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Study ID: 199201-009

Title: A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

Protocol Amendment 4 Date: 04Apr2016

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STUDY TITLE

A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

Protocol Number:	199201-009 Amendment 4
EudraCT Number (if applicable):	
Phase:	2b
Name of Investigational Products:	AGN-199201 (oxymetazoline hydrochloride ophthalmic solution) and AGN-190584 (pilocarpine hydrochloride ophthalmic solution)
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 [redacted]
Emergency Telephone Number(s):	Refer to the Study Contacts Page.
Serious Adverse Event Reporting:	[redacted]

[redacted]

Approval Date: 04-Apr-2016

Allergan Signatory: [redacted]

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

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.

Approval Date: 04-Apr-2016

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

Approval Date: 04-Apr-2016

Table of Contents

Approval Date: 04-Apr-2016

Approval Date: 04-Apr-2016

Approval Date: 04-Apr-2016

List of Tables

List of Figures

Approval Date: 04-Apr-2016

Protocol Summary

Study Compounds:

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

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

Phase: 2

Study Objective:

To identify the optimum concentrations of AGN-199201 [redacted] and AGN-190584 [redacted] when dosed in combination once a day for the improvement of uncorrected near visual acuity (UNVA) in patients with presbyopia

Clinical Hypotheses:

At least one concurrently dosed combination of AGN-199201 and AGN-190584 will:

1. demonstrate a significant improvement in UNVA over monotherapy with AGN-199201 and monotherapy with AGN-190584 when they are dosed at the same concentrations as the combination

2. produce safety and tolerability findings no worse than cumulative findings with AGN-199201 monotherapy and AGN-190584 monotherapy when they are dosed at the same concentrations as the combination

Study Design

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

Duration: 39 to 112 days per patient

Study Treatment Groups: Patients will receive AGN-199201 [redacted] and:

Group 1: AGN-190584 vehicle

Group 2: AGN-190584 ophthalmic solution, [redacted]

Group 3: AGN-190584 ophthalmic solution, [redacted]

Group 4: AGN-190584 ophthalmic solution, [redacted]

All patients will receive the fixed combination of AGN-190584 ophthalmic solution [redacted] and AGN-199201 ophthalmic solution [redacted] during one of the 5 dosing periods. See Table 1 for details of the dosing groups.

Approval Date: 04-Apr-2016

Table 1 Study Treatment Groups

Group	Nondominant eye			Dominant eye
	Unfixed Combination(s)		Fixed Combination	
1	AGN-199201,	AGN-190584, 0% (vehicle)	(AGN-190584, / AGN-199201,) + Vehicle	Vehicle + Vehicle
2	AGN-199201,	AGN-190584,	(AGN-190584, / AGN-199201,) + Vehicle	Vehicle + Vehicle
3	AGN-199201,	AGN-190584,	(AGN-190584, AGN-199201,) + Vehicle	Vehicle + Vehicle
4	AGN-199201,	AGN-190584,	(AGN-190584, / AGN-199201,) + Vehicle	Vehicle + Vehicle

Dosage/Dose Regimen: This study is a controlled comparison of the unfixed combinations of AGN-199201 and AGN-190584 ophthalmic solutions, and the fixed combination of AGN-190584 and AGN-199201) dosed in the nondominant eye. Study medication will be administered once daily in each eye during office visits at hour 0 (8 AM ± 1 hour) for 2 consecutive days during each dosing period. Dosing periods will be separated by a washout period of 14 ± 7 days.

Eyes receiving both AGN-190584 and AGN-199201 are to receive a single drop of AGN-199201, followed approximately 5 to 7 minutes later by a single drop of AGN-190584. Eyes receiving the fixed combination of AGN-190584 and AGN-199201 are to receive a single drop of the fixed combination drug, followed approximately 5 to 7 minutes later by a single drop of vehicle. Eyes receiving vehicle alone are to receive 2 drops of vehicle, separated by approximately 5 to 7 minutes (see Table 1 and Figure 1).

Randomization/Stratification: At the baseline visit of the first dosing period, patients will be randomized in a 1:1:1:1 ratio into 1 of the 4 study groups. Randomization will be stratified at baseline by UNVA ≤ 20/80 and > 20/80.

Approval Date: 04-Apr-2016

[redacted]

Study Population Characteristics

Number of Patients: Approximately 160 patients (40 per group) will be enrolled at approximately 15 sites in the United States. Approximately 35 patients per group are expected to complete the study based on an anticipated dropout rate of 12.5% (5 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, ≥ 40 and < 51 years of age

[redacted]

- Emmetropes at distance, either natural or post corneal laser refractive surgery cornea, with presbyopia in each eye and subjective complaints of poor near vision that impacts activities of daily living, as defined by

[redacted]

Approval Date: 04-Apr-2016

Key Exclusion Criteria:

- Concurrent use of any topical ophthalmic medications, including artificial tears, other than the study medications, during the course of the study
- Corneal abnormalities (including keratoconus, corneal scar, Fuchs' endothelial dystrophy, guttata, or edema) in either eye which are likely to interfere with visual acuity
- History of cataract surgery, phakic intraocular lens (PIOL surgery), corneal inlay surgery, or any intraocular
- Diagnosis of glaucoma or ocular hypertension

Response Measures

Primary Efficacy:

- Mesopic, high contrast UNVA

Approval Date: 04-Apr-2016

General Statistical Methods and Types of Analyses:

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

The per protocol (PP) population is defined as all randomized patients who have no significant protocol deviations that affect the primary efficacy variable and complete all study visits. The PP population will be determined prior to database lock. The primary efficacy variable will be analyzed using the PP population on an as-treated basis.

