NCT02780115

Study ID: 199201-010

Title: A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN-199201 and AGN-190584 in Patients With Presbyopia

Protocol Amendment 3 Date: 18Aug2016

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STUDY TITLE

A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN-199201 and AGN-190584 in Patients With Presbyopia

Protocol Number:	199201-010 Amendment 3
Phase:	2
Name of Investigational Products:	AGN-199201 (oxymetazoline hydrochloride ophthalmic solution) and AGN-190584 (pilocarpine hydrochloride ophthalmic solution)
Emergency Telephone Number(s):	Refer to the Study Contacts Page
Serious Adverse Event Reporting:	[redacted]
Allergan Medical Safety Physician Contact Information:	[redacted]
Allergan Signatory:	[redacted]

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

Approval Date: 18-Aug-2016

The following information can be found on FDA Form 1572 and/or study contacts page: 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 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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[redacted]

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Protocol Summary

Study Compounds:

AGN-199201 (oxymetazoline hydrochloride [HCl] ophthalmic solution) [redacted]

AGN-190584 (pilocarpine HCl ophthalmic solution) [redacted]

Phase: 2

Study Objectives:

- To evaluate the safety, efficacy, and tolerability of fixed combinations of AGN-199201 and AGN-190584 over a 42-day observation period when administered bilaterally, once daily (QD) for 28 days in patients with presbyopia
- To compare the safety, efficacy, and tolerability of a fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] when administered monocularly to the nondominant eye versus bilaterally over a 42-day observation period with QD dosing for the first 28 days in patients with presbyopia
- To assess the systemic pharmacokinetics of AGN-199201 [redacted] and AGN-190584 [redacted] following single and multiple (QD for 28 days) ophthalmic administrations as a fixed combination in 1 or both eyes (OU), by analysis of plasma drug concentration-time profiles (maximum observed plasma concentration-time [C_{max}], time to maximum observed plasma concentration-time [T_{max}], area under the plasma concentration curve from time 0 to the last timepoint [$AUC_{0\text{-}tlast}$], and area under the plasma concentration-time curve from time 0 to infinity [$AUC_{0\text{-}inf}$])
- To evaluate the psychometric properties of the de novo patient-reported outcome (PRO) instruments developed for this program, including the near vision presbyopia performance tasks and task-based questionnaire under mesopic and photopic conditions, the presbyopia patient satisfaction questionnaire, and the presbyopia impact and coping questionnaire

Clinical Hypotheses:

At least 1 fixed combination of AGN-199201 and AGN-190584 ophthalmic solution dosed bilaterally, QD for 28 days:

1. will demonstrate a significant improvement in uncorrected near visual acuity (UNVA) over vehicle.
2. will demonstrate acceptable safety and tolerability findings.
3. will demonstrate an acceptable pharmacokinetic profile for AGN-199201 and AGN-190584 after single and repeat administrations.

The fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] can be administered either in the nondominant eye only or bilaterally for 28 days in patients with presbyopia without any significant difference in the observed safety, efficacy, tolerability, or pharmacokinetic profiles.

Study Design:

Structure: Multicenter, double-masked, randomized, parallel-group, vehicle-controlled

Duration: 38 to 65 days per patient

Study Treatment Groups: See Table 1.

Group 1: Vehicle Control, OU

Group 2: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted] OU

Group 3: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted], OU

Group 4: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted] OU

Group 5: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted], nondominant eye and vehicle to the dominant eye

Table 1 Study Treatment Groups

Group	AGN-199201 (%)	AGN-190584 (%)	Dosing
1	Vehicle control	Vehicle control	OU
2	[redacted]	[redacted]	OU
3	[redacted]	[redacted]	OU
4	[redacted]	[redacted]	OU
5[a]	[redacted]	[redacted]	Nondominant eye

OU = both eyes

[a] Dominant eye dosed with vehicle

Dosage/Dose Regimen: This study will be a controlled comparison of fixed combinations of AGN-199201 and AGN-190584 at different concentrations and vehicle dosed in OU, and the fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] dosed in OU or in the nondominant eye only. Study medication will be administered QD in the morning. During office visits 1 through 5, study medication will be administered at hour 0 (8 AM ± 1 hour).

Patients receiving the fixed combination of AGN-199201 and AGN-190584 bilaterally will instill a single drop of the fixed combination drug into each eye. Patients receiving the fixed combination of AGN-199201 and AGN-190584 in the nondominant eye only will instill a single drop of the fixed combination drug into the nondominant eye and a single drop of the vehicle into the dominant eye. Patients receiving vehicle bilaterally will instill a single drop of the vehicle into each eye (see Table 1, Table 2, Table 3, Table 4, and Table 5).

Randomization/Stratification: At the baseline visit (visit 1), patients will be randomized in a 1:1:1:1:1 ratio into 1 of the 5 study groups. Randomization will be stratified by age (2 groups: ≤ 50 and > 50) and iris color (2 groups: brown and not-brown) at the baseline visit. Approximately two-thirds of the enrolled patients will be ≤ 50 years old.

Visit Schedule:

- Screening visit
- Dosing period: each of the 5 parallel groups will have 28 (± 3) days of dosing as shown in Figure 1
- Follow-up period: following the dosing period, all patients will be seen for a 14 (± 2)-day follow-up period as shown in Figure 1

[redacted]

Study Population Characteristics:

Number of Patients: Approximately 150 patients (30 per group) will be enrolled at approximately 15 sites in the United States (US). Approximately 26 patients per group are expected to complete the study based on an anticipated dropout rate of less than 12.5% (4 dropped patients per group).

Condition/Disease: The study population consists of adult patients who have objective and subjective evidence of presbyopia.

Key Inclusion Criteria:

- Male or female, between 40 and 55 years of age
- [redacted]
- Natural or corneal laser refractive surgery corrected [redacted] at distance with presbyopia in each eye and subjective complaints of poor near vision that impact activities of daily living, [redacted]
- [redacted]

Key Exclusion Criteria:

- Concurrent use of any topical ophthalmic medications, including artificial tears, other than the study medications during the course of the study
- Presence of any ocular condition that, in the opinion of the investigator, could affect the safety of the patient or interpretation of efficacy parameters (eg, uveitis)
- Dry eye disease (defined as total corneal staining ≥ grade 2 on the 5-point Oxford scale, or Schirmer's score [with anesthesia] < 8 mm in 5 minutes) at the screening visit

- Corneal abnormalities [redacted] in either eye that are likely to interfere with visual acuity
- History of cataract surgery, phakic intraocular lens [redacted] surgery, corneal inlay surgery, [redacted] or any intraocular surgery; [redacted]

Response Measures:

Primary Efficacy:

- Mesopic, high contrast UNVA

[redacted]

General Statistical Methods and Types of Analyses:

The modified intent-to-treat (mITT) population will be defined as all randomized patients with a baseline and at least 1 postbaseline assessment of mesopic, high contrast UNVA and will be analyzed as randomized. The efficacy variables will be analyzed using the mITT population.

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

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 analysis of covariance (ANCOVA) or 2-sample t-tests. Categorical variables will be summarized by sample size (N) frequency count, and percent and will be analyzed using Pearson's chi-square, Fisher's exact, or the Cochran-Mantel-Haenszel (CMH) test.

There will be no imputation of missing data for all analyses.

Efficacy:

The primary efficacy variable will be the weighted average change from baseline in mesopic, high contrast UNVA lines at day 28 in the nondominant eye. Baseline will be the hour 0 measure at day 1.

Safety:

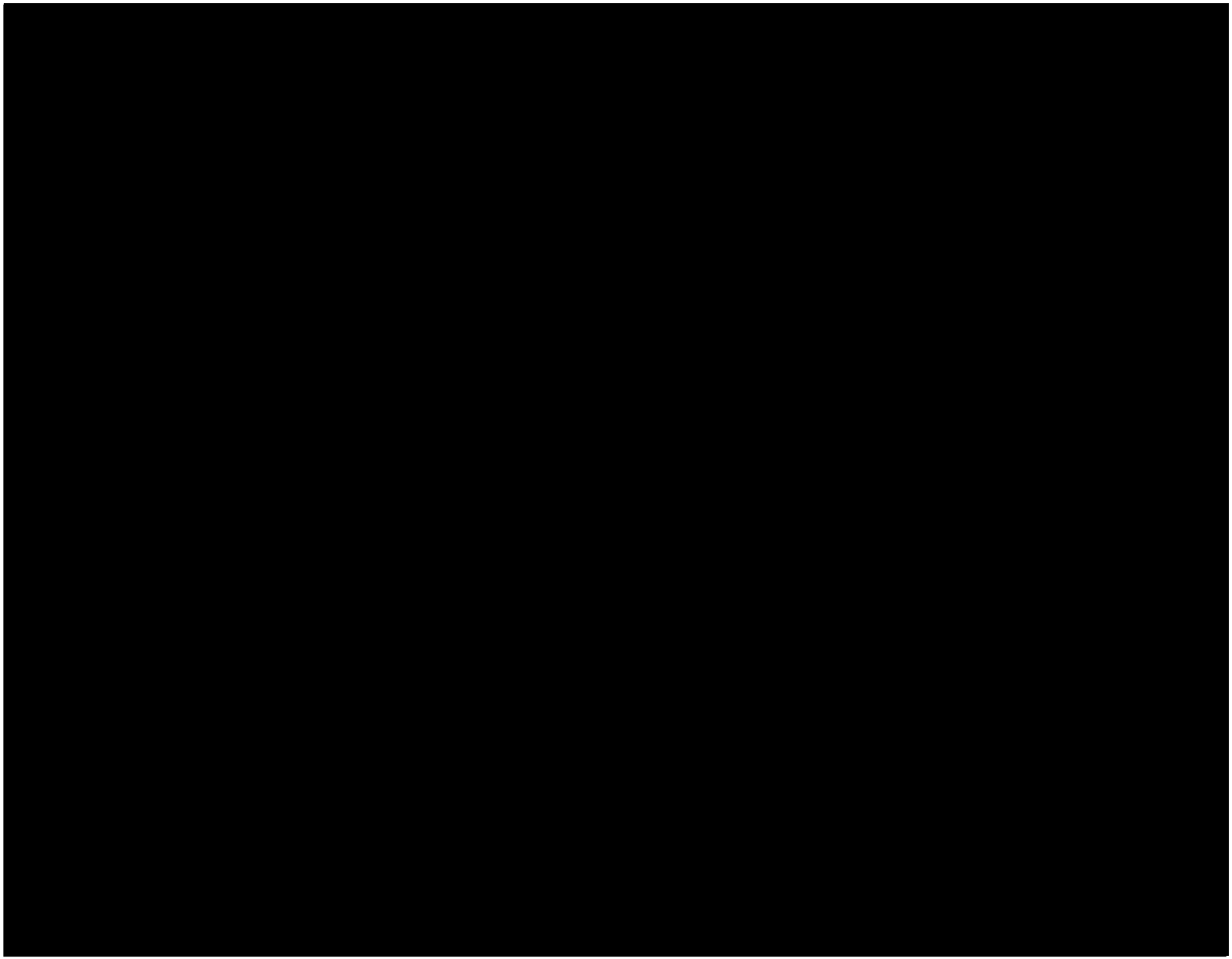
Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Incidence rates of each treatment-emergent adverse event will be summarized by primary system organ class and preferred term. Treatment-emergent adverse events will be events that occur or worsen after the treatment. 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 descriptions of the safety analyses for adverse events and other safety measures will be documented in the analysis plan (AP).

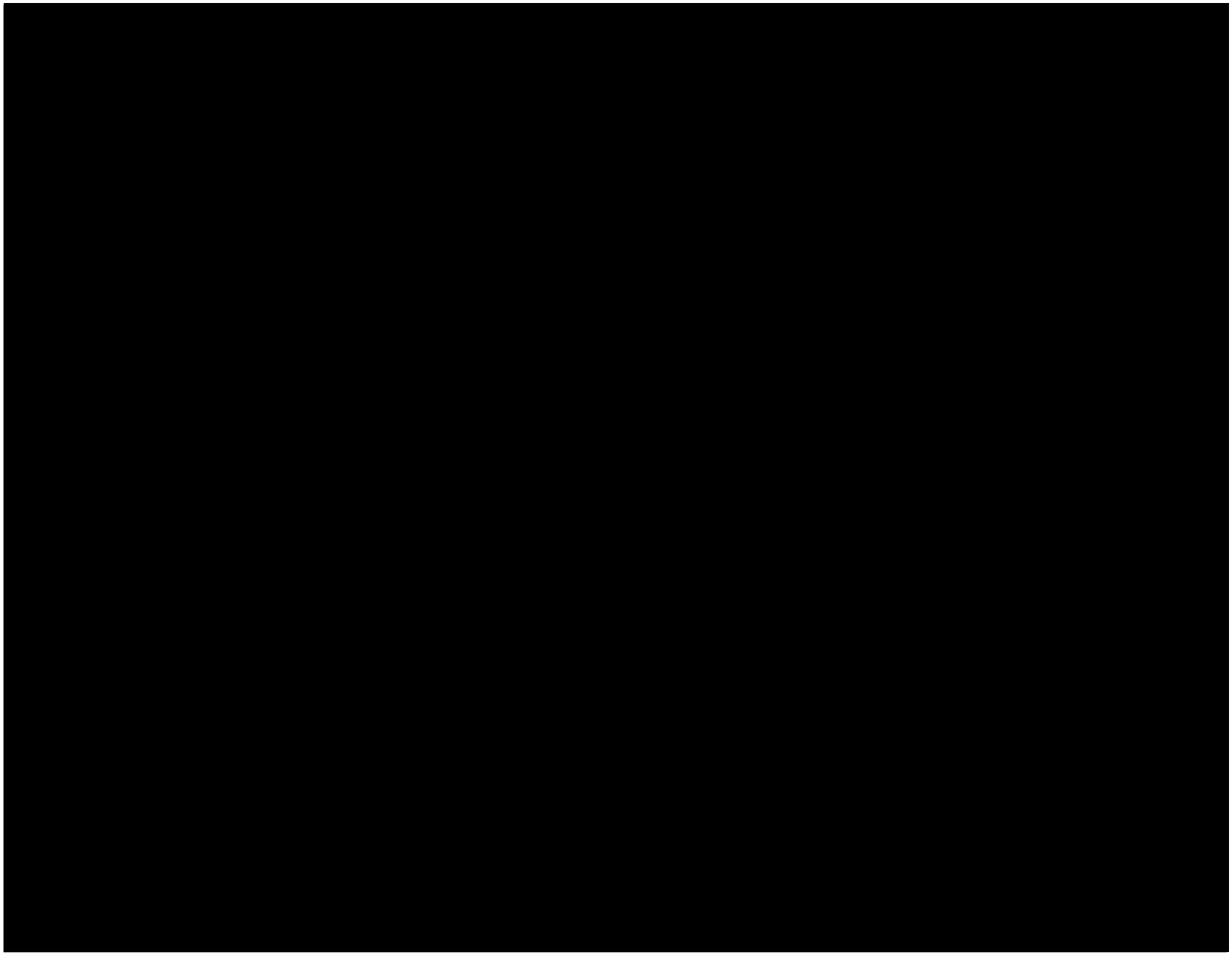
Sample Size Calculation:
A sample size of approximately 150 patients will be randomized in a 1:1:1:1:1 ratio into 1 of the 5 study groups. Approximately two-thirds of the enrolled patients will be younger patients (≤ 50 years old), and one-third of the enrolled patients will be older patients (> 50 years old).

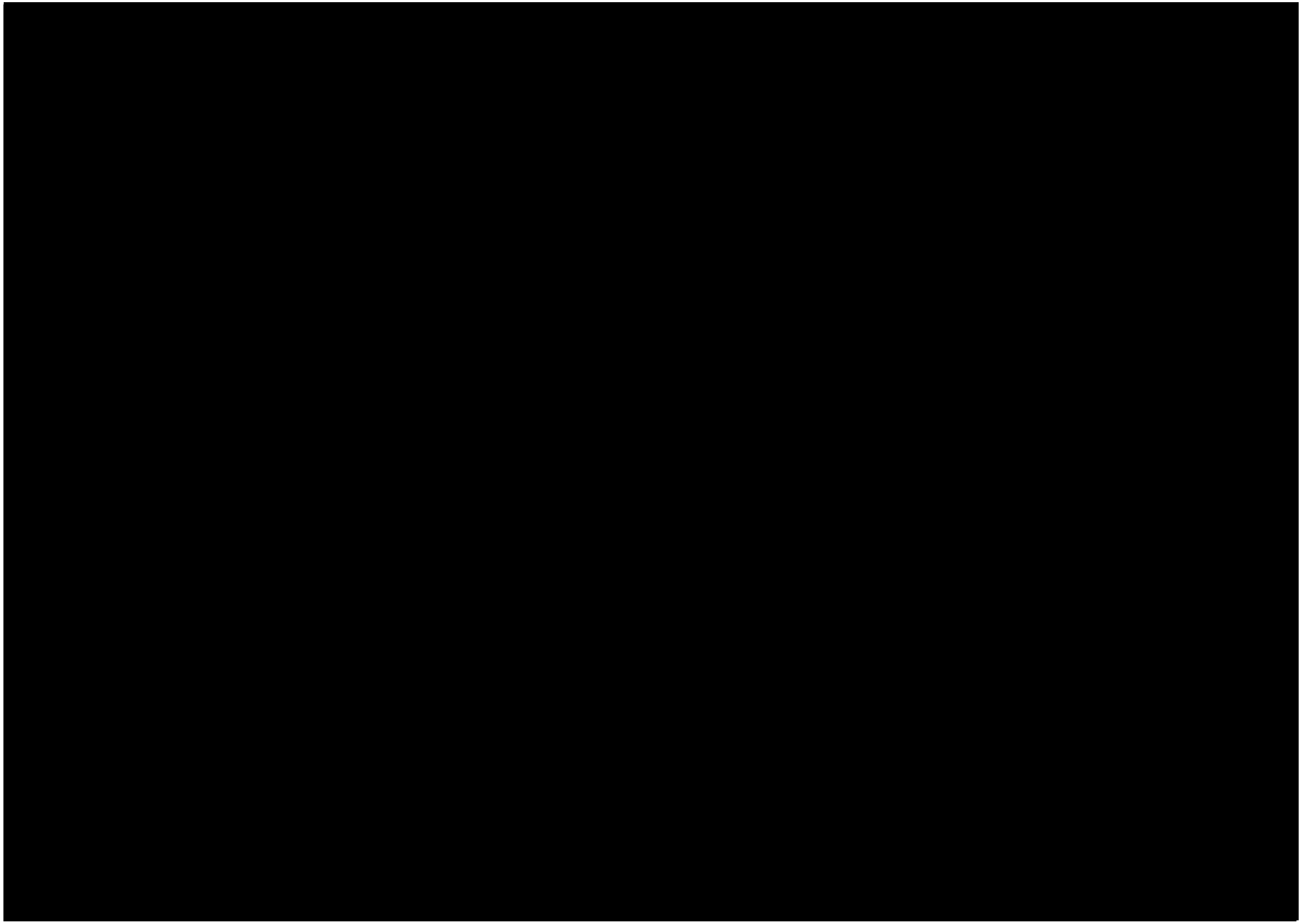
From the Study 199201-007 results, the treatment effect for the younger patients was on average 1.98 lines of change in mesopic, high contrast UNVA, with standard deviations for active and vehicle of 1.12 and 1.01,

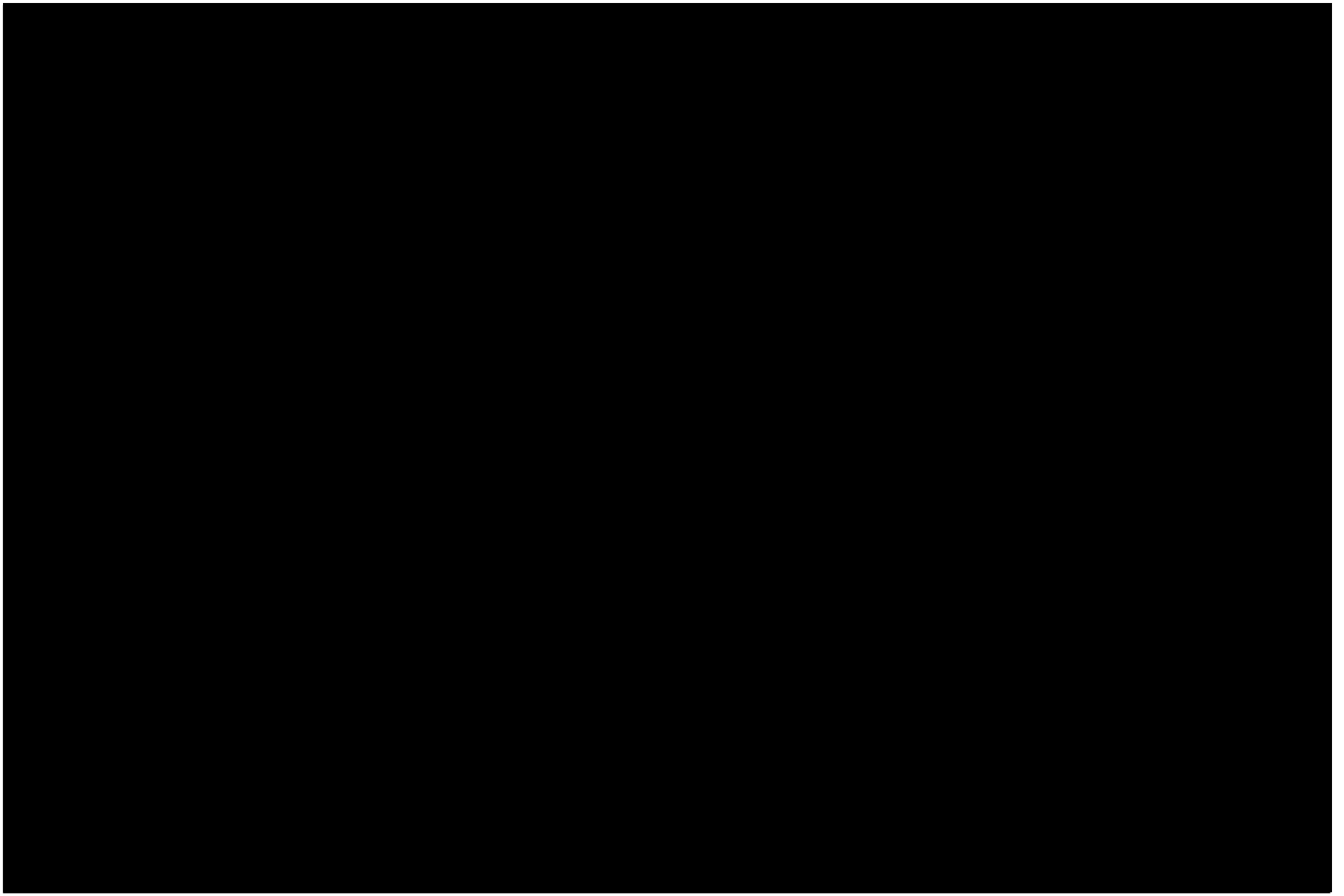
respectively. For older patients, the treatment effect was on average 0.72 lines of change in mesopic, high contrast UNVA with standard deviations for active and vehicle of 1.87 and 1.15 respectively. The treatment effect for the younger patients was on average 1.02 lines of change in photopic, high contrast UNVA, with standard deviations for active and vehicle of 1.42 and 0.67, respectively. For older patients, the treatment effect was on average 0.27 lines of change in photopic, high contrast UNVA, with standard deviations for active and vehicle of 1.10 and 0.93, respectively.

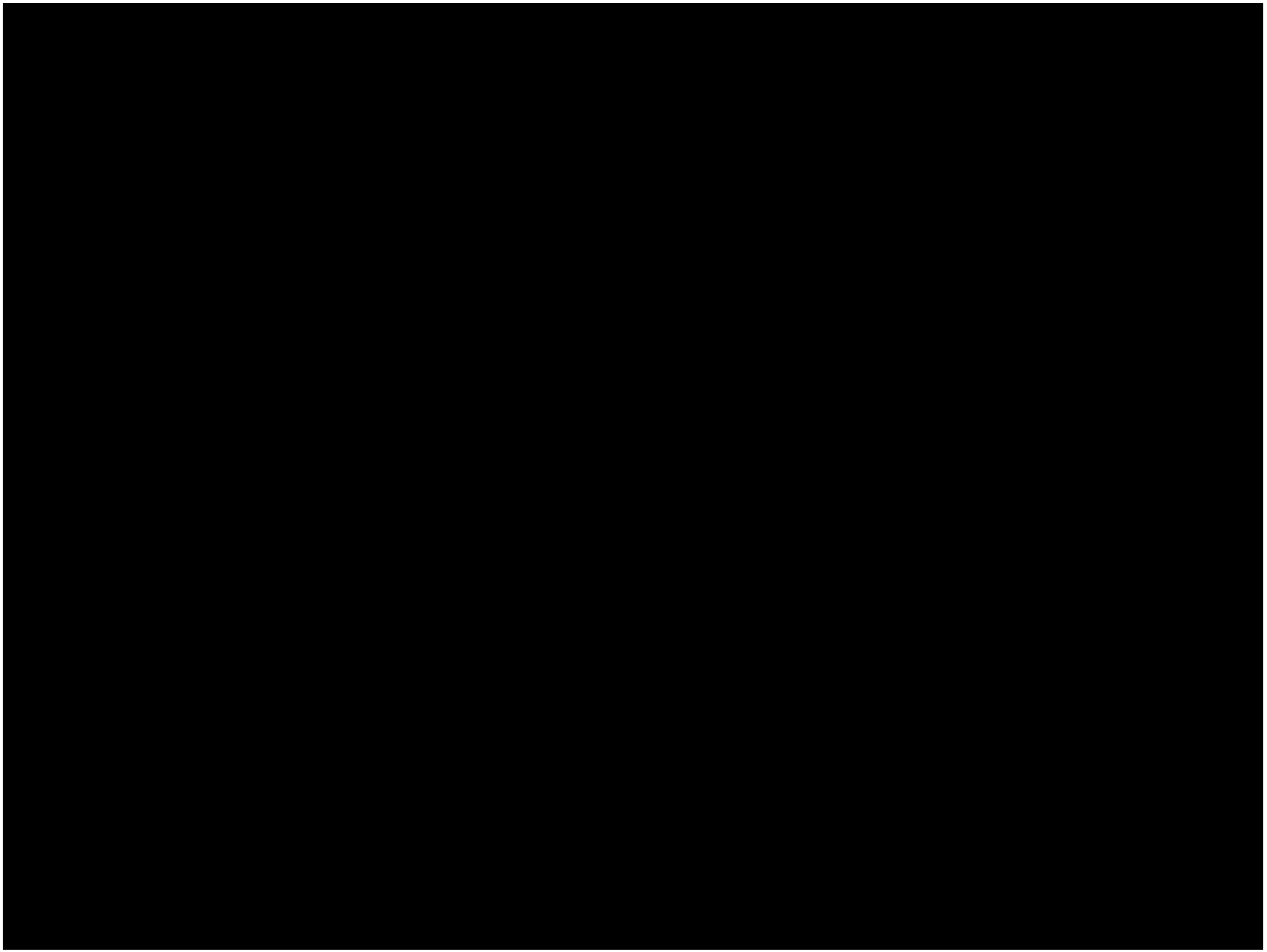
Accounting for a 12.5% dropout rate, 26 patients per treatment group will provide 99% power to observe a difference between an active group and the vehicle group for ≥ 1 line of change from baseline in mesopic, high contrast UNVA and 68% power for ≥ 1 line of change from baseline in photopic, high contrast UNVA, with a type 1 error of 0.05.

