NCT03226769

Study ID: OCUN-023

Title: Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease

Protocol Date: 01 Jun 2017

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Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease

Protocol Number: OCUN-023

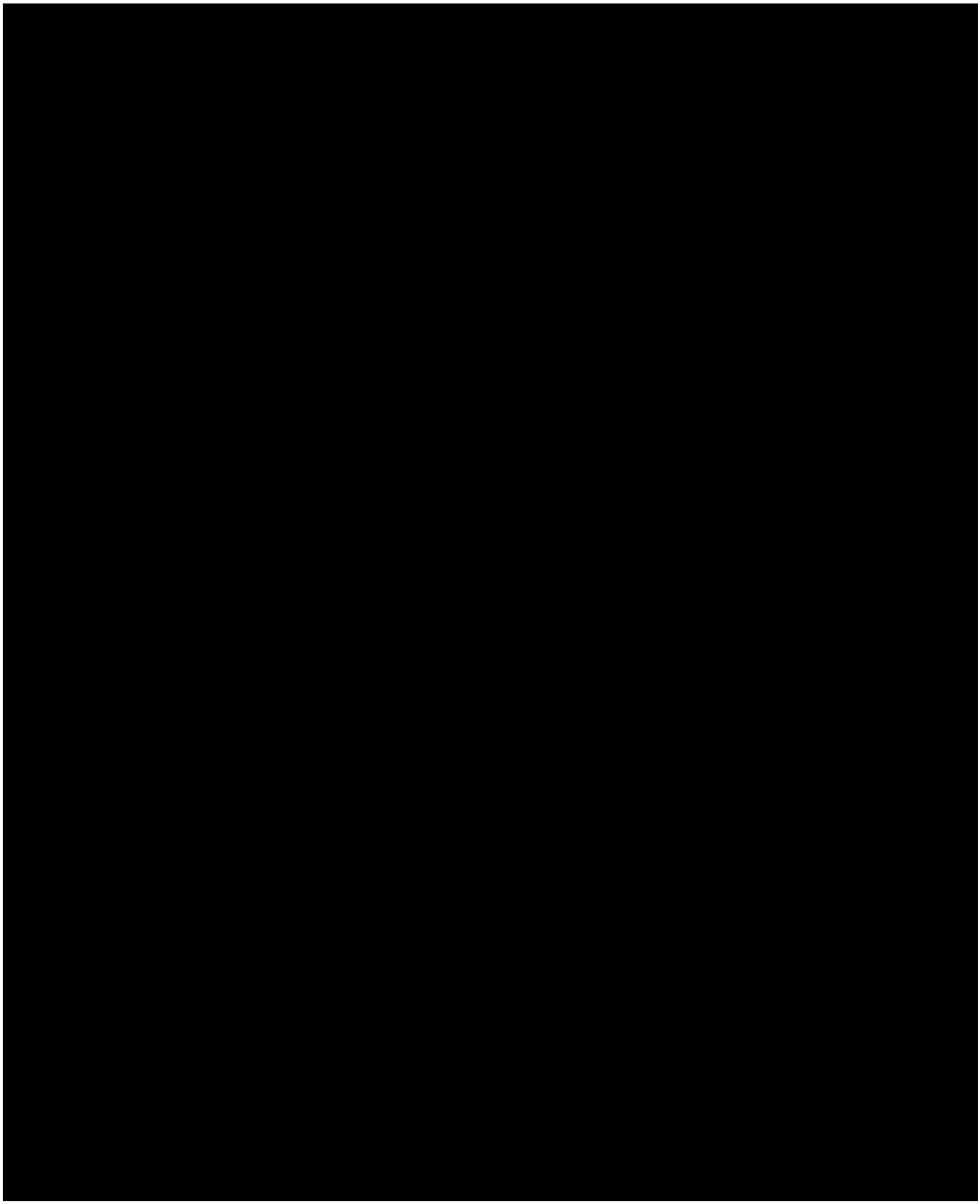
Original Protocol: June 1, 2017

Device Name: TrueTear

Sponsor: Allergan, Inc.

[redacted]

[redacted]



SYNOPSIS

Protocol Title:	Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease
Protocol Number:	OCUN-023
Study Device(s):	TrueTear
Study Objective:	The primary objective of this study is to compare the safety and efficacy of TrueTear to standardized moist heat compress (Thermalon® Dry Eye Compress) for the treatment of Meibomian Gland Disease (MGD)
Overall Study Design	
Structure:	Prospective, open-label, randomized (1:1), parallel two arm design
Duration:	An individual participant's participation is expected to last approximately 44 days
Controls:	Thermalon Dry Eye Compress [redacted]
Device Regimen:	TrueTear: • Initial in-office application of approximately 8 minutes duration at Visit 2 [redacted] • Second in-office application of approximately 3 minutes at Visit 3 [redacted] • Daily use of TrueTear per Patient Guide with assessments at Visit 3 ([redacted], Visit 4 [redacted] and Visit 5 ([redacted]
Control Regimen:	Thermalon Dry Eye Compress: • In-office applications at Visit 2 ([redacted] and Visit 3 [redacted] and daily use as per label instructions with assessments at Visit 3 [redacted] Visit 4 [redacted] and Visit 5 ([redacted]
[redacted]	[redacted]

Study Population Characteristics	
Number of Participants:	Approximately 70 participants (approximately 35 participants per arm), will be enrolled at up to two sites in the US.
Condition/Disease:	Meibomian Gland Disease
Evaluation Criteria	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

General Statistical Methods and Types of Analyses

Sample Size

As this is a proof of concept study, no formal calculation of sample size was conducted. Approximately 70 participants will be enrolled to achieve approximately 60 completed

participants.

General Statistical Methods

Statistical analyses will use a two-tailed test and will be evaluated at an α of 0.05 unless otherwise specified. The mean, standard deviation (SD), median, minimum and maximum will be presented for continuous variables such as participant age. For categorical variables, such as sex, the number for each category, the total number evaluated, and the percentage will be presented.

[redacted]

[redacted]

[redacted].

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[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
ADE	Adverse device effect
CDVA	Corrected distance visual acuity
CFR	Code of Federal Regulations
CI	Confidence interval
CN	Cranial nerve
DED	Dry eye disease
DHHS	Department of Health and Human Services
CRF	Case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
IPL	Intense pulsed light
IRB	Institutional/independent review board
LASEK	Laser-assisted sub-epithelial keratectomy
LASIK	Laser-assisted in-situ keratomileusis
LED	Light-emitting diode
LFU	Lacrimal functional unit
LLT	Lipid layer thickness
logMAR	Logarithm of the minimum angle of resolution
MGD	Meibomian gland disease
Mm	Millimeter
[redacted]	[redacted]
OTC	Over-the-counter
PP	Per protocol
PRK	Photorefractive keratectomy
SAE	Serious adverse event
SD	Standard deviation
[redacted]	[redacted]
TBUT	Tear film breakup time
TENS	Transcutaneous electrical nerve stimulation
US	United States
WOCBP	Women of childbearing potential

1.0 INTRODUCTION

1.1 Background

Meibomian gland disease (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion.[1] MGD is a common eyelid disorder that has widespread prevalence of 37% to 47% in the United States (US) alone.[2] The incidence of MGD has been found to increase with age[3-9] and is markedly higher in Asian populations (46.2% to 69.3%).[10-12] MGD may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.[13] Combined, these manifestations afflict millions of people worldwide, with more than 10 million in the US alone.[2,13]

Current recommendations for the management and treatment of MGD include: 1) lid-heating, massage, and cleaning, 2) topical antibiotic and/or topical steroids, 3) systemic anti-inflammatory antibiotics (e.g., tetracycline), 4) lubricants as adjunctive treatment, 5) LipiFlow® Thermal Pulsation System, 6) meibomian gland probing and 7) meibomian gland expression. Lid warming, lid hygiene, and lubricants are often found to be suboptimal / only partially effective.[2] Meibomian gland probing and expression can lead to patient discomfort and/or damage to the lid margin. Topical antibiotic and/or an antibiotic-steroid combination are prescribed for acute exacerbated cases or for anterior blepharitis, but are short-term and may not address the underlying cause(s) of MGD. Systemic antibiotics may lead to systemic side effects including gastrointestinal disturbance (e.g., from tetracyclines). Therefore, there remains a need for new treatment strategies targeting the treatment of MGD.

1.2 Rationale

The nasolacrimal reflex is a well-established pathway by which nasal stimuli promote both resting basal[14] and bolus tear secretion. The reflex plays a functional role in expelling foreign bodies or irritants from the nose by secreting tears into the nasal cavity via the nasolacrimal duct upon stimulation by the irritant.

Reflex activation of the lacrimal glands is also one of the body's primary compensatory mechanisms for addressing ocular surface dryness. Unfortunately, over time, an arid environment and resulting inflammation results in damage to the afferent nerves innervating the cornea, compromising the reflex response and ultimately leading to an even drier ocular surface.

Studies have demonstrated that intranasal stimulation via use of the TrueTear application results in a statistically significant increase in tear production measured by the Schirmer test.[15,16] To date, however, little is known regarding the role intranasal neurostimulation may have on secretion of meibum. The meibomian glands are not innervated directly[17] and the mechanism by which meibum that is secreted into the glands and expressed onto the eyelids is a two-stage process. First meibum is continually secreted by sebaceous cells into the meibomian glands for storage prior to expression.[18,19] Second, meibum expression is achieved though coordinated muscular activity (which can be initiated by numerous stimuli such as blinking), of the orbicularis muscle (the eyelid) contracting, and Riolan's muscle (a sphincter at the orifice of the glands just below the lid margin) relaxing. The innervation to the musculi orbicularis and

Riolan's is provided by the facial nerve (cranial nerve CN-VII) whose fibers transmit action potentials to contract said musculi upon neural activity in the superior salivatory nucleus in the brainstem.[18,20] This nucleus is responsible for the secretion of tears and tear components and shows neural activity when sensory nerve endings of the anterior ethmoidal nerve, a sub-branch of the trigeminal nerve, are stimulated.[21-23] The TrueTear stimulates the anterior ethmoidal nerve inside the nose, thereby increasing neural activity in the superior salivary nucleus, which in turn drives action potentials on the facial nerve to the lacrimal gland as well as provides the signals for coordinated activation of the orbicularis and the Riolan's muscles, thereby expressing meibum from the meibomian glands. As such, there is reason to believe that meibum expression may be achieved following stimulation of anterior ethmoidal afferences inside the nose.

A clinical study conducted by the Sponsor measuring meibomian gland activity and tear film lipid layer thickness stimulated with use of TrueTear supports this assumption. Specifically, in this study, evidence of increased meibomian gland secretion activity and increased tear film lipid layer thickness was measured following a single use of TrueTear relative to both pre-application of TrueTear and an extranasal control.[24] It is thus of interest to the Sponsor to investigate the effectiveness of TrueTear as a potential novel treatment strategy for MGD.

