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Study ID: 195263-010

Title: TOPICAL OPHTHALMIC AGN-195263 FOR THE TREATMENT OF EVAPORATIVE DRY EYE

Protocol Amendment 1 Date: October 26, 2016

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TOPICAL OPHTHALMIC AGN-195263 FOR THE TREATMENT OF EVAPORATIVE DRY EYE

Protocol Number:	195263-010 Amendment 1
EudraCT Number (if applicable):	2015-004124-57
Phase:	3
Name of Investigational Product:	0.1% [redacted] (AGN-195263)

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Approval Date: 26-Oct-2016

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Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on United States FDA Form 1572 and/or study contacts page and/or the Trial Master File: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing (Institutional Review Board (IRB); US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: 0.1% [redacted] (AGN-195263)

Phase: 3

Study Objectives:

- To evaluate the safety and efficacy of 0.1% AGN-195263 administered twice daily compared to its vehicle in patients with evaporative dry eye (EDE)
- To evaluate the systemic pharmacokinetics of 0.1% AGN-195263 administered twice daily in patients with EDE

Clinical Hypotheses:

- One drop of [redacted] 0.1% AGN-195263 administered twice daily to each eye:
  - is more effective than its vehicle as measured by the proportion of patients with complete overall ocular discomfort response at month 6
  - has an acceptable safety profile throughout the study treatment duration of 12 months

Study Design

Structure: Multicenter, global, randomized, parallel-group, vehicle-controlled study with 6 months of double-masked treatment followed by a 6 month open label treatment extension phase

Duration: The total duration of this study is up to approximately 14 months for each patient

Study Treatment Groups: 0.1% [redacted] (AGN-195263)

Controls: vehicle of 0.1% [redacted]

Dosage/Dose Regimen: One drop of 0.1% AGN-195263 [redacted] or its vehicle administered in each eye twice daily from day 1 to up to month 6. One drop of 0.1% AGN-195263 topical [redacted] in each eye twice daily from day 6 to up to month 12.

In addition to the study treatment, Allergan will supply a marketed artificial tear, which will be referred to as the study artificial tear (SAT). The brandname of the SAT may vary in each country. A full list of SAT brandnames (ie, REFRESH PLUS®, REFRESH CONTACTS®, REFRESH COMFORT®, CELLUFRESH®) is found in the Study Procedure Manual. For simplicity, throughout the study protocol, in lieu of listing by brand name, "SAT" will refer to the Allergan supplied study artificial tear.

Use of lid hygiene (ie, warm compress, lid massage, lid scrub) or artificial tears (other than the SAT) are prohibited from the standardization (day -21) visit until after the month 6 visit. Starting at the standardization (day -21) visit, all eligible patients will administer SAT twice daily in each eye for 6 days.

From the vehicle run-in (day -14) visit until the month 6 visit, use of SAT will be considered rescue therapy for intolerable symptoms. After the month 6 visit until the month 12/study exit visit, use of lid hygiene and/or any artificial tear product(s) will be unrestricted except for the use of artificial tears 24 hours prior to any study visit. The morning dose of SAT (day -21 only) or study treatment will be administered by site staff on days when there is a study visit. All other doses will be administered by the patient.

All procedures are described in Table 1 and study design is diagrammed in Figure 1.

Randomization/Stratification: Patients will be randomized to receive 0.1% AGN-195263, or its vehicle in a 1:1 ratio. The randomization will be stratified by gender and by baseline (day 1) overall ocular discomfort score (1 vs 2 to 3).

Visit Schedule: Up to 9 scheduled visits: screening (day -51), standardization (day -21), vehicle run-in (day -14), baseline (randomization, day 1), months 1, 3, 6 (primary and secondary efficacy assessment), 9, and 12/study exit (safety assessment). For patients who discontinue the study early, the month 12/study exit visit procedures should be completed when possible.

For patients not participating in the collection of blood samples for pharmacokinetic analysis: in-office study treatment should be administered in the morning at approximately the same time of day during each office visit (± 1 hour from the study administration time at baseline [day 1]). At any time, the morning dose should not exceed 1:00 pm local time.

For patients who participate in the collection of blood samples for pharmacokinetic analysis:

1) the time of the pre-dose blood sample collection should be scheduled in the morning at approximately the same time of day during each office visit (± 1 hour from the pre-dose blood sample collection time at the standardization [day -21] visit).

2) SAT or study treatment should be administered in the morning at approximately the same time of day during each office visit and within 10 min after the time the pre-dose blood sample collection was performed that day.

Study Population Characteristics

Number of Patients: Approximately 527 patients are planned to be enrolled in this study across approximately 80 global sites.

Condition/Disease: Evaporative dry eye (EDE)

Key Inclusion Criteria:

- Male, 18 years of age or older, at the screening (day -51) visit

OR

- Females, 18 years of age or older, who are naturally postmenopausal (permanent cessation of menstrual periods for at least 12 consecutive months) or are permanently sterilized (ie, eg, tubal occlusion, hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) at the screening (day -51) visit
- In at least 1 eye, all of the following objective measures of EDE must be present at the standardization (day -21) and baseline (day 1) visits. The same eye must qualify at both visits
    - Tear film break-up time (TBUT) ≥ 2 seconds and ≤ 7 seconds
    - Corneal sodium fluorescein staining score ≥ 1 and < 4 (Oxford scheme)

  - Anesthetized Schirmer's tear test score ≥ 10 mm after 5 minutes

- At the standardization (day -21) and baseline (day 1) visits, patients must have:
  - Ocular Surface Disease Index© (OSDI) score > 12 (0 to 100 scale)
  - Overall ocular discomfort score ≥ 1 and < 4 (0 to 4 scale; 0 = none, 4 = very severe)
  - Ocular burning score ≥ 1 and < 4 (0 to 4 scale; 0 = none, 4 = very severe)
  - Blurred vision score ≥ 1 and < 4 (0 to 4 scale; 0 = none, 4 = very severe)
- In at least 1 eye, the number of lower lid margin expressible meibomian glands must be ≥ 3 at the standardization (day -21) and baseline (day 1) visits. The same eye must qualify at both visits
- In at least 1 eye, a lower lid margin meibum quality global assessment score ≥ 1 at the standardization (day -21) and baseline (day 1) visits. The same eye must qualify at both visits
- Use of an artificial tear product, lid hygiene (ie, warm compress, lid massage, lid scrub), omega-3 supplementation (topical ocular or systemic), or antibiotics (ie, systemic or topical macrolides, tetracyclines, tetracycline derivatives [including doxycycline and minocycline]) for the treatment of dry eye disease, or meibomian gland disease within 1 year of the standardization (day -21) visit

Additional inclusion criteria are provided in Section 4.3

Key Exclusion Criteria:

- Male patients with a history of known, or suspected prostate cancer
- Male patients with a prostate-specific antigen (PSA) level ≥ 4 µg/L
- Female patients with a history of known or suspected breast, cervical, ovarian, or uterine cancer
- Female patients who are of child-bearing potential
- At standardization (day -21) and/or baseline (day 1) visits, a lower lid margin meibum quality global assessment score of non-expressible (NE) in either eye
- Patients who are currently using estrogen and/or progesterone containing products (including herbal and nutritional supplements) and **not** on a stable dose (at least 90 days prior to the standardization visit (day -21) and/or anticipate initiating use and/or changing use during the study
- Patients who are currently using or have used any androgen or anti-androgen treatment (including herbal and nutritional supplements), within 90 days of the standardization (day -21) visit or anticipated use during the study
- Patients who are currently using or have used any hair growth product within 90 days of the standardization (day -21) visit or anticipated use during the study
- Patients who are currently using or have used topical corticosteroids in the eyes or on the eyelids within 60 days prior to the standardization visit (day -21), or any such use anticipated prior to the month 6 visit

- Patients who are currently using or have used oral or topical macrolides, tetracyclines, tetracycline derivative drugs (including doxycycline and minocycline), retinoids (eg, isotretinoin), calcineurin inhibitors (ie, RESTASIS®, Ikervis®), oral (systemic) corticosteroids, or lifitegrast (Xiidra™) or any other therapeutic dry eye treatment within 60 days of the standardization visit (day -21), or anticipated use before the month 6 visit

Additional exclusion criteria are provided in Section 4.4.

Response Measures

Primary Efficacy:

- overall ocular discomfort score (0 to 4 scale; 0 = none, 4 = very severe)

Secondary Efficacy:

- TBUT (seconds)
- blurred vision score (0 to 4 scale; 0 = none, 4 = very severe)
- corneal sodium fluorescein staining score (0 to 5 Oxford scheme)
- ocular burning score (0 to 4 scale; 0 = none, 4 = very severe)
- derived variables based on overall ocular discomfort score (change from baseline, ≥ 1 grade improvement from baseline, ≥ 2 grade improvement from baseline, and ≥ 50% improvement from baseline)

[redacted]

[redacted]

Safety:

- adverse events
- best-corrected visual acuity (BCVA, logarithm of the minimum angle of resolution [LogMAR] chart)
- biomicroscopy
- ophthalmoscopy
- intraocular pressure (IOP)
- urine pregnancy test (female patients only)
- PSA (male patients only)
- hematology, serum chemistry, and urinalysis
- vital signs

[redacted]

General Statistical Methods and Types of Analyses:

The primary analysis will be performed after all patients complete the month 6 visit or discontinue from the study prior to the month 6 visit. The final analysis will be performed after all patients exit the study. There will be separate database locks for the primary and final analyses.

The intent-to-treat (ITT) population comprises all randomized patients. The efficacy variables will be analyzed per the randomization schedule using the ITT population.

The per-protocol (PP) population includes all randomized and treated patients who met the key inclusion and exclusion criteria; did not use artificial tears (including SAT), lid hygiene, or other prohibited treatments that could impact the overall ocular discomfort score at month 6; and had no other major protocol deviations. The

PP population will be determined prior to database lock. The primary efficacy variables will be analyzed using the PP population on an as-treated basis.

The safety population is comprised of all patients who received at least 1 dose of study medication. All safety measures will be analyzed on an as-treated basis using the safety population.

[redacted]

In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using an analysis of variance (ANOVA) model or 2-sample t-test for between-group comparisons, and paired t-test for within-group analyses. Categorical variables will be summarized by number of patients, frequency count, and percent, and will be analyzed using Pearson's chi-square or Fisher's exact test (if the expected cell count is less than 5 in 25% or more of the cells). Ordinal variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) test or the Wilcoxon rank-sum test for between-treatment comparisons and the signed-rank test for within-treatment comparisons. Descriptive statistics will be provided for the open-label treatment extension phase. No statistical testing will be performed for this phase.

Efficacy:

The primary and secondary efficacy analyses will be performed for the ITT population at the month 6 visit.

The primary efficacy variable is the complete overall ocular discomfort response at month 6. A patient will be considered to be a complete ocular discomfort responder if the overall ocular discomfort score is 0 at month 6. The between-group difference in the proportion of responders will be analyzed using the CMH method stratified by gender and baseline overall ocular discomfort score (1 vs 2 to 3).

The secondary efficacy variables include change from baseline in TBUT, complete blurred vision response, complete corneal sodium fluorescein staining response, complete ocular burning response, change from baseline in overall ocular discomfort score, at least 1 grade improvement in overall ocular discomfort score, at least 2-grade improvement in overall ocular discomfort score, and at least 50% improvement in overall ocular discomfort score. For each of blurred vision, corneal sodium fluorescein staining, and ocular burning, a complete responder is a patient with a score of 0. The continuous secondary efficacy variable, change from baseline in TBUT, will be analyzed using an analysis of covariance (ANCOVA) model with treatment, gender, baseline overall ocular discomfort score (1 vs 2 to 3) as factors and baseline TBUT as a covariate. The dichotomous secondary efficacy variables (complete blurred vision response, complete corneal staining response, and complete ocular burning response) will be analyzed using the CMH method stratified by gender and baseline value (1 vs 2 to 3) of the corresponding variable. Other dichotomous secondary efficacy variables derived from the overall ocular discomfort score at month 6 (ie, $\geq$ 1 grade improvement from baseline, $\geq$ 2-grade improvement from baseline, and $\geq$ 50% grade improvement from baseline) will be analyzed using the CMH method stratified by gender and baseline overall ocular discomfort score (1 vs 2 to 3). The change from baseline in overall ocular discomfort will be analyzed by an ANCOVA model with treatment and gender as factors and baseline overall ocular discomfort score as a covariates.

Safety:

Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Incidence rates of each treatment-emergent adverse event will be summarized by primary system organ class and preferred term. Summary tables will be generated for all treatment-emergent adverse events regardless of causality as well as for those considered to be treatment-related.

Sample Size Calculation:

The total number of patients planned for this study is 527 patients including an estimated 10% attrition rate. The sample size was estimated based on the primary efficacy analysis to compare the proportion of patients with complete overall ocular discomfort response (defined as overall ocular discomfort score equals 0) at Month 6.

Based on the final analysis of an Allergan phase 2 study (protocol 195263-006), the observed proportion of patients with complete overall ocular discomfort response over a 7-day average is 20.0% vs 9.8% (between-group difference of 10.2%) for 0.1% AGN-195263 versus vehicle, respectively. A total of 237 patients per treatment group will achieve 85% power with type I error rate of 0.05 to detect a between-group difference of 10.2% in the proportion of patients with complete overall ocular discomfort response at Month 6. This is based on the two-sided z-test (pooled variance with continuity correction), as implemented in the commercial software, PASS 2008 (Inequality Tests for Two Proportions), version 08.0.13 (Hintze, 2008). Accounting for an anticipated attrition rate of 10%, enrollment of a total of 527 patients at multiple sites is planned.