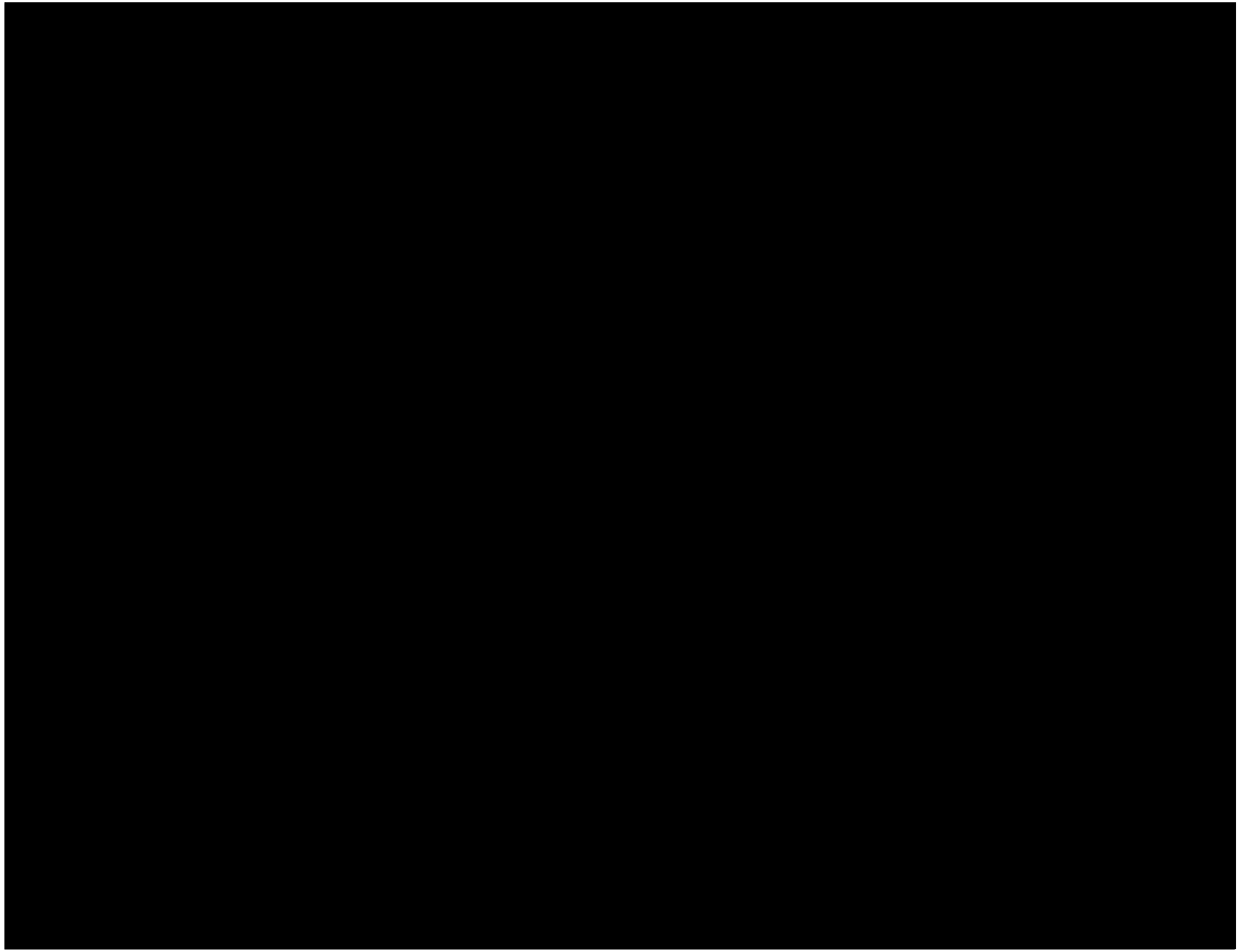












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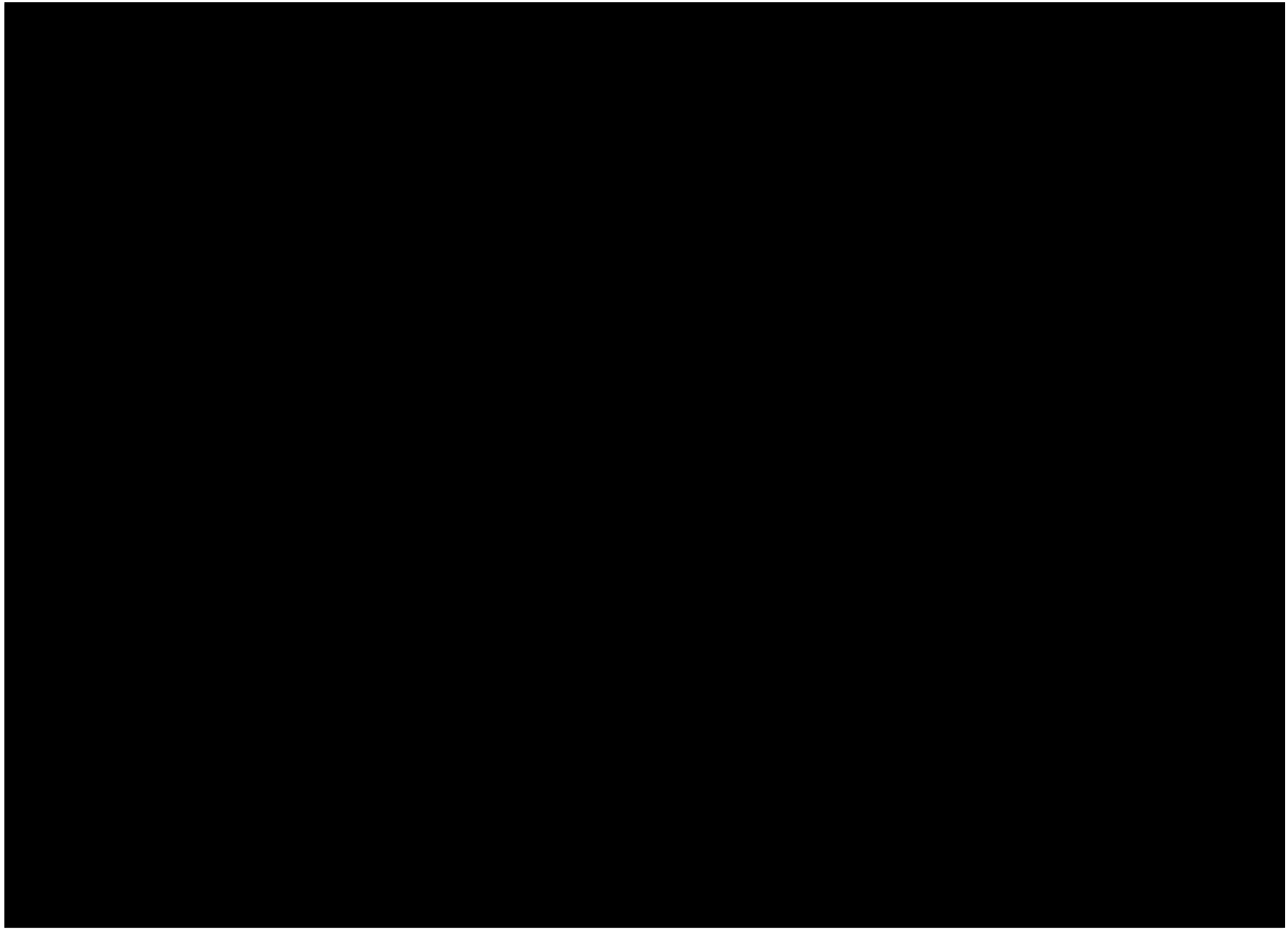


1. Background and Clinical Rationale

1.1 Background

Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with age. The exact cause of presbyopia is not known. The most likely cause of progressive presbyopia is a loss of elasticity of the crystalline lens, although changes in the lens's curvature from continual growth and loss of power of the ciliary muscles have also been postulated to contribute to its pathogenesis (Ostrin and Glasser, 2004; Radhakrishnan and Charman, 2007). The consequence of presbyopia is that the eye's near point (ie, the point nearest the eye at which an object is accurately focused on the retina when the maximum degree of accommodation is employed) gets progressively further away with age. The ability to focus on near objects declines throughout life, from an accommodation of about 20 diopters (D; ability to focus at 50 mm away) in a child, to 10 D at age 25 (100 mm), and plateaus at 0.5 to 1 D at age 60 (ability to focus down to 1 to 2 meters only). The first signs of presbyopia are eyestrain, difficulty seeing in dim light, and problems focusing on small objects and/or fine print and are usually first noticed between the ages of 40 and 50 (Ostrin and Glasser, 2004; Radhakrishnan and Charman, 2007).

Traditional nonsurgical methods of refractive correction for presbyopia include the use of dedicated reading spectacles, bifocal or varifocal spectacles, or monovision or multifocal contact lenses. Multifocal spectacles impair depth perception and edge-contrast sensitivity at critical distances for detecting obstacles in the environment (Lord et al, 2002). Varifocal lenses have a corridor of nondistorted vision. For these reasons, older people are more than twice as likely to fall when wearing multifocal spectacles (Johnson et al, 2007; Lord et al, 2002). More recently, the United States Food and Drug Administration (US FDA) has approved conductive keratoplasty for correction of presbyopia, multifocal intraocular lenses (IOLs) for visual correction of aphakia in adult patients with or without presbyopia, and the KAMRA® inlay for the improvement of near vision in presbyopic eyes. PresbyLASIK and scleral expansion bands (SEBs) have also been evaluated in presbyopia. PresbyLASIK uses laser eye surgery and reshapes the cornea to create a multifocal cornea with 3 zones for near, intermediate, and far distances. Each zone refracts light differently with the intent that the patients will learn to choose the correct zone for a given object's distance. SEBs use 4 thin segments positioned just beneath the surface of the sclera. This creates more space between the circular ciliary muscle around the lens and the lens itself, potentially allowing more tension in the ciliary muscle, leading to greater contraction and greater steepening of the lens curvature for near vision. SEBs have not been found to provide predictable or consistent results in the treatment of presbyopia

(Malecaze et al, 2001). Corneal inlays are placed within the corneal stroma beneath the surface to modify the way the cornea refracts light. The Presby Flexivue Microlens contains a refractive power that adds +1 to +3 D, the ReVision Optics Raindrop induces a change in the central corneal curvature, and the Acufocus KAMRA inlay is a pinhole aperture to facilitate greater depth of focus (Bethke, 2013; García-Lázaro et al, 2012). For each of the existing technologies, visual quality is reduced at 1 or more viewing distances, and each strategy comes with its own unique challenges. For example, zonal bifocals (eg, zonal reading glasses, contacts) produce optical aberrations, and multifocal optics (eg, PresbyLASIK) reduce image quality uniformly at all viewing distances. Thus, there remains a need for a noninvasive, reversible, pharmacological treatment for presbyopia.

Allergan is investigating the development of a noninvasive, reversible, pharmacological treatment for presbyopia based upon a fixed combination of pilocarpine hydrochloride (HCl) (AGN-190584) and oxymetazoline HCl (AGN-199201).

Pilocarpine ophthalmic solutions (1.0% to 4.0%, 1 drop administered to both eyes [OU] up to 4 times daily) are currently used for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, the management of acute-angle closure glaucoma, the prevention of postoperative elevated IOP associated with laser surgery, and for the induction of miosis (New Drug Application [NDA] 200-890, pilocarpine hydrochloride ophthalmic solution).

Pilocarpine is a muscarinic receptor agonist that mimics the actions of the parasympathetic neurotransmitter, acetylcholine, on smooth muscle. This causes 2 effects that enhance near vision: 1) constriction of the iris sphincter muscle, resulting in pupil miosis, and 2) constriction of the ciliary muscle, resulting in central lens steepening and lens accommodation (focusing from distance to near) in humans (as well as in animal models) (García-Lázaro et al, 2012). Reducing the pupil size has long been recognized as an effective way to increase the useful depth of focus, in part by reducing peripheral aberrations (Tucker and Charman, 1975). The current use of pilocarpine ophthalmic solution monotherapy for the treatment of presbyopia is limited by the commonly experienced adverse event of temporal and periorbital headache (ie, brow ache), which is believed to be due to the rapidity of the ciliary muscle contraction. The side effects of pilocarpine monotherapy for treatment of glaucoma can be intolerable due to headache and visual disturbances (blurred vision and visual impairment described as dim, dark, or jumping vision), resulting in a discontinuation rate of approximately 20% to 25% (NDA 200-890; Tsai and Forbes, 2009).

Oxymetazoline HCl is currently approved by the US FDA as over-the-counter (OTC) eye drops under the brand names Visine® LR and Ocuclear® at a concentration of 0.025% for topical (ocular) administration for relief of eye redness due to irritation and conjunctivitis, as well as an OTC nasal spray under the brand name Afrin® at a concentration of 0.05% for topical (intranasal) administration for the treatment of allergic rhinitis.

Oxymetazoline is best known as a potent and selective α1a-adrenoceptor agonist with a half maximal effective concentration (EC_{50}) in the range of 1 to 50 nM (Evans et al, 2011; Horie et al, 1995; Taniguchi et al, 1999). Oxymetazoline is also a nonselective partial α2-adrenoceptor agonist (Audinot et al, 2002; Haenisch et al, 2010; Kukkonen et al, 1998; Pauwels et al, 2000). All selective α1 agonists are vasoconstrictors, which is the basis for their therapeutic activity. In addition to its α-adrenoceptor agonism, oxymetazoline is also a potent serotonin ($5\text{-}HT_1$) receptor agonist. Oxymetazoline was shown to be a full (or partial) agonist of $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, and $5\text{-}HT_{1D}$ receptors and a weak agonist of the $5\text{-}HT_{1C}$ receptor (Schoeffter and Hoyer, 1991). $5\text{-}HT_1$ receptor agonists are also known to have vasoconstrictive properties (Hoyer et al, 1994). $5\text{-}HT_1$ receptors are mostly expressed in the central nervous system (CNS) and some peripheral nerves. Activation of central $5\text{-}HT_{1A}$ receptors are known to trigger the release or inhibition of norepinephrine depending on species, presumably from the locus coeruleus, which then reduces or increases neuronal tone to the iris sphincter muscle by modulation of postsynaptic α2-adrenergic receptors within the Edinger-Westphal nucleus, resulting in pupil dilation in rodents and pupil constriction in primates, including humans (Fanciullacci et al, 1995; Prow et al, 1996; Yu et al, 2004). A population of $5\text{-}HT_{1A}$ receptors are present in the rabbit and human ciliary processes (Chidlow et al, 1995; Yang and Latt, 1998), suggesting that oxymetazoline could directly affect lens accommodation.

$Alpha_1$ agonists are frequently coadministered with local anesthetics to delay anesthetic absorption, reduce anesthetic dosage, prolong anesthesia, and reduce systemic side effects (Burchum and Rosenthal, 2016). These effects are attributed to $alpha_1$-mediated vasoconstriction at the site of anesthetic administration. Thus, coadminstration of oxymetazoline with pilocarpine may prolong pilocarpine's duration of effect, allow for less pilocarpine administration that could improve its tolerability and enhance its ocular penetration, modulating its effect on accommodation.

Samson and colleagues (1980) evaluated the safety of oxymetazoline 0.025% in 20 normal patients and determined that topical ocular administration resulted in a small, clinically insignificant increase in pupil diameter (0.13 mm) and had no significant effect on the near point of accommodation, suggesting that oxymetazoline at concentrations of 0.025% or

lower has no direct mechanism of action for the treatment of presbyopia. Duzman and colleagues (1983) subsequently reported that oxymetazoline 0.025% had no significant effect on blood pressure, heart rate, IOP, pupil size, or visual acuity in 2 double-blind, randomized clinical trials. They attributed the lack of intraocular findings to the poor ocular penetration of oxymetazoline following topical ocular administration.

Oxymetazoline has been coadministered with dexamethasone phosphate in a trans-scleral delivery device, where it was shown to enhance the drug delivery of dexamethasone phosphate to the anterior chamber of the eye (Miller et al, 2008). Taken together, these data lend support to the hypothesis that oxymetazoline may modulate the pharmacokinetics of pilocarpine, providing synergistic benefits for the treatment of presbyopia akin to what is known for topical anesthetics.

1.2 Preclinical Summary

Besides the abundance of scientific literature available on similar products containing the 2 active ingredients, the basis for efficacy and safety in support of the proposed clinical design was established in the following animal studies.

In a 1-month ocular toxicity study, groups of 5 to 7 New Zealand White (NZW) rabbits per sex were administered a single topical drop (approximately 30 µL) of oxymetazoline 0.05%, 0.125%, or 0.25% or vehicle into the left eye twice daily (BID) (6 hours apart) for 28 days [redacted] At 2 minutes after dosing with oxymetazoline, 1 drop of pilocarpine 1.0%, a commercially available formulation containing 0.5% hypromellose (a viscosity enhancing agent that is known to increase absorption), was administered to the same eye. The vehicle-treated eye did not receive any pilocarpine treatment. All right eyes served as untreated controls. Slow iris responses were noted in several treated females at week 2 and were confirmed to be present in both genders at all concentrations in a follow-up ophthalmic examination. No histopathological findings were observed in any treatment group. Based on minimal severity, reversibility of pupil/iris findings, and a lack of correlative histopathological changes, the observed effects were considered non-adverse and pharmacologic in nature. The no-observed-adverse-effect-level (NOAEL) was 0.25% for oxymetazoline and 1.0% for pilocarpine (formulated with 0.5% hypromellose) when administered BID.

A single-dose ocular pharmacokinetic study in Dutch-belted rabbits was conducted to compare the ocular pharmacokinetics of the fixed combination formulation planned for use in this phase 2b study to the unfixed formulation used previously in phase 2a Study 199201-007. Dutch-belted rabbits were administered a single bilateral dose of

oxymetazoline 0.125% followed approximately 5 minutes later by a single bilateral dose of pilocarpine 1.0% (with 0.5% hypromellose) in the same vehicles used in Study 199201-007. A second group of rabbits was administered a single bilateral drop of a fixed combination formulation (oxymetazoline 0.125% and pilocarpine 1.0%) containing the vehicle (without hypromellose) to be used in the proposed clinical study. While only a slight reduction in pilocarpine exposure was noted with the fixed combination formulation in the iris-ciliary body (the purported site of action), this reduction was primarily driven by lower tissue concentrations at latter timepoints in the timecourse, potentially affecting clinical duration of action. Thus, to compensate, the pilocarpine high dose for the phase 2b studies was increased from 1.0% to 1.5%.

In a 14-day ocular tolerability study, groups of 5 female NZW rabbits were administered topical ocular drops (approximately 30 μL/drop) of combination formulations containing either 2% pilocarpine with 0.2 % oxymetazoline or 3% pilocarpine with 0.3% oxymetazoline, with or without 0.5% hypromellose, once daily (QD) or BID for 14 consecutive days (Study TX14097). Right eyes were dosed QD and left eyes were dosed BID. All formulations were considered well tolerated with generally no more than minimal to mild discomfort and pupil dilation, including pupils that did not fully constrict in response to light.

The data from the non-Good Laboratory Practice (GLP) tolerability study suggest that combination formulations of up to 3% pilocarpine with 0.3% oxymetazoline, with or without 0.5% hypromellose, were well tolerated when given as frequently as BID. This study and the comparison pharmacokinetic study provide further support, besides the 1-month GLP study, for the safety of testing 1.5% pilocarpine in a formulation without hypromellose in the proposed clinical study.

1.3 Clinical Summary

Four pilot clinical studies designed to evaluate the safety and efficacy of different combinations of topical pilocarpine and oxymetazoline ophthalmic solutions for the treatment of presbyopia and hyperopia were conducted between 2011 and 2013 by AltaVista Instituto del Investigation Medica at the clinic of Dr. Juan Carlos Abad (Abad, 2013). The concentration of pilocarpine tested in all 4 studies was 1.0%, while the concentrations of oxymetazoline tested ranged from 0.0125% to 0.125%. Dosing frequency ranged from a single drop to 1 drop 3 times daily for 6 months. In the clinical data reported by AltaVista, topical ocular dosing of a fixed combination of pilocarpine and oxymetazoline solutions in patients resulted in no serious adverse events. In a study of 65 patients who used a fixed

combination of pilocarpine 1.0% and oxymetazoline 0.0125% up to 3 times daily for 6 months, 3 patients (4.6%) discontinued use of the drops due to brow ache or ocular pain (Abad, 2013). This incidence is much lower than the reported 20% to 25% discontinuation rate with pilocarpine monotherapy for glaucoma and suggests that the administration of oxymetazoline with pilocarpine may improve the tolerability profile relative to pilocarpine monotherapy (NDA 200-890; Tsai and Forbes, 2009). Minor, infrequent adverse events were also reported, including a sense of decreased illumination and ocular floaters. AltaVista also reported that oxymetazoline prolonged the duration of the pilocarpine-induced improvement in uncorrected near visual acuity (UNVA) from approximately 4 to 6 hours, with the greatest difference (approximately 1 line) between the combination and pilocarpine monotherapy observed at 6 hours after dosing.

Allergan Study 199201-007 evaluated the safety and efficacy of oxymetazoline (0.125%) and pilocarpine (1.0%) in a multicenter, double-masked, randomized, vehicle-controlled study in patients with presbyopia. Oxymetazoline 0.125% and pilocarpine 1.0% ophthalmic solutions were concurrently administered as an "unfixed combination" in which the medications were administered separately. For all treatment groups, study medications were dosed QD for 3 days, and after a 5 ± 2-day washout period, BID for 3 days. All dosing was performed by trained personnel in the clinic.

A total of 65 patients were randomized, enrolled, and treated in this study. Fifteen patients were randomized to Group 1 (oxymetazoline [0.125%] dosed in the nondominant eye), 17 to Group 2 (pilocarpine [1.0%] dosed in the nondominant eye), 16 to Group 3 (oxymetazoline [0.125%]/pilocarpine [1.0%] dosed in the nondominant eye), and 17 to Group 4 (oxymetazoline [0.125%]/pilocarpine [1.0%] dosed in OU). In each group, patients were evenly distributed among the 4 strata of iris color and age. Sixty-three of the 65 patients (96.9%) completed the study. One patient in Group 2 and 1 patient in Group 4 discontinued from the study, both due to a nonocular adverse event. There were no statistically significant differences among the treatment groups in any of the demographic variables.

Concurrent dosing of pilocarpine and oxymetazoline provided a statistically significant greater response over vehicle in the percentage of patients achieving at least a 2-line improvement in mesopic, high contrast UNVA at a majority of timepoints postdose in the nondominant eye following both QD and BID dosing regimens. Pilocarpine monotherapy provided a statistically significant greater response over vehicle in the percentage of patients achieving at least a 2-line improvement in mesopic, high-contrast UNVA at a majority of timepoints postdose in the nondominant eye following QD dosing and was numerically superior following BID dosing. Across all timepoints and visits, the mean change from

baseline in lines of UNVA numerically favored the combination groups over pilocarpine monotherapy at later timepoints postdose (hour 8 of the QD dosing period and hour 11 of the BID dosing period), replicating the findings reported by AltaVista. Oxymetazoline monotherapy was found to have little effect on UNVA.

The greatest differences in favor of the combination of pilocarpine and oxymetazoline dosed in the nondominant eye (Group 3) relative to pilocarpine monotherapy dosed in the nondominant eye (Group 2) were seen with more stringent response criteria, most notably with the percentage of patients achieving at least a 3-line gain in UNVA from baseline at all timepoints postdose at the end of both the QD (31.3% versus 11.8%) and BID (12.5% versus 0%) dosing regimens, and in younger patients (ie, the 40- to 47-year age cohort per the prespecified cutoff) who robustly responded to combination with 2.8 to 3.8 lines of improvement on average. Younger patients on pilocarpine monotherapy responded with 1.2 to 2.5 lines of improvement on average. In older patients (ie, the 48- to 55-year age cohort per the prespecified cutoff), the difference was less pronounced between combination therapy and pilocarpine monotherapy. Both pilocarpine monotherapy and concurrent dosing of pilocarpine and oxymetazoline significantly reduced pupil diameter, with a maximal effect at approximately 1 hour postdose (range across visits: -2.56 to -2.73 mm) and a reduced effect 6 to 8 hours postdose (range across visits: -1.05 to -1.66 mm). Combined, these results suggest that in younger patients, the combination may be having a direct effect upon accommodation, providing a benefit over pilocarpine monotherapy for the treatment of presbyopia.

Oxymetazoline monotherapy, pilocarpine monotherapy, and concurrent dosing of pilocarpine and oxymetazoline in 1 or OU were found to be safe and well tolerated. No meaningful difference was seen between groups in the discontinuation rate or the incidence or severity of adverse events, with the exception of "eyelid retraction" that occurred most frequently in the oxymetazoline monotherapy group. No meaningful differences were seen between groups in visual analog scale (VAS) scores for temporal or supraorbital headache. It may require a larger sample size to detect ocular adverse events associated with pilocarpine monotherapy and to properly test AltaVista's finding of improved tolerability with the combination of oxymetazoline and pilocarpine relative to pilocarpine monotherapy.

The overall objective of this clinical development program is to develop a fixed-dose combination of oxymetazoline and pilocarpine for the treatment of presbyopia. To date, preclinical studies in rabbits and nonhuman primates, 4 pilot clinical studies conducted by AltaVista Instituto del Investigation Medica at the clinic of Dr. Abad, and Study 199201-007

conducted by Allergan support the combination of pilocarpine and oxymetazoline for the treatment for presbyopia.

1.4 Rationale for Study Design

The current phase 2 clinical study is designed to evaluate the safety, efficacy, and tolerability of fixed combinations of AGN-199201 and AGN-190584 over a 42-day observation period when administered QD, bilaterally, for 28 days in patients with presbyopia.

Additionally, this study will evaluate the safety, efficacy, and tolerability of a fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] when administered monocularly to the nondominant eye versus bilaterally for 28 days in patients with presbyopia. The most widely used non-spectacle methods of presbyopia correction use is monovision. In this technique, the eyes are dissociated by focusing 1 eye for distance vision and 1 eye for near vision. Unfortunately, a significant proportion of patients cannot tolerate monovision (ie, ~ 40% for contact lenses and ~ 10% for laser treatments). A pharmaceutical treatment for presbyopia that both increases depth of field by inducing miosis and enhances accommodation may allow patients to dose in 1 or OU without the significant optical limitations faced by current non-spectacle methods of presbyopia correction.