2.0 STUDY OBJECTIVES

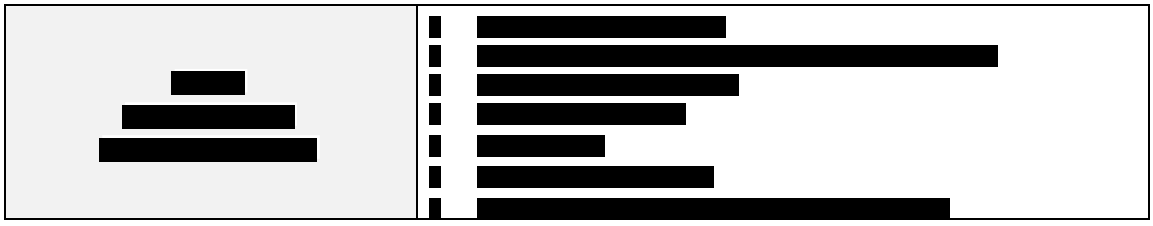
The primary objective of this study is to compare the safety and efficacy of TrueTear (intranasal tear neurostimulation) to standardized moist heat compress (Thermalon Dry Eye Compress) for the treatment of Meibomian Gland Disease (MGD).

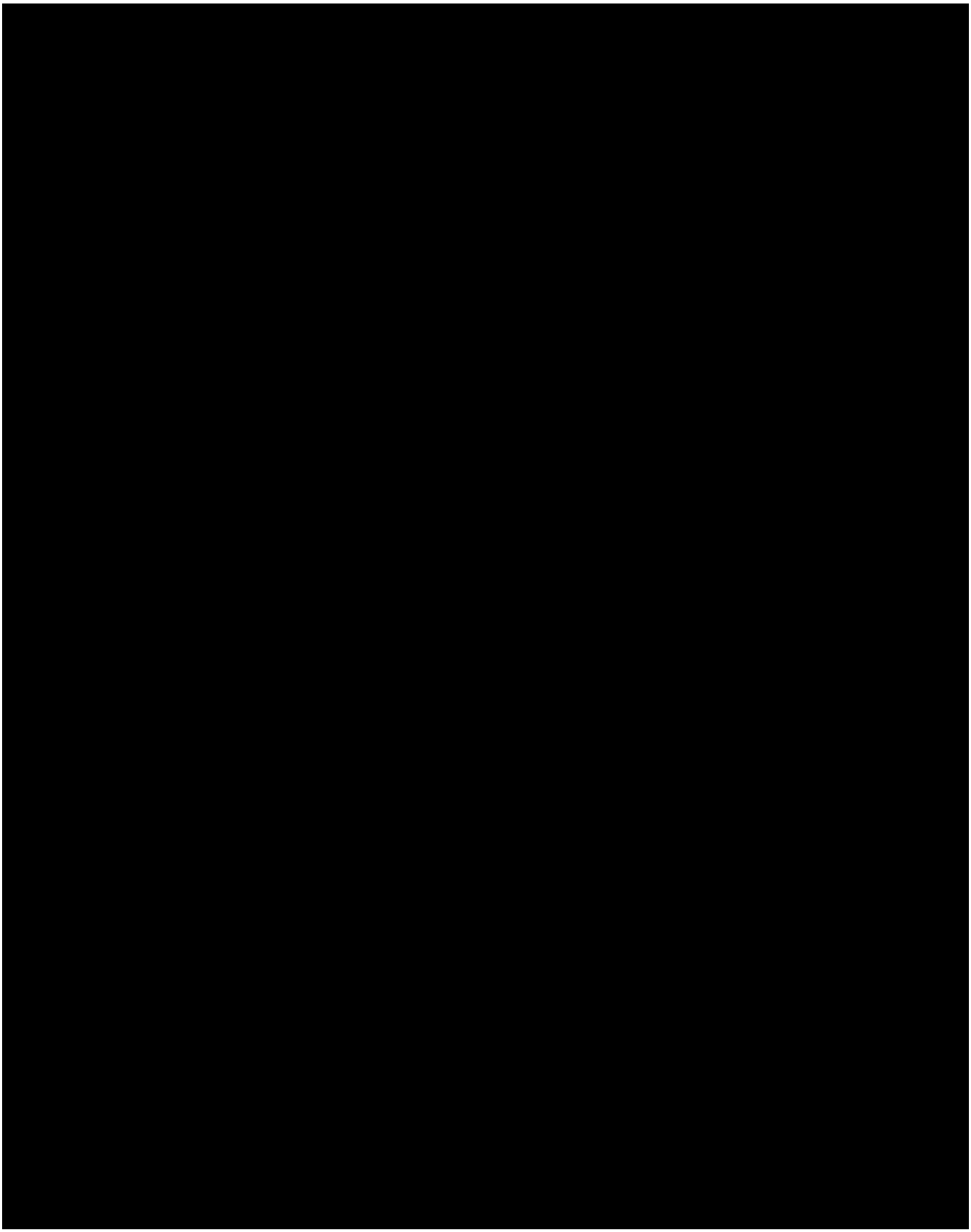
3.0 CLINICAL HYPOTHESES

Thirty days of TrueTear application provides efficacious treatment of MGD compared to moist heat compress control as measured by signs and/or symptoms of MGD.

4.0 OVERALL STUDY DESIGN

This is a prospective, randomized, parallel two-arm study conducted at up to two sites, designed to characterize the effectiveness of TrueTear on the signs and symptoms of MGD. Approximately 70 male and female participants at least 22 years of age with a participant-reported history of dry eye or MGD and meeting all other study eligibility criteria will be randomized in a 1:1 ratio to either the TrueTear or moist heat compress control treatment groups. Following the initial application of treatment in clinic at Day 0, participants will apply the randomized treatment for approximately 30 days.





5.0 STUDY POPULATION

5.1 Number of Participants

It is estimated that approximately 70 participants will be enrolled at up to two sites in the US to complete approximately 60 participants.

Participants will be randomized in a 1:1 ratio to one of two possible treatment groups:

- TrueTear
- Thermalon Dry Eye Compress (moist heat compress)

5.2 Study Population Characteristics

All participants should meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Participants should:

1. Be twenty-two (22) years of age or older at the Screening Visit

2. At the Screening and Baseline Visits, have a Standard Patient Evaluation for Dryness (SPEED) [redacted]
3. In at least one eye, meet all of the following objective measures in the same eye:
   - A basal Schirmer test [redacted]
   - [redacted]
   - [redacted]
   - Tear film breakup time (TBUT) ≥ [redacted]
4. Have used an artificial tear product, lid hygiene [redacted]; omega-3 supplementation; antibiotics [redacted] for the treatment of dry eye disease or meibomian gland disease within one year of the Screening Visit

[redacted]

5.4 Exclusion Criteria

Participants should not:

1. Have chronic or recurrent epistaxis, coagulation disorders or other conditions that, in the opinion of the Investigator, may lead to clinically significant risk of increased bleeding
2. Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas
3. Have a vascularized polyp, severely deviated septum or severe nasal airway obstruction as confirmed by intranasal examination performed at the Screening Visit
4. Have had any intraocular surgery (such as cataract surgery), extraocular surgery ([redacted]) in either eye within three months of the Screening Visit or refractive surgery [redacted] within twelve months of the Screening Visit

[redacted]

[redacted]

16. Have a cardiac demand pacemaker, implanted defibrillator, or other active implanted metallic or active implanted electronic device in the head

[redacted]

5.5 Inclusion/Exclusion Exceptions

The Investigator has the right to exclude a potential participant's enrollment in the study if s/he deems it in the best interest of the participant. Reasons for exclusion on this basis will be recorded.

5.6 Discontinuation Criteria (if applicable)

Participants are free to discontinue their participation in this study at any time and for any reason, specified or unspecified, without prejudice. In addition, the Investigator may decide to discontinue a participant from the study for safety reasons or when it is in the best interest of the participant. No constraints will be placed on ordinary patient management.

Reasons for participant withdrawal may include but are not limited to the following:

- Either at the Investigator's request, for safety reasons (e.g., serious or severe AE), or at the participant's request
- Non-compliance (e.g., failure to follow application instructions, missing visits, using prohibited medications)
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the participant; the Investigator will report all such information on the source documents/case report forms (CRFs) and decide, in conjunction with the Sponsor, whether the participant is to be withdrawn
- Sound medical reason
- A confirmed positive pregnancy test at any time during the study
- When a participant is lost to follow-up. The Investigator (or designee) will make repeated attempts to reach the participant by telephone, email and/or letter before considering the participant as lost to follow-up. These actions will be documented and recorded on the End of Study CRF. Copies of follow-up letters, if any, should be maintained in the Investigator's file.
- When a participant is erroneously admitted into the study or does not meet the eligibility criteria

In addition, the Sponsor also reserves the right to discontinue the study at any time for clinical or administrative reasons.

All early discontinuations and their reasons should be carefully documented by the Investigator on the End of Study CRF and, if applicable, on the Adverse Event (AE) CRF. Notification of a participant's discontinuation and the reason for discontinuation will be made to [redacted] and/or Sponsor. No participant who has been randomized can be replaced by another participant if the participant is discontinued prematurely for any reason.

6.0 STUDY PARAMETERS

7.0 DEVICE DESCRIPTION

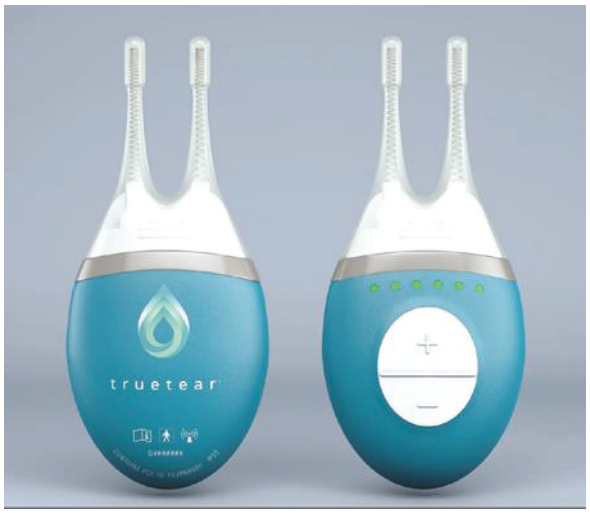
7.1 TrueTear Investigational Device

The TrueTear device delivers small electrical currents to the inner cavity of the nose, activating nerves that stimulate the body's natural tear production system.

The device consists of four distinct parts (Figure 1):

1. A reusable Base Unit which produces the electrical stimulation waveform.
2. A disposable Tip that inserts into the nasal cavity and stimulates the target intranasal tissue.
3. A reusable Cover to protect the Tip.
4. A Charger which recharges the battery inside the Base Unit.

Base Unit with Cover



Base Unit with Disposable Tips (Front and Back)

TrueTear System

Figure 1 The TrueTear System Components

7.1.1 Base Unit

When activated, the Base Unit provides electrical pulses to the Tip. The strength of these pulses is controlled by two buttons, with five different intensity levels available, indicated by the number of illuminated LEDs on the Base Unit. The device internally records the time and duration of device use.