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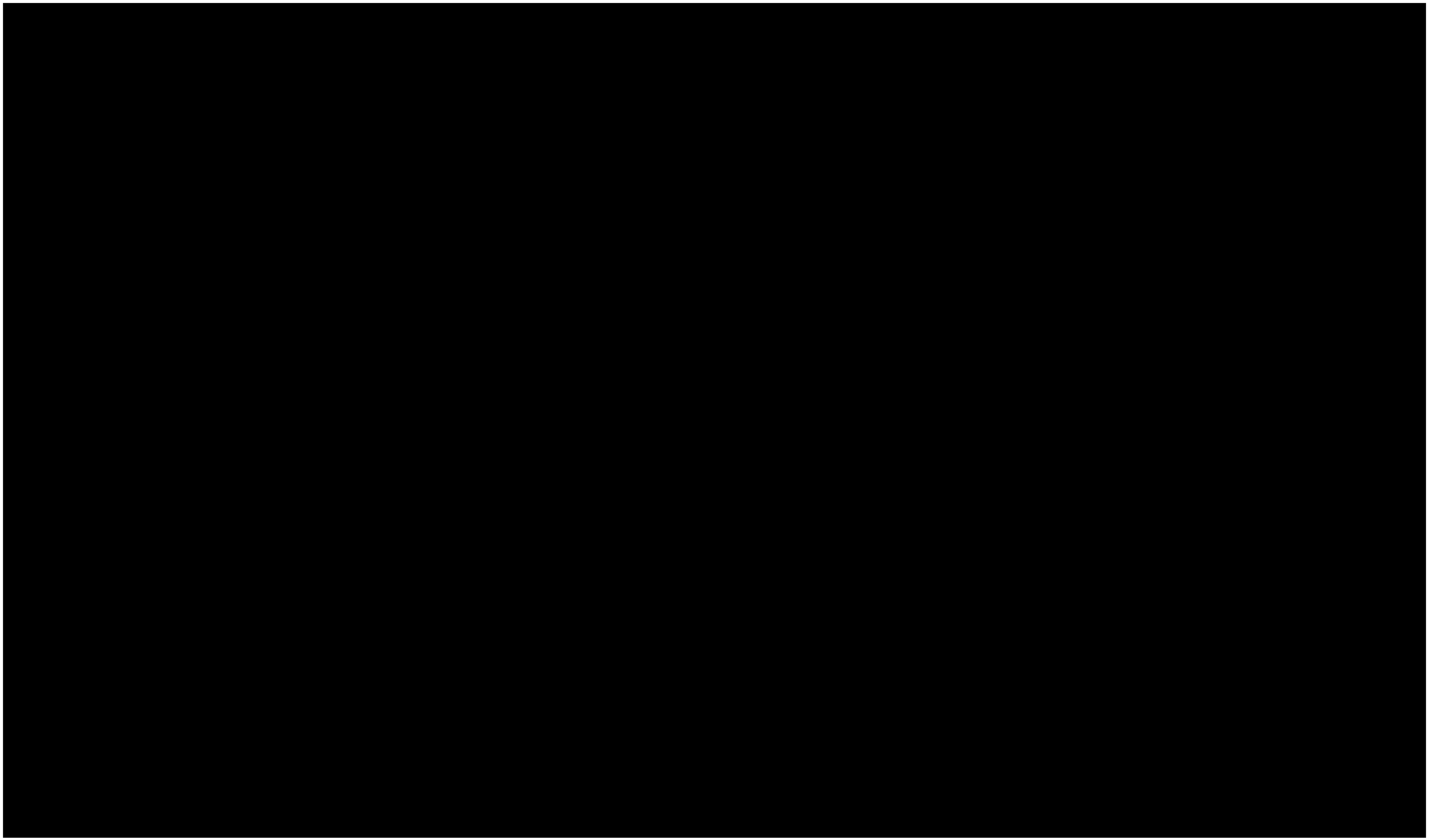
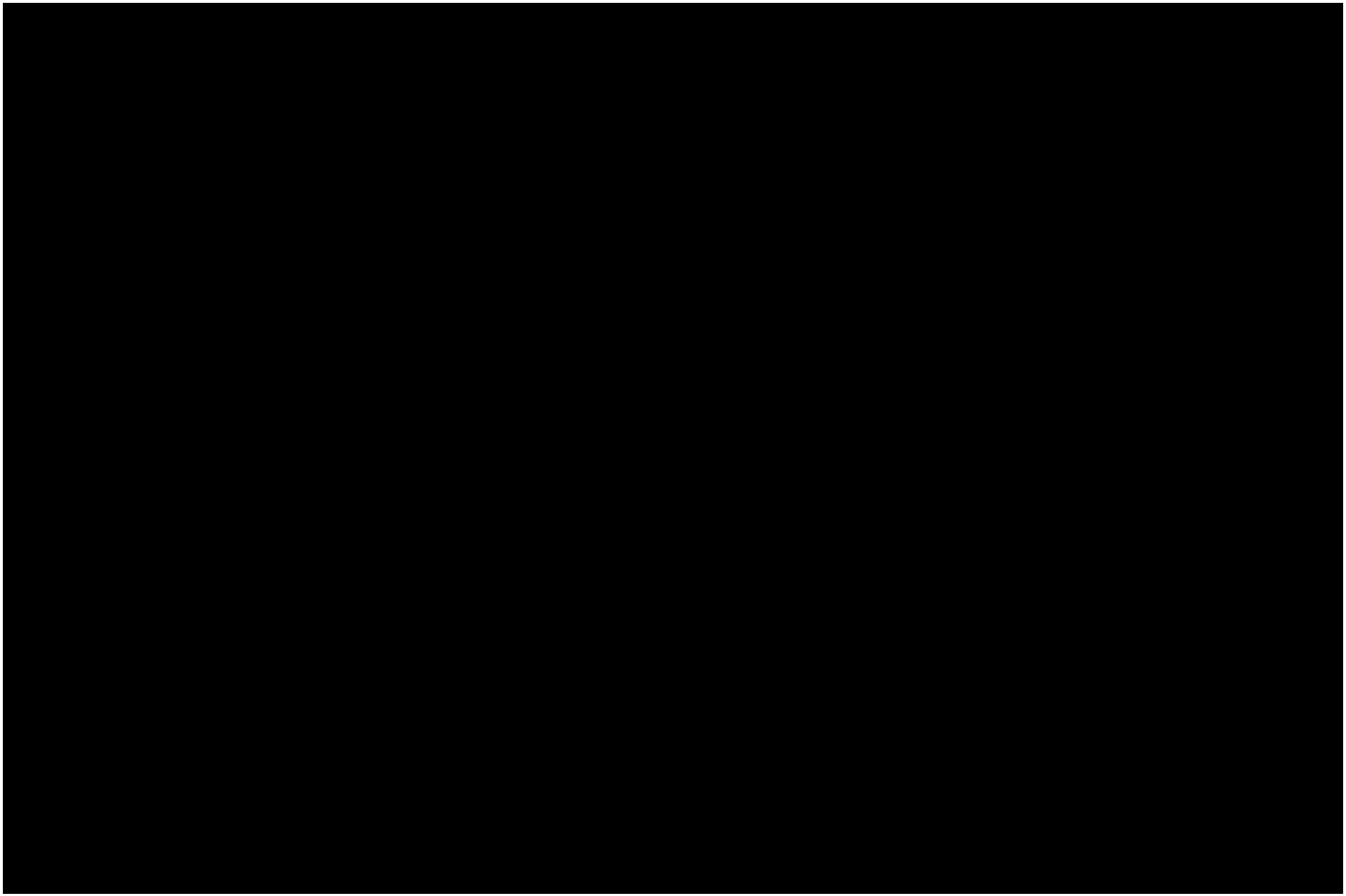
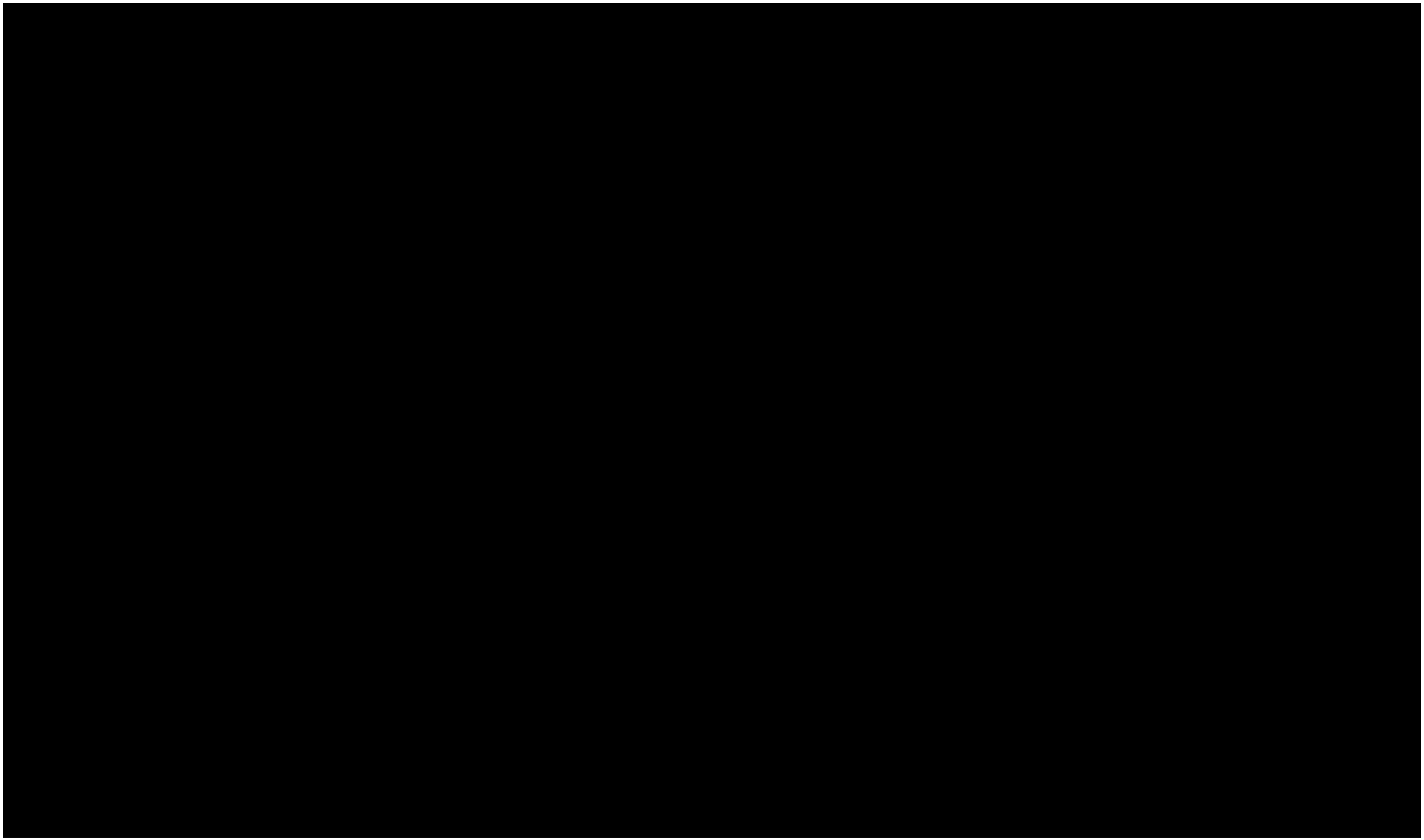
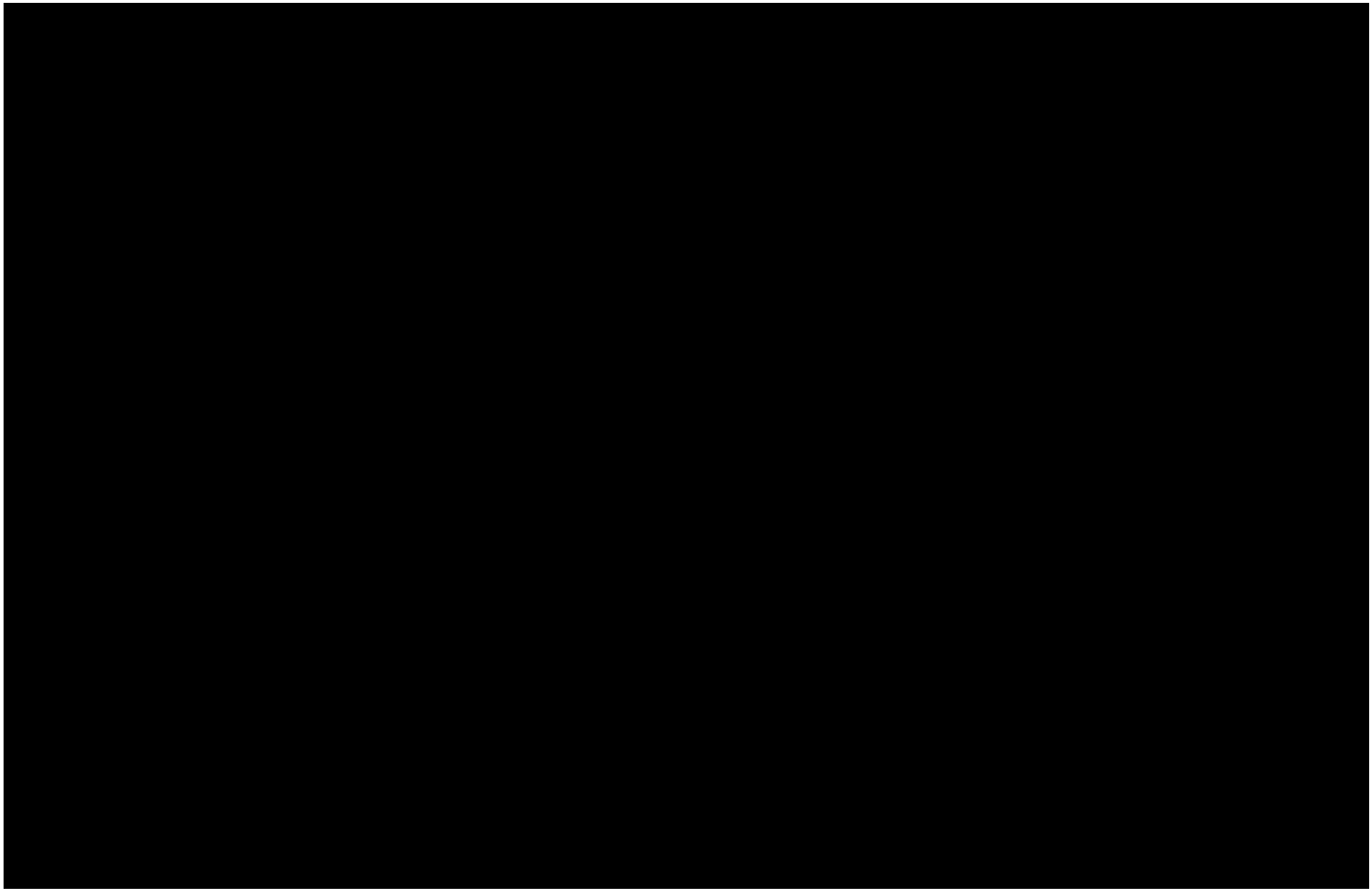








1. Background and Clinical Rationale

In 2007, the International Dry Eye Workshop (DEWS, 2007) defined dry eye disease (DED) as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

DED is broadly attributed to either impaired tear production (aqueous deficient dry eye [ADDE]) or evaporative dry eye (EDE) or both. Either of these changes to the tear film can compromise the health of the ocular surface with associated epithelial damage and symptoms of discomfort and visual disturbances. Epidemiological data suggest the prevalence of DED falls in the range of 5% to 34% of the global population ≥ 50 years (Baudouin et al, 2014; Bron et al, 2014; DEWS, 2007; Rolando et al, 2010) and contributes to approximately 25% of visits to ophthalmic clinics (Alves et al, 2013; Gayton, 2009). Epidemiological data further suggest that EDE alone may account for 30% to 47% of the overall DED population (Lemp and Nichols, 2009; Lemp et al, 2012; Rege et al, 2013). The tear film lipid layer is the major barrier to evaporation from the ocular surface. A decrease in lipid layer thickness or functional integrity is generally considered the primary mechanism leading to EDE. Such changes to the lipid layer are attributed to a reduction in the quality or quantity of meibum secretions from the meibomian glands.

Alterations in meibomian gland physiology can lead to a change in the composition of the meibum delivered to the tear film. Significant changes in meibum composition may lead to obstruction of the meibomian glands, producing meibum stagnation and potentially leading to gland atrophy. These changes can act as self-enforcing feedback loops leading to progressively larger alterations in the quality or quantity of lipid delivered to the tear film and consequently greater tear film instability and more rapid tear evaporation (Nelson et al, 2011). A shorter tear film break-up time (TBUT) based on greater tear film instability is characteristic of EDE, resulting in symptoms of ocular discomfort and impaired vision.

Current recommendations for the management and treatment of EDE include: 1) artificial tears; 2) lid hygiene (lid heating, massage, and cleaning); 3) thermodynamic treatment such as the LipiFlow® System; 4) topical antibiotic and/or topical steroids; and 5) systemic anti-inflammatory antibiotics (eg, tetracycline). To date, there is no approved pharmaceutical treatment indicated for EDE.

[redacted]

Reported risk factors for EDE and MGD have traditionally included age and female gender (particularly postmenopausal women), which are both associated with declining androgen levels (Azcarate et al, 2014; Gagliano et al, 2014; Nanavaty et al, 2014; Sullivan et al, 2009; Truong et al, 2014). In recent years, EDE has become a more frequently reported observation among younger demographics (Cuevas et al, 2012; Lemp and Nichols, 2009). In addition to age and gender, EDE has also been linked to factors which include diet, occupational habits, medications, and contact lens wear (Bron et al, 2014).

[redacted]

To date, Allergan has completed 1 phase 1 and 2 phase 2 clinical studies totaling 352 patients investigating the safety and efficacy of AGN-195263 [redacted] for DED and MGD, and an additional phase 2 study with a [redacted] formulation of AGN-195263 was completed.

The phase 1 clinical study (Study 195263-001) evaluated the safety and pharmacokinetics of AGN-195263 0.03%, 0.1%, 0.3%, and 0.6% [redacted] in postmenopausal women administered twice daily for 14 days. The first phase 2 study (Study 195263-003) evaluated the dose response relative to safety, tolerability, and efficacy of AGN-195263 0.01%, 0.1%, and 0.3% [redacted] in patients with keratoconjunctivitis sicca (KCS), also called DED, administered twice daily for 4 months.

The second phase 2 study (Study 195263-004) evaluated the safety and efficacy of AGN-195263 0.01%, 0.03%, and 0.1% [redacted] in patients with MGD administered twice daily for 6 months.

In all 3 studies with AGN-195263 [redacted], all concentrations were safe and well-tolerated. [redacted]

Efficacy data from Studies 195263-003 and 195263-004 suggested that treatment with AGN-195263 [redacted] was associated with a reduction in overall ocular discomfort and with an increase in TBUT.

[redacted]

A phase 2 study evaluating the safety and efficacy of AGN-195263 0.01%, 0.03%, and 0.1% [redacted] was recently completed. All concentrations were safe and well tolerated. Efficacy data demonstrated that the percentage of patients who were overall ocular discomfort responders at month 6 (a patient is considered to be an ocular discomfort

responder if the overall ocular discomfort score is 0 on a 0 to 4 scale; 0 = none, 4 = very severe) was numerically greater in patients receiving active compared to vehicle at month 6. In addition, an improvement in the mean change in TBUT at month 6 relative to baseline in patients receiving active compared to vehicle was also observed. Overall, the 0.1% concentration of the [redacted] formulation most consistently demonstrated improvements in both symptoms as well as in TBUT relative to vehicle. An exploratory analysis of patients with low TBUT (≤ 7 seconds) characteristics of EDE was also performed. In this subgroup of patients, the 0.1% concentration continued to demonstrate the most consistent overall improvement relative to vehicle across symptoms and TBUT after 6 months of treatment.

Overall, the clinical data collected supports the safety of the [redacted] formulation of AGN-195263 in patients with DED and patients with MGD. Data from the 2 phase 2 studies with [redacted] of AGN-195263 and 1 phase 2 study with the [redacted] formulation of AGN-195263, demonstrate improvement in overall ocular discomfort and TBUT, with the most consistent overall improvement achieved with the 0.1% concentration.

Given our current understanding of DED, 0.1% AGN-195263 ophthalmic [redacted] represents a potential therapeutic treatment option for EDE. The phase 3 pivotal superiority study proposed herein is designed to provide required safety, efficacy, and systemic pharmacokinetic data to support an indication for the treatment of EDE with 0.1% AGN-195263 ophthalmic [redacted]

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

- To evaluate the safety and efficacy of 0.1% AGN-195263 administered twice daily compared to its vehicle in patients with EDE
- To evaluate the systemic pharmacokinetics of 0.1% AGN-195263 administered twice daily in patients with EDE

2.2 Clinical Hypotheses

One drop of 0.1% AGN-195263 administered twice daily to each eye:

- Is more effective than vehicle as measured by the proportion of patients with complete overall ocular discomfort response at month 6
- Has an acceptable safety profile throughout the study treatment duration of 12 months

3. Study Design

This is a multicenter, global, randomized, parallel-group, vehicle-controlled study with 6 months of double-masked treatment followed by a 6 month open label treatment extension phase evaluating the safety, efficacy, and systemic pharmacokinetics of 0.1% AGN-195263 in patients with EDE.

Patients will be randomized to receive 0.1% AGN-195263 or its vehicle in a 1:1 ratio. The randomization will be stratified by gender and by baseline (day 1) overall ocular discomfort score (1 vs 2 to 3).

There will be up to 9 study visits including: screening (day -51), standardization (day -21), vehicle run-in (day -14), baseline (randomization, day 1), months 1, 3, 6 (primary and secondary efficacy assessments), 9, and 12/study exit (safety assessments).

The duration of the study for each patient will be up to approximately 14 months.

Use of lid hygiene (ie, warm compress, lid massage, lid scrub) or artificial tears (other than study artificial tears [SAT]) are prohibited from the standardization (day -21) visit until the end of the month 6 visit. Allergan will supply SAT (see Study Procedures Manual for further details). Starting at the standardization (day -21) visit, all eligible patients will administer SAT twice daily in each eye for 6 days. From the vehicle run-in (day -14) visit until the month 6 visit, use of SAT will be considered rescue therapy for intolerable symptoms. After the month 6 visit until the month 12/study exit visit, use of lid hygiene and/or any artificial tear product(s) will be unrestricted.

3.1 Additional Study Design Details

With respect to details described below for each study visit:

1. For patients not participating in the collection of blood samples for pharmacokinetic analysis, study treatment should be administered in the morning at approximately the same time of day during each office visit (± 1 hour from the study administration time at baseline [day 1]). At any time, the morning dose time should not exceed 1:00 pm local time.

2. For patients who participate in the collection of blood samples for pharmacokinetic analysis:
    a. the time of the pre-dose blood sample collection should be scheduled in the morning at approximately the same time of day during each office visit (± 1 hour from the pre dose blood sample collection time at the standardization [day -21] visit).
    b. SAT or study treatment should be administered in the morning at approximately the same time of day during each office visit and within 10 min after the time the pre-dose blood sample collection was performed that day.

Screening Visit (day -51): A patient may enter a screening period if, at the screening visit, applicable medications or treatments are required to be washed out or administered at a stable dose (Section 4.5), prior to commencement of the standardization (day -21) visit. If a screening period is not applicable, the screening and standardization visits may occur on the same day (day -21). For those patients who do enter the screening period, their standardization visit should be scheduled 7±1 days prior to the vehicle run-in (day -14) visit.