There is widespread belief that prolonged use of decongestant sprays like oxymetazoline can result in a condition of decreased effectiveness called tolerance. It is thought that with time they lose their effectiveness and more and more medication is needed to achieve the same level of decongestion. It has also been proposed that once stopped, the patient experiences rebound congestion (Vaidyanathan et al, 2010). Extending these finding from nasal application to ophthalmic application, the packaging for Visine LR reads, “overuse may cause more eye redness [rebound congestion].” It is unknown if the findings of tolerance and rebound with extended use of oxymetazoline for eye redness or nasal congestion will impact the efficacy of a fixed combination of AGN-199201 (oxymetazoline HCl ophthalmic solution) and AGN-190584 (pilocarpine HCl ophthalmic solution) for the treatment of presbyopia.

Allergan Study 199201-007 supports the unfixed combination of AGN-199201 [redacted] and AGN-190584 ([redacted] as a safe and effective short-term treatment for presbyopia. The current study will evaluate fixed combinations of AGN-199201 and AGN-190584 that include the concentration of AGN-199201 and AGN-190584 that were unfixed and used in Allergan Study 199201-007.

Oxymetazoline systemic exposure has been measured after a single administration of Afrin nasal spray (3 sprays [0.1 mL/spray] in each nostril of 0.05% oxymetazoline, equating to 0.3 mg/dose), which resulted in a mean observed plasma maximum concentration (C_{max}) of 0.245 ng/mL and area under the plasma concentration-time curve from time 0 to 12 hours (AUC_{0-12}) of 1.74 ng·hr/mL [redacted] No serious adverse events were reported in this study, and no patients discontinued prematurely due to an adverse event. There were no notable changes from predose to postdose in clinical laboratory tests, vital sign measurements, electrocardiograms (ECGs), or IOP during the study. This study will determine the systemic pharmacokinetics of AGN-199201 [redacted] and AGN-190584 [redacted] following single and multiple (QD for 28 days) ophthalmic administrations as a fixed combination in 1 or OU, by analysis of plasma drug concentration-time profiles (C_{max}, time to maximum plasma concentration [T_{max}], and AUC).

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

The objectives of this study will be:

- To evaluate the safety, efficacy, and tolerability of fixed combinations of AGN-199201 and AGN-190584 over a 42-day observation period when administered bilaterally QD for 28 days in patients with presbyopia
- To compare the safety, efficacy, and tolerability of a fixed combination of AGN-199201 [redacted]) and AGN-190584 [redacted] when administered monocularly to the nondominant eye versus bilaterally over a 42-day observation period with QD dosing for the first 28 days in patients with presbyopia
- To assess the systemic pharmacokinetics of AGN-199201 [redacted]) and AGN-190584 [redacted] following single and multiple (QD for 28 days) ophthalmic administrations as a fixed combination in 1 or OU, by analysis of plasma drug concentration-time profiles (C_{max}, T_{max}, AUC from time 0 to the last timepoint [AUC_{0-last}], and AUC from time 0 to infinity [AUC_{0-inf}]).
- To evaluate the psychometric properties of the de novo patient-reported outcome (PRO) instruments developed for this program, including the near vision presbyopia performance tasks and task-based questionnaire under mesopic and photopic conditions, the presbyopia patient satisfaction questionnaire, and the presbyopia impact and coping questionnaire

2.2 Clinical Hypotheses

At least 1 fixed combination of AGN-199201 and AGN-190584 ophthalmic solution dosed bilaterally QD for 28 days:

1. will demonstrate a significant improvement in UNVA over vehicle.
2. will demonstrate acceptable safety and tolerability findings.
3. will demonstrate an acceptable pharmacokinetic profile for AGN-199201 and AGN-190584 after single and repeat administrations.

The fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] can be administered either in the nondominant eye only or bilaterally for 28 days in patients with presbyopia without any significant difference in the observed safety, efficacy, tolerability or pharmacokinetic profiles.

3. Study Design

This multicenter, double-masked, randomized, parallel-group, vehicle-controlled study will be a controlled comparison of fixed combinations of AGN-199201 and AGN-190584 at different concentrations to vehicle dosed in OU, and the fixed combination of AGN-199201 [redacted]) and AGN-190584 ([redacted] dosed in OU or in the nondominant eye only. Study medication will be administered QD in the morning. During office visits 1 through 5, study medication will be administered at hour 0 (8 AM ± 1 hour). Following the treatment period, all patients will be seen for a 14 ± 2-day follow-up period as shown in Figure 1. The study duration will be 38 to 65 days per patient.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 150 patients (30 per group) will be enrolled at approximately 15 sites in the US. Approximately 26 patients per group are expected to complete the study based on an anticipated dropout rate of less than 12.5%. Approximately two-thirds of the enrolled patients will be ≤ 50 years old.

4.2 Study Population Characteristics

The study population will consist of adult patients who have objective and subjective evidence of presbyopia.

4.3 Inclusion Criteria

The following will be requirements for entry into the study:

1. Male or female, between 40 and 55 years of age

[redacted]

3. Natural or corneal laser refractive surgery corrected [redacted] at distance with presbyopia in each eye and subjective complaints of poor near vision that impact activities of daily living, [redacted]

[redacted]

[redacted]

4.4 Exclusion Criteria

The following will be criteria for exclusion from the study:

Ophthalmic:

1. Concurrent use of any topical ophthalmic medications, including artificial tears, other than the study medications, during the course of the study

[redacted]

4. Corneal abnormalities (including keratoconus, corneal scar, Fuchs' endothelial dystrophy, guttata, or edema) in either eye that are likely to interfere with visual acuity

5. History of cataract surgery, phakic intraocular lens (PIOL surgery), corneal inlay surgery, [redacted]

[redacted]

[redacted]

10. Diagnosis of any type of glaucoma or ocular hypertension

[redacted]

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

The concurrent use of nonocular medications that do not have a substantial effect on the pupil, accommodative properties, or retinal function of the eye will be permitted during the study if a stable dosing regimen is established. The dosing regimen is not considered to be stable if a patient starts, stops, or changes the dose/drug during the study.

4.5.1.1 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal (see definition below) or permanently sterilized (ie, hysterectomy).

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 women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner, or sexual abstinence.

The investigator and each patient will determine the appropriate method of contraception for the patient during their participation in the study.

4.6 Prohibited Medications/Treatments

Use of ocular medications other than study medication or medications administered to conduct study procedures (see Section 6.4) are prohibited from the screening visit until study exit.

Use of medications that may have a substantial effect on visual function or the optical properties of the eye is prohibited 2 weeks prior to the baseline visit and during the study:

- systemic medications with potential ocular side effects, including topiramate, hydroxychloroquine, ethambutol, phosphodiesterase 5 (PDE5) inhibitors (sildenafil, vardenafil, tadalafil), or tamoxifen

- ophthalmic, systemic, or intranasal anticholinergics and α-adrenergic receptor agonists with potential pupillary or accommodative effects, including oxymetazoline, pilocarpine, tetrahydrozoline, phenylephrine, naphazoline, cyclopentolate, atropine, beta-blockers, or antihistamines

- systemic maprotiline, tricyclic antidepressants, or monoamine oxidase inhibitors (MAOIs)

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

5. Study Treatments

5.1 Study Treatments and Formulations

Fixed combination AGN-199201 [redacted] weight/volume (w/v) and AGN-190584 [redacted]

Fixed combination AGN-199201 [redacted] w/v and AGN-190584 [redacted]

Fixed combination AGN-199201 [redacted] w/v and AGN-190584 [redacted]

5.2 Control Treatment

The vehicle of AGN-199201 and AGN-190584 [redacted]

5.3 Methods for Masking

Study medication will be administered to each randomized patient bilaterally by qualified site personnel during the study visits 1 to 5. The patient will be instructed to continue using the dispensed study medication on the assigned eyes between visits. The investigator, investigational staff, and patients will be fully masked to study drug and vehicle treatments. All study treatments will be provided in identical multidose bottles and cartons.

5.4 Treatment Allocation Ratio and Stratification

Patients will be randomized in a 1:1:1:1:1 ratio into 1 of 5 treatment groups:

Group 1: Vehicle control, OU

Group 2: Fixed combination AGN 199201 [redacted] and AGN 190584 [redacted], OU

Group 3: Fixed combination AGN 199201 [redacted] and AGN 190584 [redacted], OU

Group 4: Fixed combination AGN 199201 [redacted]) and AGN 190584 ([redacted], OU

Group 5: Fixed combination AGN 199201 ([redacted]) and AGN 190584 [redacted], monocular dosing to the nondominant eye and vehicle to the dominant eye

Randomization will be stratified by age (2 groups: ≤ 50 and > 50) and iris color (2 groups: brown and not brown) at the baseline visit. There will be a total of 4 strata; brown eyes and age ≤ 50 years, brown eyes and age > 50 years, not brown eyes and age ≤ 50 years, and not brown eyes and age > 50 years. For the determination of stratification group assignment for each patient, sites will be required to enter iris color (ie, brown, blue, green, gray, or hazel) and age into the Interactive Response System (IxRS), and the IxRS will assign the stratum.

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study treatment, each patient who provides informed consent will be assigned a patient number that will serve as the patient identification number on all study documents.

At the time of randomization on visit 1, eligible patients will be placed into 1 of 4 strata as described in Section 5.4, and they will be assigned to 1 of the 5 treatment groups based on the randomization scheme within the patient's stratum according to the order of enrollment. The IxRS will assign the next available randomization number for the appropriate stratum to the patient at the time the investigator requests randomization. The IxRS will report a

medication kit number to use for each patient corresponding to the randomization number. The randomization scheme will be prepared by Allergan Biostatistics.

Study medication will be labeled with the medication kit number, study number, and dominant or nondominant eye. Each medication kit (carton) will contain 2 multidose bottles of study treatment . The IxRS will provide the site with the specific medication kit number(s) for each randomized patient at the time of randomization. Sites will assign study medication kits according to the IxRS instructions. Sites will receive the IxRS confirmation notifications for each transaction. All notifications will be maintained with the study source documents.

5.6 Treatment Regimen and Dosing

Doses of study medication and/or vehicle will be instilled in the appropriate eyes by designated site personnel at hour 0 (8 AM ± 1 hour) of visits 1, 2, 3, 4, and 5. In between office visits, patients will be instructed to continue using the dispensed study medication on the assigned eyes in the morning QD.

Patients receiving the fixed combination of AGN-199201 and AGN-190584 bilaterally will instill a single drop of the fixed combination drug into each eye. Patients receiving the fixed combination of AGN-199201 and AGN-190584 in the nondominant eye only will instill a single drop of the fixed combination drug into the nondominant eye and a single drop of the vehicle into the dominant eye. Patients receiving vehicle bilaterally will instill a single drop of the vehicle into each eye (see Table 1 and Figure 1).

5.7 Storage of Study Medications/Treatments

The study product must be stored in a secure area. Only assigned study personnel, authorized by the investigator, may have access to study product. Study product will be administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

All study products must be stored upright, in a refrigerator and protected from freezing. All study products will be stored within the temperature storage range limits required to ensure study product stability during the study. Sites must report any temperature excursion to Allergan, and avoid administering the impacted study product, by isolating the product, until receiving further instructions from Allergan (see Study Procedure Manual for more information).

Patients will be instructed on the proper storage of study medication and to keep it out of the reach of children at all times.

5.8 Treatment Administration

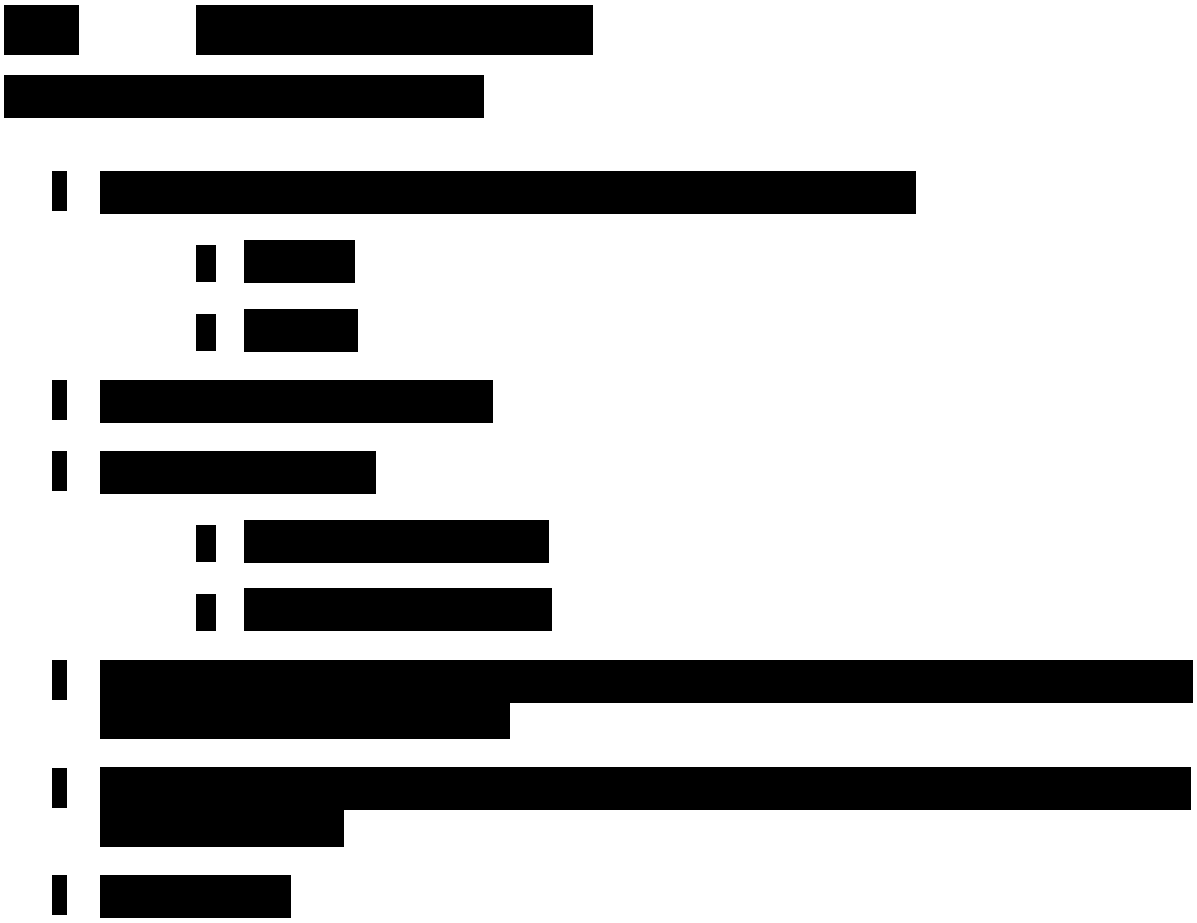
Doses of study medication and/or vehicle will be instilled in the appropriate eyes by designated site personnel at hour 0 (8 AM ± 1 hour) of visits 1, 2, 3, 4, and 5. In between office visits, patients will be instructed to apply the dispensed study medication in the morning QD into OU. See Sections 5.3 and 5.6 for more detail.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

The primary efficacy measure will be mesopic, high contrast UNVA.



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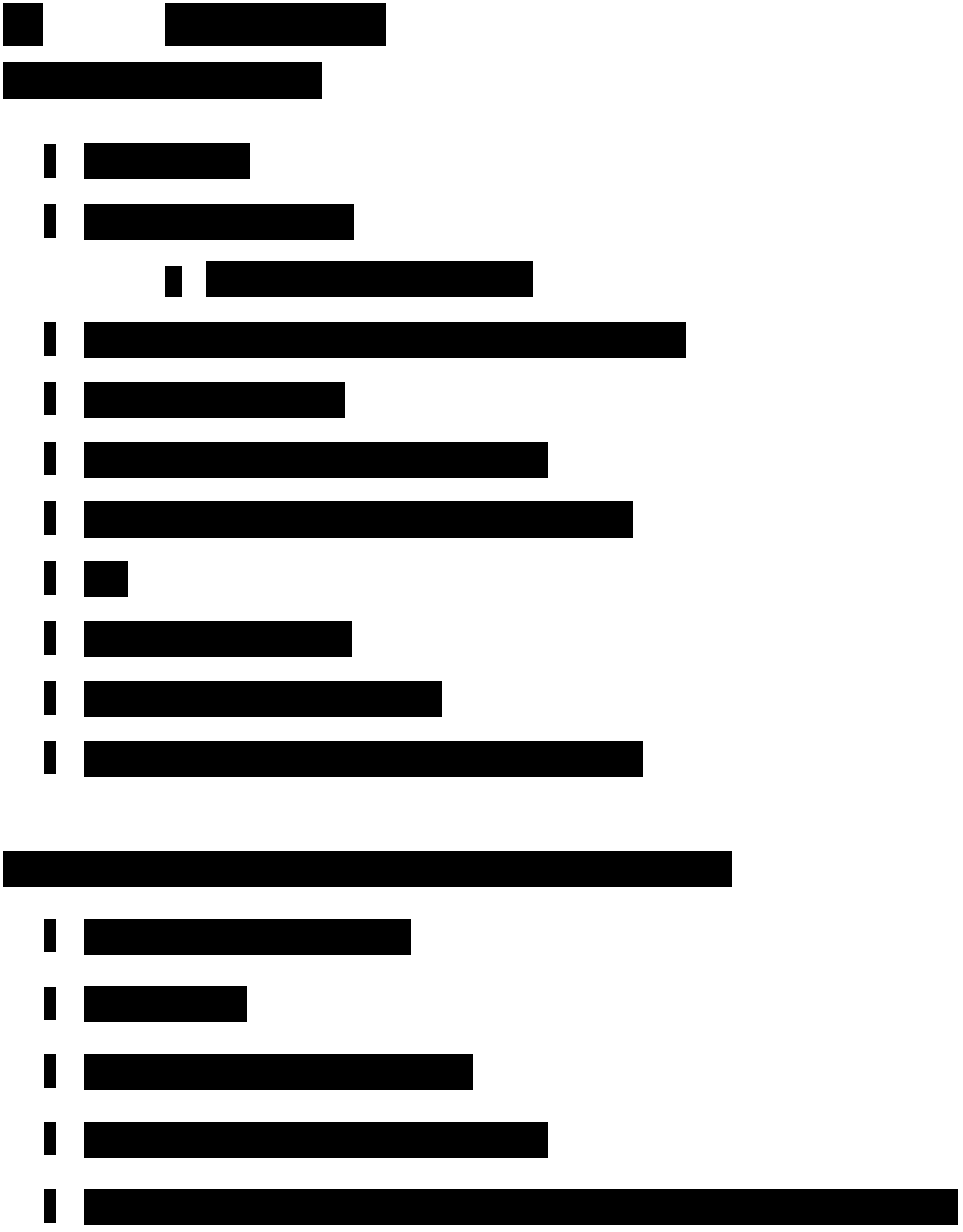

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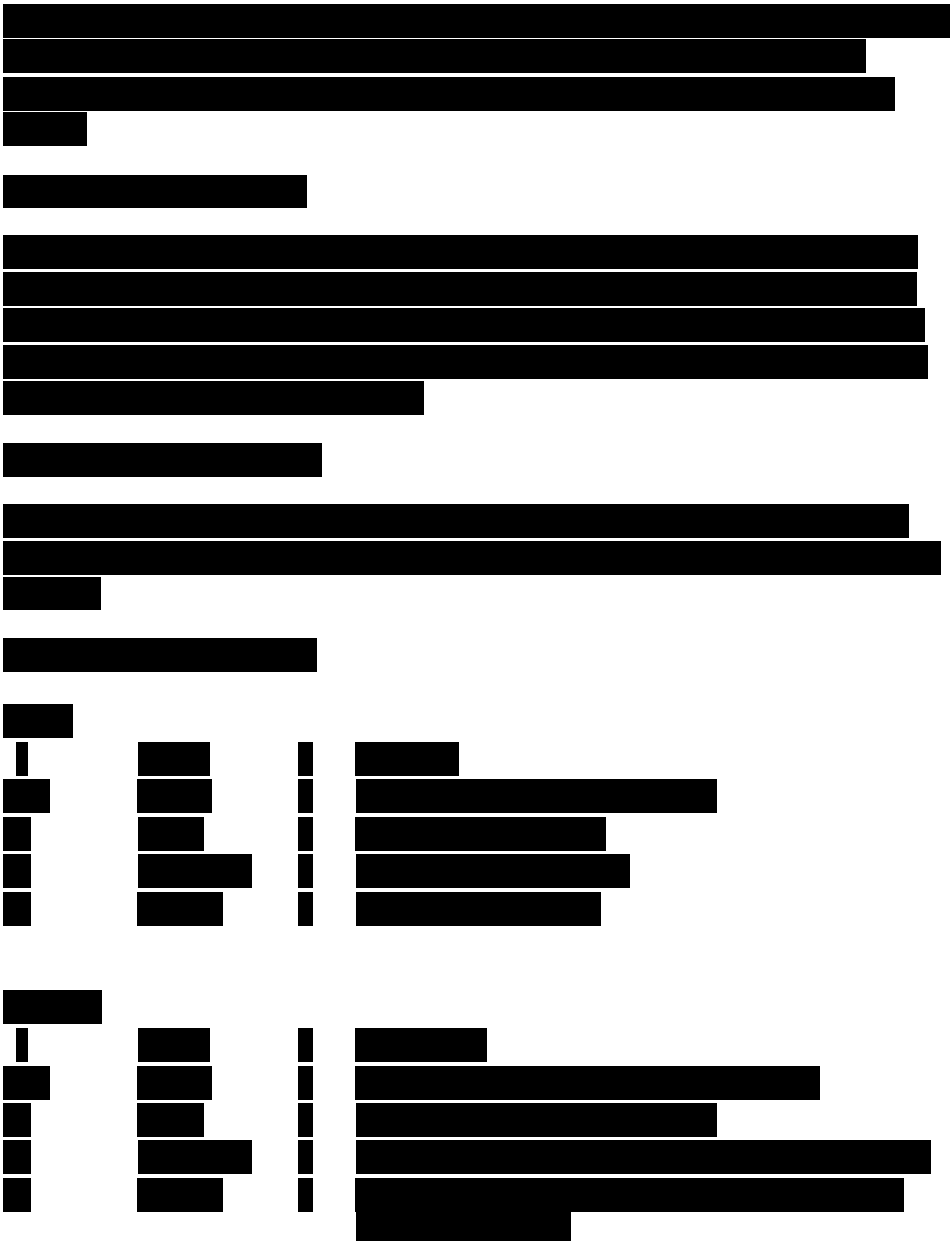
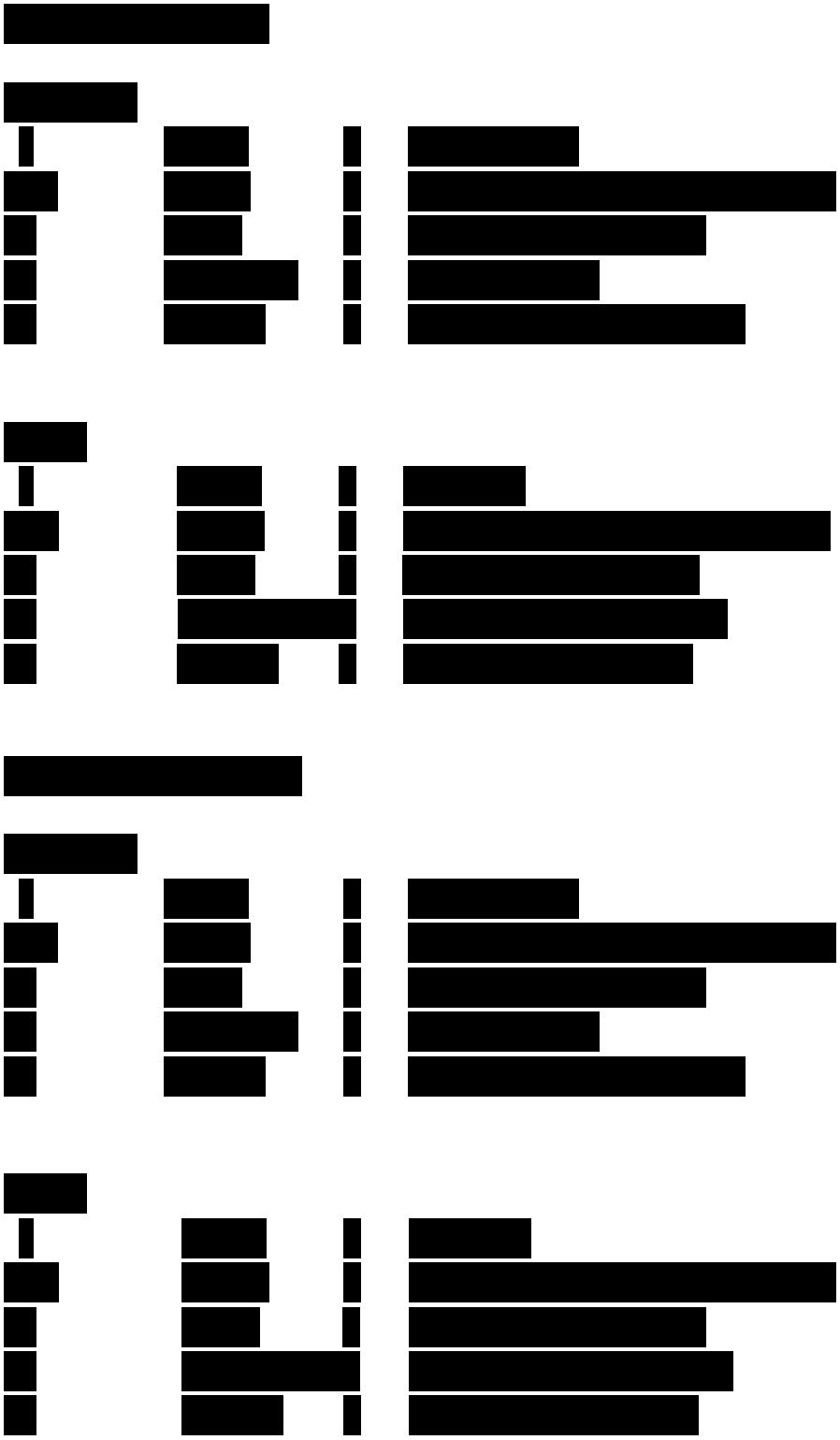
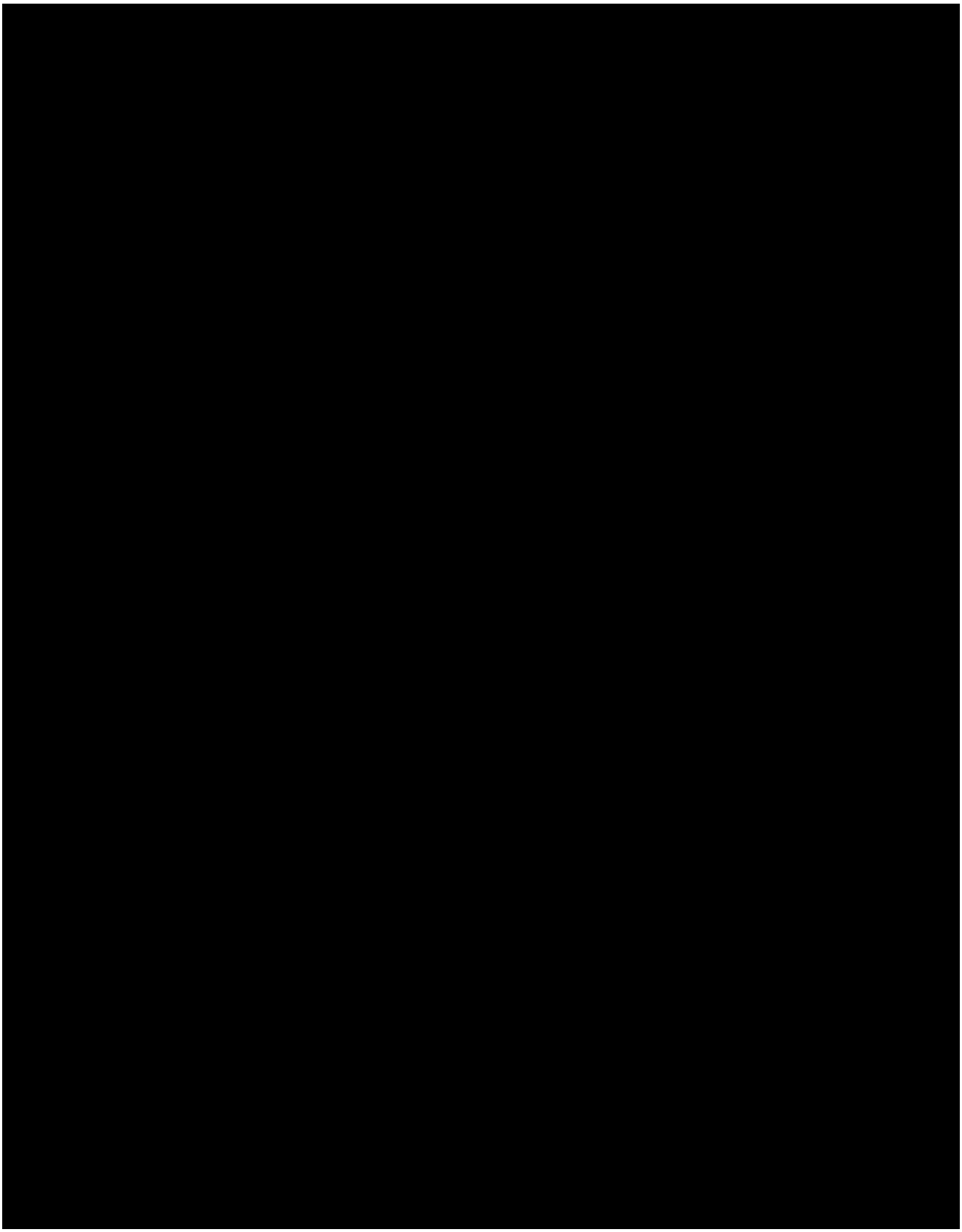
epth of focus of the measured eye. More details will be out lined in the Procedure Manual.