7.1.2 Disposable Tip

The disposable Tip is specially designed to allow the participant to easily apply stimulation to the target areas within the nose. The Tip attaches to the Base Unit and contains hydrogel (similar to the material used in contact lenses) that contacts the inside of the nose to provide stimulation. Each tip may be used up to 24 hours. After 24 hours, the used tip should be discarded and a fresh tip should be attached. A separate Cover can be used to protect the Tip and Base Unit when the device is not in use.

7.1.3 Cover

The Cover may be placed over the top of the Tip attached to the Base Unit for protection in between uses.

7.1.4 Charger

The Base Unit may be recharged by removing the Tip and placing the Base Unit onto the Charger. Charging typically takes under 4 hours, and a green LED indicates that the process has completed.

7.2 TrueTear Accountability

Each Base Unit and Charger have unique serial numbers. The serial numbers of the Base Unit/Charger used by each participant will be recorded on the appropriate case report form and device accountability log. The disposable Tip is provided in a sealed pouch, which is labeled with a lot number and expiration date. The lot number of the Tips provided to the participant will also be recorded on the appropriate case report forms and on the device accountability log. Tips should not be used beyond the expiration date provided on the pouch.

7.3 Control Description - Thermalon Dry Eye Compress

As described on the label, the Thermalon Dry Eye Compress [redacted]

[redacted].

7.4 Other Study Supplies

The following will be provided by the Investigator:

- Urine pregnancy test kits
- Schirmer test strips
- Weck-Cel eye spears
- Proparacaine
- Liquid sodium fluorescein
- Calibrated 1-10 µL pipette and sterile pipette tips

8.0 STUDY METHODS AND PROCEDURES

8.1 Participant Entry Procedures

8.1.1 Overview

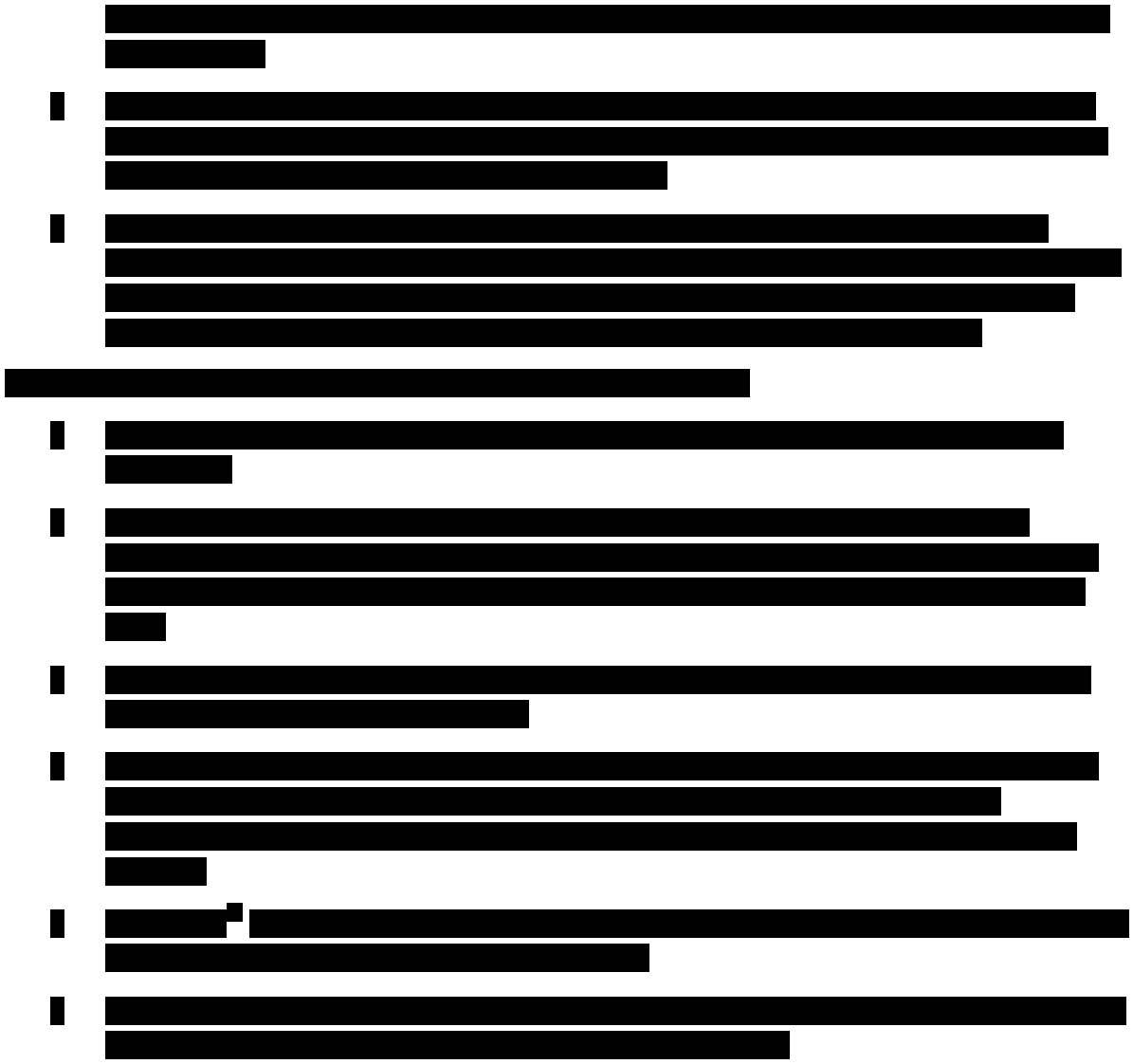
Participants as defined by the criteria in section 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a participant's participation in the trial (i.e., prior to study-related procedures), the study will be discussed with each potential participant and participants wishing to participate should give written informed consent using an IRB approved informed consent form (ICF). The ICF should be the most recent version that has received approval by a properly constituted IRB.

[redacted]

[redacted]



8.1.4 Procedures for Final Study Entry

Participants should meet all inclusion and none of the exclusion criteria.

8.1.5 Methods for Assignment to Application Groups

At the Screening Visit, participants who provide written informed consent will be assigned a unique 5-digit screening number, [redacted]. Screening numbers should be assigned in ascending consecutive order. Participants who meet all of the eligibility criteria will be scheduled to return for Visit 2 (Day 0).

At Visit 2 (Day 0), participants who meet all eligibility criteria will be randomized to one of two treatment groups (TrueTear or Thermalon Dry Eye Compress control) in a 1:1 ratio. At Visit 2 (Day 0), participants will be randomized in sequential order. The randomization number will be recorded on the CRF/source document.

8.2 Masking

Because the two devices are dissimilar and administered in very different ways, it will not be possible to mask the participant or the Investigator to the intervention assignment. As a means of minimizing bias where feasible, de-identified videos from the Tearscope assessment (lipid layer thickness) will be graded using the Guillon scale in a masked fashion.

8.3 Participant Training, Dispensing and Home Use of TrueTear

At Visit 2 (Day 0), participants randomized to the TrueTear application group will be provided a TrueTear device and disposable tips to take home with them and use daily. Participants will be instructed to use the device as described in the Patient Guide. They will receive training to perform intranasal neurostimulation and will receive a copy of the Patient Guide.

For the device application, participants will be told to turn on the unit by holding down the + button for approximately two seconds. There are five stimulation intensity levels and participants may adjust the level by pressing the + or – buttons to obtain a gentle tingling sensation. They will be instructed to fully insert the tips of the TrueTear into both nostrils simultaneously towards the top and front of the nose (as in Figure 2). Participants will be told they can cease stimulation by holding down the – button for approximately two seconds on the base unit or by withdrawing the tips from the nostrils. Participants will be instructed to replace the Tips with a new one if they do not feel any sensation.

For the initial in-office device application at Visit 2 (Day 0), each participant will be told that the application will take place for approximately eight minutes and that the entire procedure will occur while the participant is seated and positioned in a slit lamp to allow for simultaneous viewing of meibomian gland activity in the lower lid and for collection of lid and tear film temperature data.

At Visit 3 (Day 7), prior to in-office application and evaluation of tear secretion, trained clinical personnel will review procedures for the proper use of the device (e.g., correct positioning intranasally, frequency and duration of use, daily replacement and disposal of tips, etc.) with participants. As the device internally records the frequency and duration of device use, study staff may review this information with participants. Participants will be told that the in-office application of TrueTear at this visit should last for approximately three minutes.

Figure 2 Use of TrueTear

(L) Starting position and (R) Correct application position by inserting the disposable tips fully into the nasal cavity and to the front of the nose.

Note: Sponsor representatives may be present at visits to assist in training participants on the use of the device.

8.4 Participant Training, Dispensing and Home Use of Thermalon Dry Eye Compress

At Visit 2 (Day 0), participants randomized to the Thermalon Dry Eye Compress application group will be provided a Thermalon Dry Eye Compress device to take home with them and use daily. Participants will be trained to follow the instructions for proper use and storage as described on the package insert or [redacted] The following additional points will be noted:

- Between study visits, participants will be asked to use the moist heat compress daily as described on the package insert [redacted]
- If participants wish to wash their compress, instructions can be found on the package insert or [redacted]
- Participants will be reminded to fill out a diary to record daily use of the moist heat compress throughout the study duration.
- Participants will be asked to return the moist heat compress at the end of the study.

8.5 Concurrent Therapies

The use of any concurrent medication, prescription or OTC, is to be recorded on the participant's CRF along with the reason the medication was taken. Concomitant medications that are considered necessary for the participant's welfare, but will not interfere with study assessments and evaluations, will be allowed during the study at the Investigator's discretion.

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

[redacted]

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[redacted]	[redacted]

[redacted]

8.8 Completed Participants

A completed participant is one who has not been discontinued from the study and has successfully completed Day 30.

8.9 Study Termination

The study may be stopped at any time by the Investigator, the Sponsor, and/or [redacted] with appropriate notification.

8.10 Study Duration

An individual participant's participation will involve up to five visits over approximately a 44 day period.

8.11 Monitoring and Quality Assurance

8.11.1 Study Monitoring

Allergan personnel (or designees) will monitor this study in a manner consistent with applicable health authority regulations and the procedures adopted by the SOPs of Allergan. Prior to the start of the study, member(s) of [redacted] (or designees) will review the protocol, CRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Principal Investigator/Sub-Investigator(s) and pertinent study staff. Monitoring visits will occur as necessary during the course of the investigation to verify:

- The rights and well-being of participants are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, GCP and IRB/IEC requirements
- The integrity of the data
- Study device accountability

- Adequate study documentation

During the course of the study, if the Sponsor (or designee) determines that the Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor (or designee) will take written action to correct the non-compliance and to secure compliance. In addition, the Sponsor (or designee) may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions. This termination will be documented in a memo or follow-up letter to the Principal Investigator.

8.11.2 Recording of Data

Participant data recorded on CRFs during the study will be documented in an anonymous fashion. The participant will only be identified by the participant number. If, as an exception, it is necessary for safety or regulatory reasons to identify the participant, the Sponsor or its representatives, and the Investigator, are bound to keep this information confidential.