Standardization Visit (day -21): Eligible patients will discontinue use of any lid hygiene (ie, warm compress, lid massage, lid scrub) or artificial tears (other than SAT) and will begin administering 1 drop of SAT in each eye twice daily (morning and evening, spaced approximately by 12 hours) for 6 days. For selected patients, blood sample collection for systemic pharmacokinetics will occur prior to in-office administration of SAT and for 12 hours after administration of SAT at the following intervals: 5 ± 1 min; 10 ± 1 min; 30 ± 5 min; 2 hrs ± 15 min; 4 hrs ± 30 min; 6 hrs ± 30 min; 12 hrs ± 30 min. Following the 12 hour sample collection, site staff will remind patient to administer 1 drop of SAT in each eye prior to leaving site.

Vehicle Run-in Visit (day -14): All patients will enter a 2-week, patient-masked run-in on vehicle, where 1 drop of 0.1% AGN-195263 vehicle will be administered twice daily (morning and evening, spaced approximately by 12 hours) in each eye.

Baseline Visit (Randomization to Study Treatment and Initiation of Twice Daily Dosing [day 1]): Patients will be randomized on day 1 to receive either 0.1% AGN-195263 or its vehicle, administered as a single drop, twice daily (morning and evening, spaced approximately by 12 hours) in each eye. Both patient and investigator will be masked.

Month 1 Visit: Office visit during the randomized study treatment period. For selected patients, blood sample collection for systemic pharmacokinetics will occur (at same time ± 1 hour of pre-dose blood sample collection at the standardization (day -21) visit) prior to in-office administration of study treatment and for 12 hours after administration of study treatment at the following intervals**:** 5 ± 1 min; 10 ± 1 min; 30 ± 5 min; 2 hrs ± 15 min; 4 hrs ± 30 min; 6 hrs ± 30 min; 12 hrs ± 30 min. Following the 12 hour sample collection, site staff will remind patient to administer 1 drop of study treatment in each eye prior to leaving site.

Month 3 Visit: Office visit during the randomized study treatment period. For selected patients, a single blood sample collection for systemic pharmacokinetics will occur (at same time ± 1 hour of pre-dose blood sample collection at the standardization (day -21) visit) prior to in-office administration of study treatment.

Month 6 Visit: Primary and secondary efficacy will be assessed at the month 6 visit, after which the open-label treatment extension period starts. All patients will receive 0.1% AGN-195263, administered as a single drop, twice daily (morning and evening, spaced approximately by 12 hours) in each eye. Both patient and investigator will be unmasked. For select patients, blood sample collection for systemic pharmacokinetics will occur (at same time ± 1 hour of pre-dose blood sample collection at the standardization (day -21) visit) prior to in-office administration of study treatment and 10 ± 1 min after administration of study treatment.

Month 9 Visit: Office visit during the open-label treatment extension period. For selected patients, a single blood sample collection for systemic pharmacokinetics will occur (at same time ± 1 hour of pre-dose blood sample collection at the standardization (day -21) visit), prior to in-office administration of study treatment.

Month 12 / Study Exit / Early Exit Visit: For selected patients, a single blood sample collection for systemic pharmacokinetics will occur (at same time ± 1 hour of pre-dose blood sample collection at the standardization (day -21) visit), prior to in-office administration of study treatment.

The patient or patient's caregiver may instill the study treatment. Patients will be instructed to not administer their morning dose of study treatment the day of each study visit. The morning dose of SAT at the standardization visit (day -21) and of study treatment at the vehicle run-in (day -14), baseline (day 1) and month 1, 3, 6 and 9 visits will be administered by site staff.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 527 patients are planned to be enrolled in this study across approximately 80 global sites.

4.2 Study Population Characteristics

Evaporative dry eye (EDE)

4.3 Inclusion Criteria

The following are requirements for entry into the study:

[redacted]

3. Male, 18 years of age or older, at the screening (day -51) visit

   OR

   Females, 18 years of age or older, who are naturally menopausal (permanent cessation of menstrual periods for at least 12 consecutive months) or are permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) at the screening (day -51) visit

4. In at least 1 eye, <u>all</u> of the following objective measures of EDE must be present at the standardization (day -21) and baseline (day 1) visits. The <u>same eye</u> must qualify at both visits.

   - TBUT ≥ 2 seconds and ≤ 7 seconds
   - Corneal sodium fluorescein staining score ≥ 1 and < 4 (Oxford scheme)
   - Anesthetized Schirmer's tear test score ≥ 10 mm after 5 minutes

5. At the standardization visit (day -21) and baseline (day 1) visits, patients must have:

   - Ocular Surface Disease Index© (OSDI) score > 12 (0 to 100 scale)

- Overall ocular discomfort score ≥ 1 and < 4 (0 to 4 scale; 0 = none, 4 = very severe)
- Ocular burning score ≥ 1 and < 4 (0 to 4 scale; 0 = none, 4 = very severe)
- Blurred vision score ≥ 1 and < 4 (0 to 4 scale; 0 = none, 4 = very severe)

6. In at least 1 eye, a lower lid margin meibum quality global assessment score ≥ 1 at the standardization (day -21) and baseline (day 1) visits. The same eye must qualify at both visits.
7. In at least 1 eye, the number of lower lid margin expressible meibomian glands must be ≥ 3 at the standardization (day -21) and baseline (day 1) visits. The same eye must qualify at both visits.

[redacted]

11. Use of an artificial tear product, lid hygiene (ie, warm compress, lid massage, lid scrub), omega-3 supplementation (topical ocular or systemic), or antibiotics (ie, systemic or topical macrolides, tetracyclines, tetracycline derivative drugs [including doxycycline and minocycline]) for the treatment of dry eye disease or meibomian gland disease within 1 year of the standardization (day -21) visit.

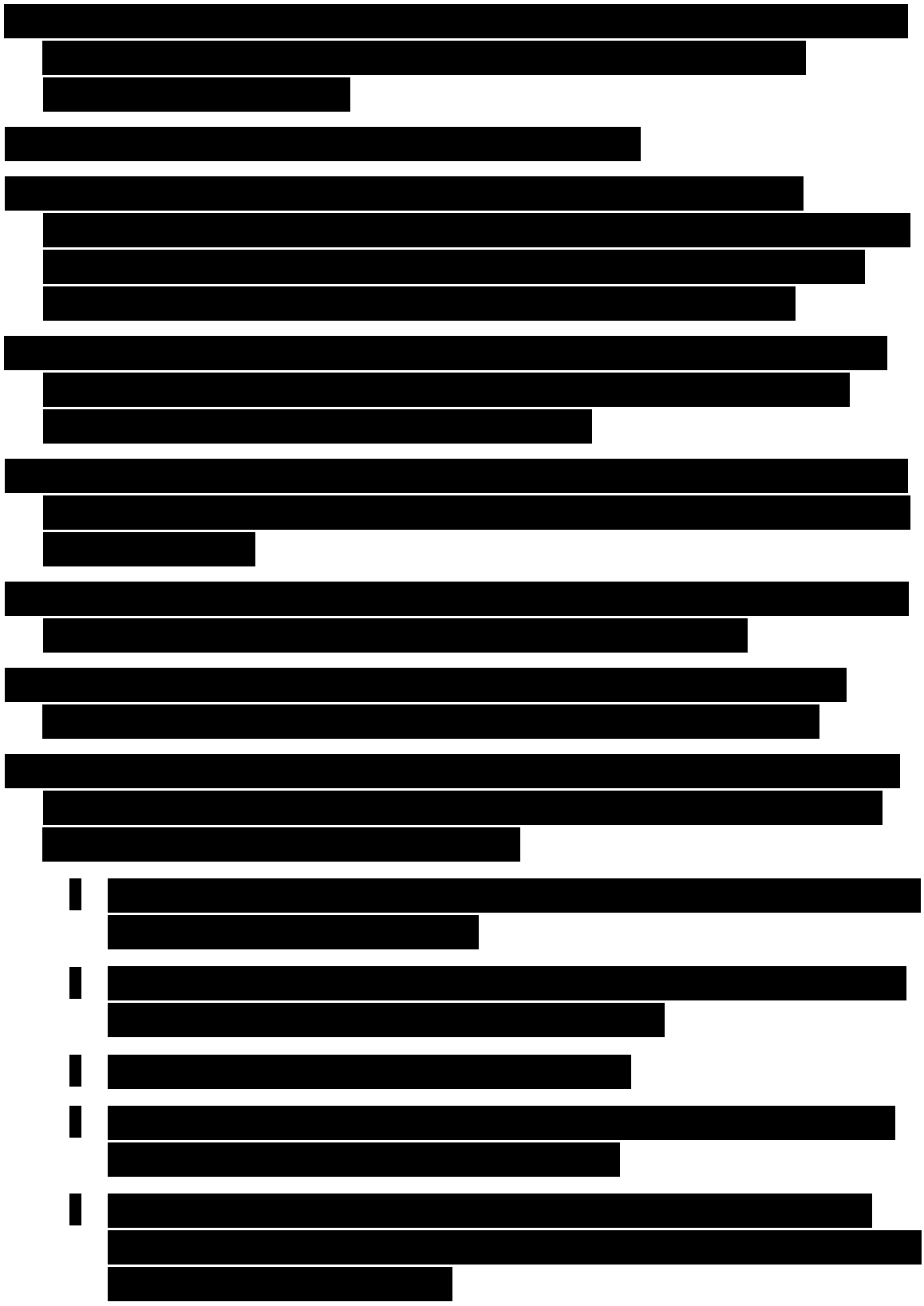
4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

[redacted]

2. At standardization (day -21) and/or baseline (day 1) visits, a lower lid margin meibum quality global assessment score of NE (non-expressible) in either eye

[redacted]



[redacted]

16. Male patients with a history of, known, or suspected prostate cancer
17. Male patients with a prostate-specific antigen (PSA) level ≥ 4 µg/L

[redacted]

19. Female patient who is of child-bearing potential
20. Female patients with a history of known or suspected breast, cervical, ovarian or uterine cancer

[redacted]

[redacted]

25. Patients who are currently using or have used any androgen or anti-androgen treatment (including herbal and nutritional supplements) [redacted]

[redacted]

27. Patients who are currently using or have used systemic or topical macrolides, tetracyclines, tetracycline derivative drugs (including doxycycline and minocycline), retinoids (eg, isotretinoin) or calcineurin inhibitors (ie, RESTASIS, Ikervis), or oral (systemic) corticosteroids , lifitegrast (Xiidra™) or any other therapeutic dry eye treatment within 60 days of the standardization (day -21) visit, or anticipated use before the month 6 visit

28. Patients who are currently using or have used any hair growth product within 90 days of the standardization (day -21) visit or anticipated use during the study

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

The following medications listed in Table 2 are permissible during the interval between the standardization (day -21) visit and the month 12/study exit visits if they have been taken for the minimum number of days listed in Table 2 prior to the standardization (day -21) visit and anticipated continuation on the same dose until at least the month 6 visit:

Table 2 Permissible Medications That Require Stable Dosing Prior to the Standardization (Day -21) Visit and Anticipated Continuation on the Same Dose Until at Least the Month 6 Visit

30 Days Before Standardization (day -21) Visit	60 Days Before Standardization Visit	90 Days Before Standardization Visit
Systemic antihistamines	Systemic beta-blocking agents	
Systemic antimuscarinics	Systemic cholinergic agonists	Estrogen and/or progesterone containing products (including herbal and nutritional supplements)
	Systemic medications used to treat mild to moderate systemic autoimmune disorders[1]	
Diuretics		
Tricyclic antidepressants	Inhaled corticosteroids	
Phenothiazines		
Systemic vitamins and/or systemic supplements containing: omega 3 fatty acids; vitamins A, B, and E; fish oil; biotin or Evening Primrose oil		

Note: any medication previously noted as an exclusion criteria (ie: systemic corticosteroids, calcineurin inhibitors, etc) must follow details noted for prohibited medications.

In addition, the following medications are permissible during the interval between the standardization (day -21) visit and the month 12/study exit visits:

- oral nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen (as needed)
- dermal or nasal corticosteroids (as needed)

The use of any artificial tear product is permissible after the month 6 visit to the month 12/study exit visit.

The use of lid hygiene (ie, warm compress, lid massage, lid scrub) on either eye is permissible after the month 6 visit to the month 12/study exit.

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

4.5.1.1 Definition of Females of Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, tubal occlusion, hysterectomy,

bilateral salpingectomy, and/or bilateral oophorectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause.

For male patients with a pregnant partner or a female partner of child bearing potential, it is recommended that a barrier method of contraception be employed for the entire duration of the phase 3 study and for 24 hours following the last dose of study treatment.

If a female partner of a male patient becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed. The investigator will (1) obtain consent from the female partner 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.

4.5.2 Prohibited Medications/Treatments/Procedures

Lid hygiene (ie, warm compress, lid massage, lid scrub) on either eye is prohibited during the interval between the standardization (day -21) visit and month 6 visit.

Contact lens wear in either eye is prohibited during the interval between the standardization (day -21) visit and month 12/study exit visit.

The following facial hair removal procedures applied to chin, cheek, upper lip, and/or brow are prohibited for female patients during the interval prior to each study visit:

- plucking or shaving within 14 days of any study visit
- laser, waxing, sugaring depilatory product, or any other removal process within 30 days of any study visit

The following procedures are prohibited in either eye during the interval between the screening (day -51) visit and month 12/study exit visit:

- punctal cautery
- anterior segment surgery in either eye which could affect corneal sensitivity (eg, cataract surgery, corneal refractive surgery, or any surgery involving a limbal or corneal incision)
- use of any type of punctal plug (eg, nondissolvable or collagen)

- use of any type of scleral lenses
- use of LipiFlow or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression
- use of sealed compartment ocular frames
- upper or lower lid tattooing

The following medications listed in Table 3 are prohibited during the interval between the standardization (day -21) visit and the month 6 visit:

Table 3 Prohibited Medications Within the Period Indicated Prior to the Standardization (Day -21) Visit to Month 6 Visit

At the Standardization Visit	Within 60 Days Before Standardization Visit[a]
All artificial Tears except SAT	Systemic or topical macrolides Topical corticosteroids in the eyes or on the eyelids Oral (systemic) corticosteroids Tetracycline Tetracycline derivatives (eg, doxycycline, minocycline) Retinoids (eg, isotretinoin) Calcineurin inhibitors (eg, RESTASIS, Ikervis) Lifitegrast (Xiidra) Other therapeutic treatments of dry eye

[a] all medications listed in table are permissible following the Month 6 visit.

The following medications listed in Table 4 are prohibited during the interval between the standardization (day -21) visit and the month 12/study exit visits:

Table 4 Prohibited Medications Within the Period Indicated Prior to the Standardization (Day -21) Visit and Throughout the Duration of the Study

Within 30 Days Before Standardization (day -21) Visit	Within 60 Days Before Standardization (day -21) Visit	Within 90 Days Before Standardization (day -21) Visit
Topical ocular glaucoma medications Topical ocular allergy medications (includes herbal and nutritional supplements)	Eyelash growth stimulators (eg, LATISSE)	Androgen or anti-androgen treatment (includes herbal and nutritional supplements) 5-alpha reductase inhibitors (eg, finasteride, dutasteride, bexlosteride, epristeride, izonsteride, lapisteride, turosteride) Spironolactone Inhibitors of steroidogenesis (eg, ketoconazole, abiraterone) Androgen receptor antagonists (eg, flutamide, bicalutamide, nilutamide, galeterone, MDV3100) GnRH agonists (eg, deslorelin, nafarelin, leuprolide, buserelin, goserelin, triptorelin, histrelin, deslorelin) Cyproterone acetate Hormone replacement therapy program or other use of estrogen or progesterone (includes herbal and nutritional supplements) Hair growth products

GnRH = gonadotropin-releasing hormone

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

4.5.3 Rescue Medications or Treatments

Allergan provided artificial tears (SAT, see Study Procedures Manual) may be used during the study (from the vehicle run-in (day -14) visit until the month 6 visit) only as needed as rescue medication for intolerable symptoms. In order to avoid dilution of the study medication, SAT should be instilled at least 30 minutes before or 30 minutes after each use of the study treatment.

Patients will be asked to refrain from use of SAT for 1 day prior to each study visit. "One day prior to each study visit" is defined as the morning of the day before the study visit and continues until the end of the study visit.

At each visit, patients will be asked about their use of artificial tears (SAT) by responding to the following 2 questions: 1) number of times used during the day prior to the study visit, and 2) how many times used per day on average over the week prior to the study visit.

5. Study Treatments

5.1 Study Treatments and Formulations

0.1% [redacted] (AGN-195263) (10192X) [redacted]

5.2 Control Treatment

The control treatment in this study is a vehicle of 0.1% [redacted] (AGN-195263) [redacted] The vehicle contains the same inactive ingredients as that of the 0.1% AGN-195263, but does not contain the drug substance.

5.3 Methods for Masking

During the vehicle run-in period (days -14 to -1), the patient will be masked to the run-in study treatment he/she receives. In order to maintain the masking of study vehicle during the vehicle run-in period (and to obtain unbiased ocular symptoms), patients will be informed and consented that they will receive vehicle for a 2-week period during their study participation. Following the vehicle run-in period, the investigator and patient will be masked during the randomized study treatment phase (baseline (day 1) to month 6 visit). All study treatments will be provided in identical unit dose vials and cartons to maintain masking of the study. From the end of the month 6 visit until the month 12/study exit visit (the open-label treatment extension phase), the investigator and patient will be unmasked.

5.4 Treatment Allocation Ratio and Stratification

At the time of randomization (baseline, day 1), patients will be randomly assigned in a 1:1 ratio to receive either 0.1% AGN-195263 [redacted] or its vehicle

during the randomized study treatment phase. Patients will be stratified by gender and baseline (day 1) overall ocular discomfort score (1 vs 2 to 3). There will be 4 stratification groups as shown in Table 5.

Table 5 Stratification Groups

Stratification Group	Gender	Baseline Overall Ocular Discomfort Score
1	Male	1
2	Male	2 to 3
3	Female	1
4	Female	2 to 3

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of screening procedures, each patient will provide informed consent. At the standardization (day -21) visit the site will call the interactive voice response system (IVRS) or log onto the interactive web response system (IWRS) to obtain the patient number that will serve as the patient identification number on all study documents.

An automated interactive (telephone or web) response system (IxRS) will be used to manage the run-in and randomization study treatment assignment based on randomization schemes prepared by Allergan Biostatistics. Study medication, including the run-in vehicle, will be labeled with medication kit numbers and shipped to each site.

At the time of enrollment at the vehicle run-in visit (day -14), all eligible patients will be assigned vehicle. At the patient's vehicle run-in visit, the IxRS system will provide the site with the specific medication kit number(s) to use for each qualified patient.

At the time of the baseline visit (randomization, day 1), patients meeting the inclusion/exclusion criteria (Sections 4.3 and 4.4) will be placed into 1 of 4 stratification groups as described in Section 5.4. Eligible patients will be randomly assigned to receive either 0.1% AGN-195263 [redacted] or its vehicle in a 1:1 treatment allocation. Based on the randomization scheme, a randomization number associated with 1 of the 2 treatment arms will be assigned to each patient sequentially according to the order of enrollment within the patient's stratification group. That is, IxRS will assign the next available randomization number for the stratification group to the patient at the time the investigator requests randomization. IVRS/IWRS will report a medication kit number to use for each patient corresponding to the randomization number.