[redacted]

[redacted]







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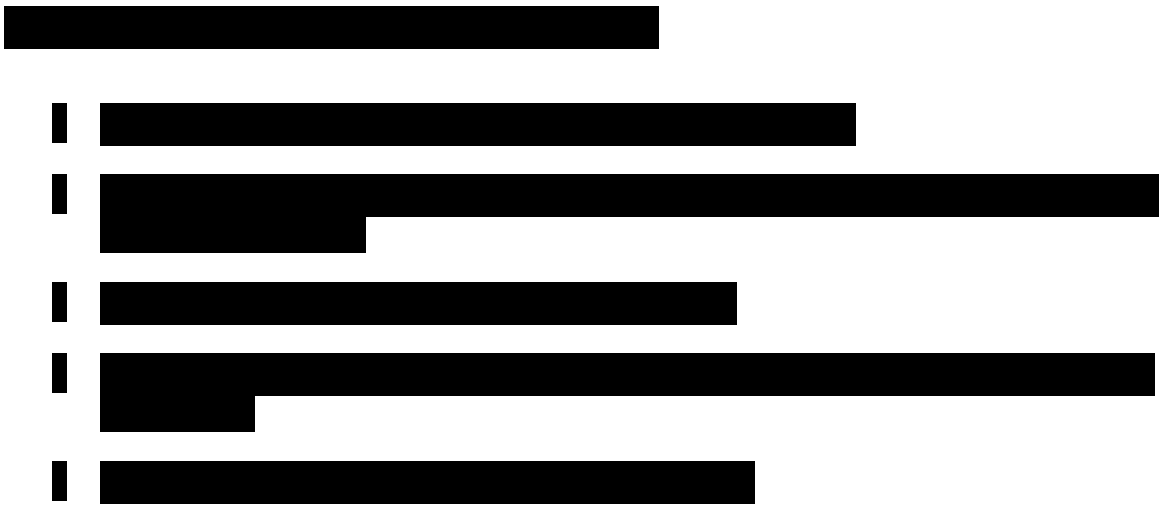


6.6 Summary of Methods of Data Collection

This protocol will use 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 will be responsible for ensuring that data are properly recorded on each patient's eCRF and related documents. Data will be entered on the eCRFs in a timely manner and on an ongoing basis. 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

One database lock is planned at the completion of the study. A detailed analysis plan (AP) will be approved prior to database lock.

7.1 Analysis Populations

The modified intent-to-treat (mITT) population will be defined as all randomized patients with a baseline and at least 1 postbaseline assessment of mesopic, high contrast UNVA and will be analyzed as randomized. The efficacy variables will be analyzed using the mITT population.

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

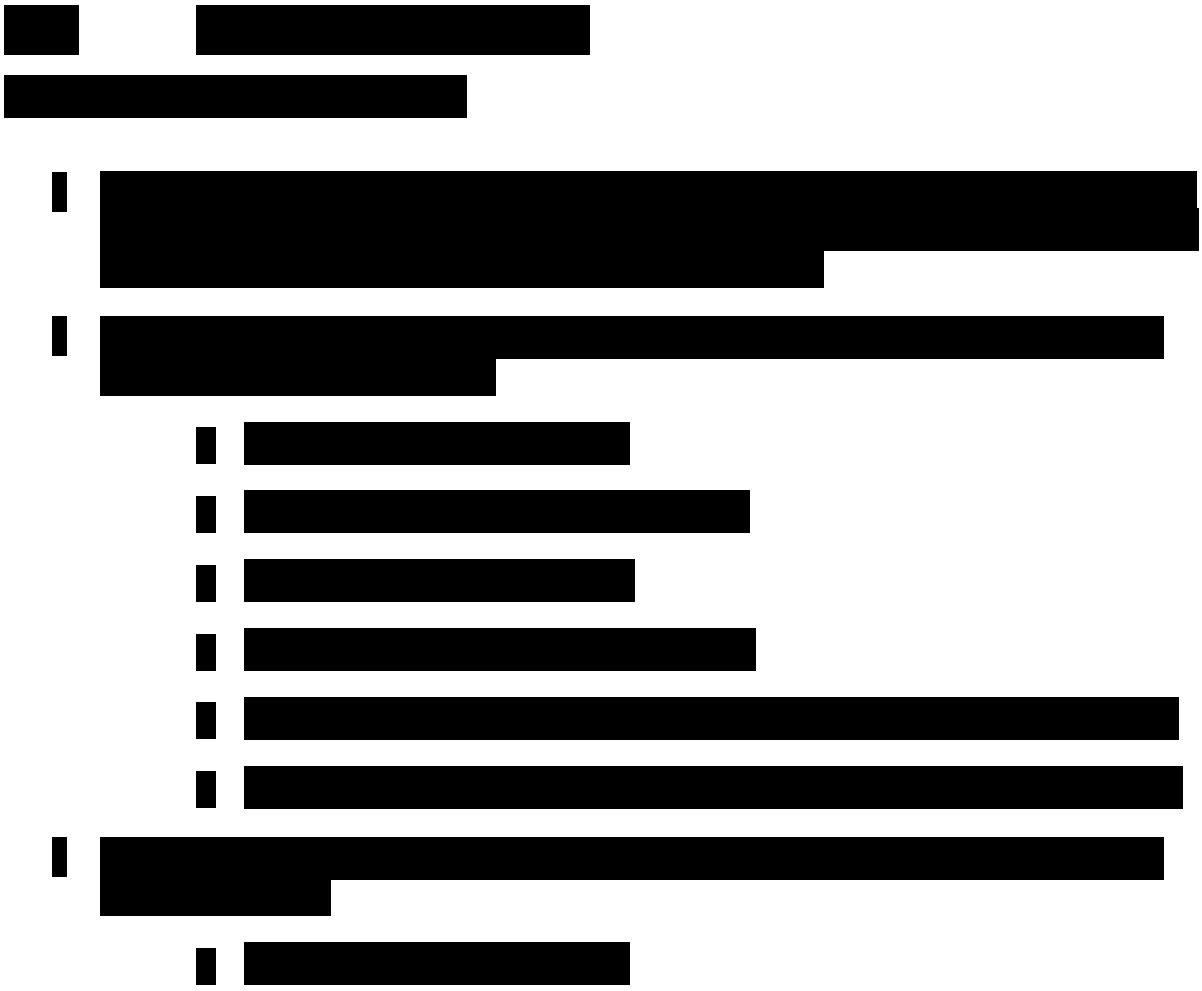
In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using analysis of covariance (ANCOVA) or 2-sample t-tests. Categorical variables will be summarized by sample size (N), frequency count and percent, and will be analyzed using Pearson's chi-square, Fisher's exact, or the Cochran-Mantel-Haenszel (CMH) test.

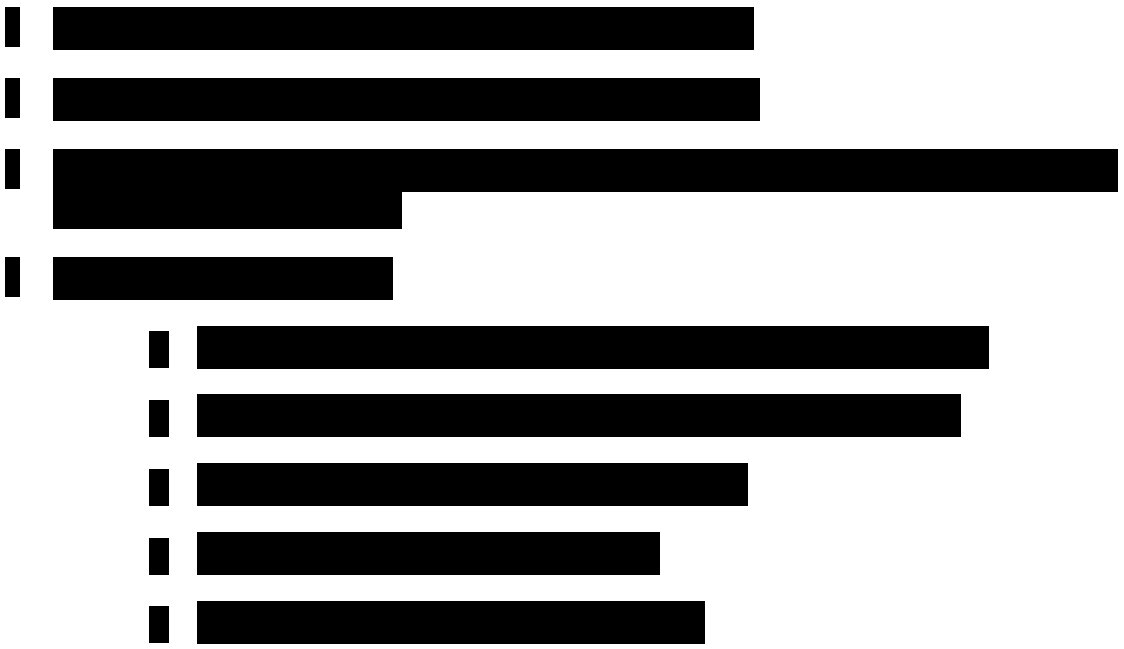
There will be no imputation of missing data for all analyses.

7.2 Collection and Derivation of Primary and Other Efficacy Assessments

7.2.1 Primary Efficacy Variable

The primary efficacy variable will be the weighted average change from baseline in mesopic, high contrast UNVA lines at day 28 in the nondominant eye. Baseline will be the hour 0 measure at day 1.





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 ANCOVA techniques or 2-sample t-tests (for between-group comparisons) and paired t-tests (for within-group analyses). Categorical variables will be analyzed using the CMH test.

There will be no adjustment of type 1 error rate for the multiple tests. There will be no imputation of missing data for all analyses.

7.3.1 Primary Efficacy Analyses

For the primary efficacy analysis, the weighted average change from baseline will be analyzed by ANCOVA with treatment group, age group, and iris color as fixed effects. A detailed algorithm for the derivation of the primary efficacy variables will be documented in the AP.

[redacted]

7.4 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy variable by UNVA at baseline (20/40 to 20/80 and 20/100 to 20/200), age group, and iris color (brown or not brown).

7.5 Sample Size Calculation

A sample size of approximately 150 patients will be randomized in a 1:1:1:1:1 ratio into 1 of the 5 study groups. Approximately two-thirds of the enrolled patients will be younger patients (≤ 50 years old), and approximately one-third of the enrolled patients will be older patients (> 50 years old).

From the Study 199201-007 results, the treatment effect for the younger patients was on average 1.98 lines of change in mesopic, high contrast UNVA, with standard deviations for active and vehicle of 1.12 and 1.01, respectively. For older patients, the treatment effect was on average 0.72 lines of change in mesopic, high contrast UNVA, with standard deviations for active and vehicle of 1.87 and 1.15, respectively. The treatment effect for the younger patients was on average 1.02 lines of change in photopic, high contrast UNVA, with standard deviations for active and vehicle of 1.42 and 0.67, respectively. For older patients, the treatment effect was on average 0.27 lines of change in photopic, high contrast UNVA, with standard deviations for active and vehicle of 1.10 and 0.93, respectively.

Accounting for a 12.5% dropout rate, 26 patients per treatment group will provide 99% power to observe a difference between an active group and the vehicle group for ≥ 1 line of change from baseline in mesopic, high contrast UNVA and 68% power for ≥ 1 line of change from baseline in photopic, high contrast UNVA, with a type 1 error of 0.05.

7.6 Interim Analyses

There will be no interim analyses.

8. Study Visit Schedule and Procedures

Please see Table 2, Table 3, Table 4, and Table 5 for a schematic of the schedule of visits and procedures and Figure 1 for a flowchart of the study visits.

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 authorization US only), data protection consent (Europe 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.

Each patient that provides informed consent and/or assent will be assigned a patient number that will be used on patient documentation throughout the study.

8.2 Washout Intervals/Run-In

This study will not include a washout period.

8.3 Procedures for Final Study Entry

The results from screening ocular examinations must be evaluated and determined to be acceptable to the investigator prior to the patient's entry into the study. Furthermore, all female patients of childbearing potential MUST have a negative urine pregnancy test at screening and baseline (day 1) prior to randomization and initiation of study treatment. Each patient's ocular examination findings at screening and baseline (day 1) will be evaluated with respect to the entry criteria specified in Sections 4.3 and 4.4 for final determination of eligibility before the patient is randomized.

Patients will be considered to have enrolled in the study when they are randomized.

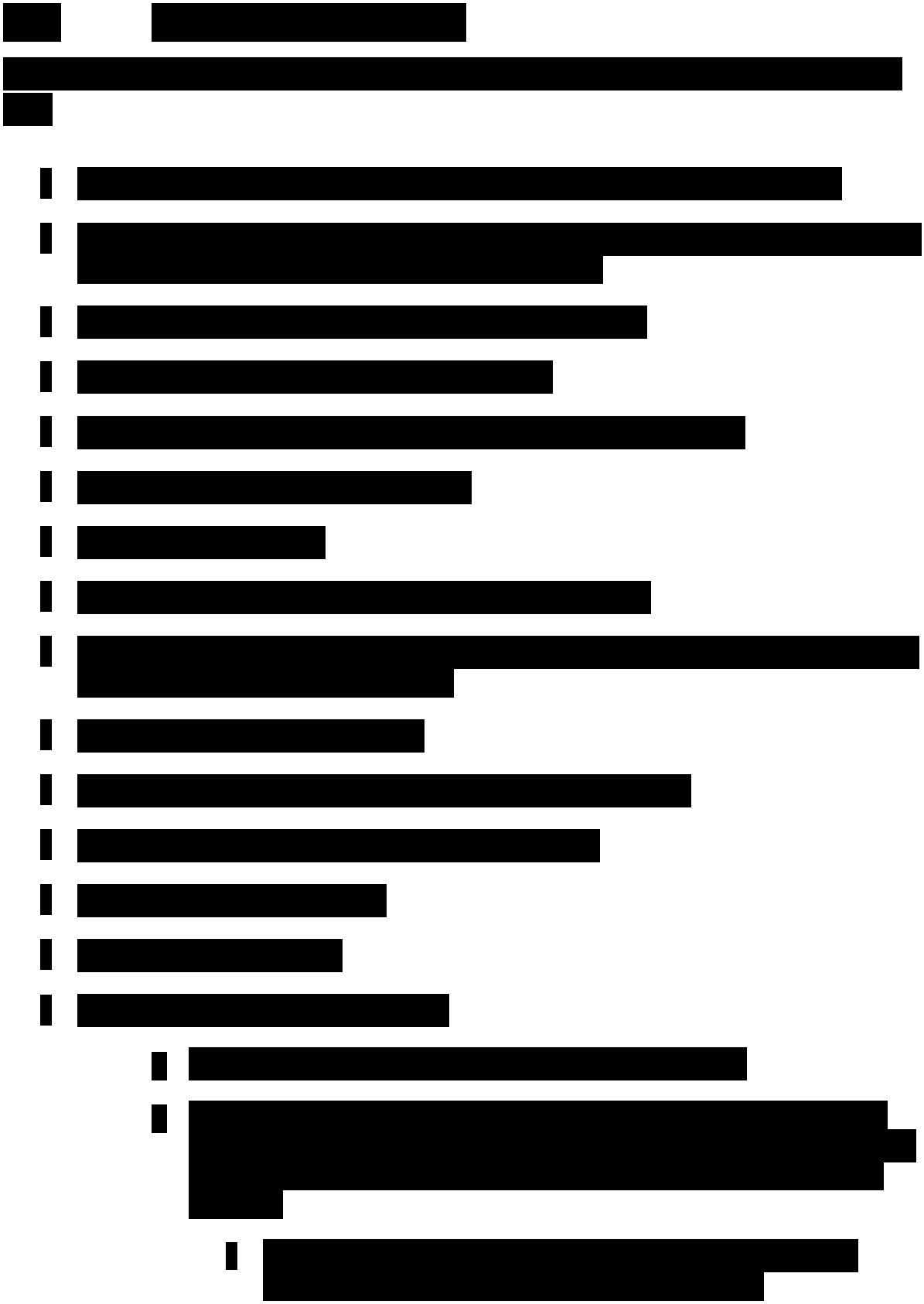
See Section 5.5 for the method for assignment to treatment groups/randomization.

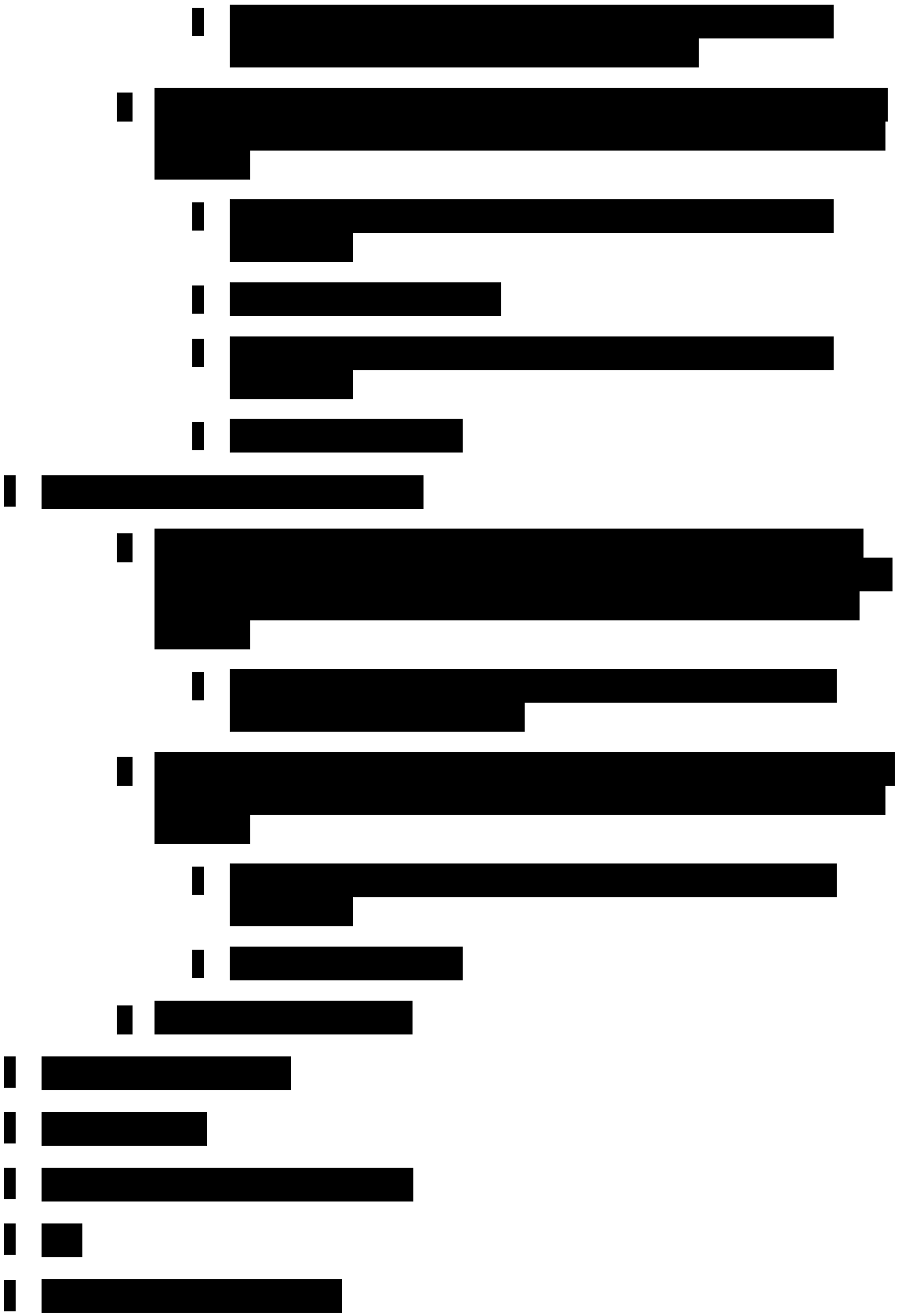
8.4 Visits and Associated Procedures

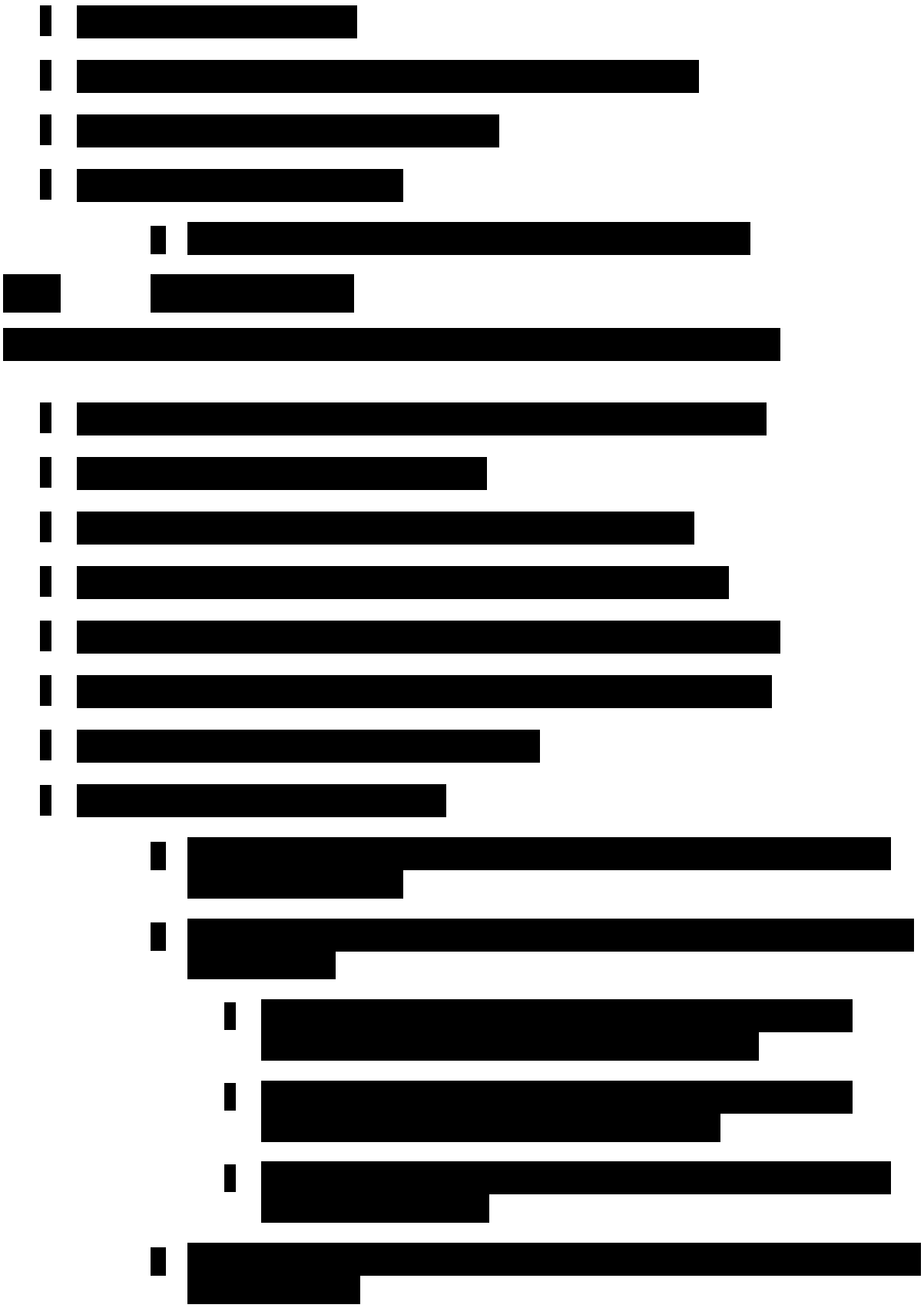
Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, then evaluations should overlap (examine the patient together and discuss findings) for at least 1 visit.