9.0 ADVERSE EVENTS

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding) symptom, or disease temporally associated with the use of an investigational product but not necessarily related to the investigational product. An AE may also be called a complication. The capture of AEs will begin with the participant's entry into the study.

9.1 Adverse Event Recording

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

9.2 Adverse Event Evaluation

The Investigator should evaluate if each AE is serious, related to the applicable study device and anticipated using the following definitions.

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- It results in death (i.e., the AE actually causes or leads to death);
- It is life threatening (i.e., the AE places the participant at immediate risk of death);
- It requires or prolongs inpatient hospitalization. If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a participant is hospitalized to undergo coronary bypass surgery, the

heart condition that necessitated the bypass should be recorded. Hospitalizations for diagnostic or elective surgical procedures or hospitalizations required to allow outcome measurement for the study should not be recorded as SAEs:

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions);
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational device;
- It is considered a significant medical event by the Investigator based on medical judgment (e.g. may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above);
- It is considered sight-threatening by the Investigator.

9.3 Relationship of the AE to the investigational device

Definite	A clear-cut causal relationship with the study device and no other possible cause
Probable	A causal relationship with the study device is likely although alternate etiologies are also possible
Possible	A causal relationship with study device is not definite, alternate etiologies are also possible
Not related	The AE has no causal relationship to study device and/or there is evidence of alternative etiology such as concurrent medication or illness.
Not applicable	The participant has not been exposed to the study device.

The AE will be determined to be device related, making it an adverse device effect (ADE), if it is identified to have had a definite, probable or possible causal relationship to the study device.

An AE is unanticipated if the nature, severity, or frequency of the event is not consistent with either the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, user manuals and the current IRB-approved informed consent document, and (b) other relevant sources of information such as product labeling and package inserts; or the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the AE and the participant's predisposing risk factor profile for the AE.

9.4 Serious and Unanticipated Adverse Device Effects

A serious and unanticipated adverse device effect is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of

incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants."

9.5 Adverse Event Reporting

All AEs that occur during the course of the study should be reported on the Adverse Event CRF. The Investigator should determine the intensity of the event.

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities

All SAEs and adverse device effects (ADEs) should be reported by the Investigator to [redacted] and the Sponsor in writing within 24 hours from the point in time when the Investigator becomes aware of the event.

It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB) of all unanticipated SAEs and unanticipated problems, per the IRBs reporting requirements.

Throughout the course of the proposed study, all efforts will be made to remain alert to possible adverse experiences or untoward findings. If adverse experiences occur, the first concern will be the safety and welfare of the participant. Appropriate medical intervention will be made.

[redacted] and the Sponsor will immediately conduct an evaluation of any unanticipated adverse device effect. The results of the evaluation will be reported to the IRB within 10 days of [redacted]. and/or the Sponsor becoming aware of the event. If it is determined by [redacted] and the Sponsor to present an unreasonable risk to study participants, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. Termination will occur not later than five working days after [redacted]. and the Sponsor makes this determination, and not later than 15 working days after first receiving notice of the event. [redacted] and the Sponsor will not resume an investigation terminated under these conditions without an additional IRB approval.

Contact information for reporting Serious Adverse Events:

[redacted]

9.6 Anticipated Adverse Events

The following is a list of potential AEs associated with the use of the device:

- Nasal discomfort or pain
- Epistaxis
- Excessive sneezing
- Nasal irritation, paresthesia or numbness post-stimulation
- Nasal infection, abrasion or inflammation
- Skin irritation or hypersensitivity
- Headache (e.g., tension, migraine, etc.)
- Facial pain
- Excessive salivation
- Sensation of teeth vibrating
- Excessive rhinorrhea
- Temporary aggravation of nasal allergies
- Allergic reaction to contact materials

As described on the Thermalon Dry Eye Compress label, the following potential AE associated with the use of Thermalon Dry Eye Compress may occur:

- Blurry vision

10.0 PREGNANCY

Women of Childbearing Potential (WOCBP) include any females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or are not postmenopausal at least 12 months since last menses. WOCBP will be required to use designated methods of birth control during the course of the study such as abstinence, sterile male partner, oral contraceptive pills, contraceptive patches, injectable contraception, vaginal rings, intrauterine contraception, or barrier methods. All women who are pregnant, nursing an infant, or planning a pregnancy during the duration of this study will be excluded from participation.

If a participant or Investigator suspects that the participant may be pregnant prior to study device administration, the study device should be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the participant should not administer the study device and should not be enrolled in the study.

If a female participant becomes pregnant during the study, the Investigator will notify Allergan immediately after the pregnancy is confirmed. The Investigator will (1) obtain a consent from the female participant for pregnancy follow-up and (2) follow the progress of the pregnancy to term. The Investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

11.0 STATISTICAL HYPOTHESIS AND METHODS OF ANALYSES

11.1 Power Calculation and Determination of Sample Size

As this is a proof of concept study, no formal calculation of sample size was conducted. Approximately 70 participants will be enrolled to achieve approximately 60 completed participants.

11.2 Statistical Hypotheses and Level of Significance

The null hypothesis is that there is no difference between the two devices, TrueTear and Thermalon, in the outcome of the exploratory measures. The alternative hypothesis is there is a difference in the outcome.

The hypothesis can be expressed as:

$$H_0: E_N = E_T$$

$$H_A: E_N \neq E_T$$

where E_N represents the exploratory outcome result for the TrueTear neurostimulation group and E_T represents the result for the Thermalon application group.

11.3 Randomization

A computer-generated randomization will be used to assign study participants to their device application group. Study participants who meet the eligibility criteria and return for Visit 2 (Day 0) will be randomized in a 1:1 ratio to either application of the TrueTear or the Thermalon device.

11.4 GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses will use a two-tailed test and will be evaluated at an α of 0.05 unless otherwise specified. The mean, standard deviation (SD), median, minimum and maximum will be presented for continuous variables such as participant age. For categorical variables, such as sex, the number for each category, the total number evaluated, and the percentage will be presented.

11.5 Participant Accountability and Missing Data

Participants who withdraw from the study will be tabulated with the reasons for the withdrawal. Missing data will not be imputed.

11.6 Participant Demographic and Baseline Characteristics

The demographic and baseline characteristics of the study population observed will be summarized by device group and for both groups combined.

11.7 Effectiveness Analyses

This study does not include any effectiveness measures.

12.0 FINAL CLINICAL STUDY REPORT

A final clinical study report will be prepared after completion of the study.

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

13.1 Protection of Human Participants

13.1.1 Participant Informed Consent

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

All ICFs should be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form 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 Sponsor and [redacted] prior to submission to the governing IRB and that it is read, signed and dated by all participants 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 should be determined by [redacted] and/or study Sponsor and provided in writing by [redacted] and/or study Sponsor prior to the consent process.

13.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The Investigator should obtain appropriate IRB approval before initiating the study and re-approval at least annually.

13.1.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonisation (ICH) Guidelines, and the ethical principles that originated with the Declaration of Helsinki.

13.1.4 Participant Confidentiality

All personal study participant data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions 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 Allergan, [redacted] IRB approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and other domestic government agencies, will be granted direct access to the study participant'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 study device may ultimately be marketed, but the participant's identity will not be disclosed in these documents.

13.2 Documentation

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

13.2.1 Retention of Documentation

All study-related correspondence, participant records, consent forms, record of the distribution and use of all study device and copies of CRFs should be maintained on file for at least two 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 study device. 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 should be transferred to a person who will accept the responsibility. The Sponsor should be notified in writing of the name and address of the new custodian.

13.3 REGULATORY STATUS

A previous version of the TrueTear (formerly known as the Oculeve Intranasal Lacrimal Neurostimulator) received [redacted] It has been approved for marketing in Canada and Australia as well. The current version of TrueTear is an investigational device in the US.

The Thermalon Dry Eye Compress is legally sold by its manufacturer [redacted] as a class I device in the USA and does not require premarket approval or notification.

13.4 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Device

All investigational devices will be clearly labeled "For Investigational Use Only." The distribution and return of all devices will be recorded. Used disposable tips should be discarded after use; unused disposable tips should be returned to the Sponsor at the conclusion of the study.

A device accountability log will be maintained by the site and will be filed in the Trial Master File.

13.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Thermalon Dry Eye Compresses

Thermalon Dry Eye Compresses will be purchased commercially and will be dispensed to participants in commercial packaging with a study label. Participants will be referred to the package insert or [redacted] for product use and storage information. At the end of the study, participants will be asked to return their compress.

13.6 Recording of Data on Source Documents and Case Report Forms (CRFs)

All participant data will be captured in the participant CRFs (i.e. source document). The Investigator is responsible for ensuring that study data is completely and accurately recorded on each participant's CRF and all study-related materials. All study data should also be attributable, legible, contemporaneous, original and accurate. 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.

13.7 Amendments to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the participants) should be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the Sponsor.

13.8 Publications

Information collected during this clinical study concerning TrueTear and results of the data obtained are proprietary and strictly confidential. The Sponsor reserves all rights to any such information. Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Sponsor and [redacted] will have the final decision regarding the manuscript and publication.

