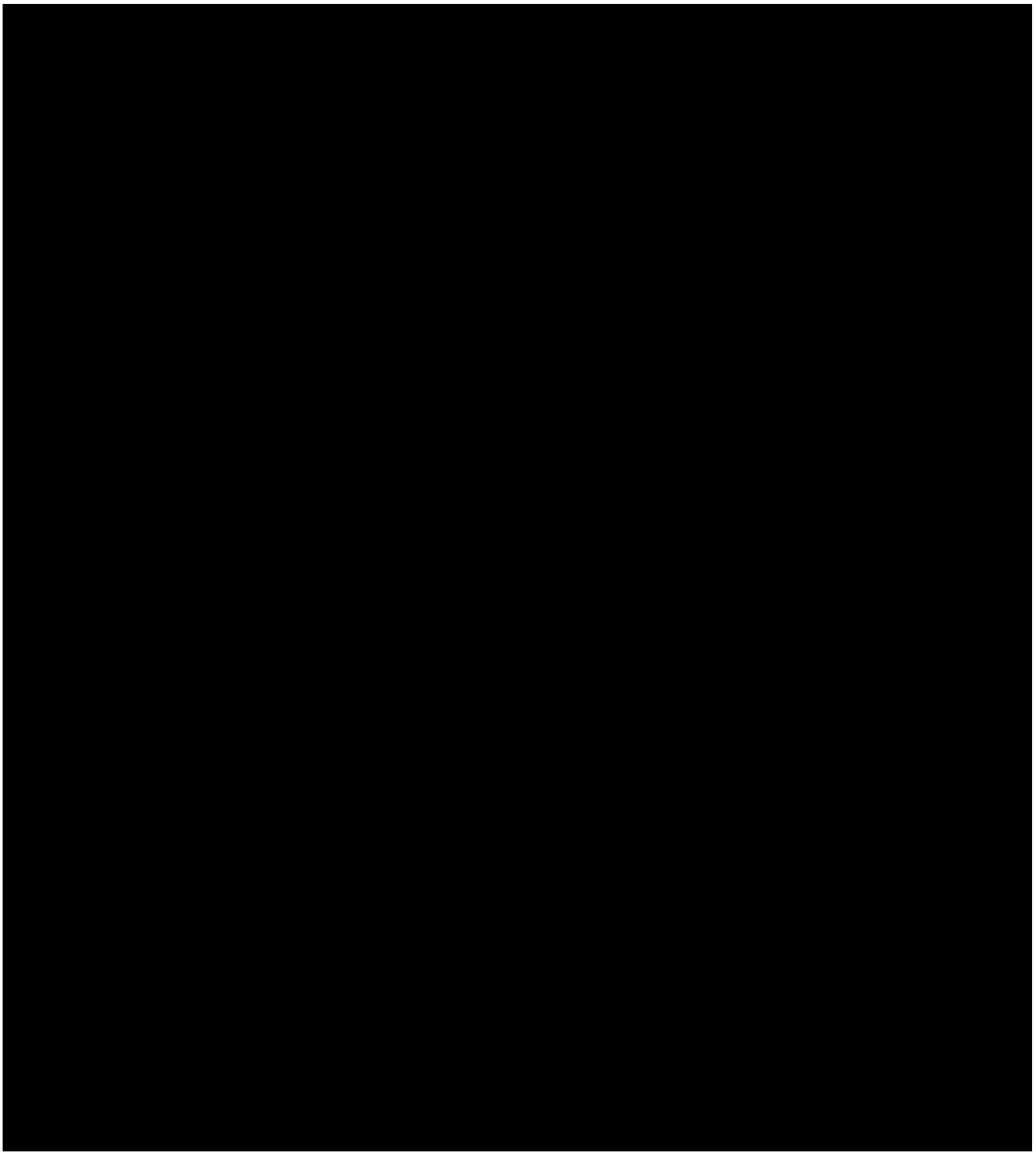

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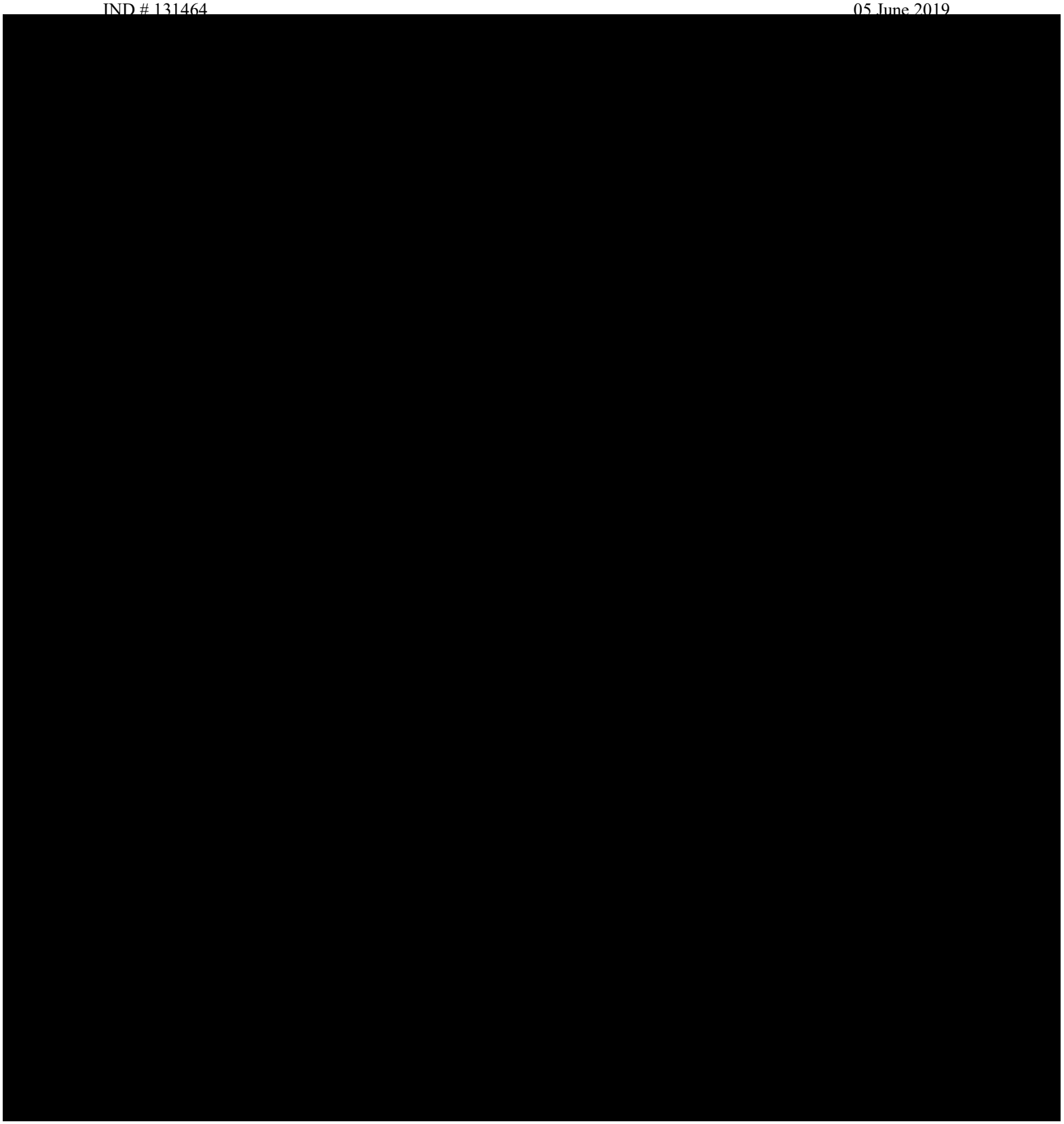

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Appendix 5: Sponsor and [redacted] Approvals

Protocol Title:	A Multi-Center, Double-Masked Evaluation of the Efficacy and Safety of CSF-1 in the Treatment of Presbyopia
Protocol Number:	18-150-0006
Final Date:	05 June 2019

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signature:_____ Date:_____

[redacted]
Orasis Pharmaceuticals

Signature:_____ Date:_____

[redacted]

[redacted]_____ [redacted]_____

[redacted]

[redacted]_____ Date:_____

[redacted]
Chief Scientific Officer and Senior Vice President of Strategic Scientific Consulting
[redacted]

Appendix 5: Sponsor and [redacted] Approvals

Protocol Title:	A Multi-Center, Double-Masked Evaluation of the Efficacy and Safety of CSF-1 in the Treatment of Presbyopia
Protocol Number:	18-150-0006
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Signature:_____ Date:_____

[redacted]
Orasis Pharmaceuticals

Signature:[redacted] Date: 6/5/2019

Signature:[redacted] 6/5/2019

Signature:[redacted] Date: 6/5/2019

Appendix 6: Investigator's Signature

Protocol Title:	A Multi-Center, Double-Masked Evaluation of the Efficacy and Safety of CSF-1 in the Treatment of Presbyopia
Protocol Number:	18-150-0006
Final Date:	05 June 2019

I agree to implement and conduct the study diligently and in strict compliance with the protocol, Good Clinical Practices and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the sponsor in confidence and, when this information is submitted to an institutional review board (IRB), ethical review committee or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

[Name]
Principal Investigator
[Affiliation]

Signature Page for VV-CLIN-000221 v1.0

Approval	[redacted] 07-Jun-2019 10:44:45 GMT+0000

Signature Page for VV-CLIN-000221 v1.0