The site will dispense the study medication kit assigned by the IxRS according to the IVRS/IWRS instructions. Sites will also call the IVRS or log onto the IWRS at all subsequent visits to obtain a study medication kit number for dispensing study medication. Sites will receive the IxRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

5.6 Treatment Regimen and Dosing

All eligible patients will receive a 2-week (days -14 to -1) patient-masked run-in on vehicle instilled as a single drop twice daily in each eye. At baseline (randomization, [day 1]), upon meeting inclusion/exclusion criteria, patients will be randomized to 0.1% AGN-195263 or its vehicle to be administered as a single drop, twice daily (morning and evening) in each eye for 6 months (baseline [day 1] to month 6 visits). Starting at the month 6 visit, all patients will administer 0.1% AGN-195263 as a single drop, twice daily (morning and evening) in each eye for an additional 6 months (month 6 to month 12).

The patient or patient's caregiver may instill the SAT (during standardization period) and study treatment. Twice-daily (morning and evening) SAT (during standardization period) and study medication should be instilled approximately 12 hours apart each day at approximately the same times. Patients will be instructed to not administer their morning dose of SAT (prior to Vehicle Run-In (day -14) visit) or study treatment on the day of each study visit.

5.7 Storage of Study Medications/Treatments

The study treatment and SAT must be stored in a secure isolated area (ie, with no other medication, supplies, documents, etc) and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol. Since the active study treatment includes [redacted], the site and all principal/sub-investigators must have the appropriate national prescribing registration for handling controlled substances for the same location (ie, address) where patient visits take place or per applicable country regulations.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Sites should monitor temperature conditions and report any temperature excursions to their site monitor or Allergan personnel. Please refer to the Procedure Manual for further details on drug storage and instructions on reporting temperature excursions. Study treatment and SAT are not to be frozen.

Allergan or Allergan designee will perform reconciliation on unused study treatment.

6. Response Measures and Summary of Data Collection Methods

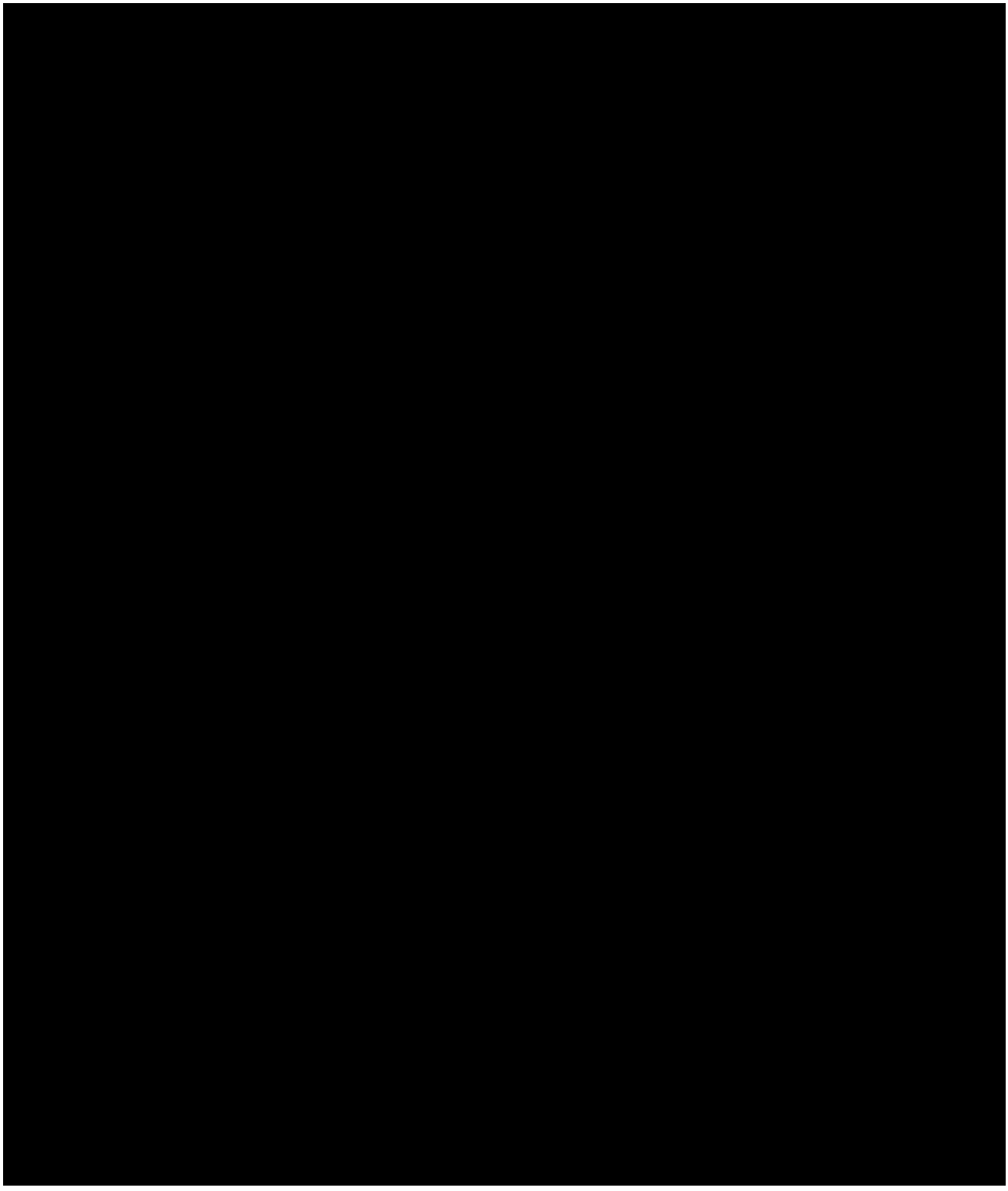
6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

- Overall ocular discomfort score (0 to 4 scale; 0 = none, 4 = very severe)

6.1.2 Secondary Efficacy Measures

- TBUT (seconds)
- blurred vision score (0 to 4 scale; 0 = none, 4 = very severe)
- corneal sodium fluorescein staining (0 to 5 Oxford scheme)
- ocular burning score (0 to 4 scale; 0 = none, 4 = very severe)
- derived variables based on overall ocular discomfort score (change from baseline, ≥ 1 grade improvement from baseline, ≥ 2 grade improvement from baseline and ≥ 50% improvement from baseline)



- [redacted]

[redacted]

6.3 Safety Measures

- adverse events
- BCVA (LogMAR)
- biomicroscopy
- ophthalmoscopy
- intraocular pressure (IOP)
- urine pregnancy test (female patients only)
- PSA (male patients only)
- hematology, serum chemistry, and urinalysis
- vital signs
- male scalp hair evaluation assessed by the investigator using the Norwood Male Pattern Baldness grading scale
- female hair evaluation (upper lip, chin, cheeks, and scalp) assessed by the investigator using the Ferriman and Gallwey scoring (0 to 4) scale for facial hair and the Female Androgenetic Alopecia Ludwig grading scale for the scalp

6.5 Summary of Methods of Data Collection

This protocol will use electronic case report forms (eCRFs) with remote data capture through a qualified third-party vendor. Data entered into the eCRF will correspond to, and be supported by, source documentation maintained at the sites. The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. The data will be entered on the eCRFs in a timely manner and on an ongoing basis. Site data and images will be transferred to Allergan via electronic media.

An IxRS will be used to assign patient identification numbers, randomize patients, and manage study medication inventory. Data will be transferred to Allergan on a periodic basis throughout the study.

7. Statistical Procedures

The primary efficacy analysis will be performed after all patients complete the month 6 visit or discontinue from the study prior to the month 6 visit. The final analysis will be performed after all patients exit the study. There will be separate database locks for the primary analysis and final analysis. Prior to the first database lock a detailed analysis plan (AP) will be approved.

7.1 Analysis Populations

There are 3 analysis populations defined for this study: intent-to-treat (ITT), per-protocol (PP), and safety.

The ITT population comprises all randomized patients. The efficacy variables will be analyzed using the ITT population. The analyses will be performed per the randomization schedule.

The PP population comprises all randomized and treated patients who met the key inclusion and exclusion criteria; did not use artificial tears (including SAT), lid hygiene, or other prohibited treatments that could impact the overall ocular discomfort score at month 6; and had no other major protocol deviations. The PP population will be determined prior to database lock. The primary efficacy variable will be analyzed using the PP population on an as-treated basis.

The safety population is defined as all patients who received at least 1 dose of study medication. Safety analyses will be performed on an as-treated basis. All safety measures will be analyzed using the safety population.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

Patients will have both eyes treated although only 1 eye is required to qualify based on the inclusion/exclusion criteria. For patients with only 1 qualified eye, the qualified eye will be designated as the study eye. For patients with both eyes qualified, the study eye will be the eye with the lower TBUT at the baseline (day 1) visit. For patients having both eyes qualified and the same TBUT in both eyes, the study eye will be the right eye. Efficacy analyses will be based on the data of the study eye.

7.2.1 Primary Efficacy Variable

The primary efficacy variable is complete overall ocular discomfort response at month 6. The overall ocular discomfort will be assessed on a questionnaire using a 0 to 4 scale on which 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. A patient with the score of 0 will be considered to be a complete overall ocular discomfort responder.

7.2.2 Secondary Efficacy Variables

There are total 8 secondary efficacy variables evaluated at month 6 as listed below.

- ***Change from Baseline in TBUT***

  The change from baseline in TBUT will be analyzed as the first secondary efficacy variable. For TBUT, the mean of 3 measurements will be computed at each visit for each eye. The mean value of the study eye will be used for the analysis.

- ***Complete Blurred Vision Response***

  Similar to overall ocular discomfort, blurred vision will be assessed by each patient based on a 0 to 4 scale. Proportion of patients with complete blurred vision response defined as a blurred vision score of 0 will be analyzed as a secondary efficacy variable.

- ***Complete Corneal Sodium Fluorescein Staining Response***

  The complete corneal sodium fluorescein staining response is defined as a secondary efficacy variable. A responder is defined as a patient with a corneal sodium fluorescein staining score of 0 based on the Oxford scheme.

- ***Complete Ocular Burning Response***

  Similar to overall ocular discomfort and blurred vision, a 0 to 4 scale will be used to assess the burning symptom experienced by patients. Proportion of patients with complete ocular burning response defined as a burning score of 0 will be analyzed as a secondary efficacy variable.

- ***Change from Baseline in Overall Ocular Discomfort Score***

  In addition to the responder analysis, the change from baseline in overall ocular discomfort score will be computed and analyzed as a secondary efficacy variable.

- ***≥ 1 Grade Improvement from Baseline in Overall Ocular Discomfort Score***

  The proportion of patients who achieved ≥ 1 grade improvement in overall ocular discomfort score from baseline (ie, change from baseline in raw score ≤ -1) will be analyzed as a secondary efficacy variable.

- ***≥ 2 Grade Improvement from Baseline in Overall Ocular Discomfort Score***

  The proportion of patients who achieved ≥ 2 grade improvement from baseline (ie, change from baseline in raw overall ocular discomfort score ≤ -2) will be analyzed as a secondary efficacy variable.

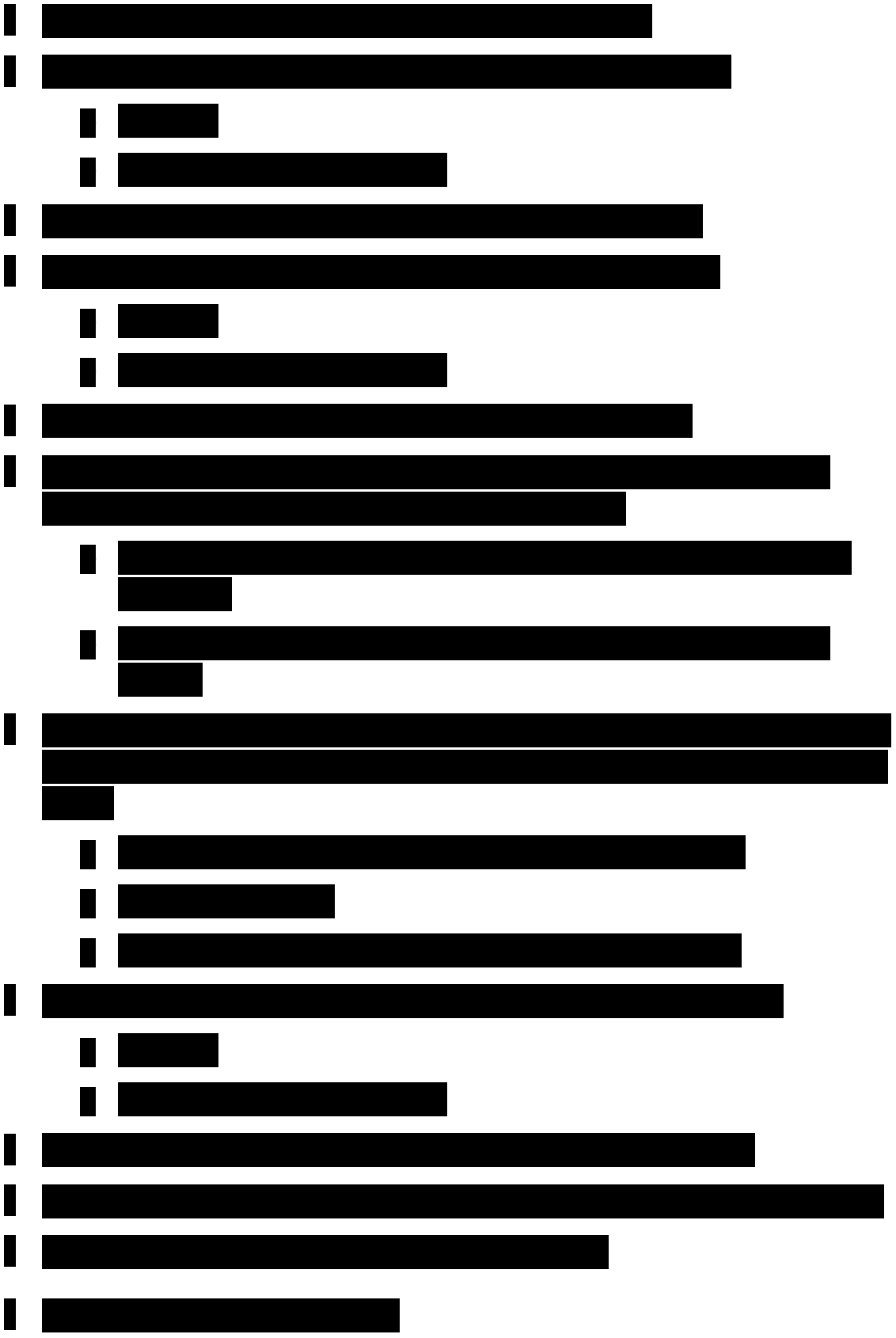
- ***≥ 50% Improvement from Baseline in Overall Ocular Discomfort Score***

  The percent change in overall ocular discomfort score (OODS) defined as below will be computed for each patient:

  [(OODS at month 6 - OODS at baseline)/OODS at baseline]x100

  Patients with a percent change ≤ -50% (ie, improvement ≥50%) will be considered as responders and the proportion of responders will be analyzed as a secondary efficacy variable.

[redacted]



[redacted]

7.3 Hypothesis and Methods of Analysis

In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using an analysis of variance (ANOVA) model or 2-sample t-test for between-group comparisons and paired t-test for within-group analyses. Categorical variables will be summarized by number of patients, frequency count, and percent, and will be analyzed using Pearson's chi-square or Fisher's exact test (if the expected cell count is less than 5 in 25% or more of the cells). Ordinal variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) test or the Wilcoxon rank-sum test for between-treatment comparisons and the signed-rank test for within-treatment comparisons.

A 2-sided test with a p-value ≤ 0.05 will be considered statistically significant unless otherwise stated.

SAT and Prohibited Treatments Impacting Efficacy Assessment

Usage of SAT or prohibited treatments described below will be considered to impact the efficacy assessments for the visit immediately following the use of SAT or prohibited treatments. The subsequent visits will not be impacted, unless the SAT or prohibited treatments are used again prior to any subsequent visits within the timeframe specified below. The efficacy data that are determined to be impacted by the usage of SAT or prohibited treatment will be considered as missing for the continuous variables with the missing data imputation method described below to be implemented. For the analysis of complete response in ocular symptoms, patients will be analyzed as nonresponders for the visits impacted by SAT or prohibited treatments.

- artificial tears (including SAT): use within 24 hours before each scheduled visit (vehicle run-in visit to month 12 visit)
- lid hygiene: use at least 8 days out of the 30-day window preceding each scheduled visit or any use within 14 days before each office visit
- any use during the study after the randomization visit of oral or topical macrolides, tetracyclines, tetracycline derivative drugs

Missing Data Imputation

ITT analyses of the efficacy variables described below will use the following rules to impute the missing data:

- If the data is missing because the patient discontinued the study due to lack of efficacy or use of SAT or other prohibited treatments that impacts the efficacy assessments,
    - Responder analyses: the patient will be considered a non-responder at all subsequent visits
    - Other analyses: the missing data will be imputed using the last observation carried forward (LOCF) method
- If the data is missing because the patient discontinued the study due to reasons other than lack of efficacy, the missing data will be imputed using the LOCF method.
- The intermittent missing data will be imputed using the LOCF method.
- The missing data at baseline visit will be imputed by the mean value across all patients who had non-missing baseline assessment of the variable analyzed regardless of treatment group

7.3.1 Primary Efficacy Analyses

The primary efficacy analyses will be performed for month 6 visit using the ITT population. The null hypothesis for the primary efficacy variable, complete overall ocular discomfort response, is that 0.1% AGN-195263 is no different than vehicle with respect to the proportion of patients who are complete overall ocular discomfort responders at month 6. The alternative hypothesis is that a between-group difference exists. As described above, patients who discontinued from the study due to lack of efficacy or used SAT or other prohibited treatments within the impact intervals specified will be counted as non-responders in the analysis. Missing data due to other reasons including intermittent missing visits, early discontinuation due to reasons other than lack of efficacy will be imputed by the LOCF method. The achievement of complete overall ocular discomfort response will be determined including the imputed data. The null hypothesis will be tested using the CMH method stratified by gender and baseline overall ocular discomfort score (1 vs 2 to 3). The between-group difference in the responder rate will be reported with the confidence intervals estimated based on the normal approximation for the binary variable.