14.0 REFERENCES

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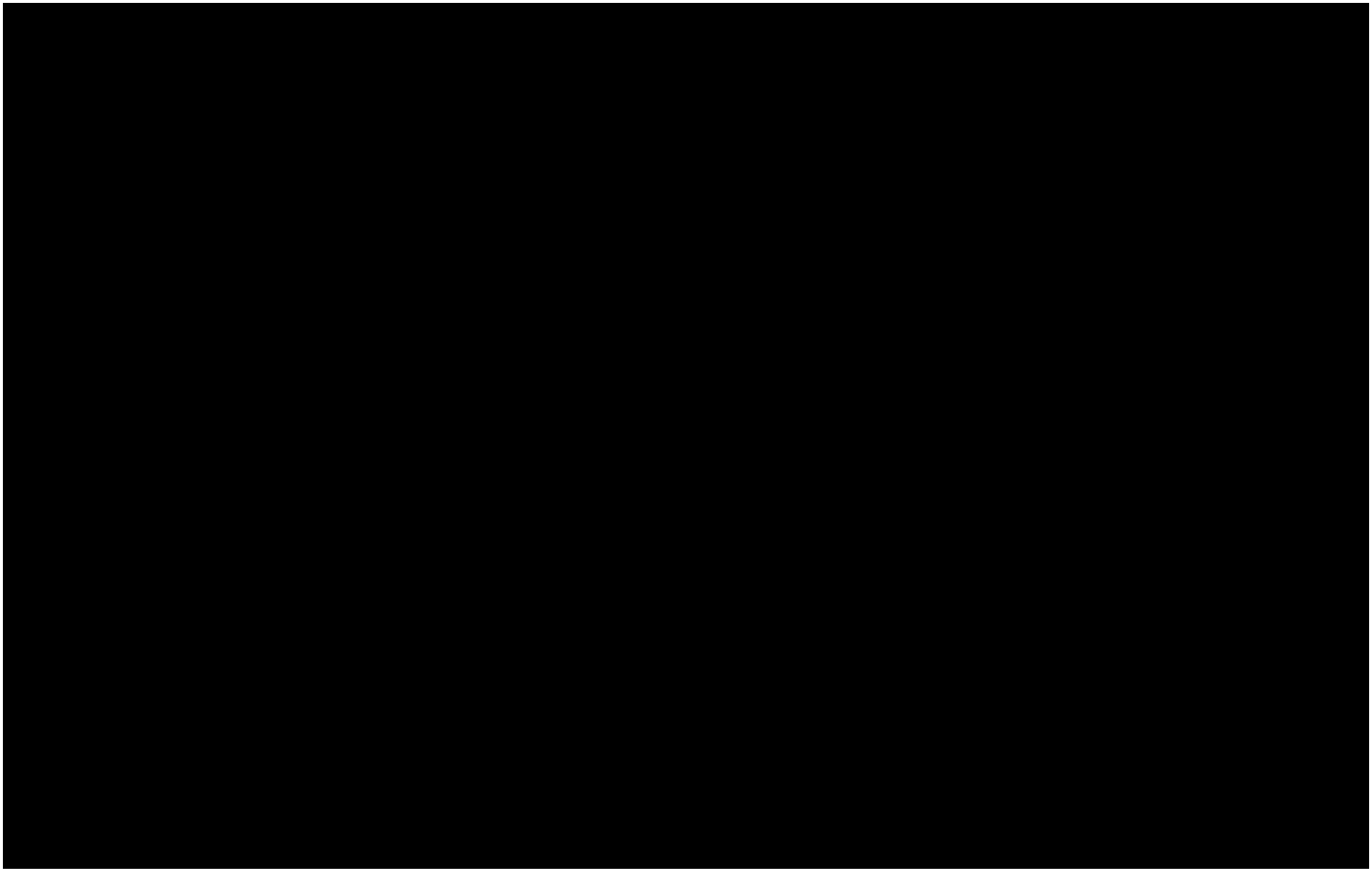
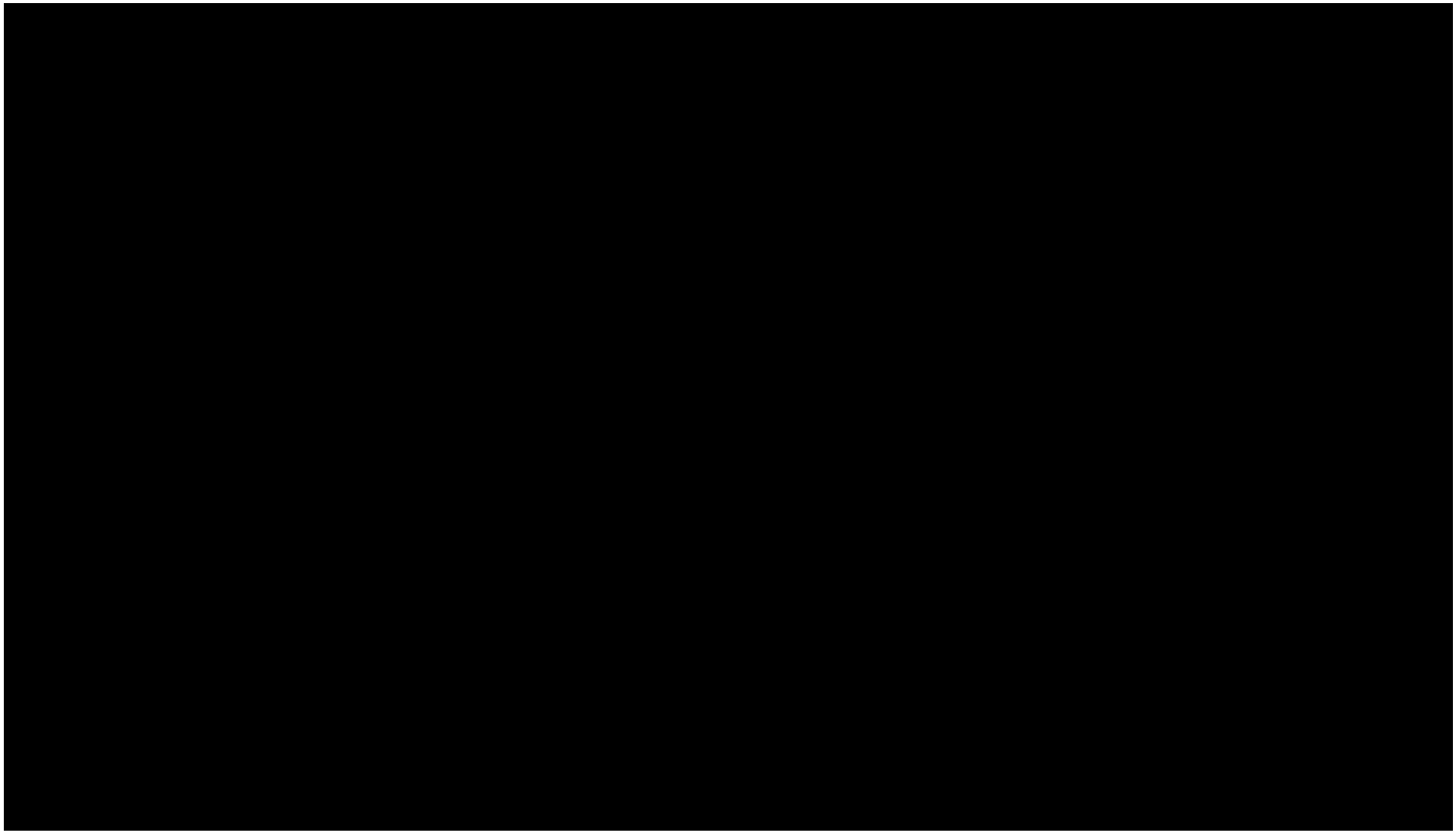
15.0 APPENDICES





15.2 Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

15.2.1 Visual Acuity Procedures

LogMAR visual acuity should be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Participants should use the most recent correction to attain their corrected distance visual acuity (CDVA); if they forget their spectacles, this prescription can be placed in a trial frame.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the participant viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites should use only ETDRS Series 2000 Chart 1 & 2, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and be well illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The participant should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The participant should be told that the chart has letters only, no numbers. If the participant reads a number, s/he should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The participant should be asked to read slowly to achieve the best identification of each letter. S/he is not to proceed to the next letter until s/he has given a definite response.

If the participant changes a response (e.g., 'that was a "C" not an "O"') before s/he has read aloud the next letter, then the change should be accepted. If the participant changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the participant says s/he cannot read a letter, s/he should be encouraged to guess. If the participant identifies a letter as one of two letters, s/he should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters

missed up to and including the last line read. This total sum represents the logMAR visual acuity for that eye.

Example: Participant correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR visual acuity	= 0.18

Repeat the procedure for the left eye.

To provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site should be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a participant broke his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from the Screening Visit (Visit 1) should be evaluated by the Investigator as a potential AE.

15.2.2 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described. The following will be examined at each visit:

- Cornea
- Conjunctiva
- Anterior Chamber
- Lid

15.2.3 Tear Film Breakup Time Evaluated

Slit-lamp settings should be adjusted to a magnification of 10x to 16x using a cobalt blue filter

and yellow barrier filter placed directly in front of the objective lens of the slit lamp.

Participants will be asked to tilt their heads slightly back and, starting with the right eye, 5 µL of 2% preservative-free liquid sodium fluorescein will be applied to the lower cul-de-sac using a micropipette and sterile disposable tip. To thoroughly mix the fluorescein with the tear film, the participant will be instructed to blink several times over approximately 15 seconds. The participant will be instructed to blink three times naturally, then stare and not blink. Using a stopwatch, TBUT will be measured by the Investigator as the time from the last blink until one or more black (dry) spots appear in the precorneal tear film. The time is to be recorded to two significant digits. After the first measurement, the participant will be instructed to blink naturally three additional times and a second measurement will be taken. The procedure will be repeated for a third measurement. After a 60-second rest period, the entire procedure will be repeated for the left eye.

15.2.4 Corneal and Conjunctival Sodium Fluorescein Staining

Immediately following completion of TBUT evaluation for both eyes, the entire cornea will be evaluated for staining, starting with the right eye. The examination will be performed with the slit lamp at approximately 10x magnification using a cobalt blue filter and yellow barrier filter placed directly in front of the objective lens of the slit lamp. Grading of the resulting corneal staining will be based on the National Eye Institute (NEI) grading system (score between 0 and 3), where 0 corresponds to no staining, 1 corresponds to mild staining, 2 corresponds to moderate staining, and 3 corresponds to severe staining.

The schematic representations of the five corneal and six conjunctival regions per eye are shown below. The upper eyelid is lifted slightly to grade the entire corneal surface. For corneal staining, the maximum possible score per eye is 15. This procedure should then be repeated in the other eye. Once grading of the cornea is complete, grading of the conjunctiva can occur.

To grade conjunctival staining, the six nasal and temporal conjunctival regions will be graded. To grade the temporal zone, the participant should be instructed to look nasally; to grade the nasal zone, the participant should be instructed to look temporally. A standardized grading system of 0 to 3 is used for each for the six areas depicted per eye as shown in the diagram below. For conjunctival staining, the maximum possible score per eye is 18. This procedure should then be repeated in the other eye.

[redacted]