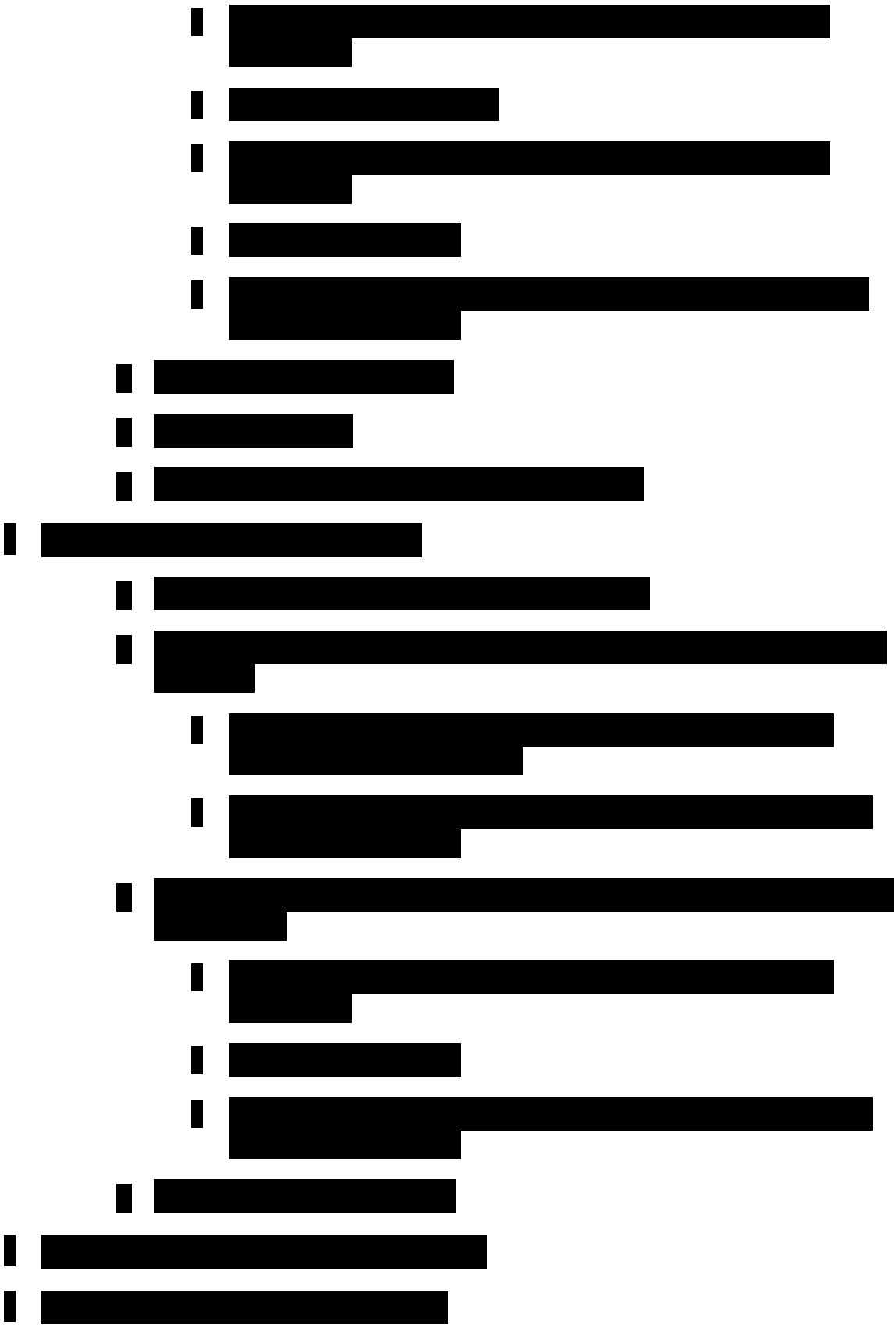
[redacted]

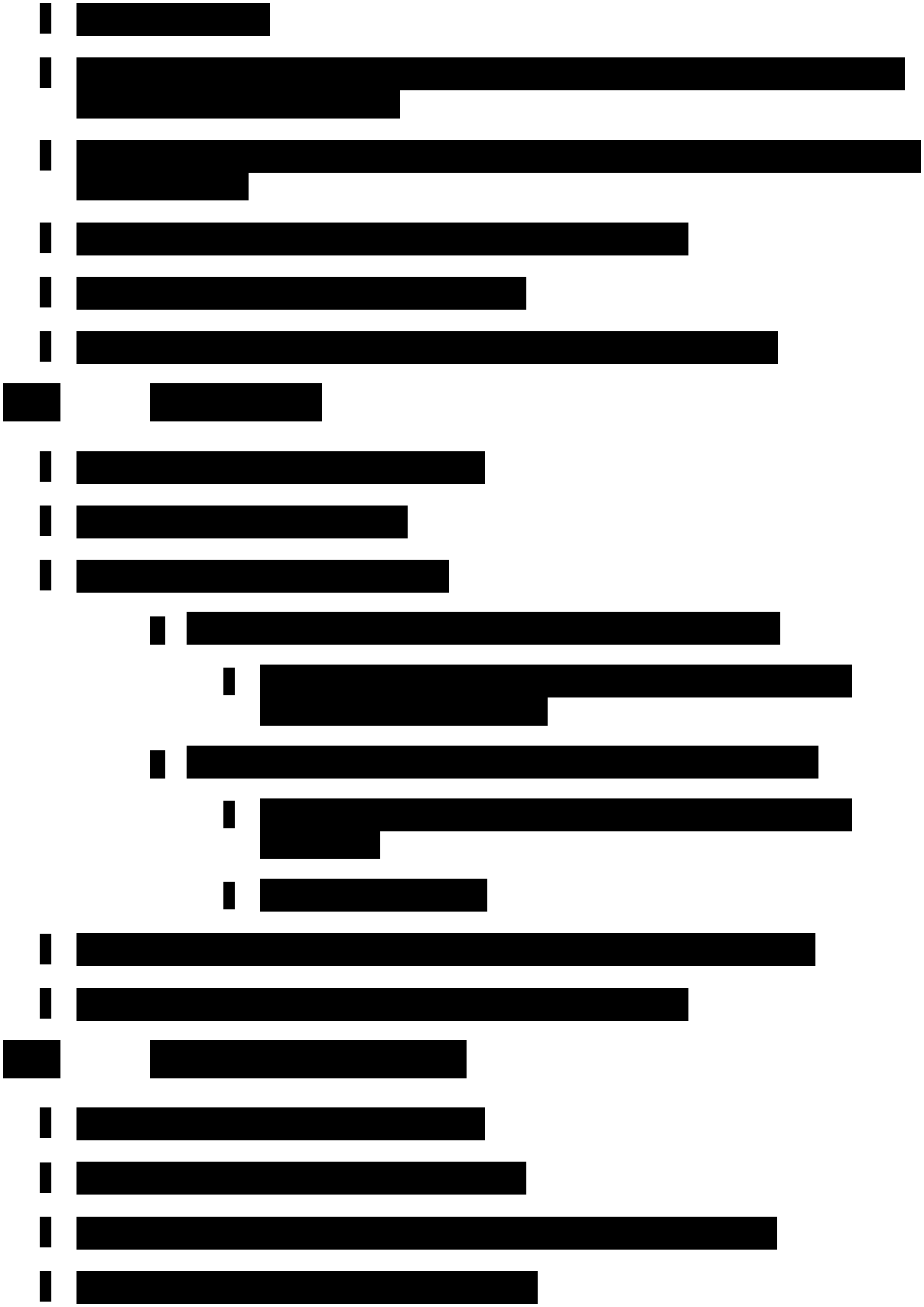
The following section provides a list of procedures for each scheduled visit. All ophthalmic procedures should be performed for each eye, unless otherwise noted. It is recommended, but not required, that the procedures occur in the order presented. Additional information on the examination procedures, equipment, and techniques for the measures listed in this section are presented in Section 6.4 and the Procedure Manual.