7.3.2 Secondary Efficacy Analyses

There are total 8 secondary efficacy variables. Change from baseline in TBUT described in Section 7.2.2 will be analyzed using an analysis of covariance (ANCOVA) model with treatment, gender, and baseline overall ocular discomfort score (1 vs 2 to 3) as factors and the baseline TBUT value as a covariate. The complete blurred vision response, complete corneal sodium fluorescein staining response, and complete ocular burning response will be analyzed using the CMH method stratified by gender and baseline score (1 vs 2 to 3) of the corresponding variable.. In addition, there are 4 secondary efficacy variables derived based on the overall ocular discomfort score. Change from baseline in overall ocular discomfort score will be analyzed by an ANCOVA model with treatment and gender as factors and baseline overall ocular discomfort score as a covariate. The proportion of patients with ≥ 1-grade improvement from baseline, ≥ 2 grade improvement from baseline and ≥ 50% improvement from baseline in overall ocular discomfort score as defined in Section 7.2.2 will be analyzed by the CMH method stratified by gender and baseline overall ocular discomfort score (1 vs 2 to 3).

7.3.4 Safety Analyses

Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. The treatment-emergent adverse events will be summarized for randomized study treatment phase. In addition, treatment emergent adverse events attributed to 0.1% AGN-195263 treatment will be summarized for randomized study treatment phase and open-label treatment extension phase by the treatment received during the randomized study treatment phase and combined. This analysis will be performed for the subset of safety population who received 0.1% AGN-195263 during the study. Incidence rates for each treatment-emergent adverse

event will be summarized separately by (1) preferred term, (2) by primary system organ class and preferred term, and (3) by primary system organ class, preferred term and maximum severity. Summary tables will be generated for all treatment-emergent adverse events regardless of causality as well as for those considered to be treatment-related.

Detailed methods for the analyses of safety variables will be described in the AP.

7.4 Subgroup Analyses

Subgroup analyses will be performed for the primary and secondary efficacy variables by baseline overall ocular discomfort score (1, 2 to 3), baseline TBUT(≤ 2, > 2 to ≤ 4.5, > 4.5 to ≤ 7, and > 7), age group, gender, and race.

7.5 Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed on AGN-195263 treated patients only for post drug treatment analysis. To enable only bioanalysis of samples from patients who receive active AGN-195263 treatment, the randomization codes will be made available based on Allergan internal procedures. [redacted] If the serum concentrations of a given analyte are measurable, pharmacokinetic parameters, including peak or maximum drug concentration (C_{max}), time to achieve the peak concentration (T_{max}), and the area under the concentration-time curve from time 0 (baseline, prior to study treatment administration) to time of last quantifiable concentration ($AUC_{0\text{-}last}$), will be calculated for individual patient concentration and time profiles using standard model-independent techniques. Descriptive statistics (eg, mean, standard deviation), if applicable, will be computed for all pharmacokinetic parameters calculated.

7.6 Sample Size Calculation

The total number of patients planned for this study is 527 patients including an estimated 10% attrition rate. The sample size was estimated based on the primary efficacy analysis to compare the proportion of patients with complete overall ocular discomfort response (defined as overall ocular discomfort score equals 0) at Month 6.

Based on the final analysis of an Allergan phase 2 study (protocol 195263-006), the observed proportion of patients with complete overall ocular discomfort response over a 7-day average is 20.0% vs 9.8% (between-group difference of 10.2%) for 0.1% AGN-195263 versus vehicle, respectively. A total of 237 patients per treatment group will achieve 85% power with type I error rate of 0.05 to detect a between-group difference of 10.2% in the proportion of patients with complete overall ocular discomfort response at Month 6. This is based on the two-sided z-test (pooled variance with continuity correction), as implemented in the commercial software, [redacted]. Accounting for an anticipated attrition rate of 10%, enrollment of a total of 527 patients at multiple sites is planned.

7.7 Interim Analyses

There will be no interim analysis.

8. Study Visit Schedule and Procedures

This study will be comprised of a 6-month double-masked treatment phase followed by a 6-month open label treatment extension phase evaluating safety, efficacy, and systemic pharmacokinetics of 0.1% AGN-195263 in patients with EDE. There will be 9 study visits: screening (day -51), standardization (day -21), vehicle run-in (day -14), baseline (randomization, day 1), months 1, 3, 6, 9, and 12/study exit. See Table 1 for a schematic of the schedule of visits and procedures and Figure 1 for schematic diagram of the study design.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give written authorization (US sites only), data protection consent (European sites only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

8.2 Procedures for Final Study Entry

Each patient's medical and ophthalmic history as well as medication usage will be evaluated and determined to be acceptable to the investigator prior to patient enrollment in the study.

A patient is considered to have entered the study once they have met the inclusion and exclusion criteria and are assigned a study enrollment number at the enrollment visit (day 1). See Section 5.5 for the method for assignment to treatment groups/randomization.

8.3 Visits and Associated Procedures

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, it is preferred that evaluations should overlap and the evaluators will examine the patient together and discuss findings for at least 1 visit.

The following section provides a list of procedures for each scheduled visit. Additional information on the examination procedures, equipment, and techniques for the measures listed in this section is presented in Section 12. Unless otherwise specified, procedures should be performed on both eyes. The procedures listed below are recommended to be performed in the order shown unless otherwise specified. If the patient does not qualify at a study visit, the remaining procedures for that visit should not be performed.

8.3.1 Screening Visit (Day -51)

The following procedures and assessments will be performed during the screening visit:

- Informed consent/authorization
- Demographics (including height, weight)

- Inclusion/exclusion criteria review
- Medical and ophthalmic history
- Medication history/concomitant medications. Ensure to query use of:
    - Lid hygiene (ie, warm compress, lid massage, lid scrub)
    - Any artificial tear products
    - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Contact IxRS
- Adverse events

8.3.2 Standardization Visit (Day -21 [± 1 day])

The following procedures and assessments will be performed during the standardization visit:

- Inclusion/exclusion criteria review (reassessment only for patients whose screening and standardization visits are on separate days)
- Medical and ophthalmic history (reassessment only for patients whose screening and standardization visits are on separate days)
- Concomitant medications (reassessment only for patients whose screening and standardization visits are on separate days). Ensure to query use of:
    - Lid hygiene (warm compress, lid massage, lid scrub)
    - Any artificial tear products
    - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Vital signs (pulse rate, blood pressure)
- Hair evaluation (all patients asked to report any use of hair growth products or hair removal procedures)

[redacted]

- Visual acuity (manifest refraction)
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)

- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer tear test with anesthesia
- Lower lid margin meibomian gland secretion evaluation
- IOP
- Ophthalmoscopy (eyes should be dilated)
- Contact IxRS
- Blood and urine collection sample for hematology, blood chemistry, PSA measurement (males only), and urinalysis
- [redacted]
- In-office administration of SAT
- Post-dose blood sample collection for systemic pharmacokinetics (5 minutes ± 1 minute, 10 minutes ± 1 minute, 30 minutes ± 5 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes and 12 hours ± 30 minutes) (for selected patients) (To facilitate the 12 hour time course of blood draws for pharmacokinetic analysis at the standardization (day -21) and month 1 visits, sites may "split" the visit, and perform the serial blood draws at a separate visit (the "split visit"). The split visit must occur within 5 days from the scheduled visit.)
- Adverse events
- SAT dispensing

8.3.3 Vehicle Run-in Visit (Day -14 + [3 days])

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

The following procedures and assessments will be performed during the vehicle run-in visit:

- Concomitant medications. Ensure to query use of:
  - Lid hygiene (ie, warm compress, lid massage, lid scrub)
  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Ocular symptoms questions: overall ocular discomfort, blurred vision, ocular burning
- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- IOP
- Contact IxRS
- In-office administration of study treatment
- Adverse events
- Study treatment dispensing
- SAT dispensing
- Collect unused study treatment

8.3.4 Baseline Visit (Randomization, Day 1)

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to

each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

The following procedures and assessments will be performed during the baseline visit:

- Inclusion/exclusion criteria review
- Concomitant medications. Ensure to query use of:
  - Lid hygiene (warm compress, lid massage, lid scrub)
  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Vital signs (pulse rate, blood pressure)
- Pregnancy test (females patients only)
- Hair evaluation
- [redacted]
- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer tear test with anesthesia
- Lower lid margin meibomian gland secretion evaluation
- IOP
- Ophthalmoscopy (during examination, eyes to be undilated)
- Contact IxRS (randomization)

- In-office administration of study treatment
- Adverse events
- Study treatment dispensing
- SAT dispensing
- Collect unused study treatment

8.3.5 Month 1 Visit (± 5 days)

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

The following procedures and assessments will be performed during the month 1 visit:

- Concomitant medications. Ensure to query use of:
  - Lid hygiene (ie, warm compress, lid massage, lid scrub)
  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Hair evaluation

[redacted]

- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer's tear test with anesthesia

- IOP
- Contact IxRS
- Blood and urine sample collection for hematology, blood chemistry, PSA measurement, and urinalysis
- Pre-dose blood sample collection for pharmacokinetic analysis (testosterone, DHT, SHBG) (performed for selected patients); time of the collection should align ± 1 hour to the pre-dose collection performed at the standardization (day -21) visit.
- In-office administration of study treatment (If patient is not participating in pharmacokinetic blood draws, time of in-office administration should be scheduled to align to the baseline (day 1) administration time of day ± 1 hour. For all patients participating in blood sampling for pharmacokinetic analysis, study treatment should be administered at approximately the same time of day during each office visit and within 10 min after the time the pre-dose blood sample collection was performed at the current visit)
- Post-dose blood sample collection for systemic pharmacokinetics (5 minutes ± 1 minute, 10 minutes ± 1 minute, 30 minutes ± 5 minutes, 2 hours ± 15 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes and 12 hours ± 30 minutes) (for selected patients)
- Adverse events
- Study treatment dispensing
- SAT dispensing
- Collect unused study treatment

8.3.6 Month 3 Visit (± 7 days)

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

The following procedures and assessments will be performed during the month 3 visit:

- Concomitant medications. Ensure to query use of:
    - Lid hygiene (warm compress, lid massage, lid scrub)

  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Vital signs (pulse rate, blood pressure)
- Hair evaluation
- [redacted]
- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer's tear test with anesthesia
- IOP
- Contact IxRS
- Blood and urine sample collection for hematology, blood chemistry, PSA measurement, and urinalysis
- Pre-dose blood sample collection for pharmacokinetic analysis [redacted] (performed for selected patients); time of the collection should align ± 1 hour to the pre-dose collection performed at the standardization (day -21) visit.
- In-office administration of study treatment (If patient is not participating in pharmacokinetic blood draws, time of in-office administration should be scheduled to align to the baseline (day 1) administration time of day ± 1 hour. For all patients participating in blood sampling for pharmacokinetic analysis, study treatment should be administered at approximately the same time of day during each office visit and within 10 min after the time the pre-dose blood sample collection was performed at the current visit)

- Adverse events
- Study treatment dispensing
- SAT dispensing
- Collect unused study treatment

8.3.7 Month 6 Visit (± 7 days)

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

The following procedures and assessments will be performed during the month 6 visit:

- Concomitant medications. Ensure to query use of:
  - Lid hygiene (ie, warm compress, lid massage, lid scrub)
  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Vital signs (pulse rate, blood pressure)
- Hair evaluation

- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer's tear test with anesthesia

- Lower lid margin meibomian gland secretion evaluation
- IOP
- Ophthalmoscopy
- Contact IxRS
- Blood and urine sample collection for hematology, blood chemistry, PSA measurement, and urinalysis
- Pre-dose blood sample collection for pharmacokinetic analysis (testosterone, DHT, SHBG) (performed for selected patients); time of the collection should align ± 1 hour to the pre-dose collection performed at the standardization (day -21) visit.
- In-office administration of study treatment (If patient is not participating in pharmacokinetic blood draws, time of in-office administration should be scheduled to align to the baseline (day 1) administration time of day ± 1 hour. For all patients participating in blood sampling for pharmacokinetic analysis, study treatment should be administered at approximately the same time of day during each office visit and within 10 min after the time the pre-dose blood sample collection was performed at the current visit)
- Post-dose blood sample collection for systemic pharmacokinetics (for selected patients); the sample collection should be performed at 10 minutes ± 1 minute only
- Adverse events
- Study treatment dispensing
- SAT dispensing
- Collect unused study treatment

8.3.8 Month 9 Visit (± 14 days)

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

The following procedures and assessments will be performed during the month 9 visit:

- Medication history/concomitant medications. Ensure to query use of:

  - Lid hygiene (warm compress, lid massage, lid scrub)
  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivative drugs
- Vital signs (pulse rate, blood pressure)
- Hair evaluation
- [redacted]
- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer's tear test with anesthesia
- IOP
- Contact IxRS
- Blood and urine sample collection for hematology, blood chemistry, PSA measurement, and urinalysis
- Pre-dose blood sample collection for pharmacokinetic analysis ([redacted]) (performed for selected patients); time of the collection should align ± 1 hour to the pre-dose collection performed at the standardization (day -21) visit.

- In-office administration of study treatment (If patient is not participating in pharmacokinetic blood draws, time of in-office administration should be scheduled to align to the baseline (day 1) administration time of day ± 1 hour. For all patients participating in blood sampling for pharmacokinetic analysis, study treatment should be administered at approximately the same time of day during each office visit and within 10 min after the time the pre-dose blood sample collection was performed at the current visit)
- Adverse events
- Study treatment dispensing
- SAT dispensing
- Collect unused study treatment

8.3.9 Month 12/Study Exit (Early Exit) (± 14 days)

Patients will be instructed to not administer morning dose of study treatment the day of a study visit. In addition, patients will be asked to refrain from use of SAT for 1 day prior to each study visit. One day prior to each study visit begins on the morning of the day before the study visit and continues until the end of the study visit.

Patients who exit early from the study should complete the month 12/study exit visit procedures when possible. The following procedures and assessments will be performed during the month 12/study exit visit:

- Concomitant medications. Ensure to query use of:
  - Lid hygiene (warm compress, lid massage, lid scrub)
  - SAT
  - Any artificial tear products other than SAT
  - Oral or topical macrolides, tetracyclines, tetracycline derivatives
- Vital signs (pulse rate, blood pressure)
- Hair evaluation

[redacted]

- Visual acuity
- Biomicroscopy (includes upper and lower lid margin appearance evaluation)
- TBUT
- Sodium fluorescein corneal staining (Oxford scheme)
- Sodium fluorescein conjunctival staining (Oxford scheme)
- At least 10-minute wait
- Schirmer's tear test with anesthesia
- Lower lid margin meibomian gland secretion evaluation
- IOP
- Ophthalmoscopy
- Contact IxRS (only for patients who are exiting early from the study)
- Blood and urine sample collection for hematology, blood chemistry, PSA measurement, and urinalysis
- Blood sample collection for pharmacokinetic analysis [redacted] (performed for selected patients); time of the collection should align ± 1 hour to the pre-dose collection performed at the standardization (day -21) visit.
- Adverse events
- Collect unused study treatment

8.4 Instructions for the Patients

- Non-PK patients: Return to the study site for study visits at days -21, -14, 1 and months 1, 3, 6, 9, and 12. Visits should be scheduled so that in-office administration of study treatment at months 1, 3, 6, 9, and 12 will be ± 1 hour from the time of day established at baseline (day 1).
- PK patients: Return to the study site for study visits at days -21, -14, 1, and months 1, 3, 6, 9, and 12. Visits should be scheduled so that the time of the pre-dose blood sample collection in the morning will be at approximately the same time of day during each office visit (± 1 hour from the pre-dose blood sample collection time at the standardization (day -21) visit).

- Patients should remain at the site for the duration of the visit to complete the study-related procedures as explained to them by the study site personnel.
- If glasses are worn for vision correction, patients should remember to bring their glasses each time they visit the doctor's office.
- Follow the study visit schedule and to report all changes in their medical condition to the site.
- Maintain a stable dose if any concomitant medication is taken.
- Report any changes to their medication at their next study visit or report any new medication(s) initiated during the study. Patients should also be reminded to contact the study site if they are experiencing any difficulties during their study participation.

DOSING INFORMATION

- Directions will be provided on proper dosing technique and storage of study treatment. For study treatment dosing, patients will be instructed that each vial from their kit is for single-use dosing; 1 drop should be instilled in each eye from the first vial for the morning dose and a second (new) vial should be used to instill one-drop in each eye for the evening dose.
- If SAT is required for intolerable symptoms, any use of SAT should be instilled at least 30 minutes before or 30 minutes after study treatment whenever both medications are used.
- Patients are NOT to administer SAT or study treatment on the morning of study days -14, -1 and months 1, 3, 6, 9, and 12, as the first (morning) dose on these days will be administered by site staff.
- To administer 1 drop of SAT in each eye on the evening of study day -21 and 1 drop of study treatment in each eye on the evening of study days -14 and 1 and months 1, 3, 6, and 9.
- Save all unused study treatment vials in their study treatment kit and to bring their study treatment kit(s) with them on day 1 and months 1, 3, 6, 9 and 12.
- During the open-labl period beginning after the month 6 visit and through month 12/study exit, patients may resume lid hygiene or artificial tears as needed, but use of artificial tears will continue to be prohibited within 24 hours of any study visit.

8.5 Unscheduled Visits

Patients may experience adverse events that necessitate their returning to the study site for unscheduled visits. The adverse event and all required information should be recorded on the appropriate eCRF and the patient's record should include all relevant information.

Unscheduled visits may be performed as necessary to ensure the safety and wellbeing of patients during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit. An assessment of any adverse event should be completed.

8.6 Compliance with Protocol

Patients must be able to adhere to the study visit schedule, testing parameters, and appropriate inclusion, exclusion, and treatment criteria as described in the protocol.

At each study visit, patients will be asked if they have used any concomitant medications/therapies or had any concurrent procedures since the previous visit.

8.7 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate case report form.

8.8 Withdrawal Criteria

Patients may voluntarily withdraw from the study at any time. Table 6 describes the applicable follow-up depending on whether an enrolled study patient decides to discontinue voluntarily, or is discontinued by the investigator or by Allergan.

Table 6 Early Discontinuation Requirements

Reason for Discontinuation	Study Procedures and Visits Requirements
Patient elects to not complete a full study visit	Early exit procedures, as described in Table 1, should be completed before the end of that visit, whenever possible.
Patient elects to discontinue after completion of enrollment visit and assignment into a study cohort but before exit visit is initiated	No additional procedures or study visits are required.
Patient is discontinued after completion of the enrollment visit due to patient not qualifying for a study cohort or cohort is full (and thus patient is not asked to return for additional study visits)	No additional procedures or study visits are required.
Patient discontinued at the investigator's discretion	Early exit procedures, as described in Table 1, should be completed before the end of that visit, whenever possible.
Patient discontinued at Allergan's discretion	Early exit procedures, as described in Table 1, should be completed before the end of that visit, whenever possible.

Notification of patient's early discontinuation from the study and the reason for discontinuation will be made to Allergan or to the site in the case of patient not qualifying for a cohort or if cohort enrollment goal is met, and will be clearly documented on the eCRF.