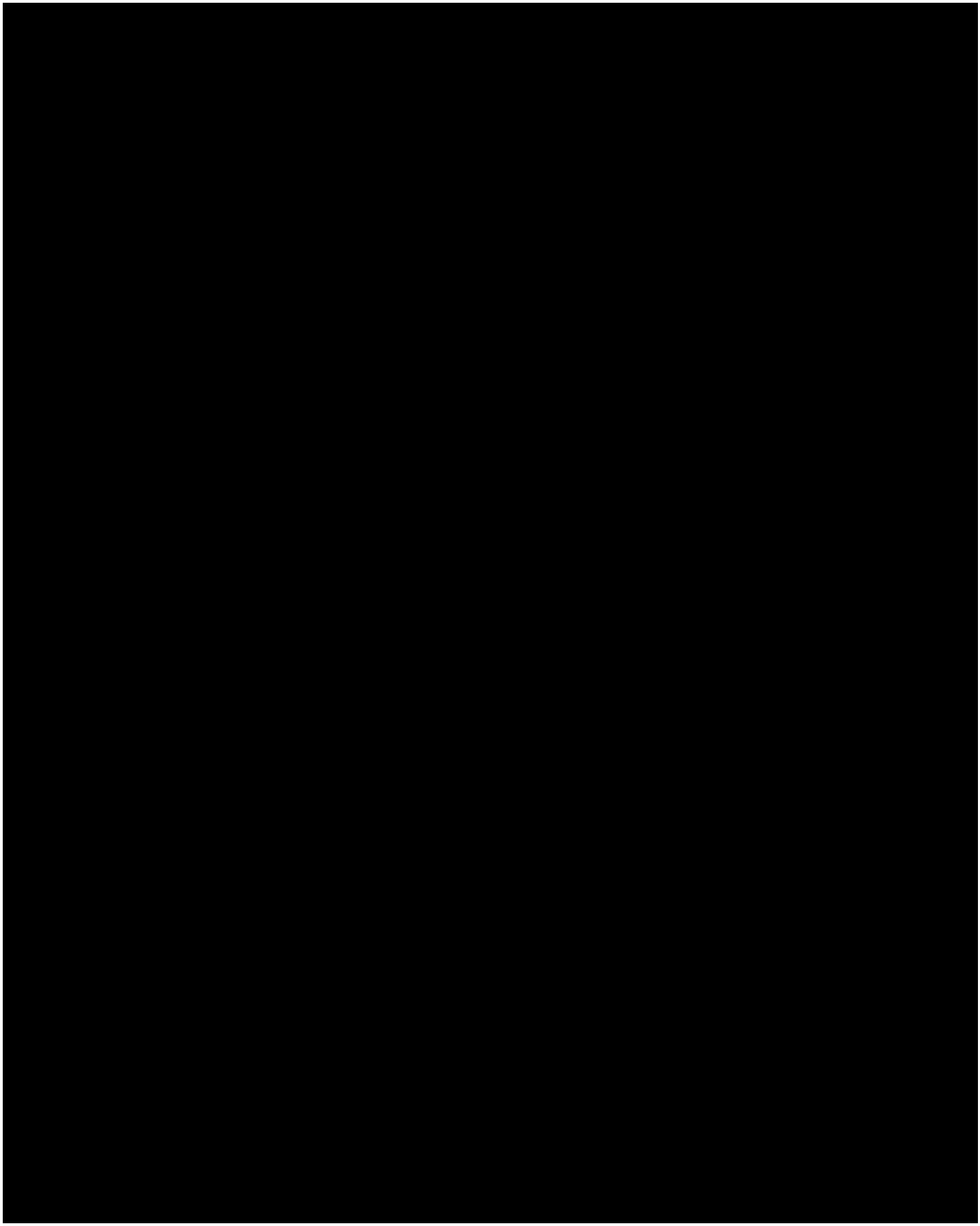
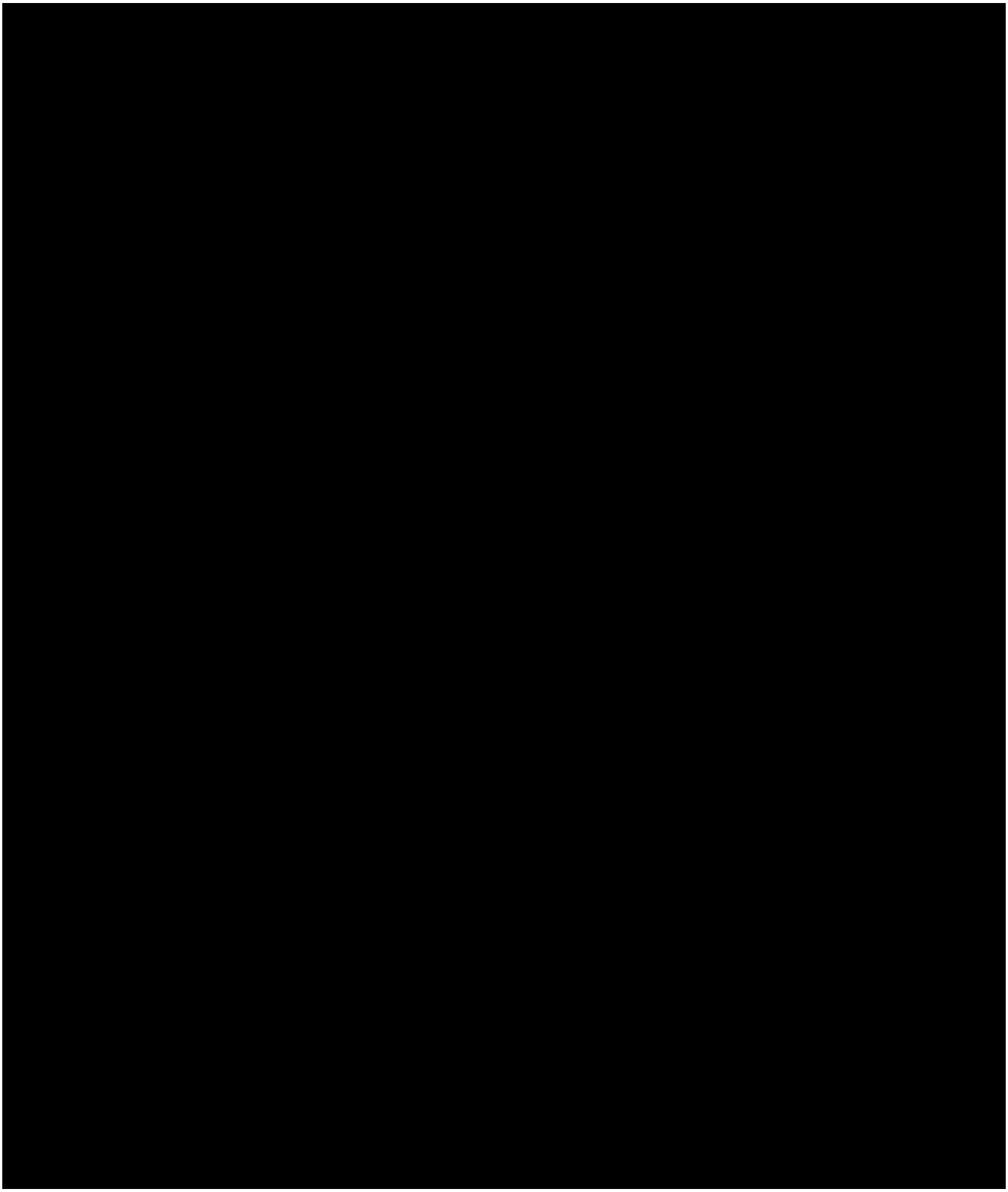
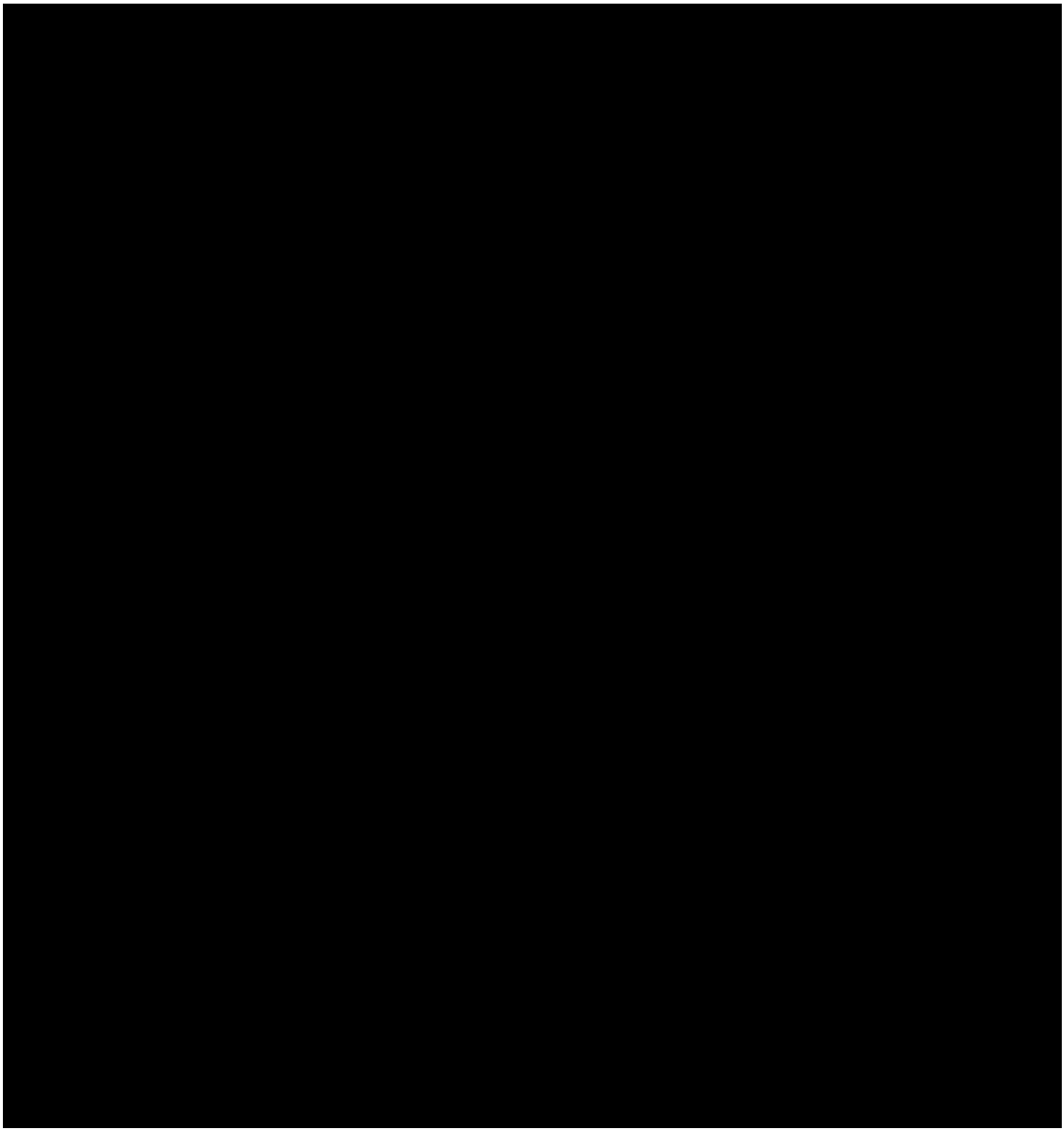


Figure 3 Target Area of Cotton Swab Nasal Stimulation

15.2.6 Symptom Questionnaires

[redacted]