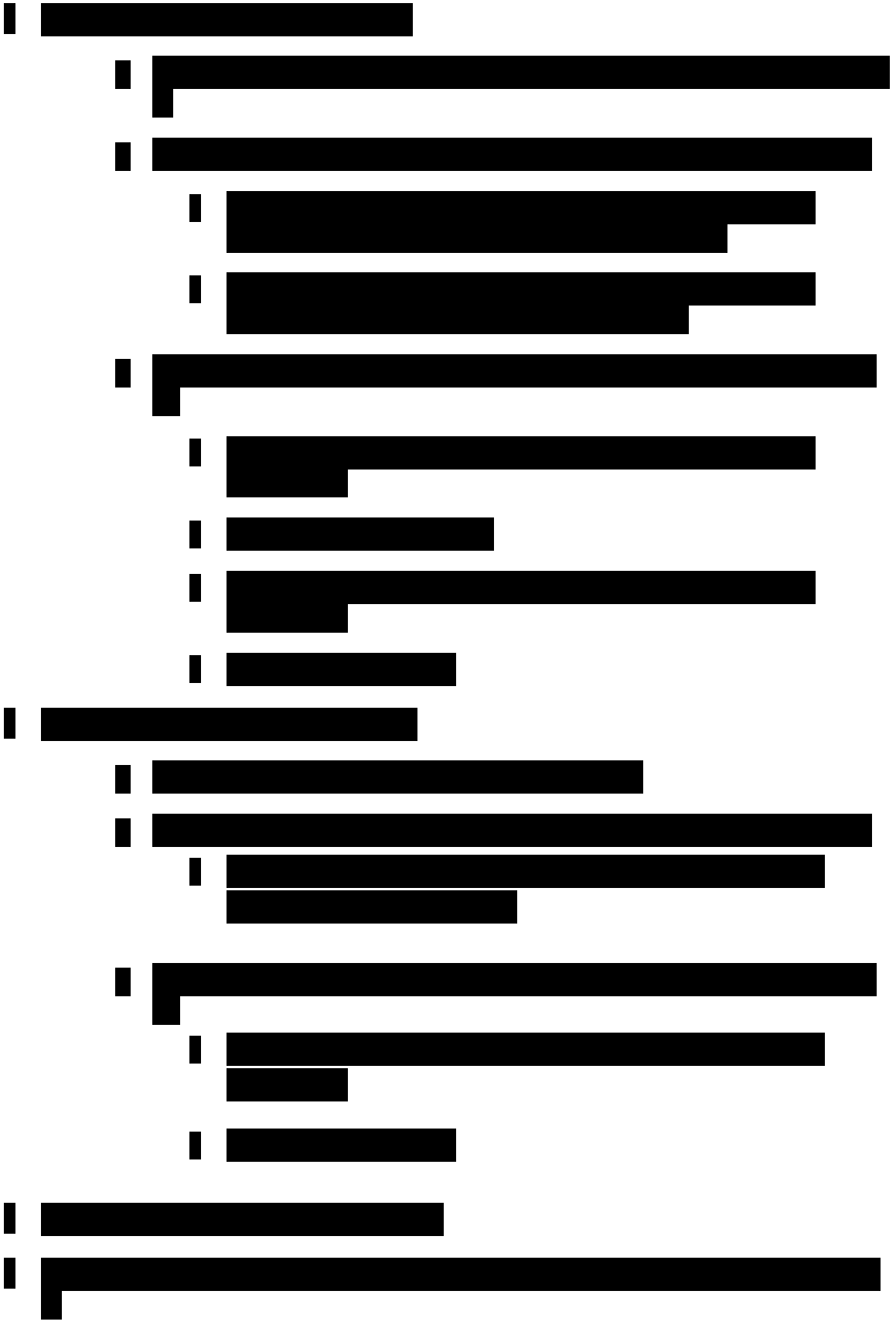


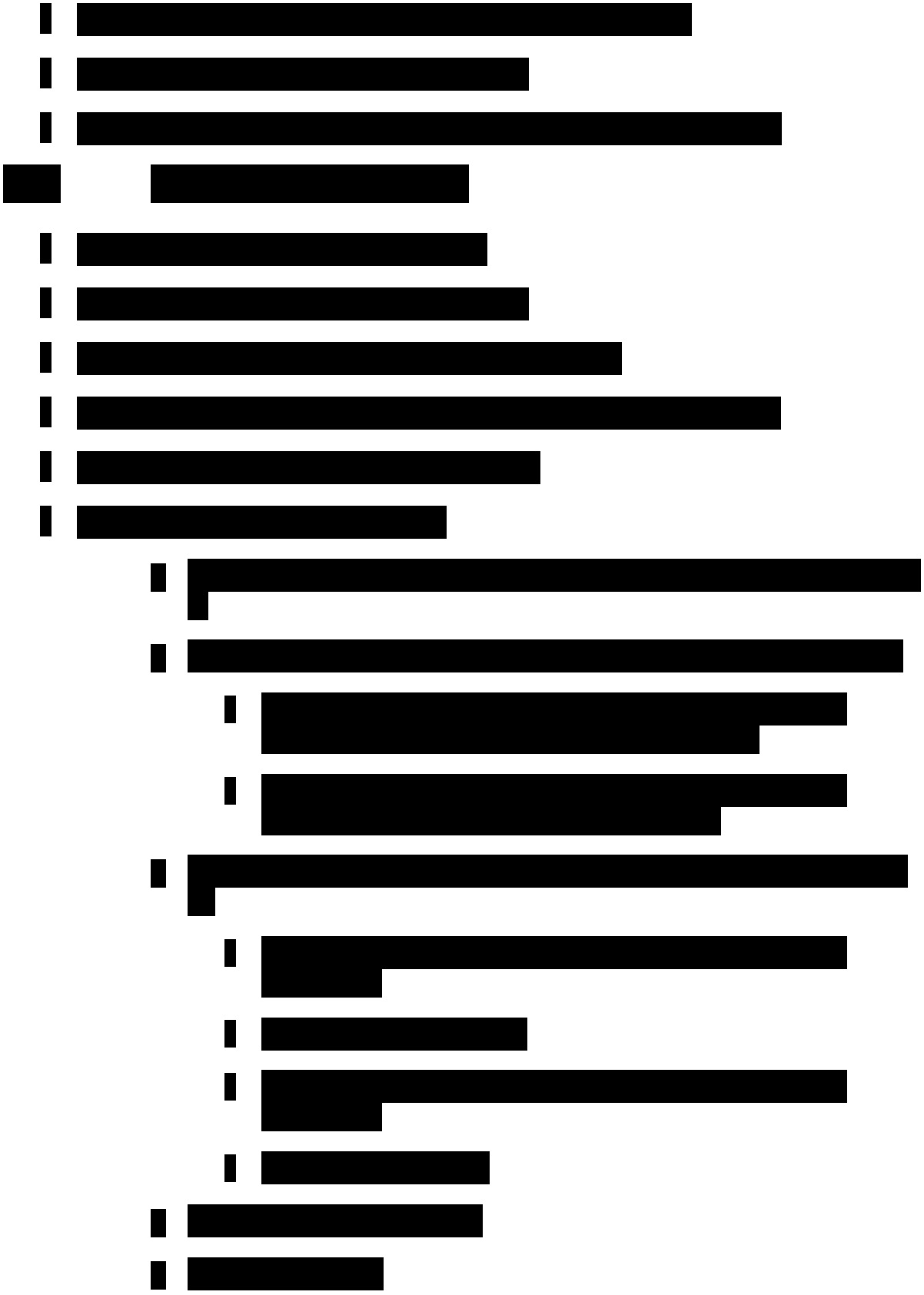


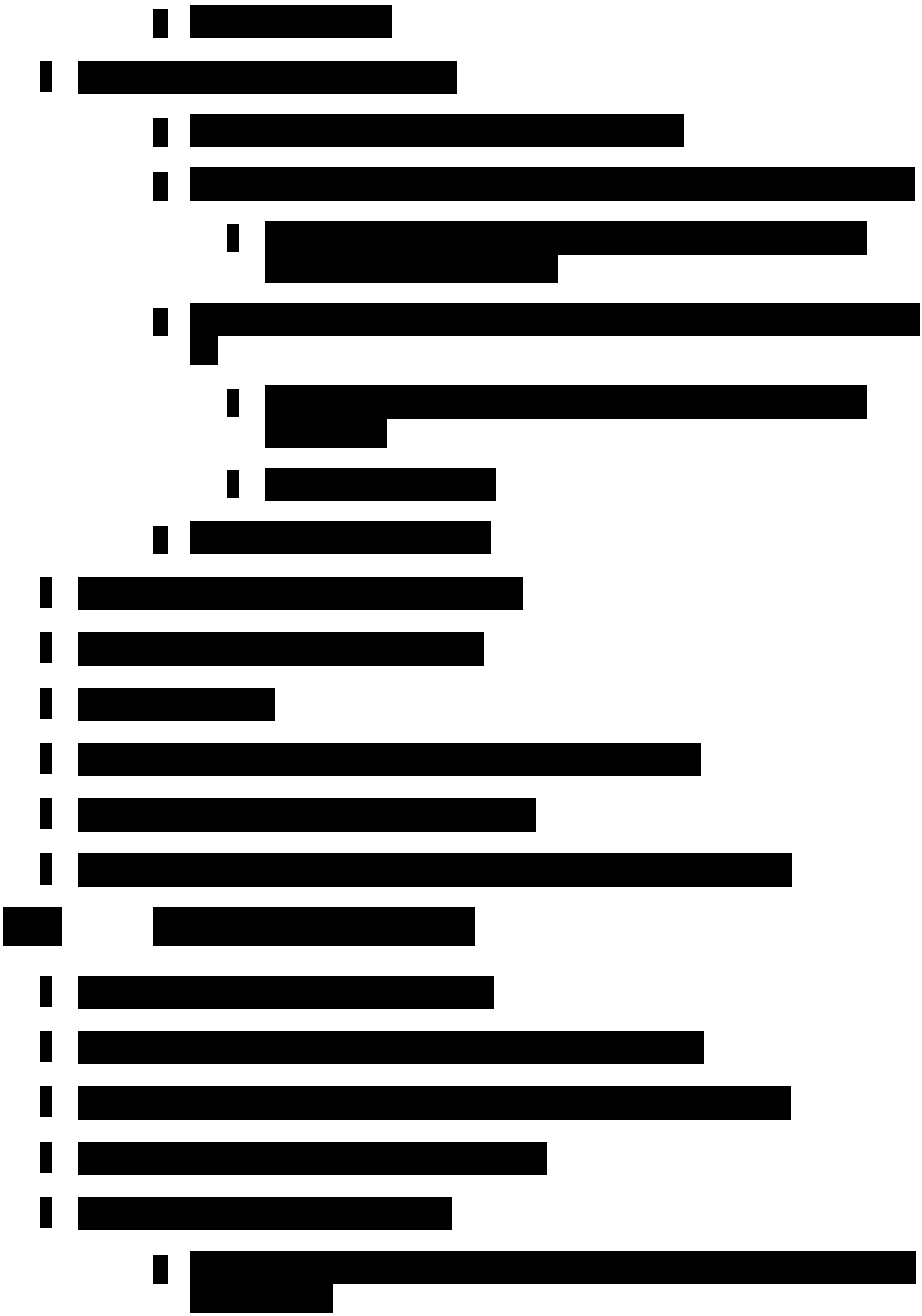


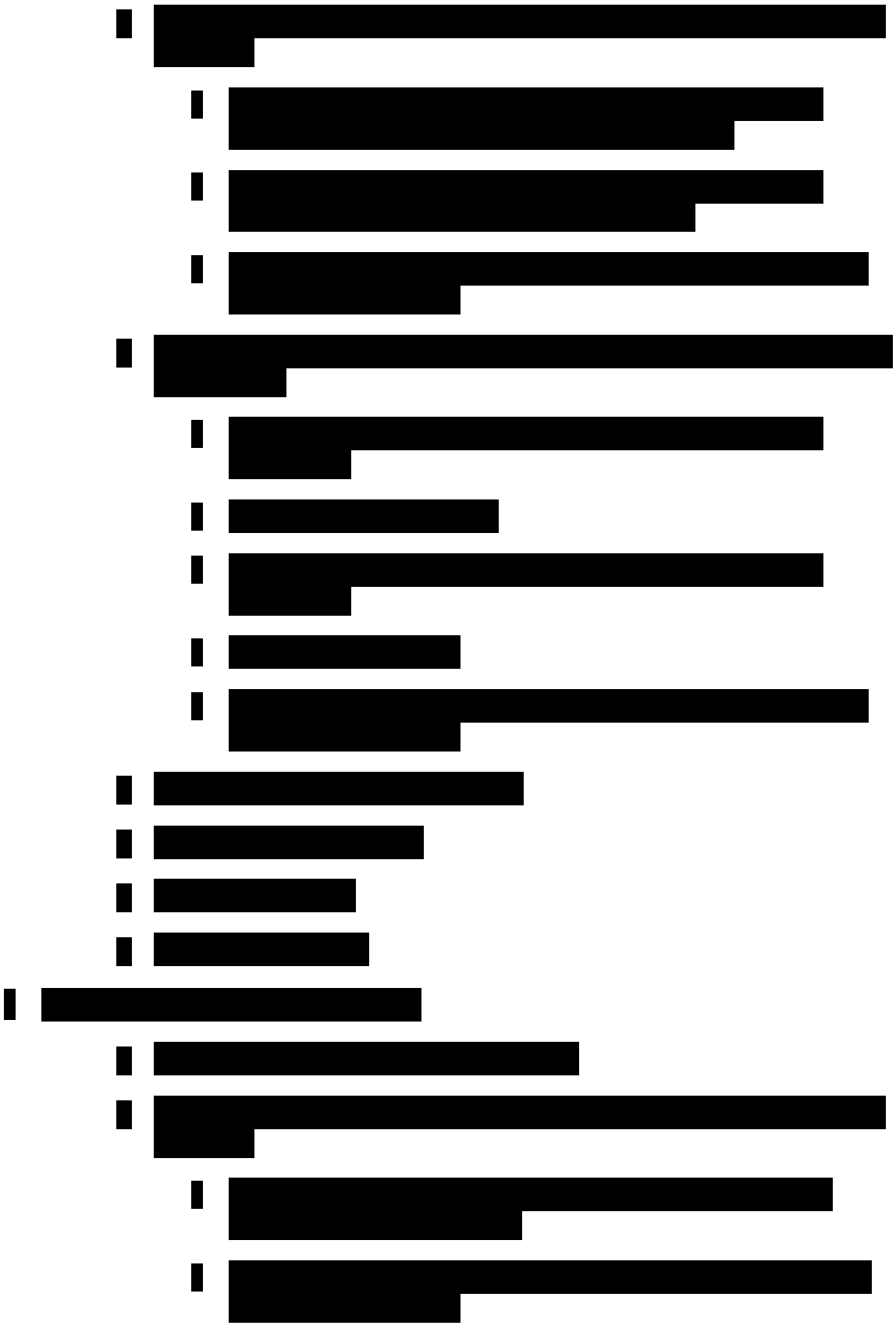


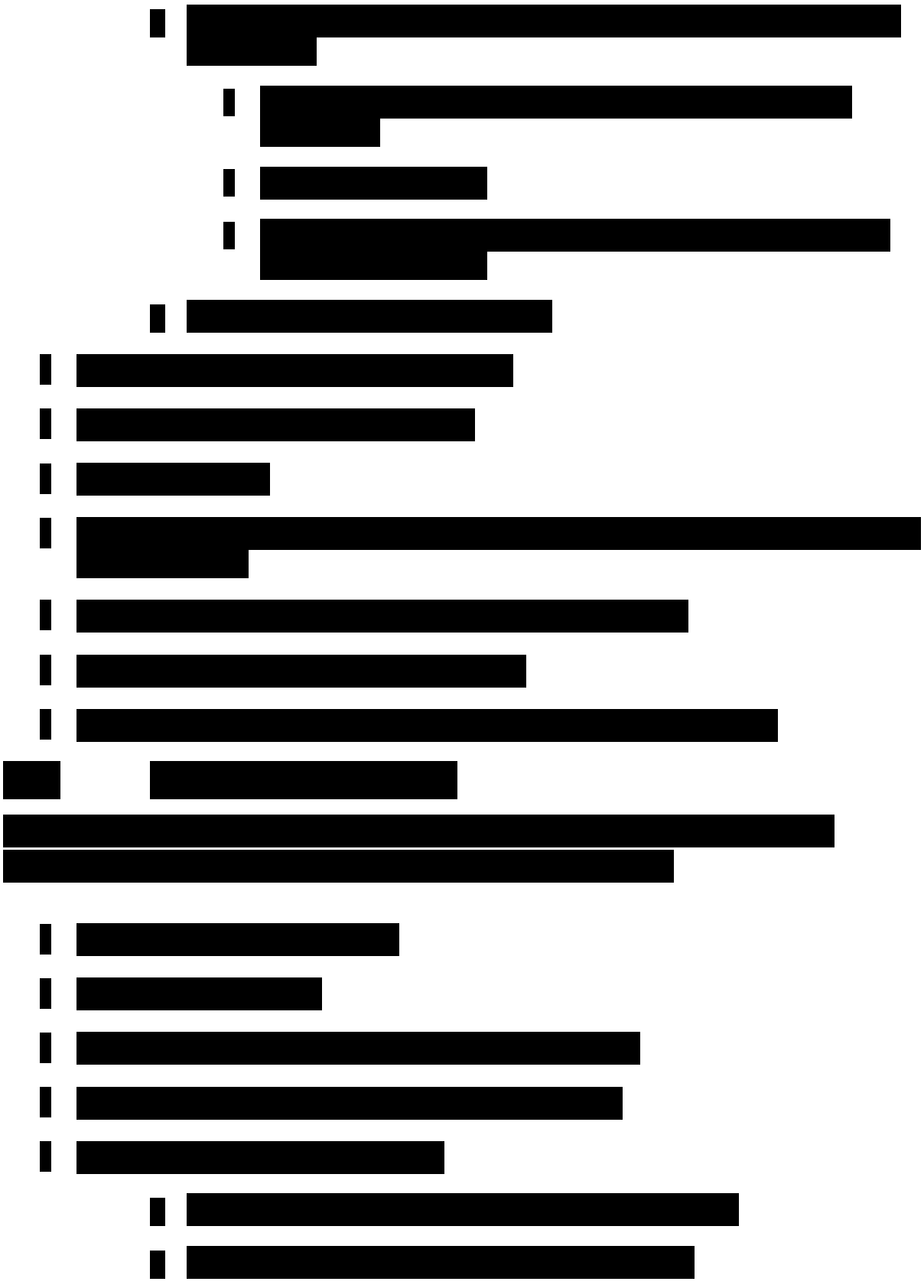


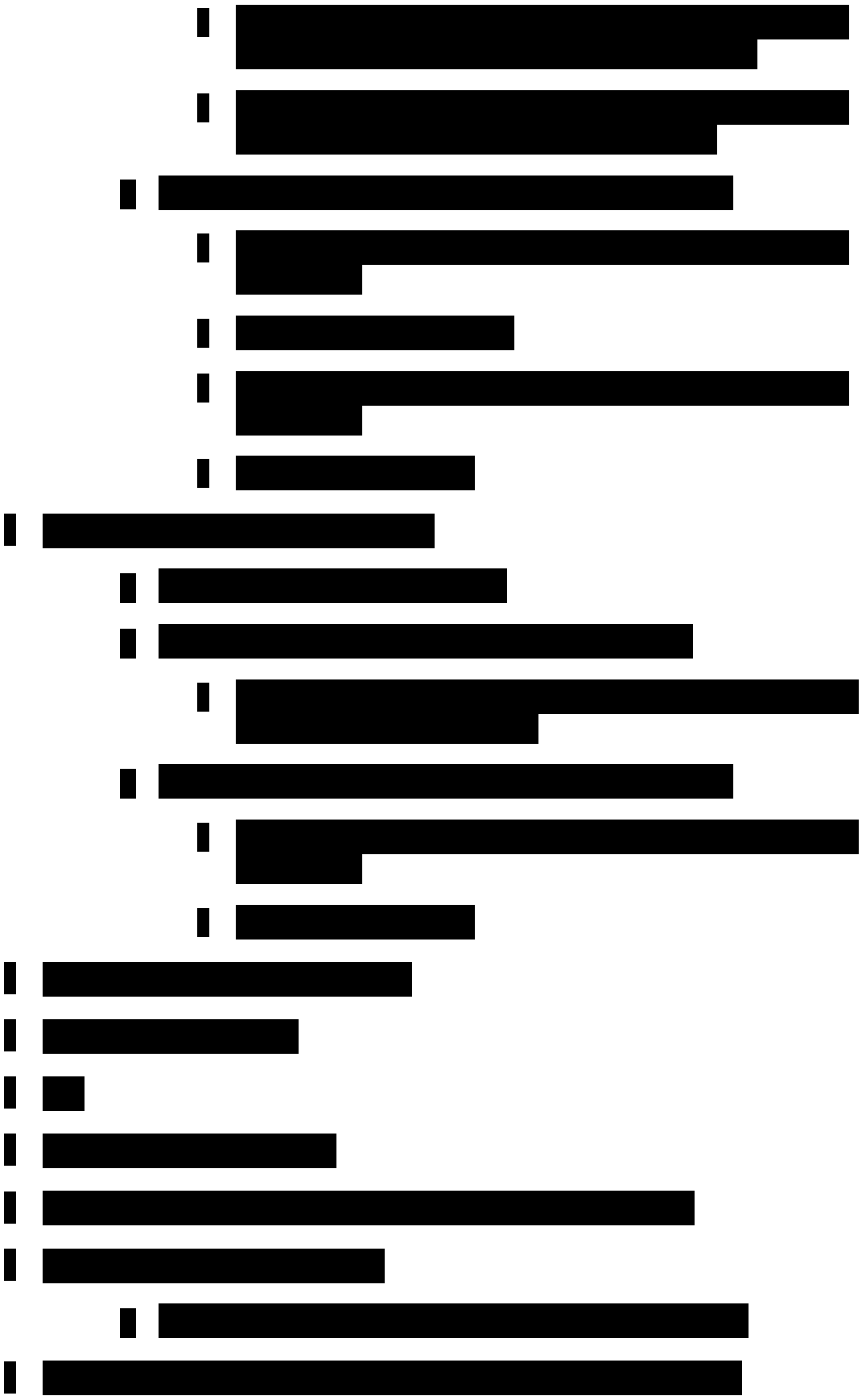


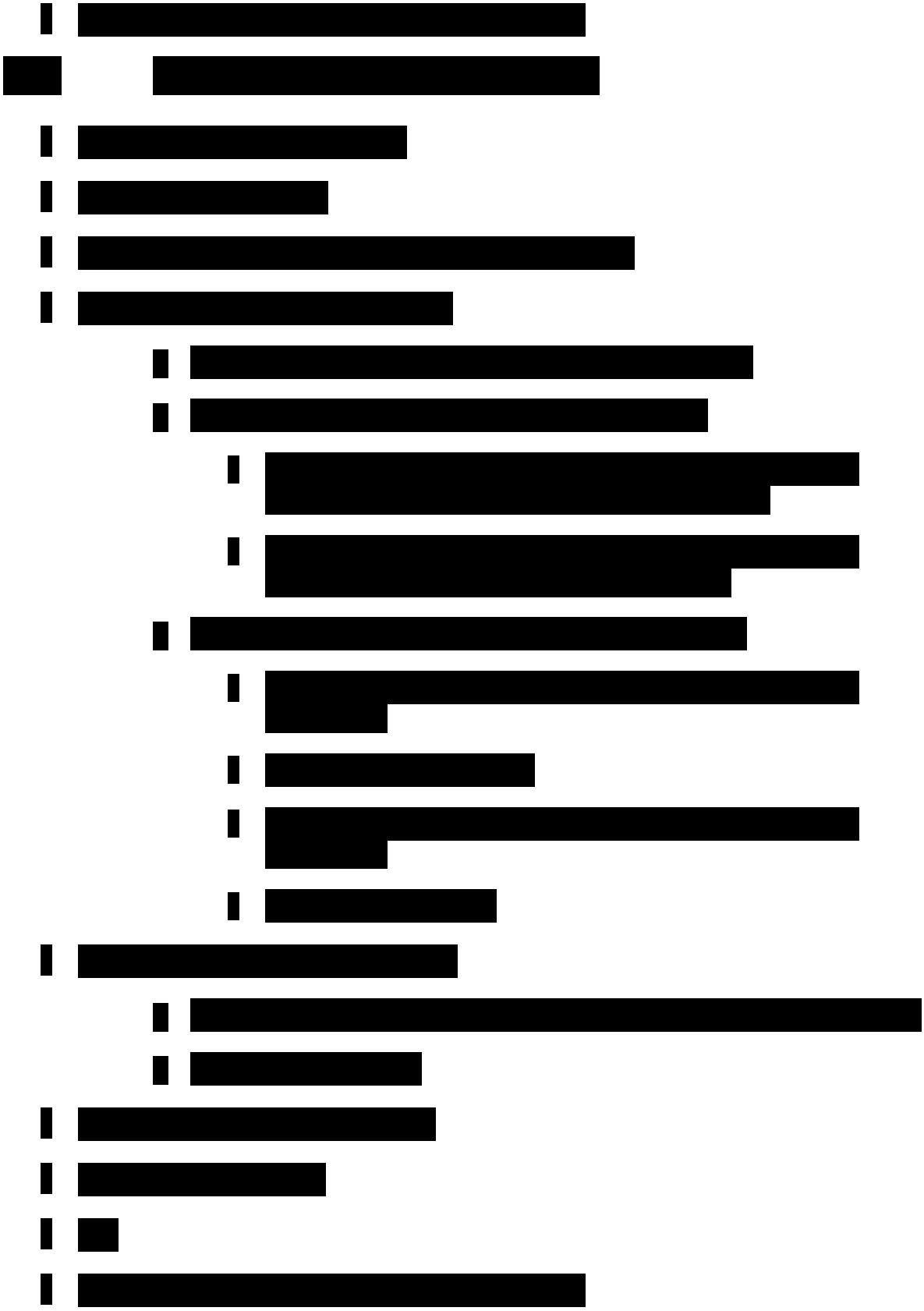


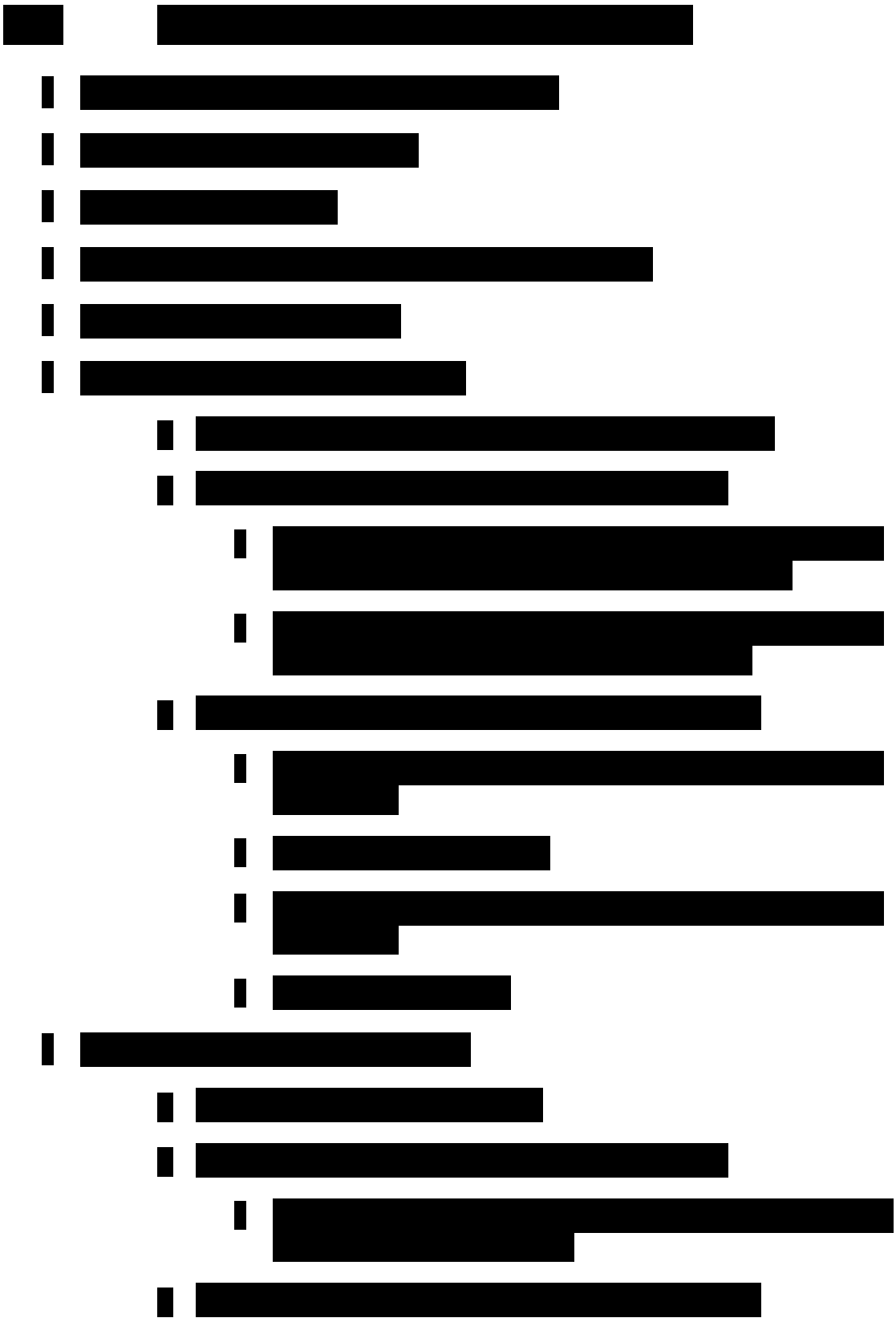












8.5 Instructions for the Patients

After patients have signed the informed consent, they will be instructed as follows:

- Patients will be instructed to complete the study-related procedures as explained to them by the study site personnel.
- Patients will be instructed to refrain from swimming, being exposed to smoke, or other exposure that might cause eye irritation during the study.
- If glasses are worn for vision correction, patients should remember to bring the glasses each time they visit the doctor's office.
- Patients must not read, use the computer, or look at cell phones/tablets without the use of reading glasses during any portion of the study visits. Note: Patients will be required to refrain from using their glasses during the near-vision tasks and associated near-vision task questionnaires, but *may* use their glasses to fill out other study related questionnaires.
- Patients will be instructed to strictly follow the study visit schedule and to report all changes in condition to the site.
- Patients will be instructed to maintain a stable dose of any concomitant medication used chronically.
- Patients will be instructed to report any changes to their medication at their next study visit, or to report any new medication(s) initiated during the study. Patients will also be reminded to contact the study site if they are experiencing any difficulties during their study participation.
- Patients will be reminded of the systemic and ocular medications/treatments that are prohibited for the duration of the study (see Section 4.6).

- Patients will be reminded that study medication must be stored out of the reach of children at all times.
- Patients will be provided a dosing card for additional instructions on study drug administration.

8.6 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and well-being of the patients during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit. For all parameters not measured, indicate "not done".

8.7 Compliance With Protocol

Patients will be scheduled for follow-up visits, and these should occur as close as possible to the day specified in the visit schedule.

At each postbaseline visit, the investigator or designee will ask patients if they have been compliant with study medication use, have used any concomitant medications, or have had any medical procedures performed since the previous visit.

8.8 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 Allergan and will be clearly documented on the appropriate eCRF.

8.9 Withdrawal Criteria

A patient may be withdrawn from the study if it is deemed by the investigator or Allergan that it is unsafe for the patient to continue in the study. Patients who are withdrawn from the study will not be replaced.

If the patient withdraws prior to completing the study, the procedures outlined for the visit 8/study exit should be performed at the last visit attended (see Section 8.4.9).

If a female patient becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study (see Section 4.5.1.1).

8.10 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 eCRF. 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 eCRF 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 eCRF.

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 patient 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.

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

Any preplanned 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 eCRF.