8.9 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event case report form. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the

medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the CRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event 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. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the

study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate case report form.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or Agent of Allergan eg, CRO as listed on the Allergan Study Contacts Page and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must

supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.
2. 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 patient.
3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unmasking study medication. The investigator should inform the sponsor (Allergan Medical Safety Physician) of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Patients

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the

IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

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 drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (US sites only), data protection consent (European sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

10.4 Documentation

10.4.1 Source Documents

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

The following information should be entered into the patient's medical record:

- Patient's name
- Patient's contact information

- The date that the patient entered the study, patient number, and patient randomization [or medication kit] number
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- Dates of all patient visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any adverse events
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- The results of laboratory tests performed by the site (eg, results of urine pregnancy tests)
- Key study variables

Source documentation practices must follow Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and ALCOA, ie, records must be **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal and **A**ccurate.

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's case report forms and related documents. An investigator who has signed the protocol signature page should personally sign for the case report forms (as indicated in the case report forms) to ensure that the observations and findings are recorded on the case report forms correctly and completely. The case report forms are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

[redacted]

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the patients, the number of unused units returned to the investigator by the patient (if applicable), and the number of unused units returned to Allergan or Allergan's designee during and at the completion of the study. A detailed inventory must be completed for the study medication. The study treatment must be dispensed or administered only by an appropriately qualified person to patients in the study. The study treatment is to be used in accordance with the protocol for patients who are under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All unused clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by the Sponsor

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Blood samples collected for pharmacokinetic analysis will be processed into serum samples at the clinical sites, submitted to a central laboratory for processing and/or storage, prior to shipment to a bioanalytical laboratory for analysis utilizing a validated method.

Details of sample collection, handling, storage, and shipping procedures are found in Appendix 12.1 (Attachments) as well as the appropriate Study Procedure Manuals.

10.8 Publications

Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

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12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

For each patient, their visits for ophthalmic examinations should be scheduled at approximately the same time of the day, such that study treatment can be administered in the morning at approximately the same time of day during each office visit (± 1 hour from the study administration time at baseline). In addition, for sites that participate in the collection of blood samples for pharmacokinetic analysis, the time of the pre-dose blood sample collection should be scheduled to align to time sample was collected at the standardization (day -21) visit ± 1 hour. Procedures should be performed in the order described in Table 1. Below is a brief description of selected procedures.

12.1.1 Pregnancy Test

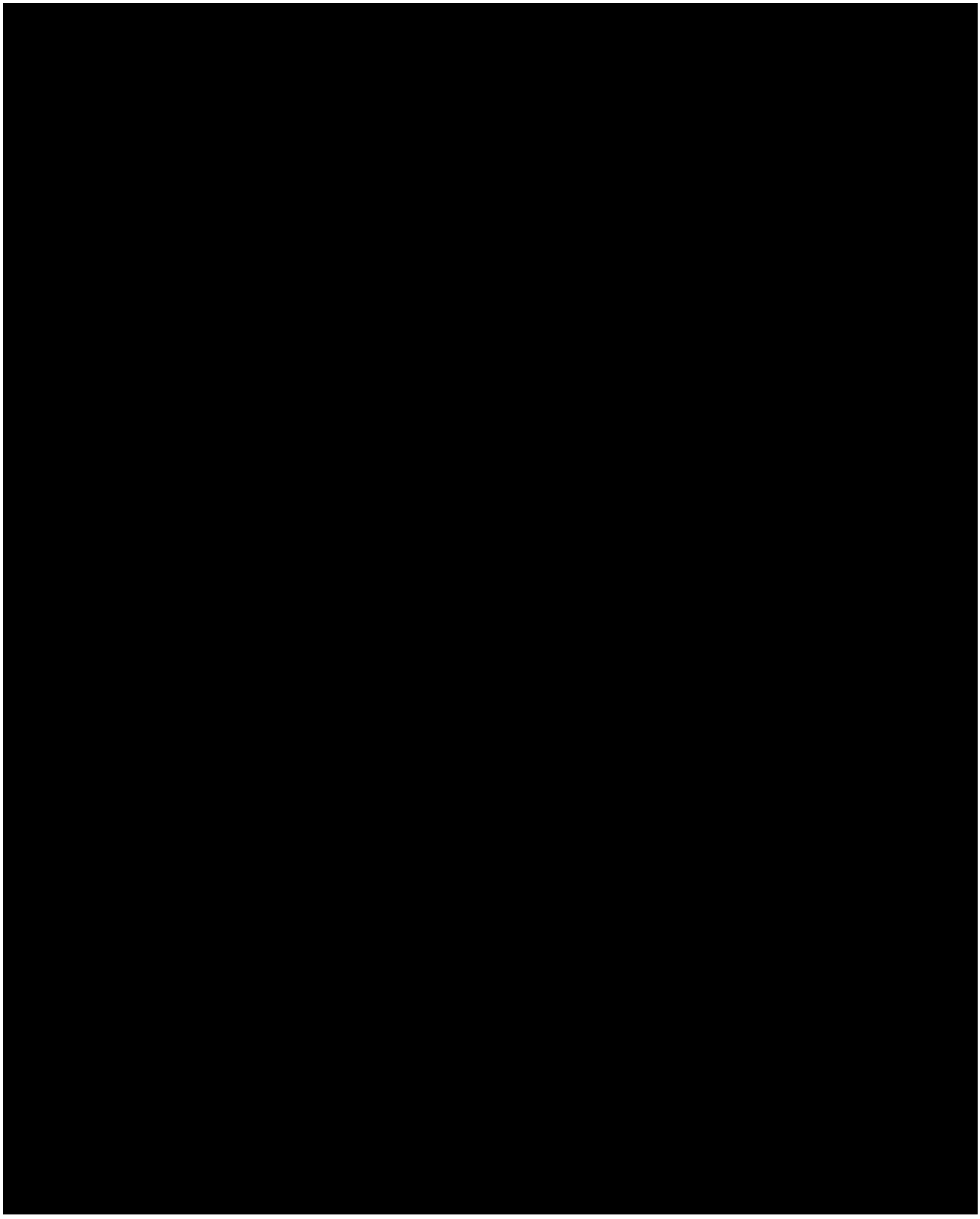
All female patients will have a urine pregnancy test performed at the baseline (day 1) visit.

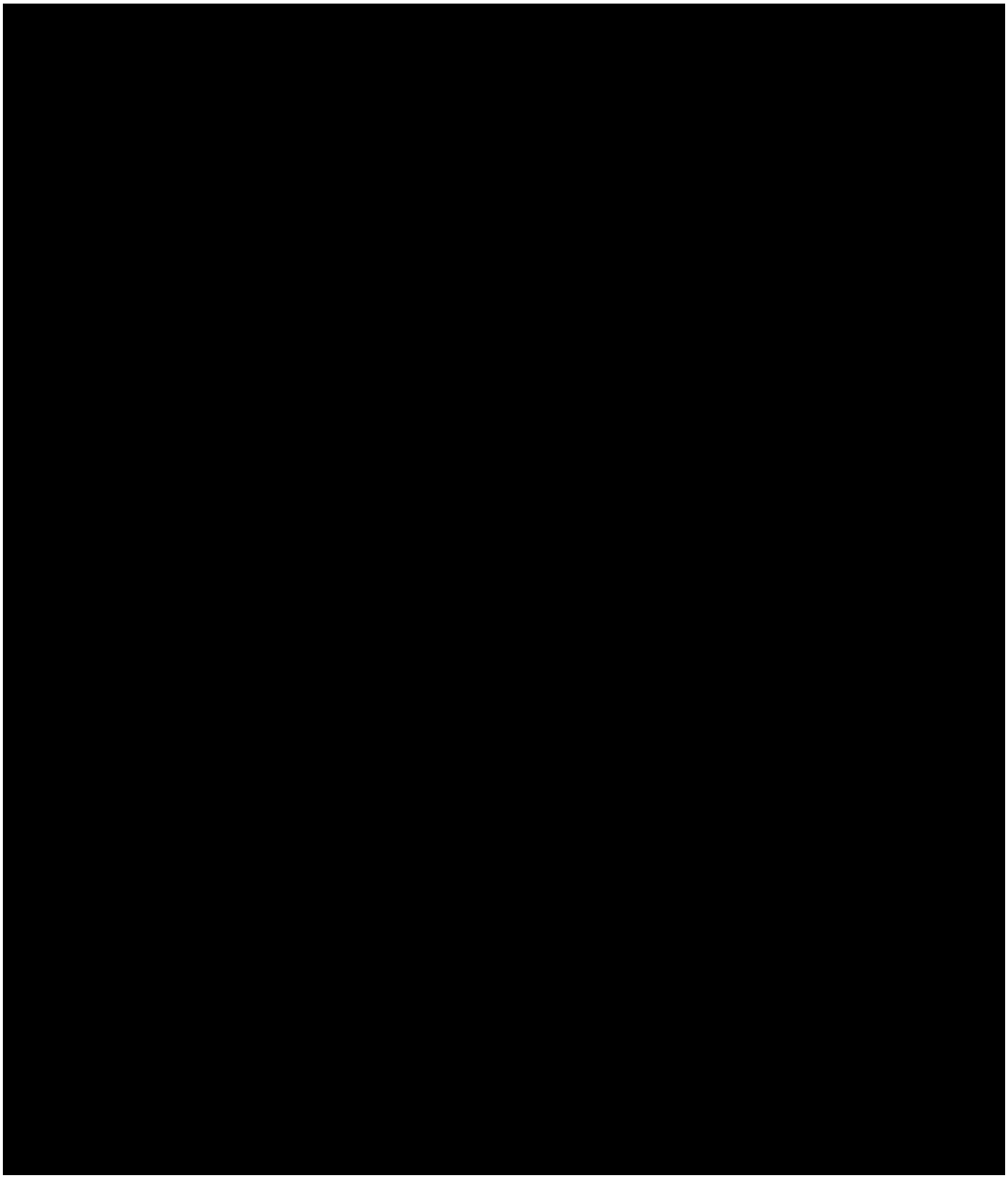
Females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, tubal occlusion, hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. However, all females in this study will undergo a pregnancy test as per Table 1.

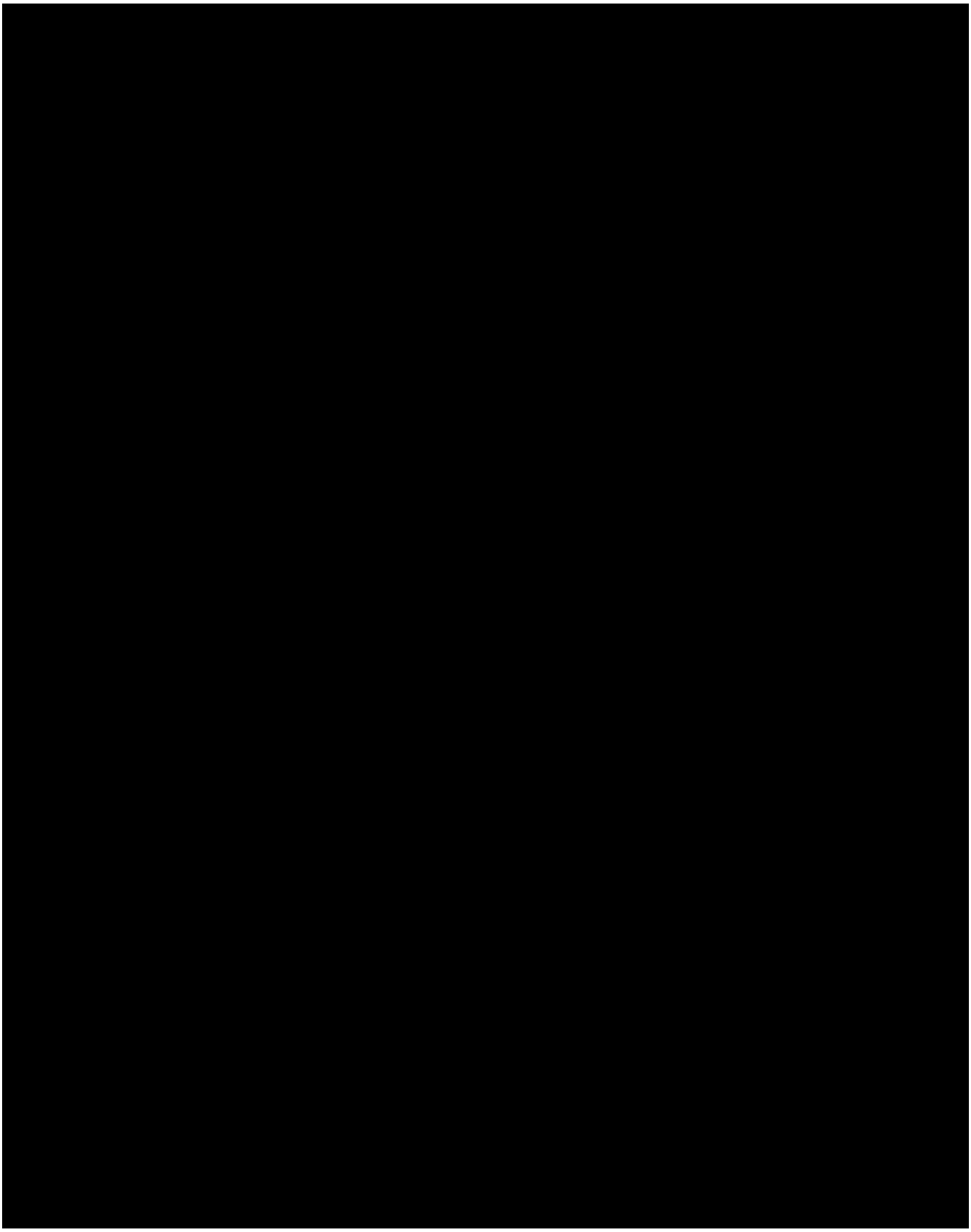
12.1.2 Vital Signs

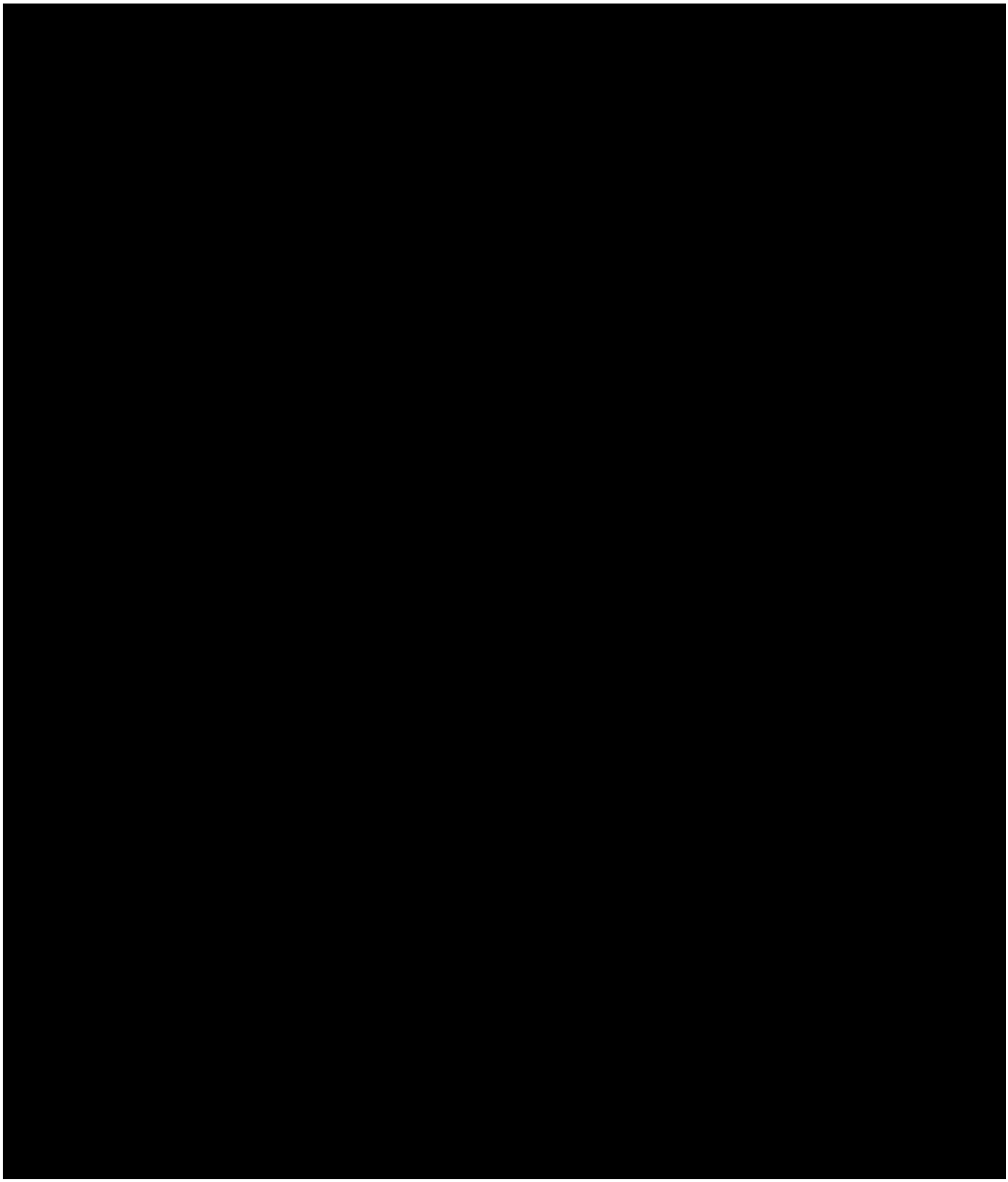
Pulse rate: The patient should be in a resting state (seated) for at least 5 minutes. Pulse will be counted for 30 seconds, multiplied by 2, and recorded in beats per minute.

Systolic and diastolic blood pressure: blood pressure will be measured in the same arm each time using a sphygmomanometer with the patient in resting state (seated) for at least 5 minutes. Blood pressure will be recorded in millimeters of mercury (mm Hg).