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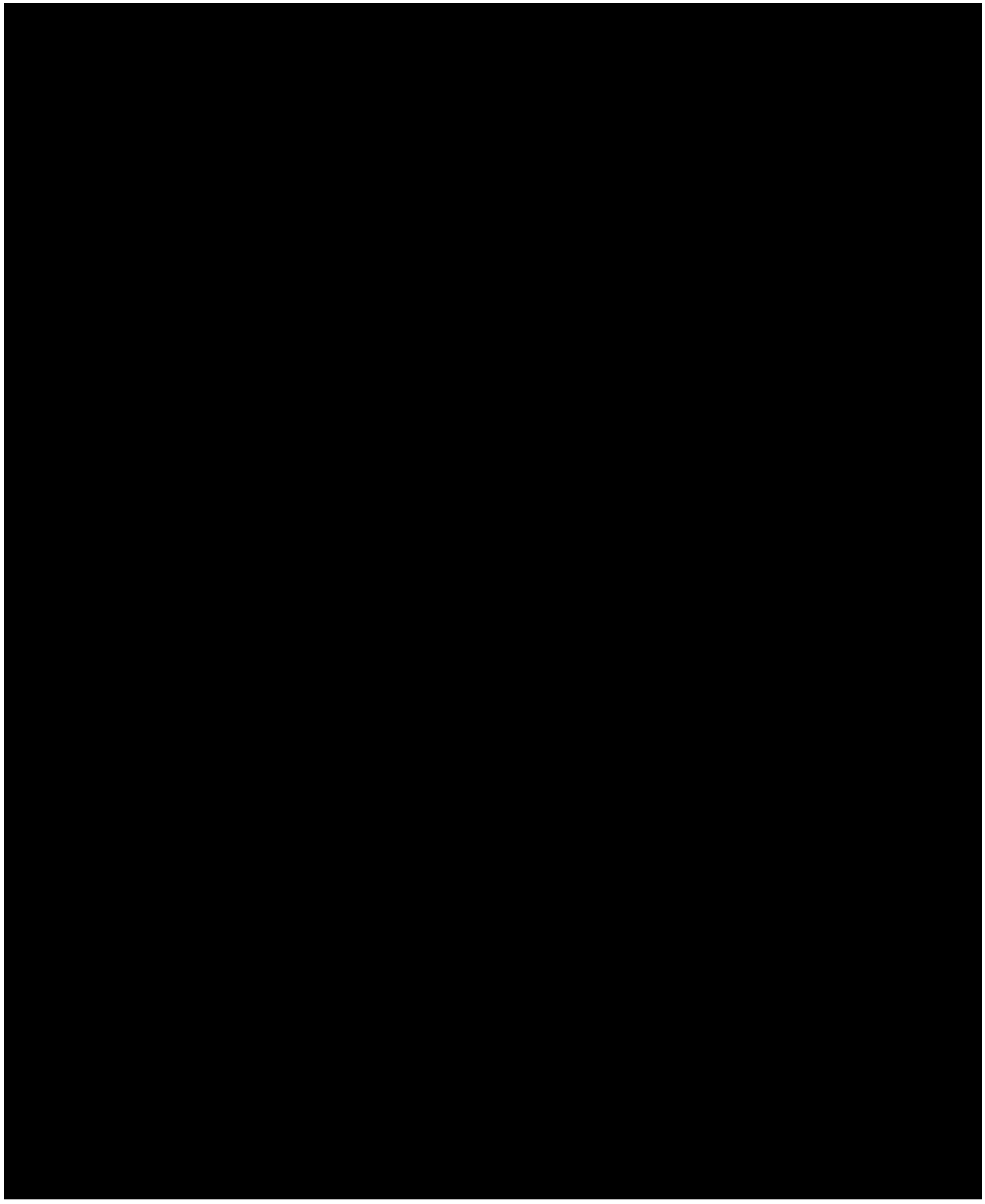