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 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 Allergan 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 IxRS via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

9.5 Procedures for Pregnancy Follow-up and Reporting (If Applicable)

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed, and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was enrolled in this study and treated with an investigational drug ocular oxymetazoline, ocular pilocarpine, or the combination of oxymetazoline and pilocarpine, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

It is not known if the investigational products may have teratogenic or mutagenic effects, as studies to evaluate these effects in humans have not been done. There are no adequate and well-controlled studies of pilocarpine or oxymetazoline administration in pregnant women. In addition, it is not known if these products are excreted in human milk.

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 Code of Federal Regulations [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.

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 21 CFR 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 ECGs. The investigator's copy of the eCRFs 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 (ie, the 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 Attributable, Legible, Contemporaneous, Original, and Accurate.

10.4.2 Case Report Form Completion

This protocol will use electronic data capture (EDC) through a qualified third party vendor. The data will be entered in the EDC system in a timely manner on an ongoing basis.

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for eCRFs (as indicated in the case report forms) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs 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 eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, the Allergan-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 Allergan.

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

10.5.1 Labeling/Packaging

The study medication will be packaged and supplied by Allergan. The medication will be identified as an investigational compound.

The study medication will be provided in sealed study kits containing 2 multidose bottles of study treatment; 1 bottle will be labeled Dominant ([redacted] and 1 bottle will be labeled Non-Dominant ([redacted] The study number and kit number, at a minimum, will be printed on the outer carton and bottle labels. Additional labeling will be in accordance with local regulations.

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 units returned to the investigator by the patient (if applicable), and the number of units returned to

Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed or administered only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol for patients who are under the direct supervision of an investigator. A unit is defined as a study kit that is comprised of 2 multidose bottles of study medication.

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

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

10.6 Monitoring by the Sponsor

A representative of Allergan 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 onsite 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 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 a 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.

10.8 Coordinating Investigator

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

11. References

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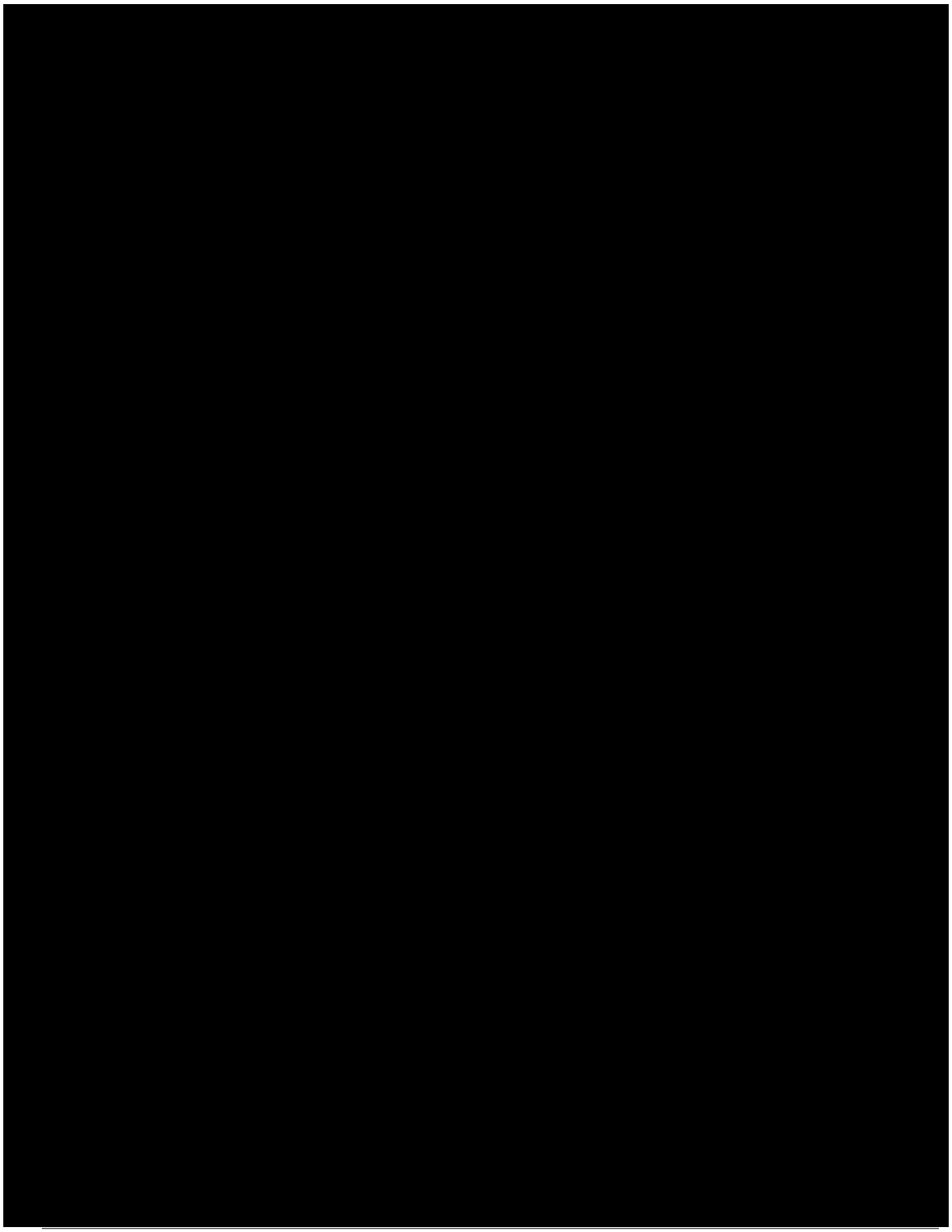
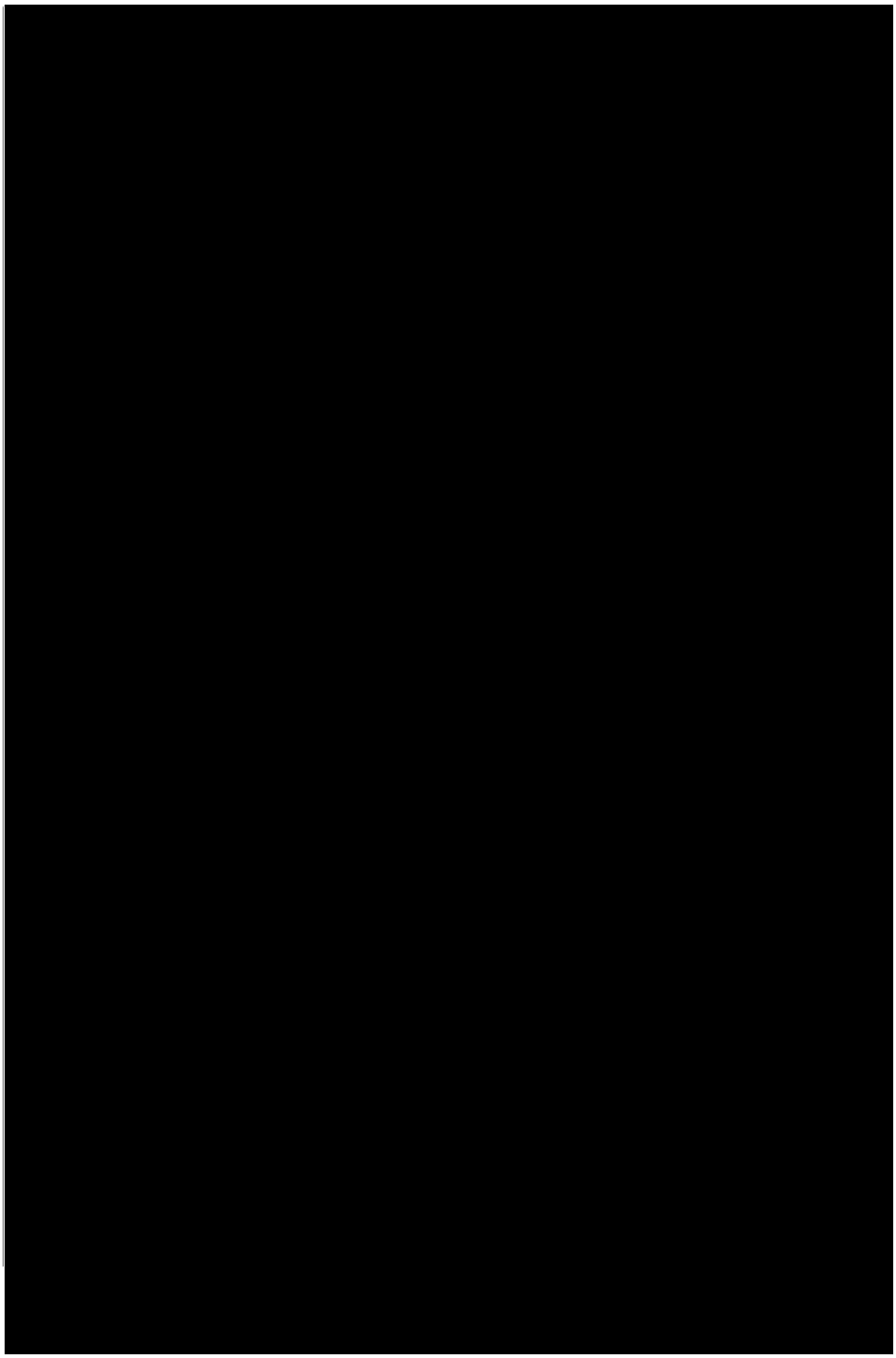
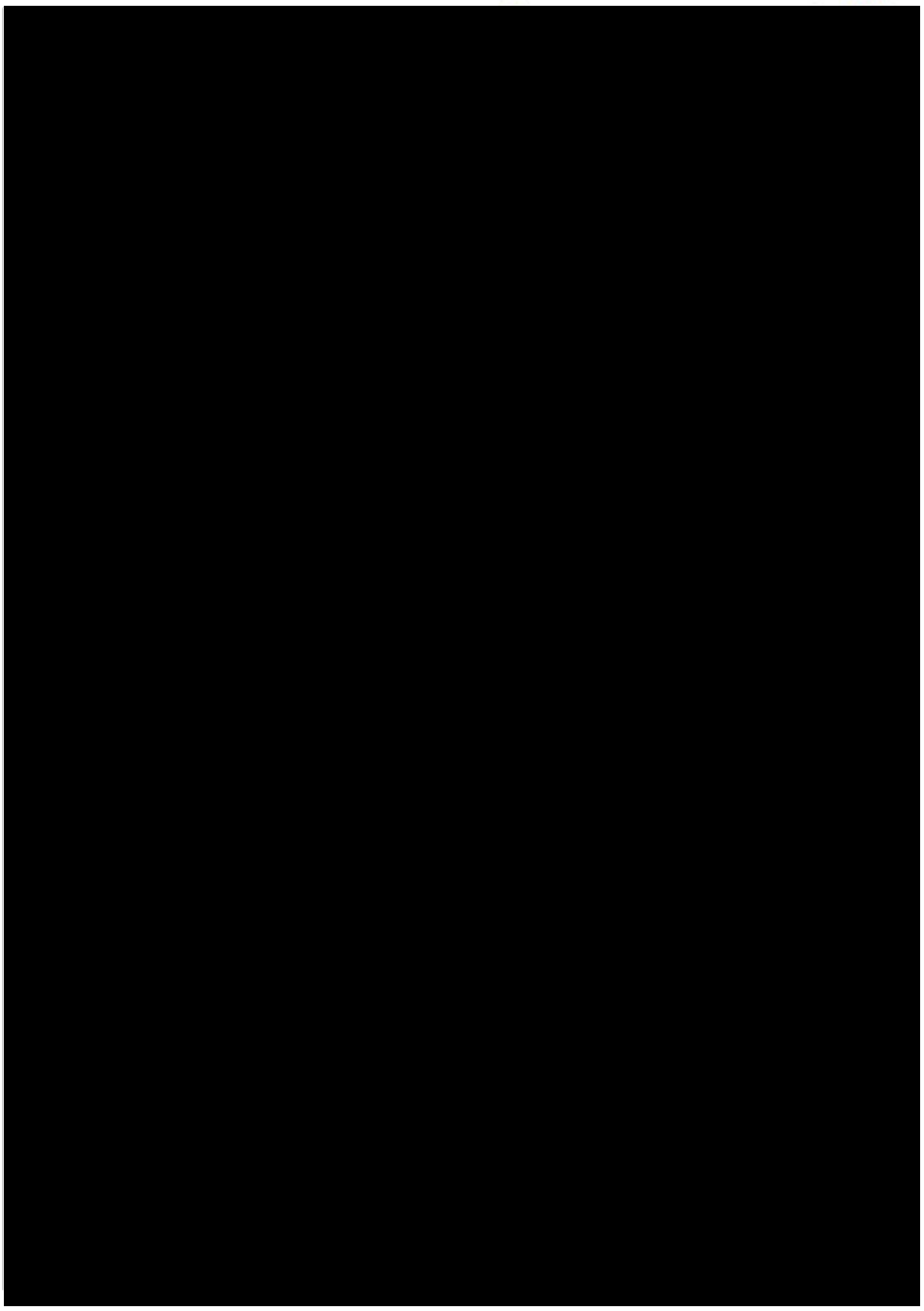
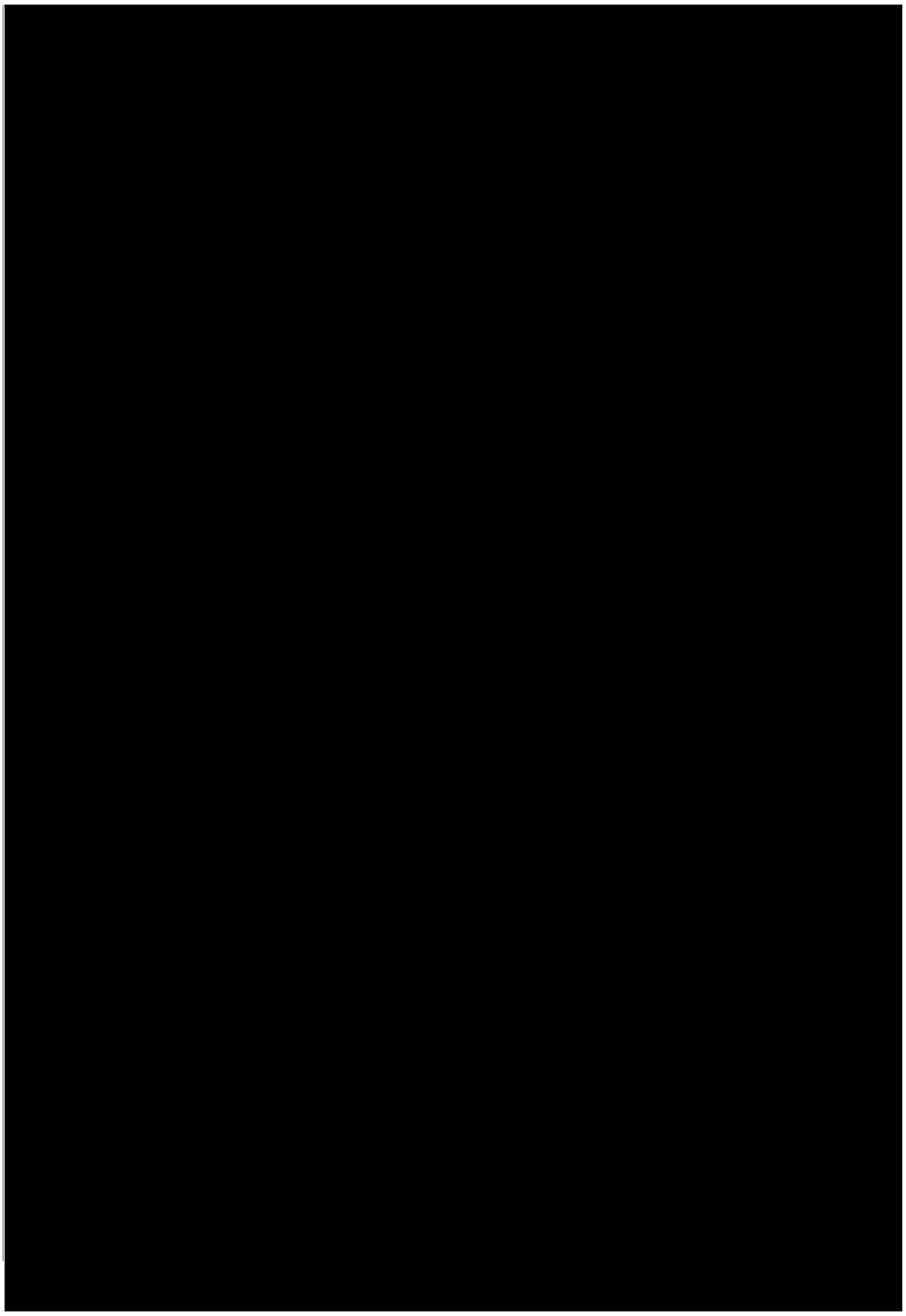
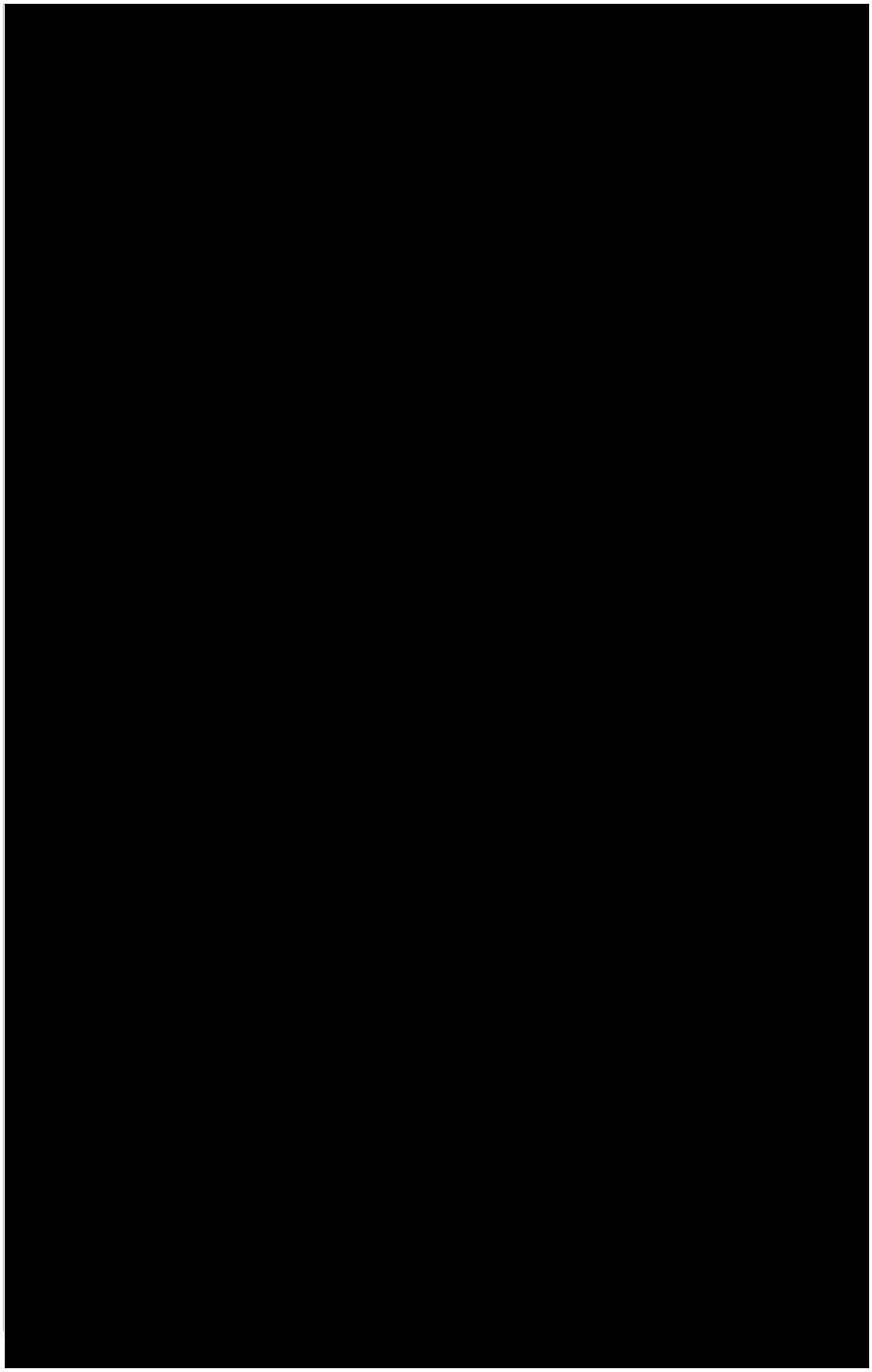
12. Attachments