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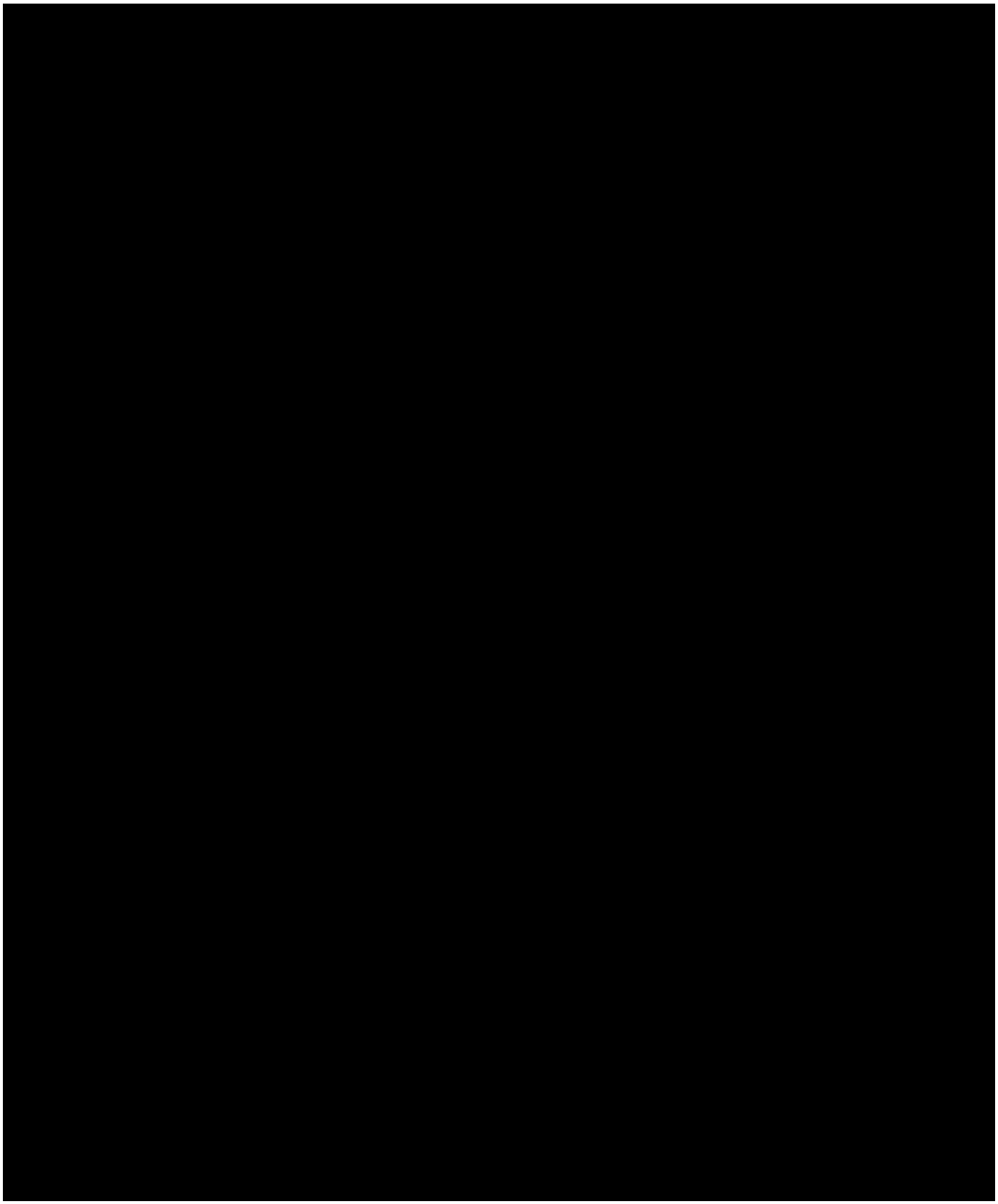

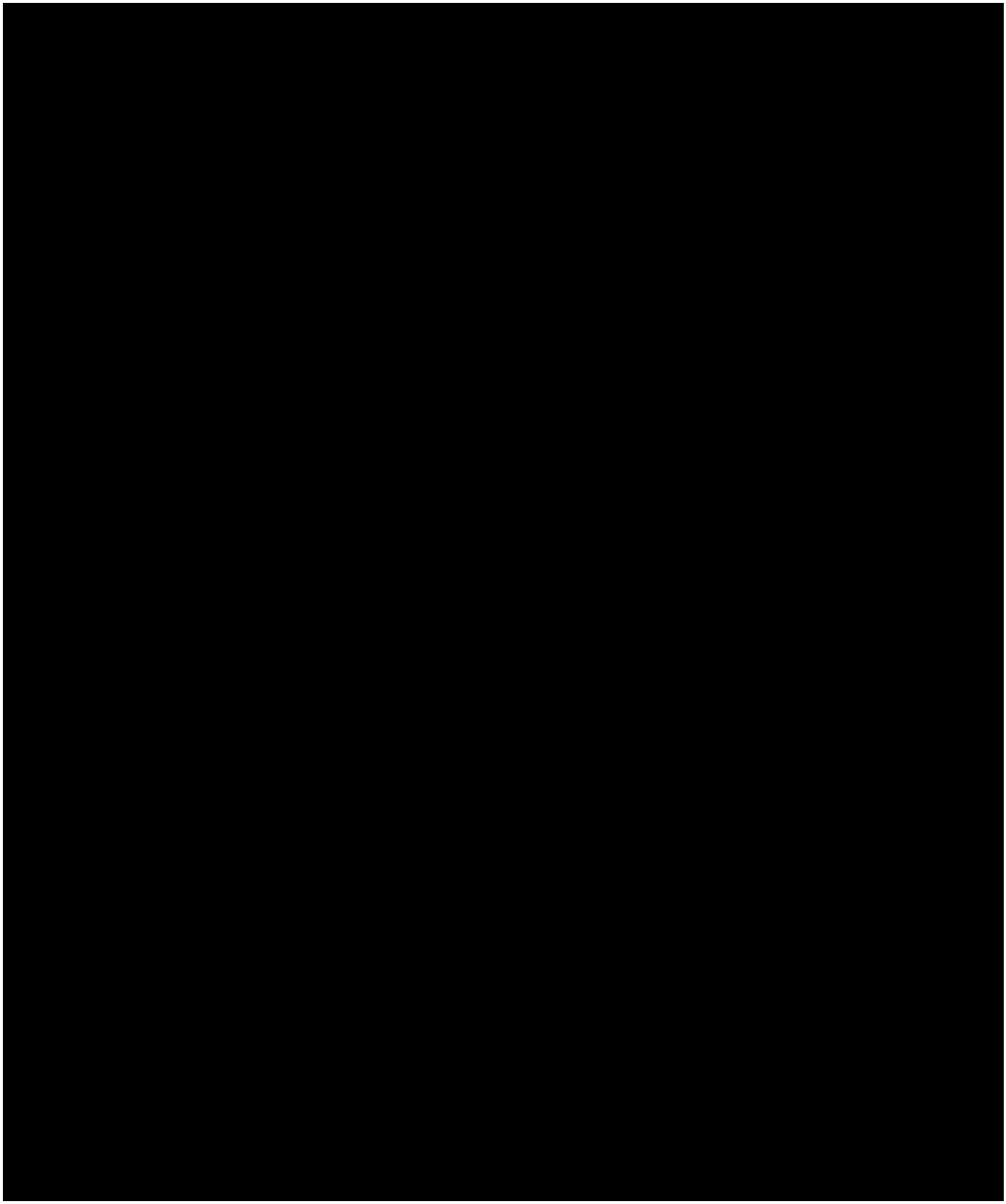

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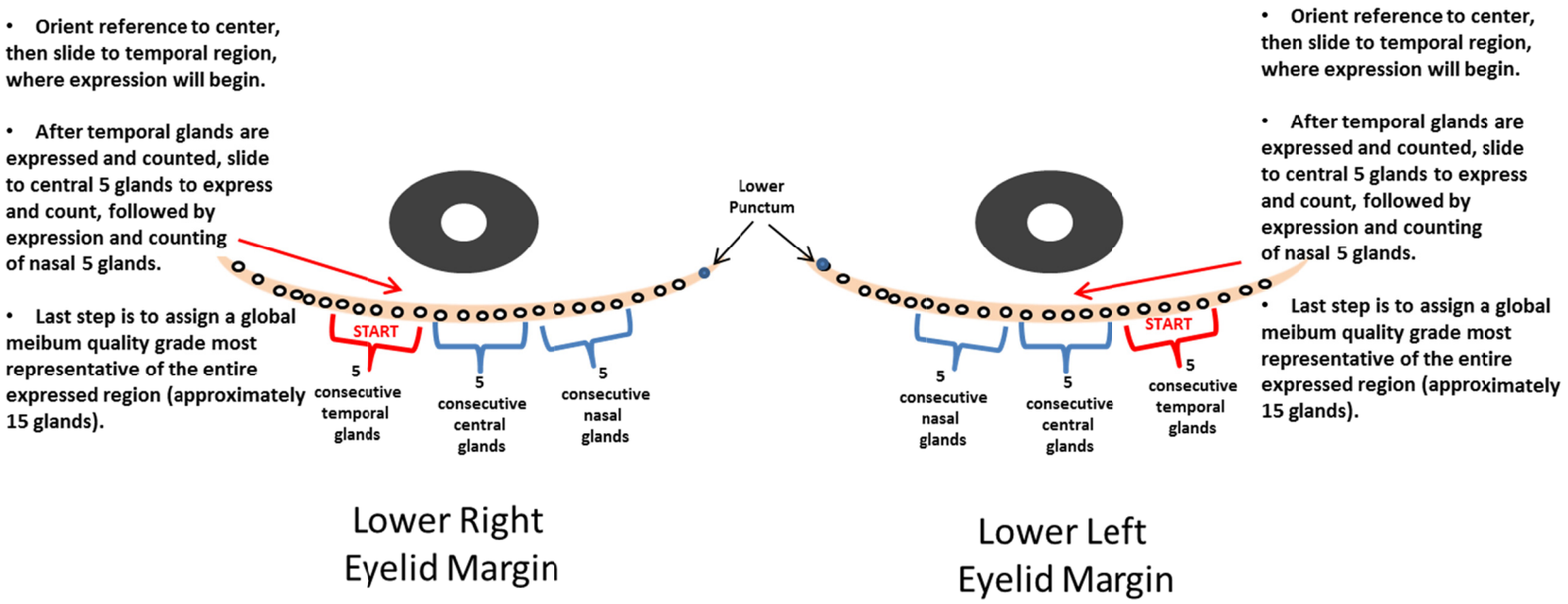