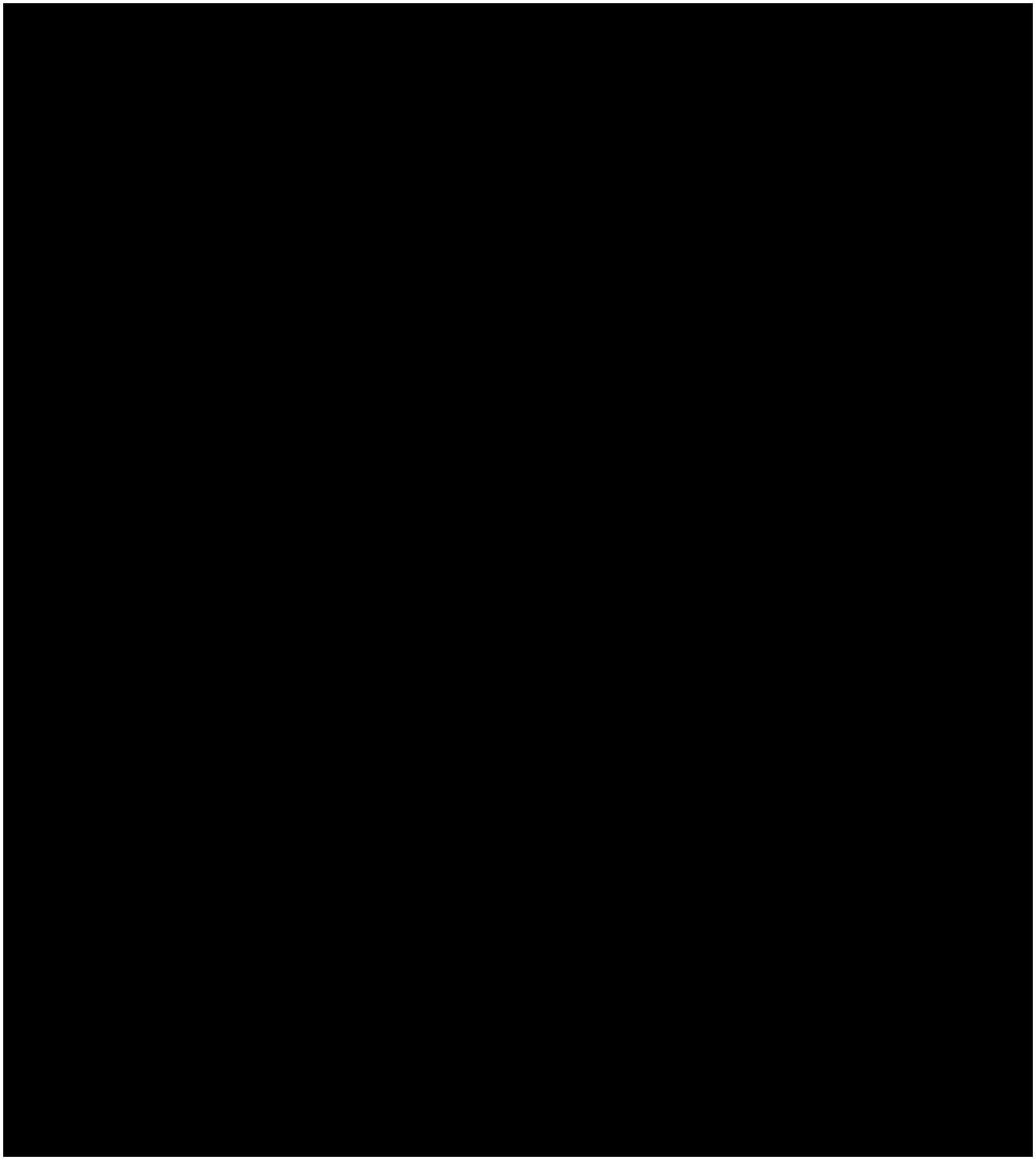

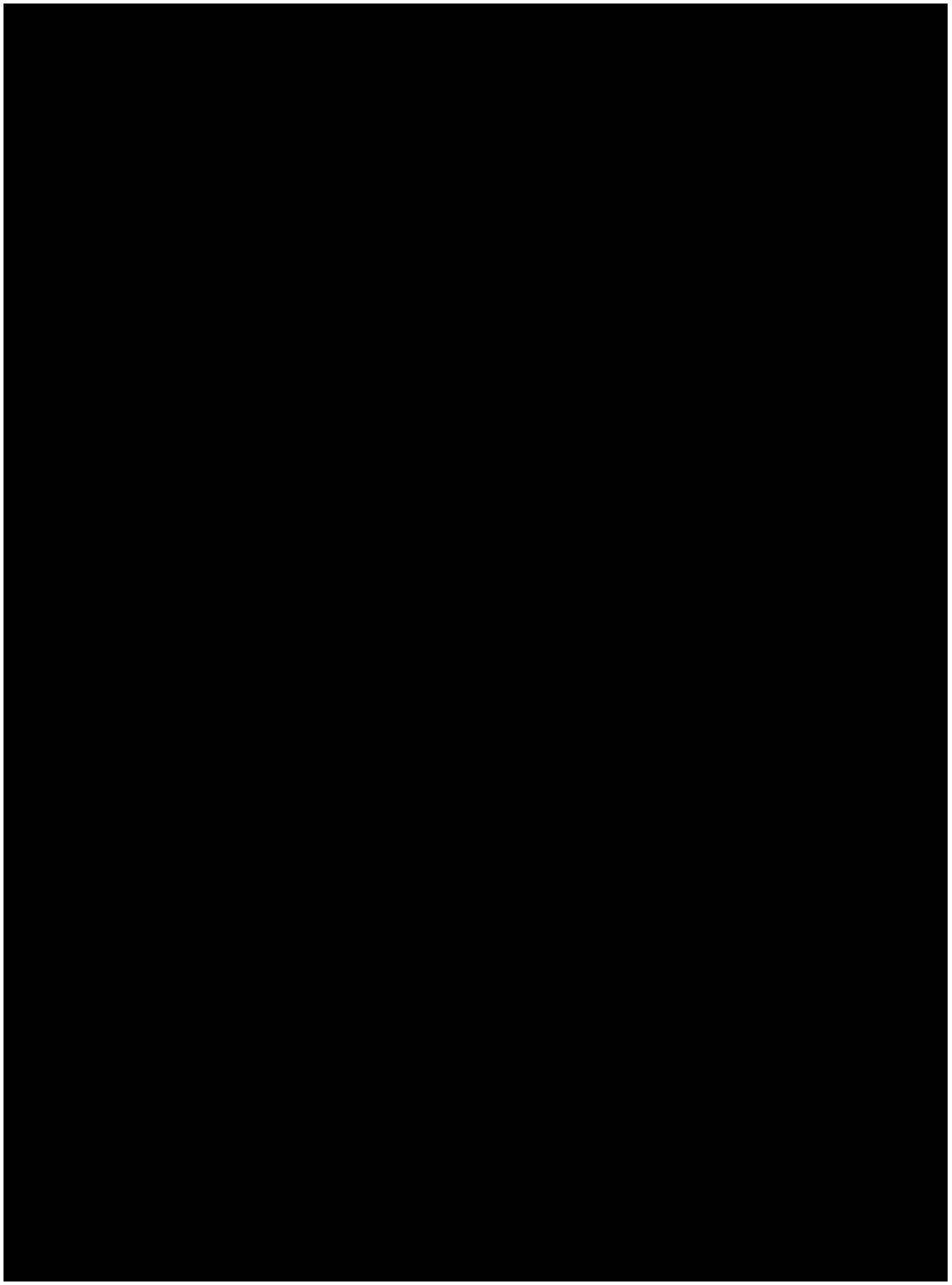

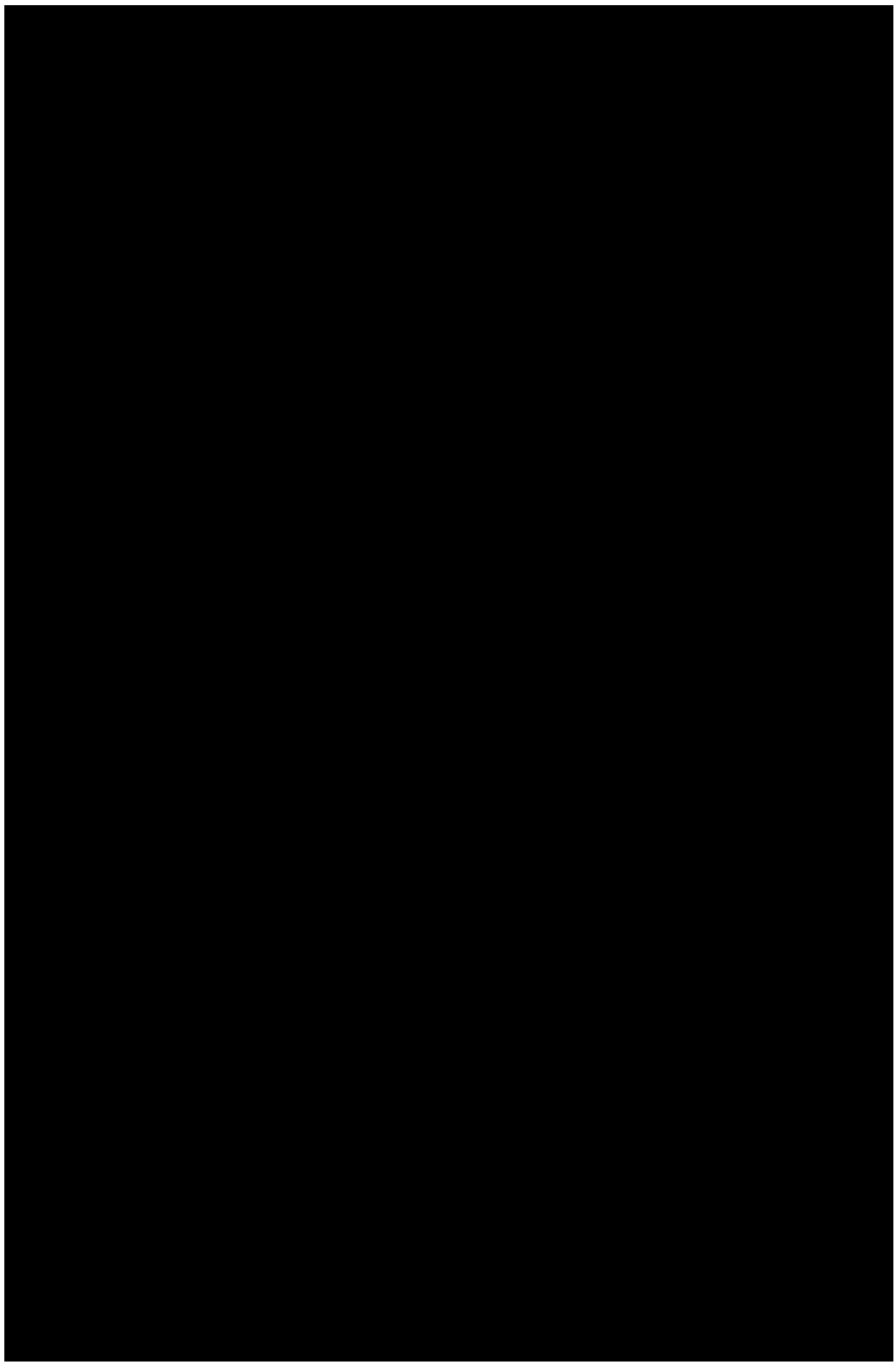

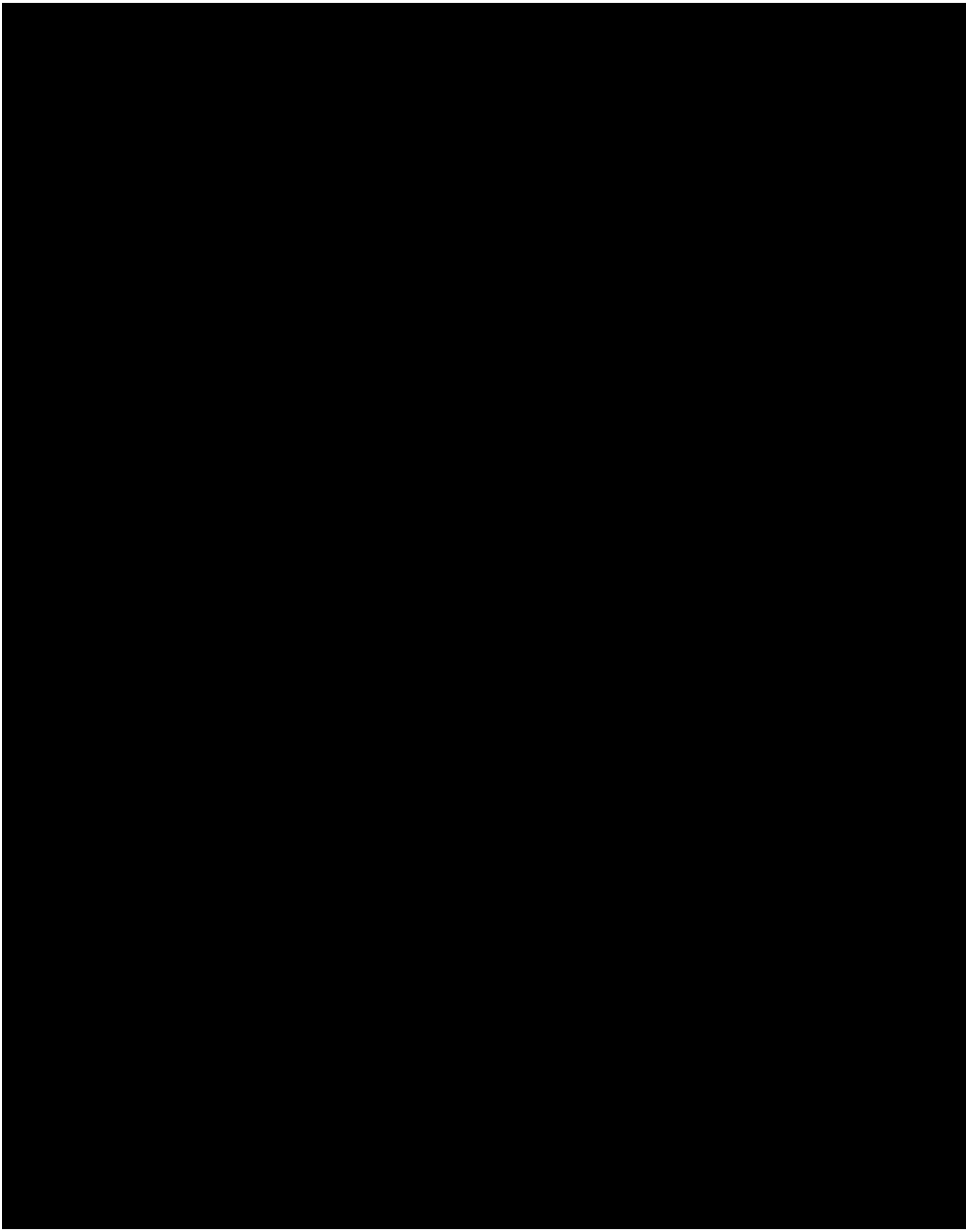

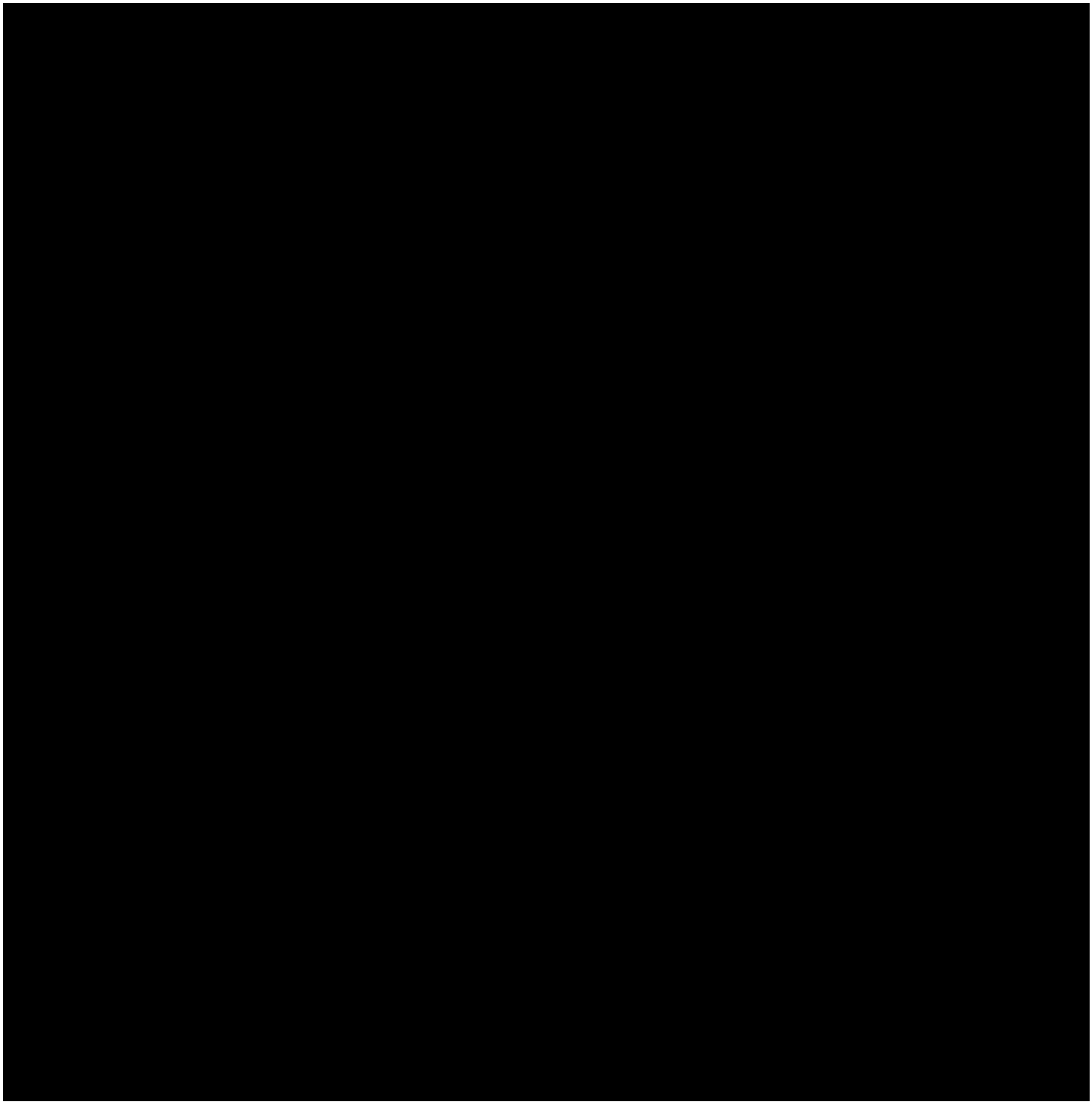

[redacted]

[redacted]

15.3 Appendix 3: Sponsor and [redacted] Approvals

Protocol Title: Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease

Protocol Number: OCUN-023

[redacted]

15.4 Appendix 4: Investigator's Signature

Protocol Title: Prospective, Open-Label, Randomized, Proof of Concept Study Exploring Application of TrueTear™ for the Treatment of Meibomian Gland Disease

Protocol Number: OCUN-023

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) 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: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____