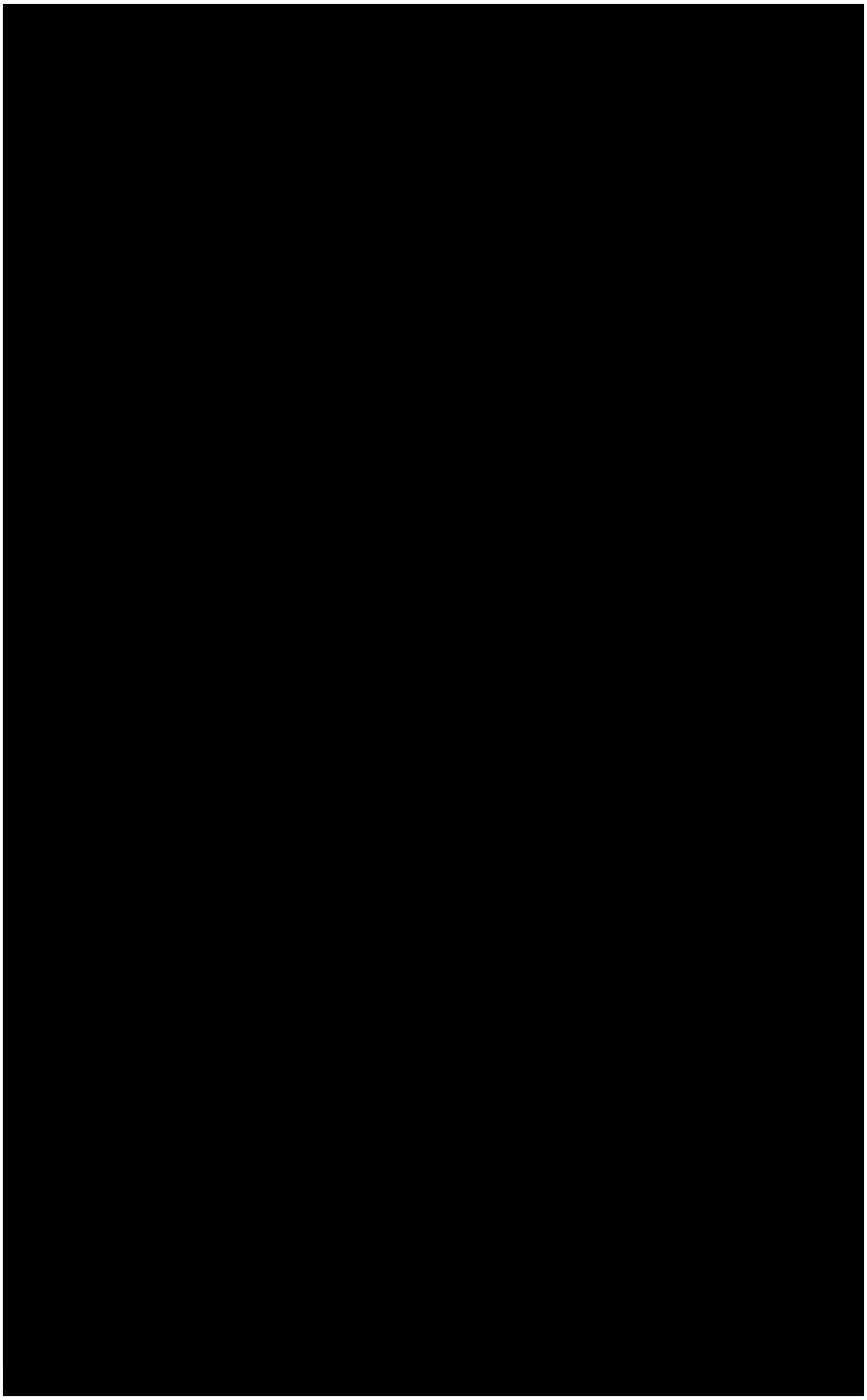


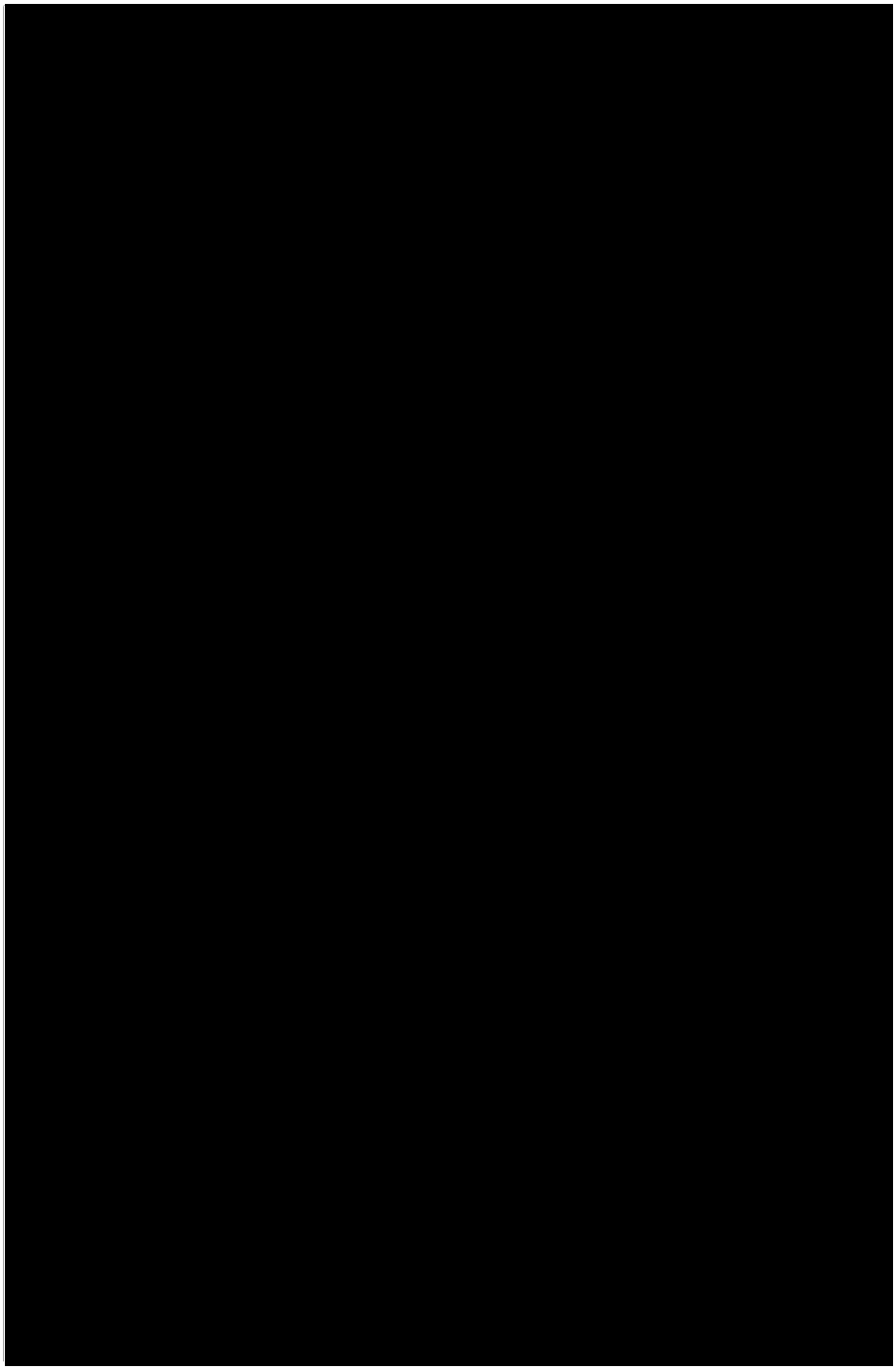


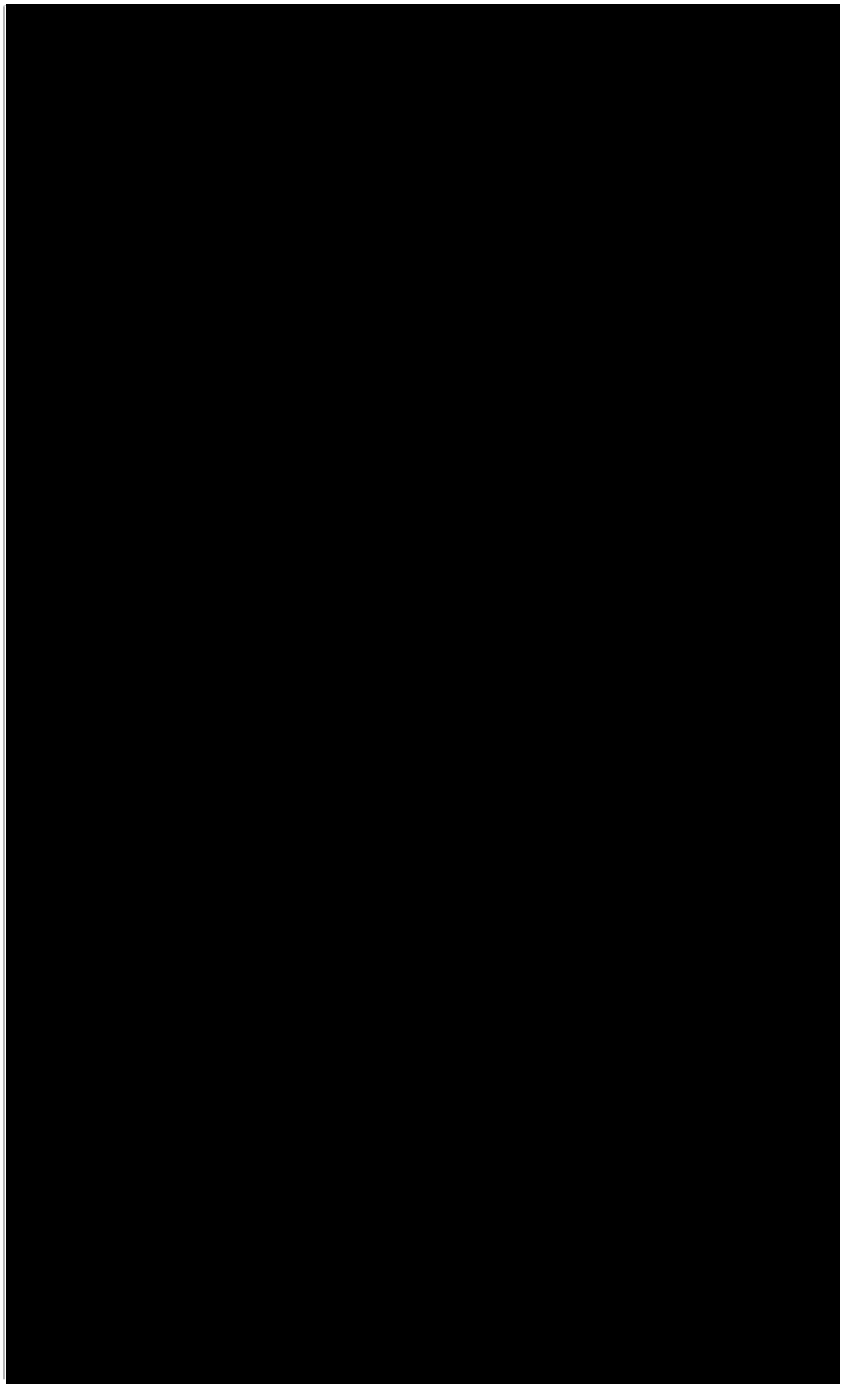


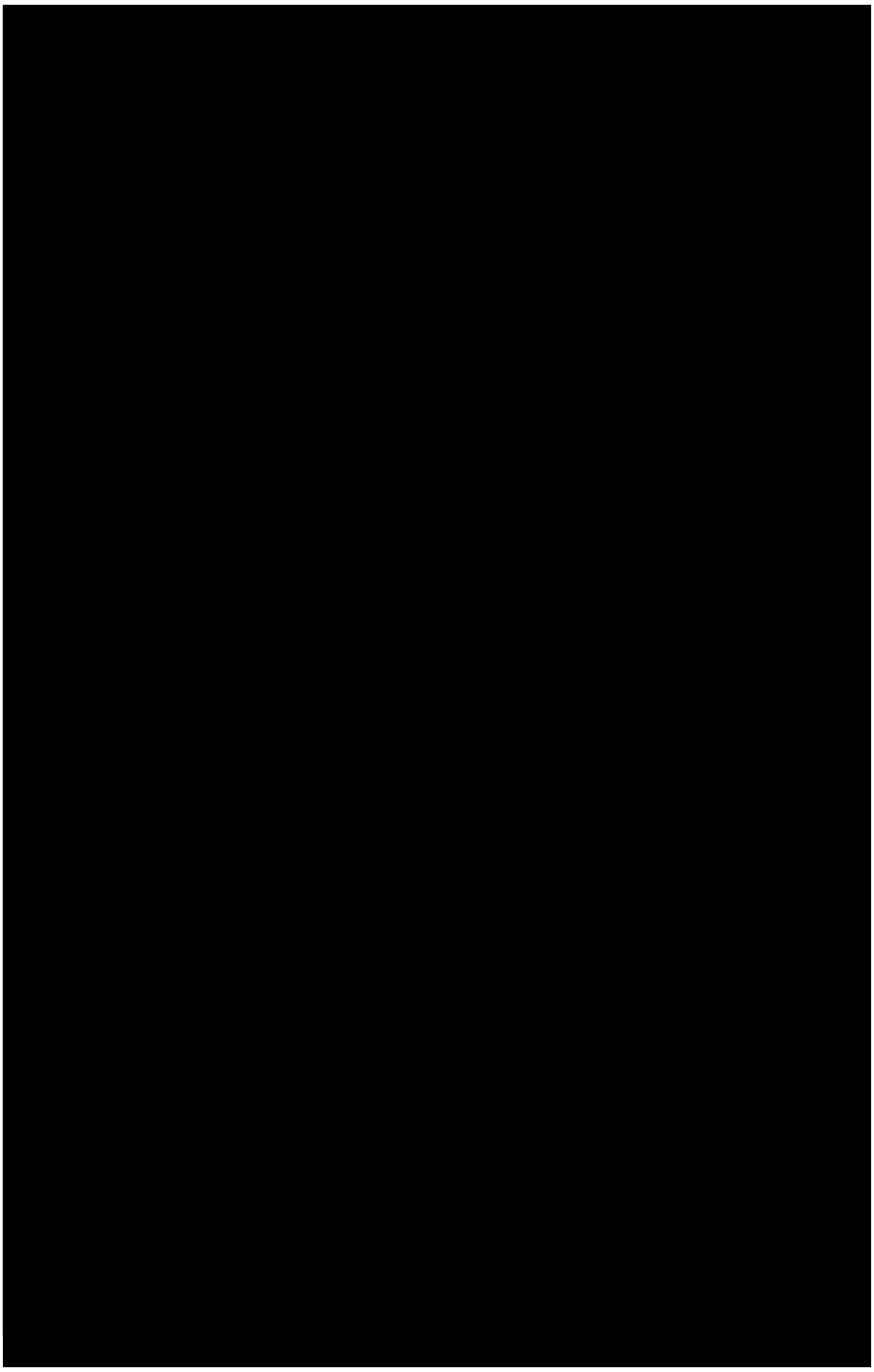


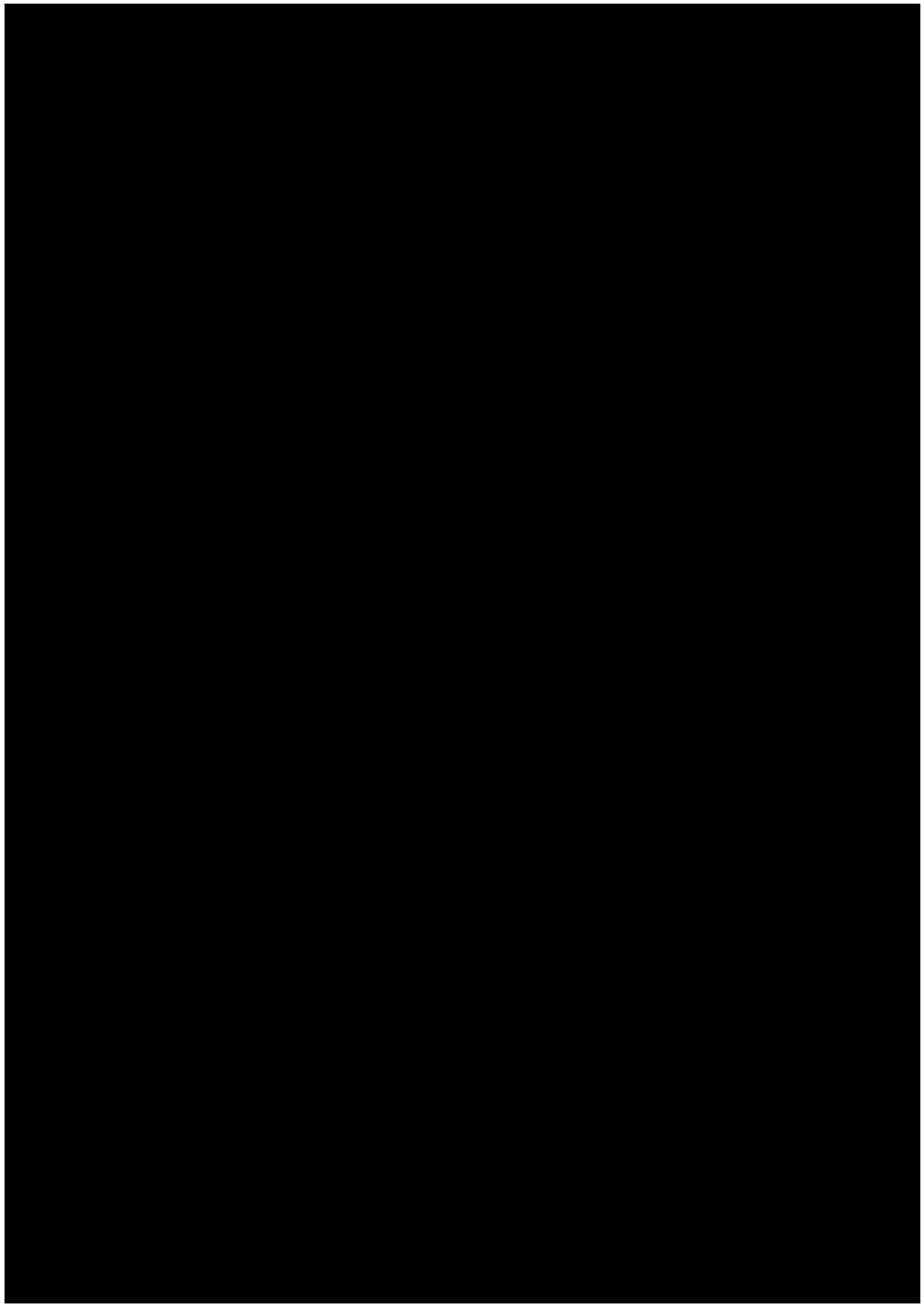


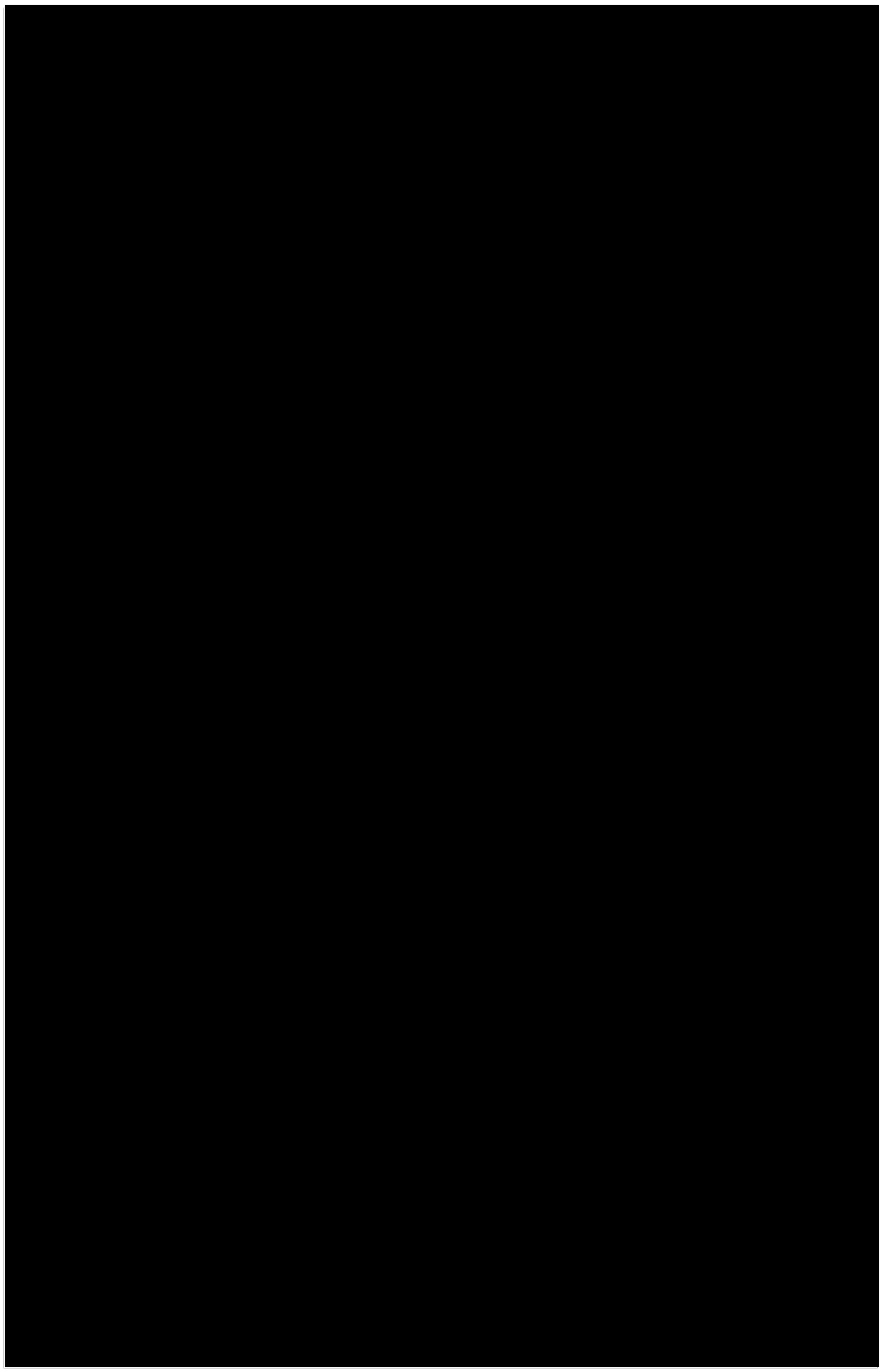


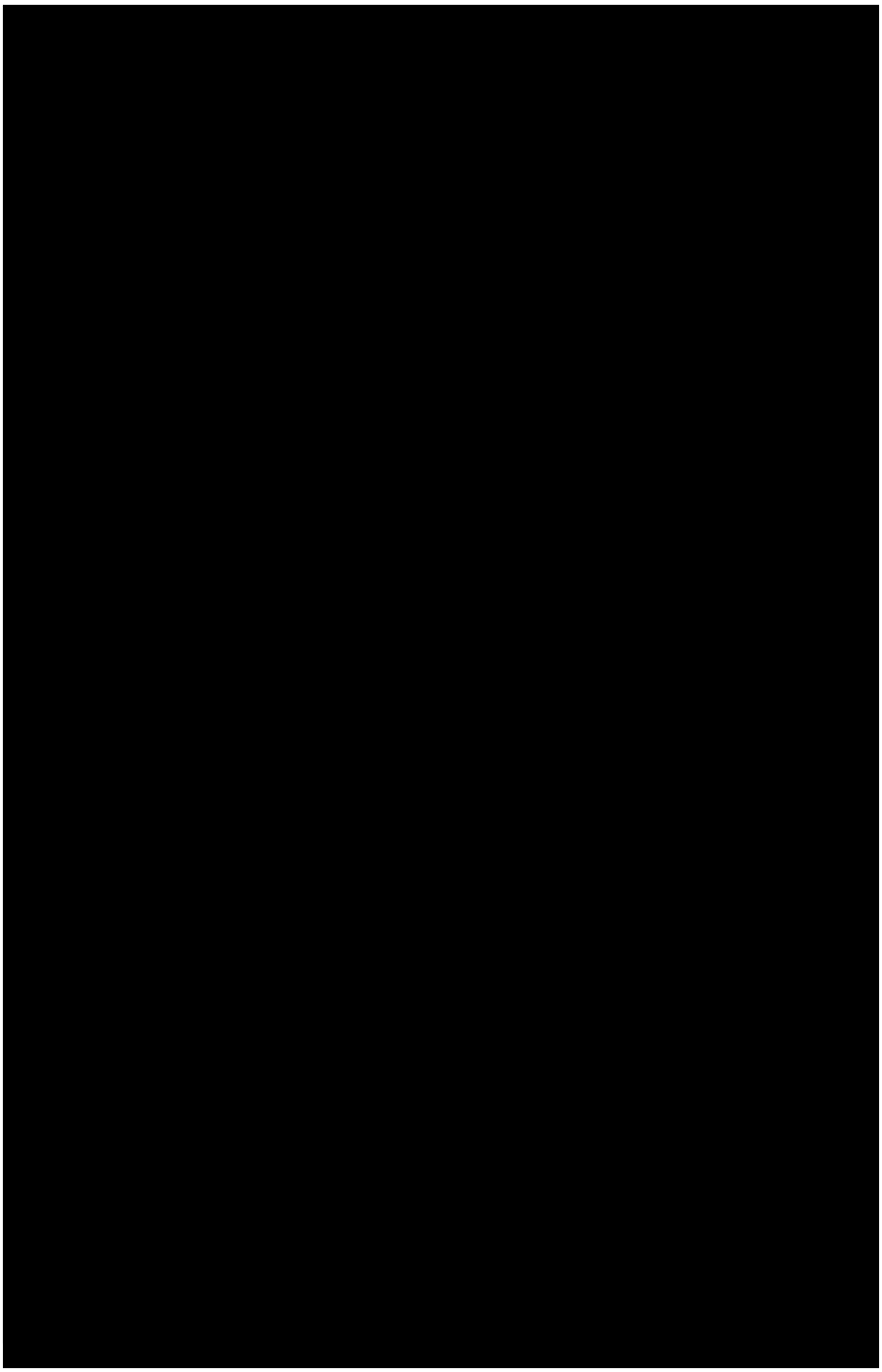


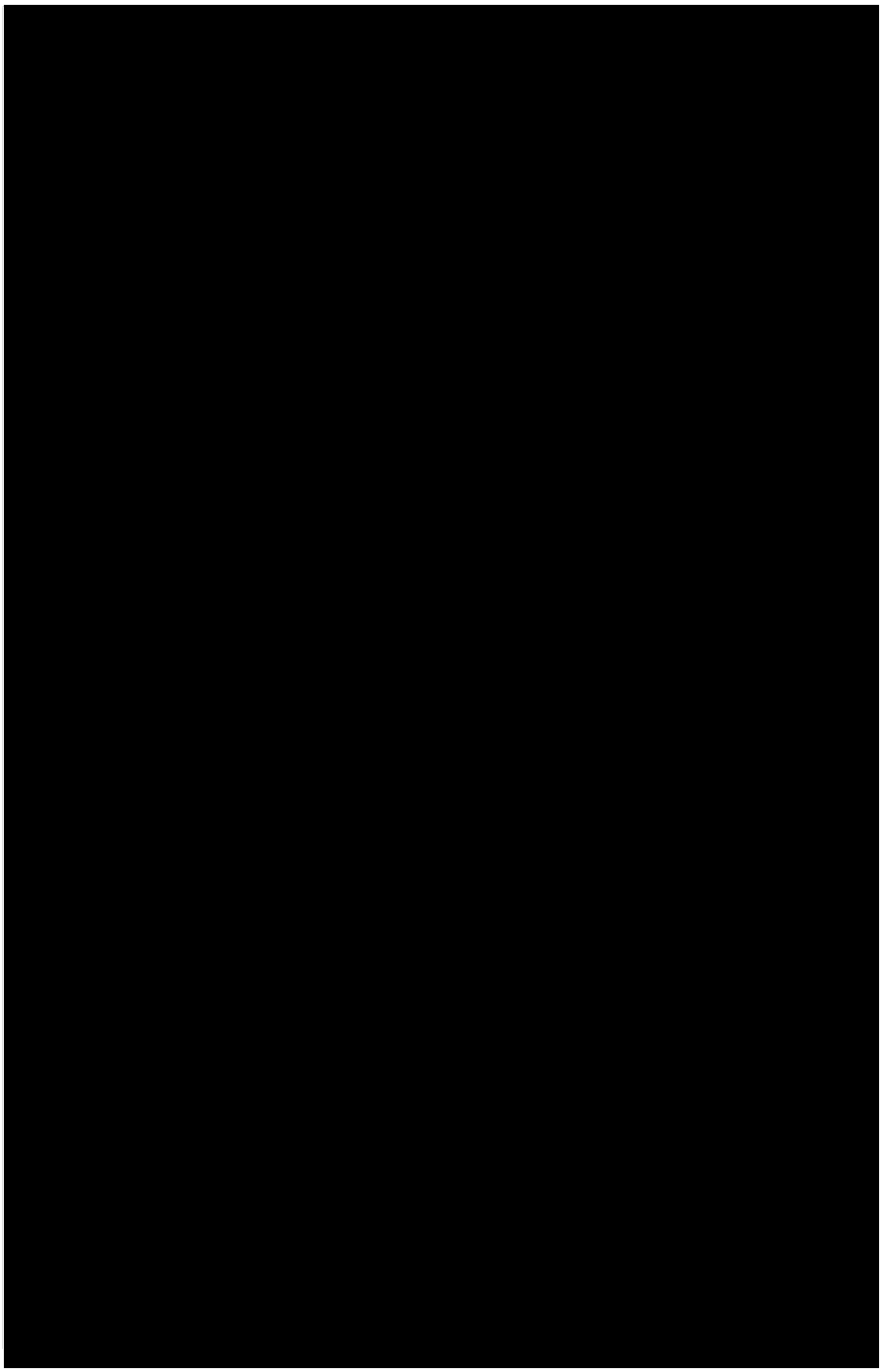


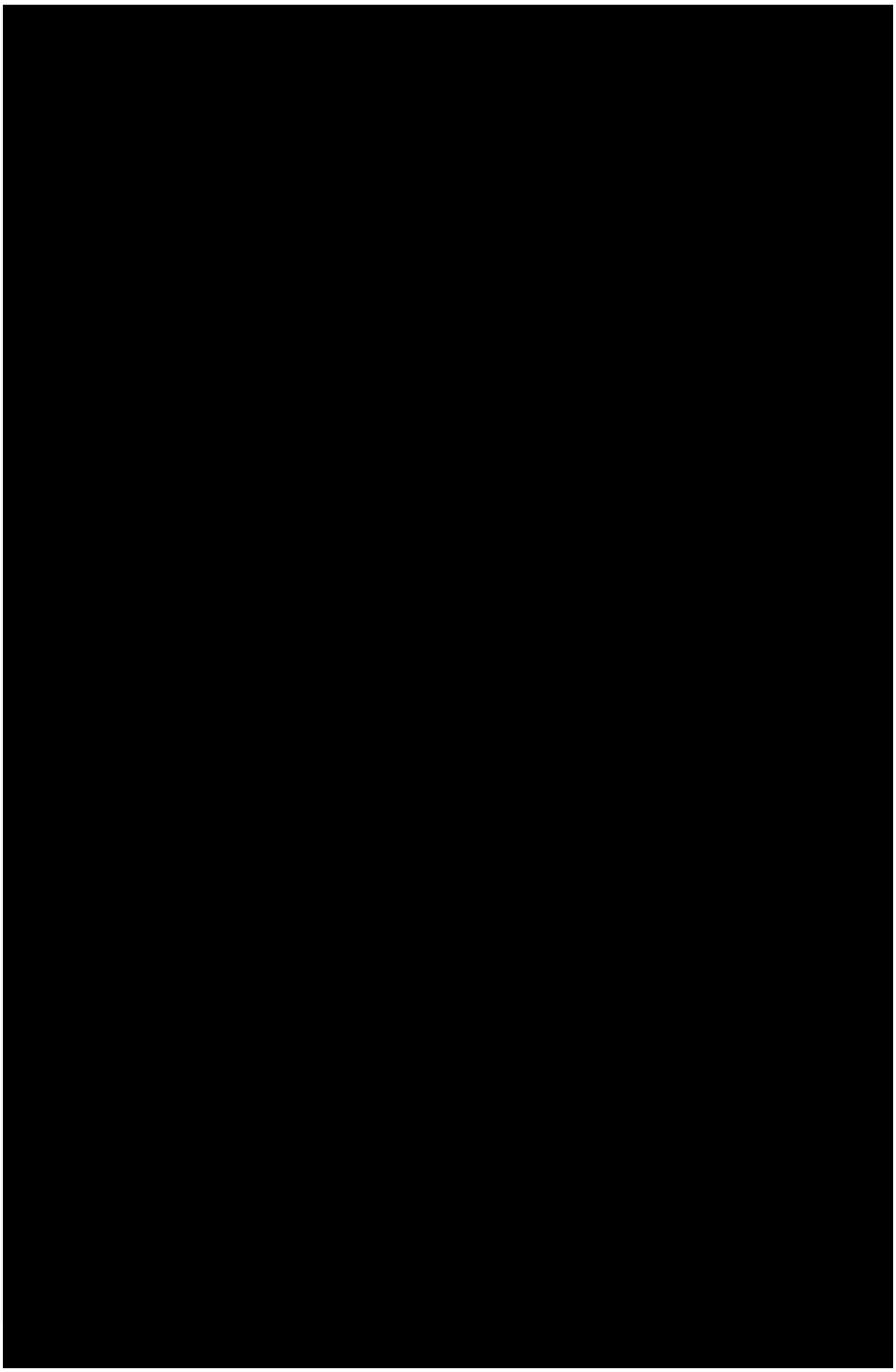


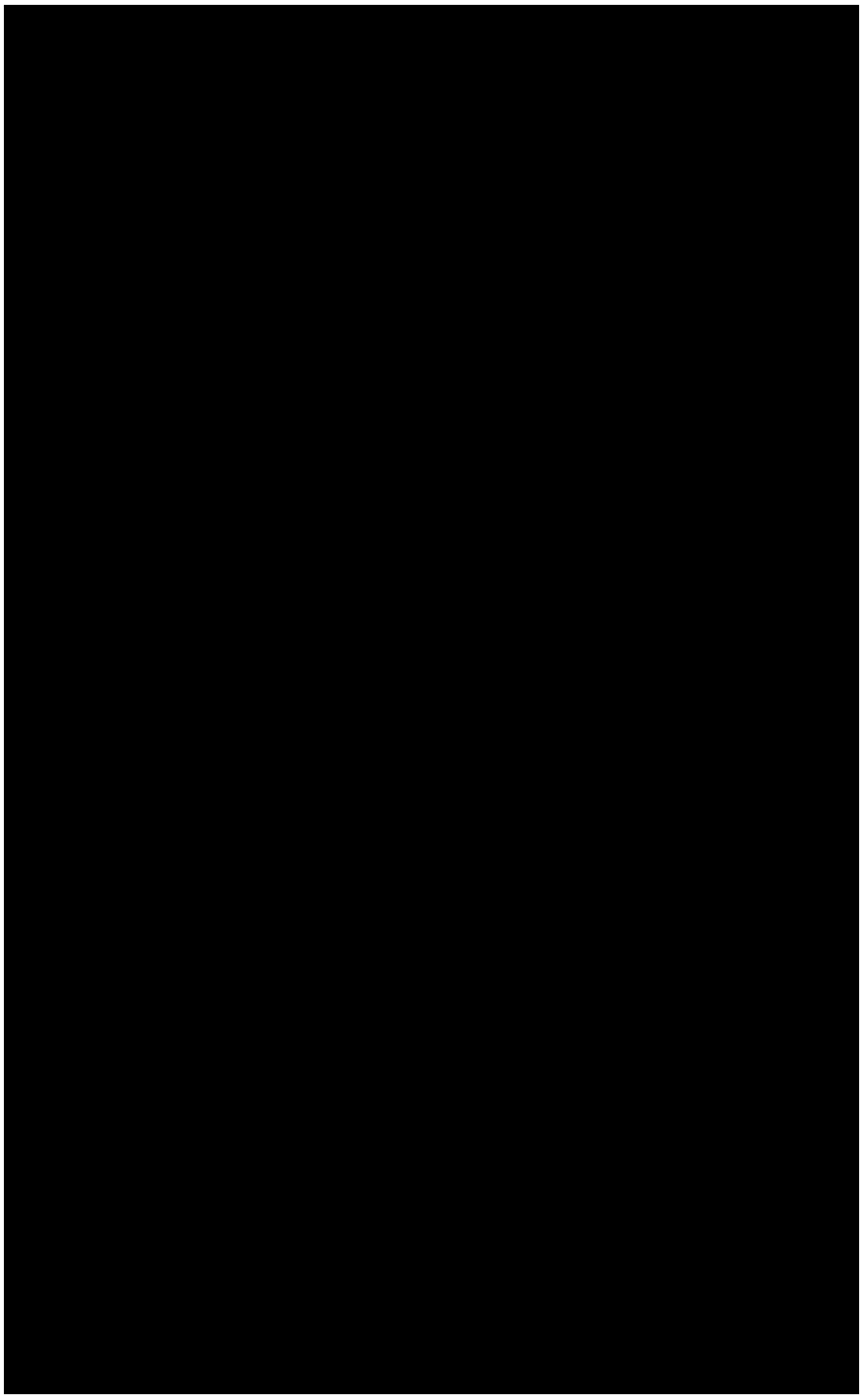


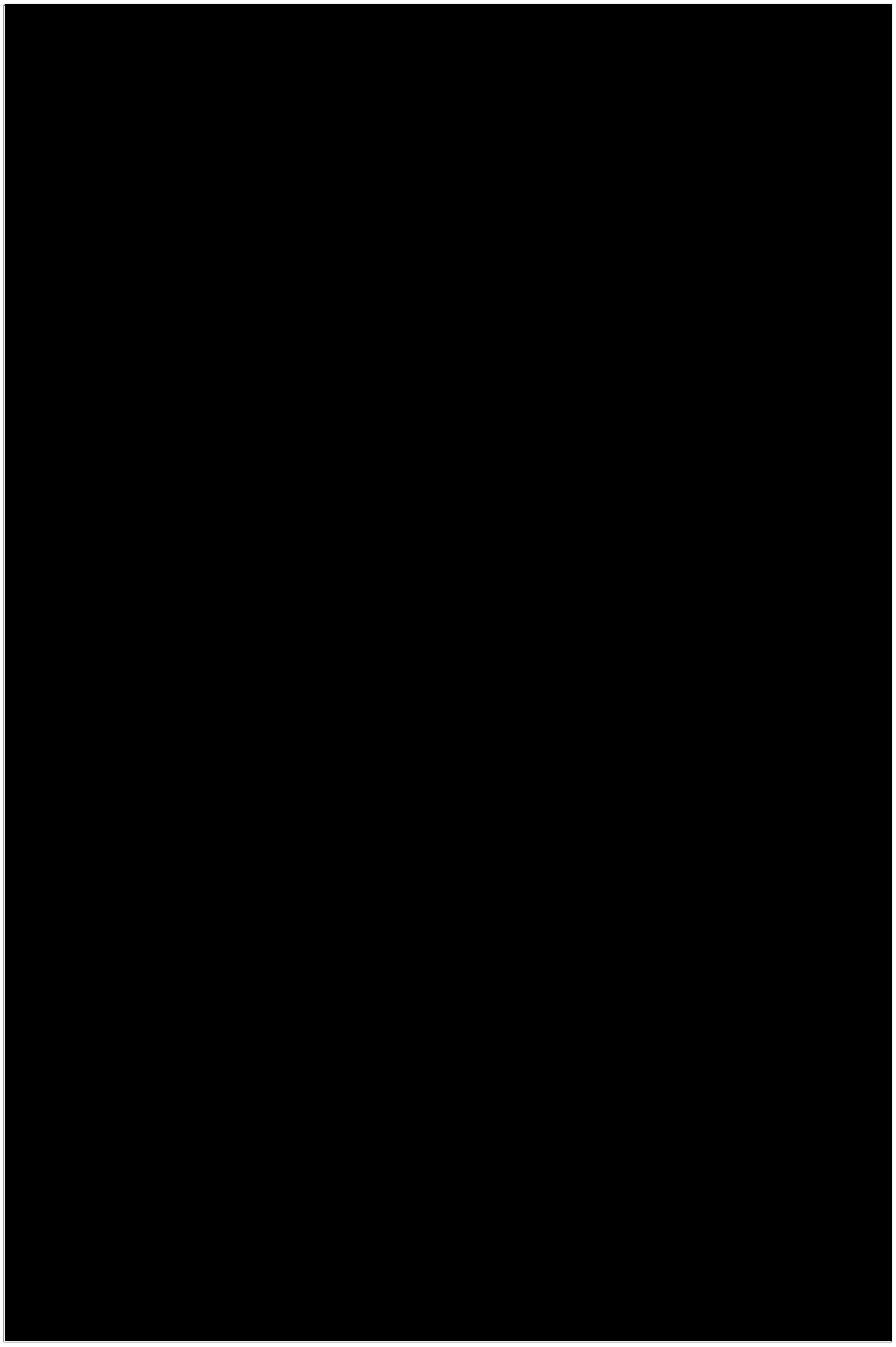












12.2 Package Insert

The appropriate package insert will be supplied to investigators in countries where the product is marketed.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
5-HT	serotonin
ANCOVA	analysis of covariance
AP	analysis plan
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from time 0 to 12 hours
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0-tlast}$	area under the plasma concentration curve from time 0 to the last timepoint
BID	twice daily
bpm	beats per minute
C_{max}	plasma maximum concentration
C/D	cup to disc
cd/m^2	candelas per square meter
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
D	diopters
DET	dry eye test
EC_{50}	maximal effective concentration
ECGs	electrocardiograms
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
HCl	hydrochloride
HIPAA	Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOLs	intraocular lenses

IOP	intraocular pressure
IRB	Institutional Review Board
IxRS	interactive response system
LASIK	laser-assisted in situ keratomileusis
LC-MS/MS	liquid chromatography tandem mass spectrometry
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NDA	New Drug Application
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
NOAEL	no-observed-adverse-effect-level
NVPT	near vision task-based presbyopia
NZW	New Zealand White
OCT	Optical Coherence Tomography
OD	right eye
OS	left eye
OTC	over-the-counter
OU	both eyes
PDE5	phosphodiesterase 5
PGIC	Patient Global Impression of Change
PIOL	phakic intraocular lens
PRK	photorefractive keratectomy
PRO	patient-reported outcome
QD	once daily
RK	radial keratotomy
SEB	scleral expansion band
$T_{1/2}$	half-life
UDVA	uncorrected distance visual acuity
UNVA	uncorrected near visual acuity
US	United States
VAS	visual analog scale
w/v	weight/volume

12.4 Protocol Amendment 1 Summary

Title: A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN 199201 and AGN 190584 in Patients With Presbyopia

Protocol 199201-010 Amendment 1

Date of Amendment: February 2016

Amendment Summary

This summary includes changes made to Protocol 199201-010 (October 2015). Grand Seiko autorefraction is no longer a mandated method for pupil diameter measurement, since not all sites have this autorefractor. Only selected sites will use this measurement.

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
Title Page	The Allergan Signatory was changed, an e-mail address was added for serious adverse event reporting, and the Allergan Medical Safety Physician contact information was changed	To reflect the current Therapeutic Area Head and Safety Physician and to facilitate serious adverse event reporting
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Section4.5.1.1	~~If a female becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed, and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was enrolled in this study and treated with an investigational drug ocular oxymetazoline, ocular pilocarpine, or the combination of oxymetazoline and pilocarpine, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.~~	To be consistent with the Informed Consent Form
Section 5.7	Text referring to a temperature monitoring device was deleted	To apply to sites that may not have a temperature monitoring device
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Section 8.5	Deleted instruction for patients to remain at the study site for the duration of the visit	To minimize patient inconvenience
Section 9.5	This section was added to describe the procedures for pregnancy follow-up and reporting	To be consistent with the Informed Consent Form

12.5 Protocol Amendment 2 Summary

Title: A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN-199201 and AGN-190584 in Patients With Presbyopia

Protocol 199201-010 Amendment 2

Date of Amendment: March 2016

Amendment Summary

This summary includes changes made to Protocol 199201-010 Amendment 1 (February 2016). The order of the Grand Seiko automated refraction was corrected in Table 2, the description of the primary efficacy variable was clarified, and selected sites are now to use only the Zeiss Visante OCT model.

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, Key Inclusion Criteria	• Natural or corneal laser refractive surgery corrected [redacted] presbyopia in each eye and subjective complaints of poor near vision that impact activities of daily living, [redacted]	For clarification
Protocol Summary, Efficacy, and Section 7.2.1	The primary efficacy variable will be the weighted average change from baseline in <u>mesopic, high contrast UNVA</u> lines at day 28 in the nondominant eye.	For clarification

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Photopic pupil diameter (both eyes, ~~distance and~~ near)	Correction
Section 4.3	3. Natural or corneal laser refractive surgery corrected [redacted] presbyopia in each eye and subjective complaints of poor near vision that impact activities of daily living, [redacted]	For clarification

Section	Revision	Rationale
[redacted]		

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 8.5	• Patients must not read, use the computer, or look at cell phones/tablets without the use of reading glasses during any portion of the study visits. Note: Patients will be required to refrain from using their glasses during the near-vision tasks and associated near-vision task questionnaires, *but may use their glasses* to fill out other study-related questionnaires.	For clarification

12.6 Protocol Amendment 3 Summary

Title: A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN-199201 and AGN-190584 in Patients With Presbyopia

Protocol 199201-010 Amendment 3

Date of Amendment: June 2016

Amendment Summary

This summary includes changes made to Protocol 199201-010 Amendment 2 (March 2016). Mesopic and photopic DCNVA in the nondominant eye was added at baseline and day 28, and a statement was added that the investigator should note if the pupil dialated normally after the funduscopic examination at screening and visit 6.

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
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]d
Section 7.3.1	A detailed algorithm for the derivation of the primary efficacy variables will be documented in the AP.	For clarification
[redacted]	[redacted]	[redacted]
Section 7.4	Subgroup analyses will be performed for the primary efficacy variable by UNVA at baseline (20/40 to 20/80 and 20/100 to 20/200), age group, and iris color (brown or not brown)~~, gender, race, and ethnicity~~.	Gender, race, and ethnicity subgroup analyses will not be performed
Sections 8.4.2 [redacted]	[redacted]	[redacted]

ALLERGAN

Protocol 199201-010 Amd 3

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