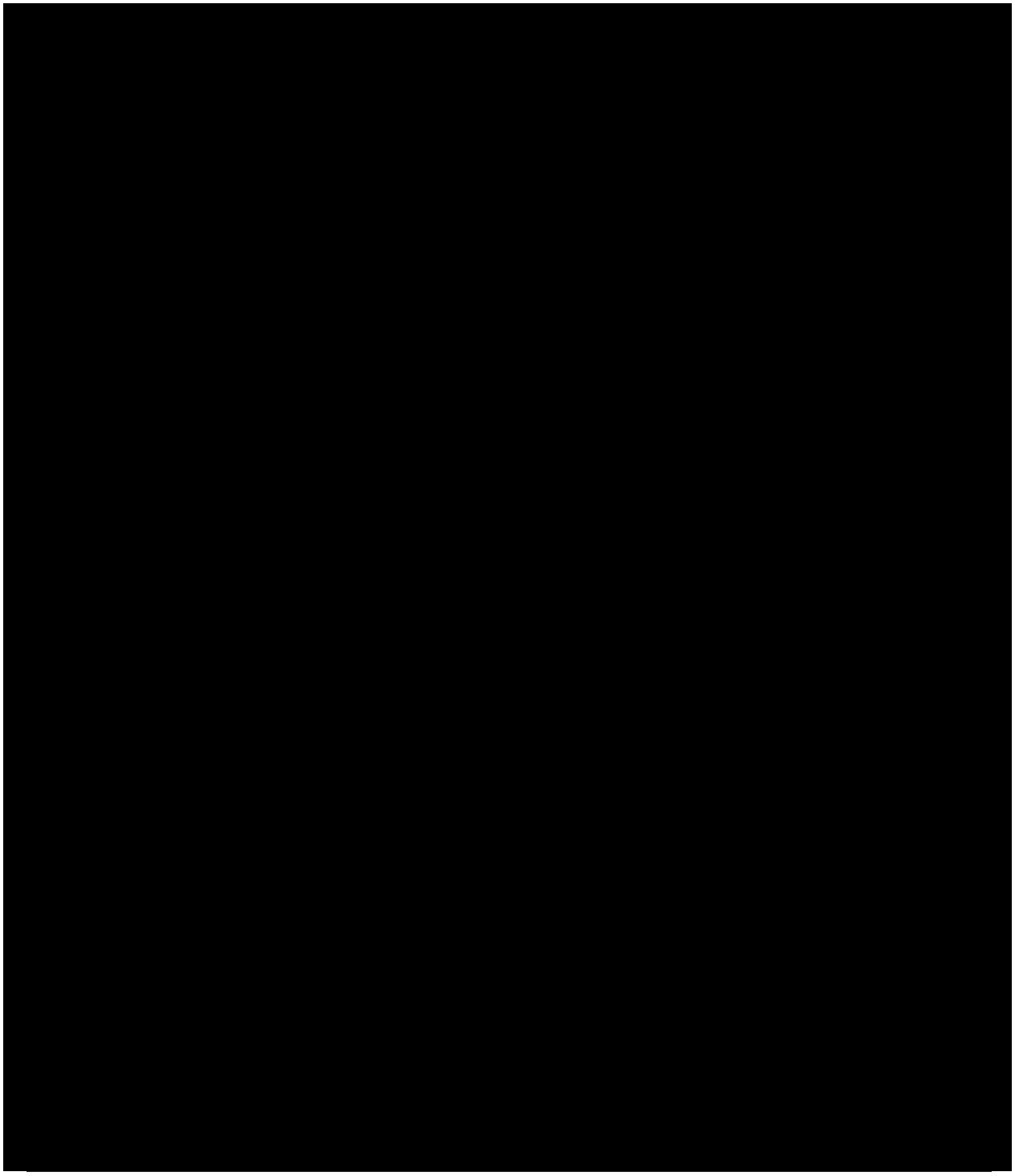

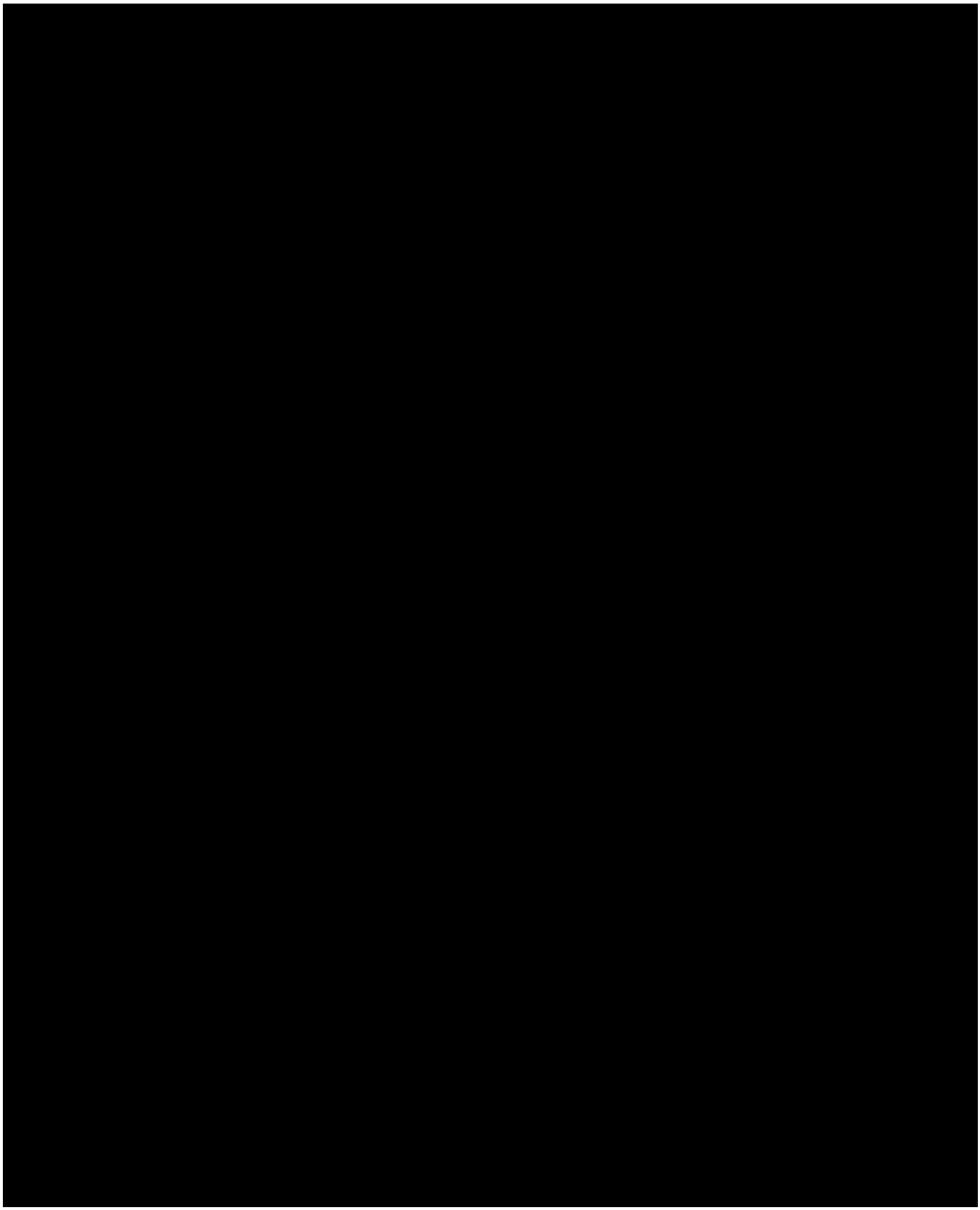

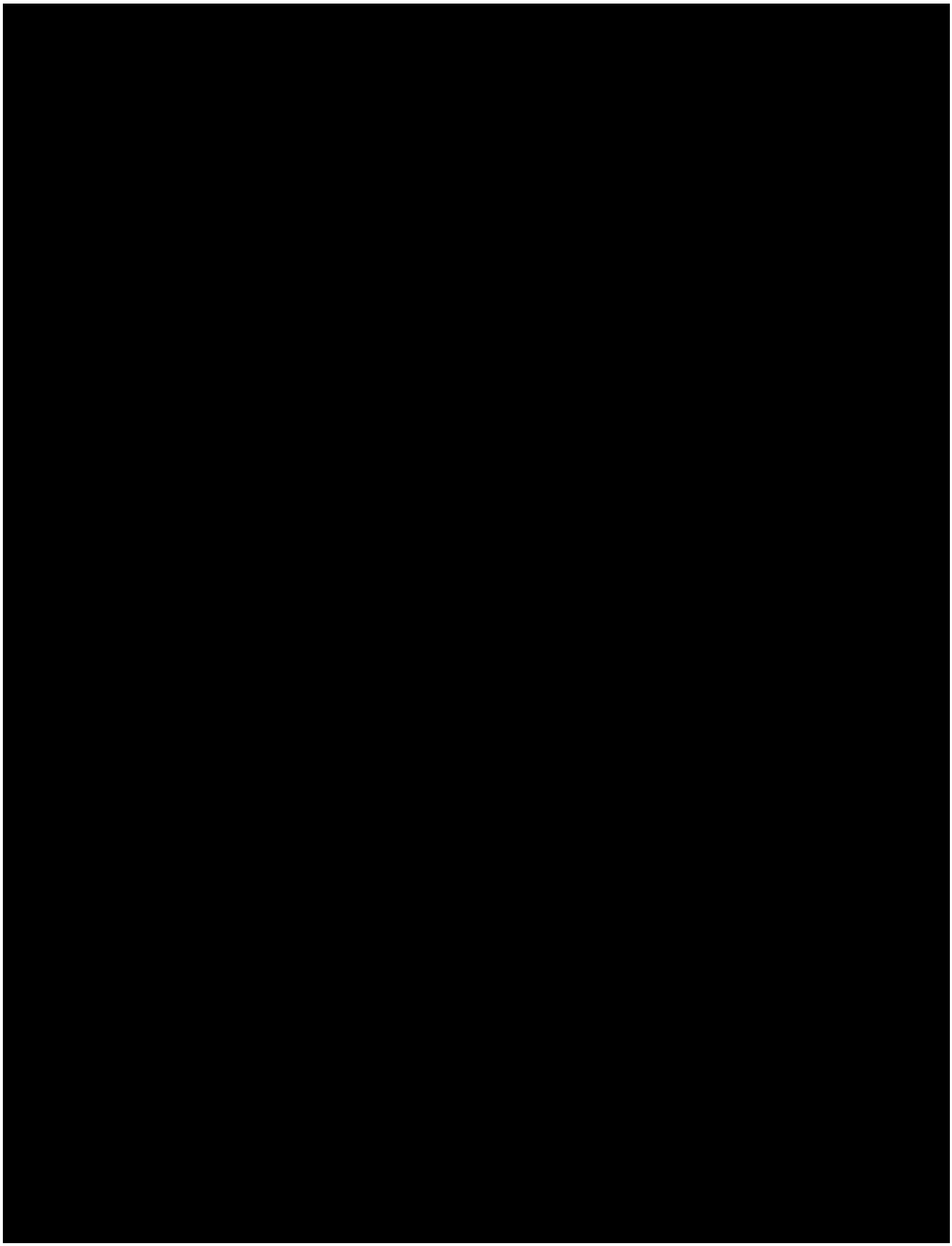

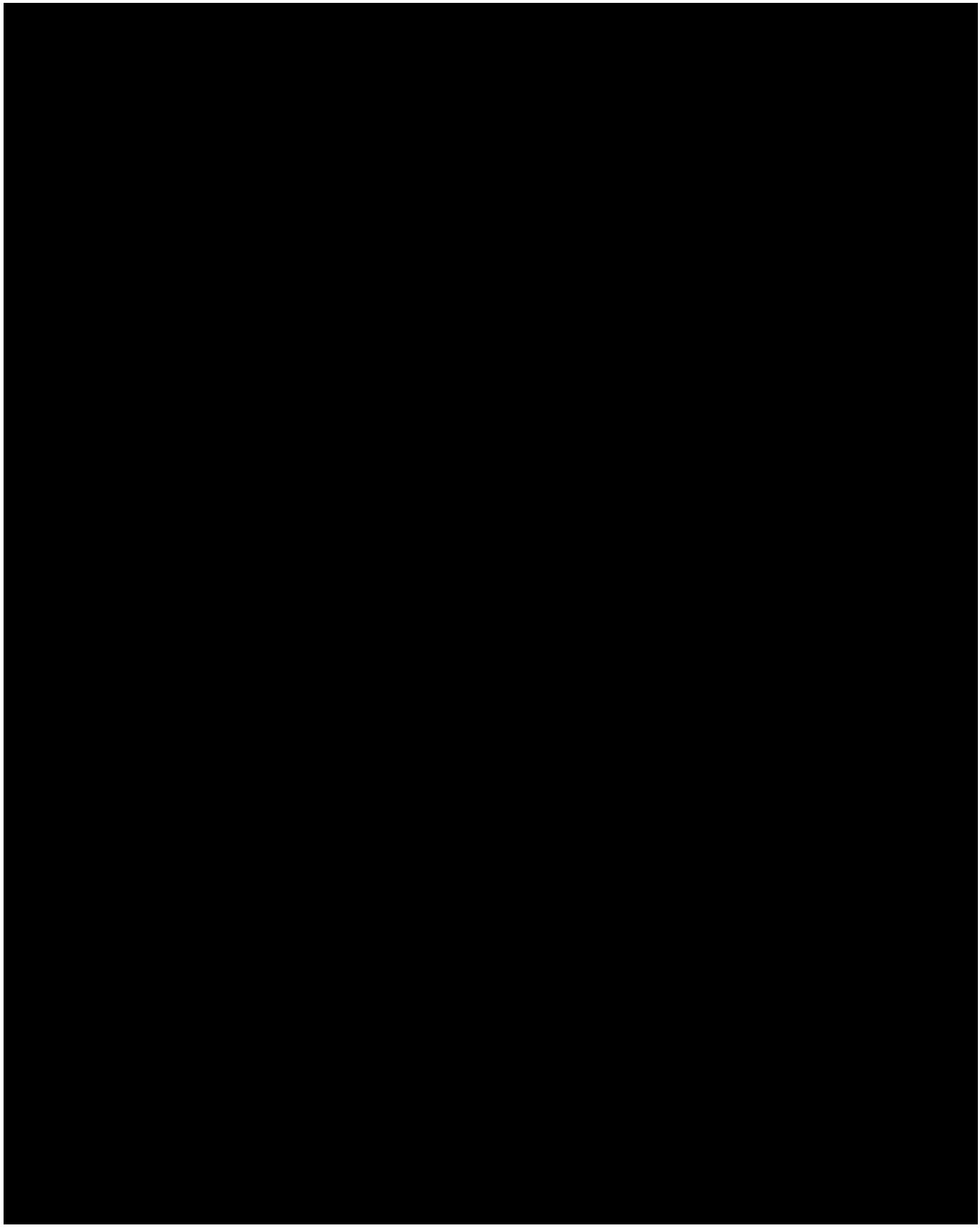

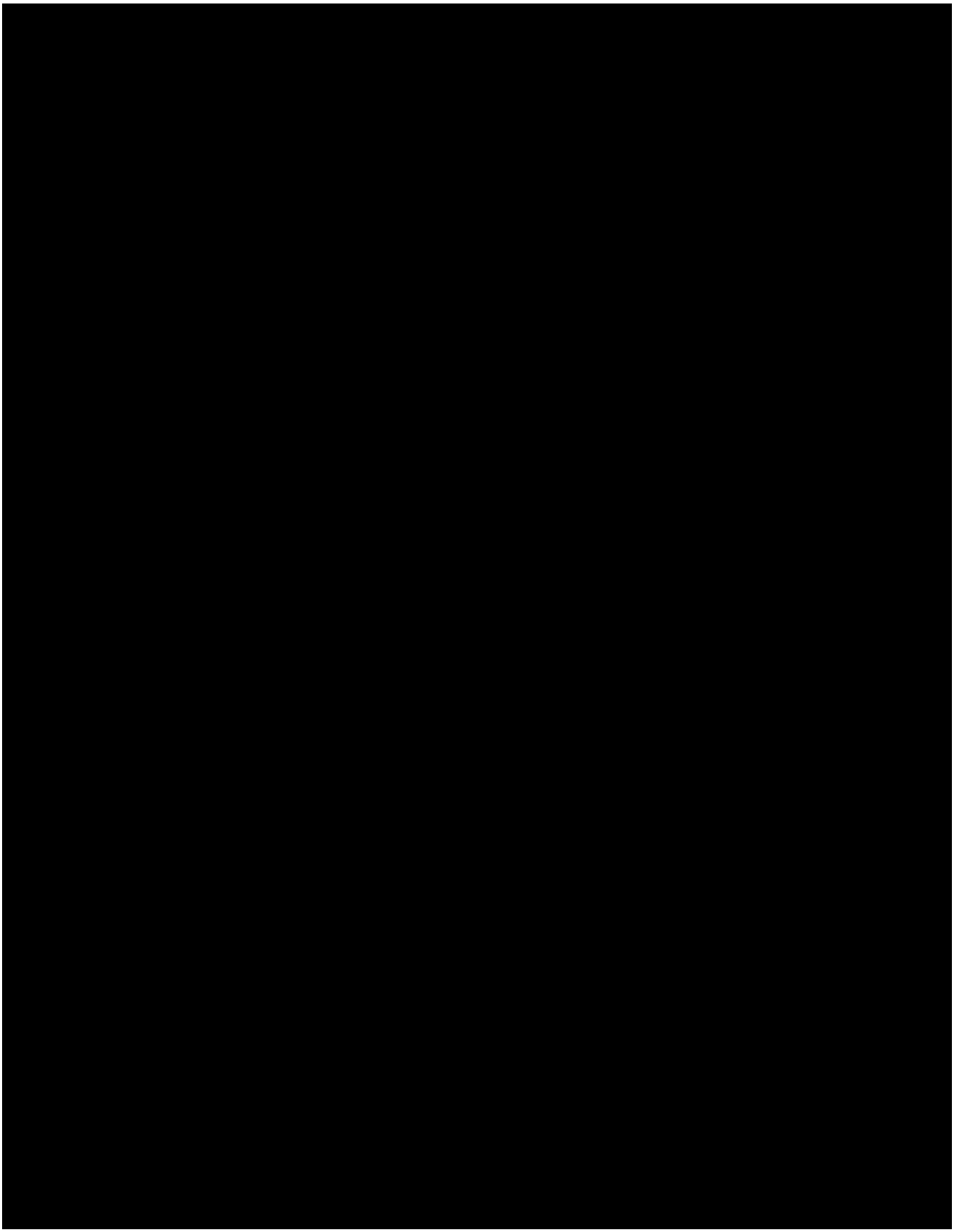

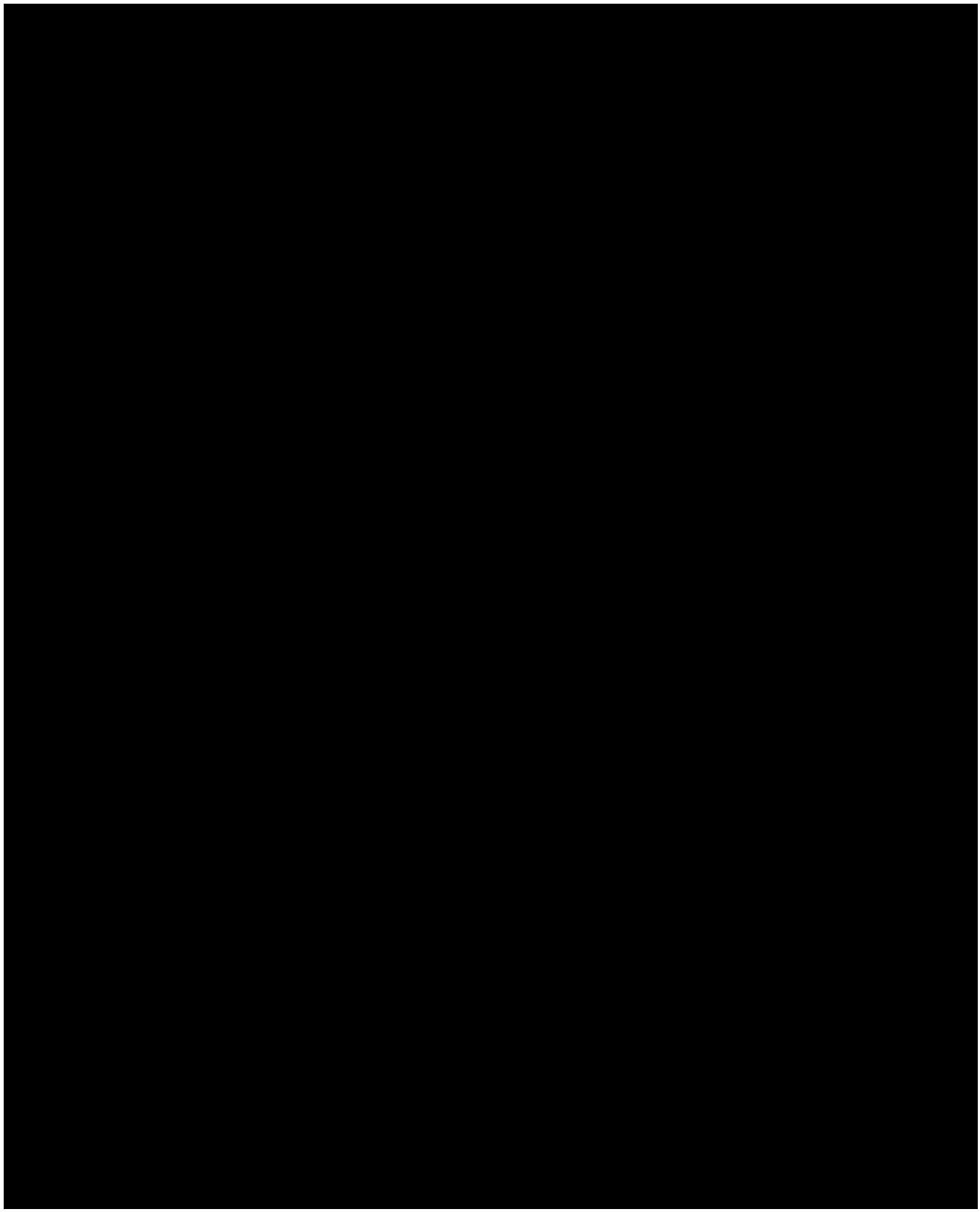

12.1.15 Blood and Urine Samples for Blood Chemistry and Urinalysis

Laboratory specimens for blood chemistry panel, hematology including complete blood count with differential, and urinalysis will be sent to a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification) to be assayed using validated methods. All blood and urine samples will be stored at the centralized clinical laboratory following testing, and will be discarded after a time period indicated by Allergan. Allergan shall have full ownership rights to any biological specimens/samples derived from the study. The following analyses will be performed by the central laboratory:

- Hematology parameters will include hematocrit, hemoglobin (Hb), HbA1c, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count, and differential (neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils).
- Serum chemistry parameters will include albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, bicarbonate, calcium, chloride, creatinine, creatine kinase, direct bilirubin, glucose, indirect bilirubin, magnesium, phosphorous, potassium, sodium, total bilirubin, total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides, total protein, urea nitrogen, uric acid
- Urine will be analyzed for specific gravity, pH, color, protein, glucose, blood, bilirubin, and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts, and crystals).
- PSA for male patient samples only

12.1.16 Blood Sample Collection for Pharmacokinetic Analysis

Blood samples obtained for selected patients for pharmacokinetic analysis will be processed and stored frozen until shipped to a facility for analysis.

Prior to the start of collection, sites must ensure that all required pre-labeled tubes are available for each collection timepoint as described in the Blood Sample Collection for Pharmacokinetic Analysis Procedures Manual.

For each collection timepoint, the investigator will draw approximately 3 mL of blood.

12.2 Glossary of Abbreviations

Term / Abbreviation	Definition
[redacted]	[redacted]
ADDE	aqueous deficient dry eye
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AP	analysis plan
BCVA	best-corrected visual acuity
BID	twice-daily administration
CMH	Cochran-Mantel-Haenszel
DED	dry eye disease
[redacted]	[redacted]
eCRF	electronic case report form
EDE	evaporative dry eye
GnRH	gonadotropin-releasing hormone
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
IxRS	automated interactive (telephone or web) response system
KCS	keratoconjunctivitis sicca
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LOCF	last observation carried forward
LogMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MGD	meibomian gland dysfunction
NE	non-expressible
NSAID	nonsteroidal anti-inflammatory drug
OODS	overall ocular discomfort score
OSDI	Ocular Surface Disease Index
PK	pharmacokinetic

Term / Abbreviation	Definition
PP	per-protocol
PSA	prostate-specific antigen
RBC	red blood cell
SAT	study artificial tears
SHBG	sex hormone-binding globulin
TBUT	tear film break-up time
US(A)	United States (of America)
WBC	white blood cell

12.3 Protocol Amendment Summary

Title: Topical Ophthalmic AGN-195263 for the Treatment of Evaporative Dry Eye

Protocol 195263-010 Amendment 1

Date of Amendment: October 2016

Amendment Summary

This summary includes changes made to Protocol 195263-010 (29 July 2016). Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Summary/Study Design	Study artificial tears (SAT) will be used twice daily for 6 days following the standardization (day -21) visit	Clarification of 6 days, not 7, as SAT are prohibited 24 hours prior to any study visit.
Protocol Summary/Key Exclusion Criteria	Hormone replacement therapy will be permitted so long as dosing has been stable for 90 days prior to the standardization visit and is anticipated to remain stable throughout the study.	Revised to be consistent with previous phase 2 study 195263-006.
Protocol Summary/Key Exclusion Criteria	Use of oral or topical corticosteroids in the eyes or eyelids will be prohibited within 60 days of the standardization visit and until the month 6 visit.	Revised from a window of 30 days to be consistent with previous phase 2 study 195263-006.
Table 1 Schedule of Procedures	Order of procedures: IOP measurement moved to after staining, Schirmer's, and lower lid margin meibomian gland evaluation. Ophthalmoscopy moved to follow IOP measurement.	To minimize possible effects of ocular contact from IOP measurement on Schirmer's and staining.
Section 4.3/ Inclusion Criteria	Inclusion criterion #11 expanded to include additional treatments for dry eye disease or meibomian gland disease.	To broaden criteria to include use of pharmacologic treatments for dry eye or meibomian gland disease.
Section 4.5.1/ Permissible Medications	Inhaled corticosteroids must be stable for at least 60 days prior to the standardization visit and until the month 6 visit. Dermal and nasal corticosteroids will be permitted as needed.	Revised to accommodate chronic inhaled corticosteroid use, and clarified that dermal corticosteroids, in addition to nasal, will be permitted as needed.
Section 4.4/ Exclusion Criteria	Lifitegrast (Xiidra) and any other therapeutic treatments for dry eye prohibited 60 days prior to the standardization visit through month 6 visit.	Updated to exclude this recently marketed treatment for dry eye, and any therapeutic treatments which may be approved during the course of the study.
Section 4.4/	Exclusion criterion #29 added to	To exclude procedures that may confound hair

Section	Revision	Rationale
Exclusion Criteria	exclude hair weaves and scalp hair transplants.	growth evaluations.
Section 4.4/ Exclusion Criteria	Exclusion criterion #30 added to outline prohibited female hair removal practices and windows around study visits.	To exclude procedures that may confound hair growth evaluations.
Section 7.2.3/ Other Efficacy Variables	Expanded other efficacy variables to include change from baseline assessments of corneal and conjunctival staining scores, upper and lower lid margin appearance measures, global meibum quality scores, and ocular symptom scores	Addition of exploratory analyses.

ALLERGAN

Protocol 195263-010 Amd 1

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]