The safety population is defined as all patients who received at least 1 dose of study treatment and will be analyzed as treated. 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 mixed model techniques or 2-sample t-tests (for between-group comparisons) and paired t-tests (for within-group analyses). Categorical variables will be summarized by sample size (N), frequency count and percent, and will be analyzed using Pearson's chi-square test, Fisher's exact test, or Cochran-Mantel-Haenszel (CMH) test.

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

Efficacy:

The primary efficacy variable is the weighted average change from baseline in UNVA letters in the nondominant eye over two-day dosing periods between hour 1 and hour 10. Baseline will be the hour 0 measure for each dosing period. For the primary efficacy analyses, the weighted average change from baseline will be analyzed by response surface approach using a mixed model with treatment group, dosing period, baseline UNVA, and iris color as fixed effects.

A UNVA responder is defined as a patient with at least a 3 line improvement in mesopic, high contrast, UNVA from baseline (hour 0 of visit 1) at most of the postdose time points in the nondominant eye. The proportion of the UNVA responders will be compared by frequency distribution.

There will be no adjustment for multiple tests.

Detailed descriptions will be documented in analysis plan.

Approval Date: 04-Apr-2016

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 are 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. The adverse events will be classified into ocular and nonocular types and will be summarized separately as described below. Ocular adverse events and other ocular evaluations will be summarized using eye as the experimental unit by dosing group and dosing period. Nonocular adverse events and other nonocular assessments (eg, vital signs) will be summarized using patient as the experimental unit by dosing group and dosing period.

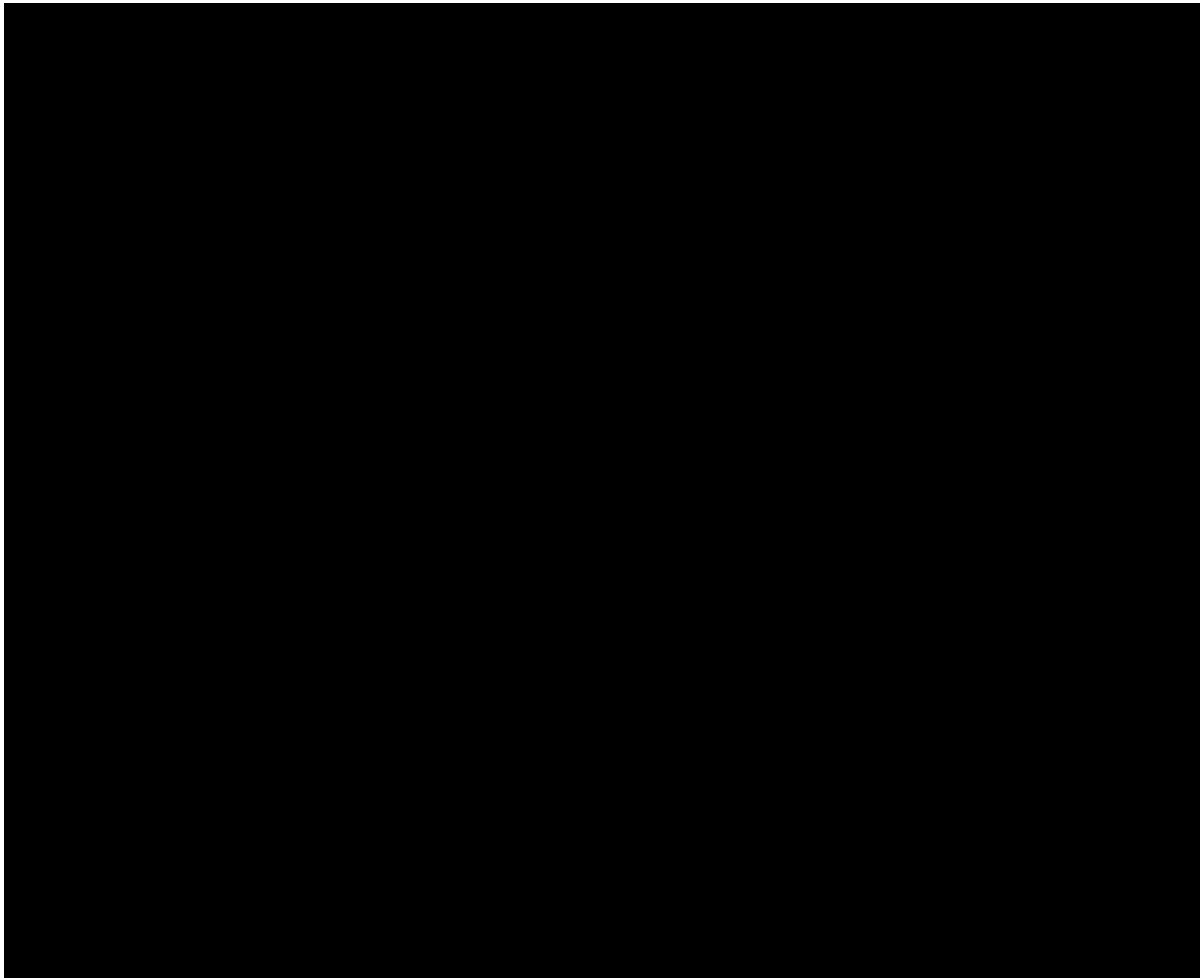
Detailed descriptions of the safety analyses for adverse events and other safety measures will be documented in analysis plan.

Sample Size Calculation:

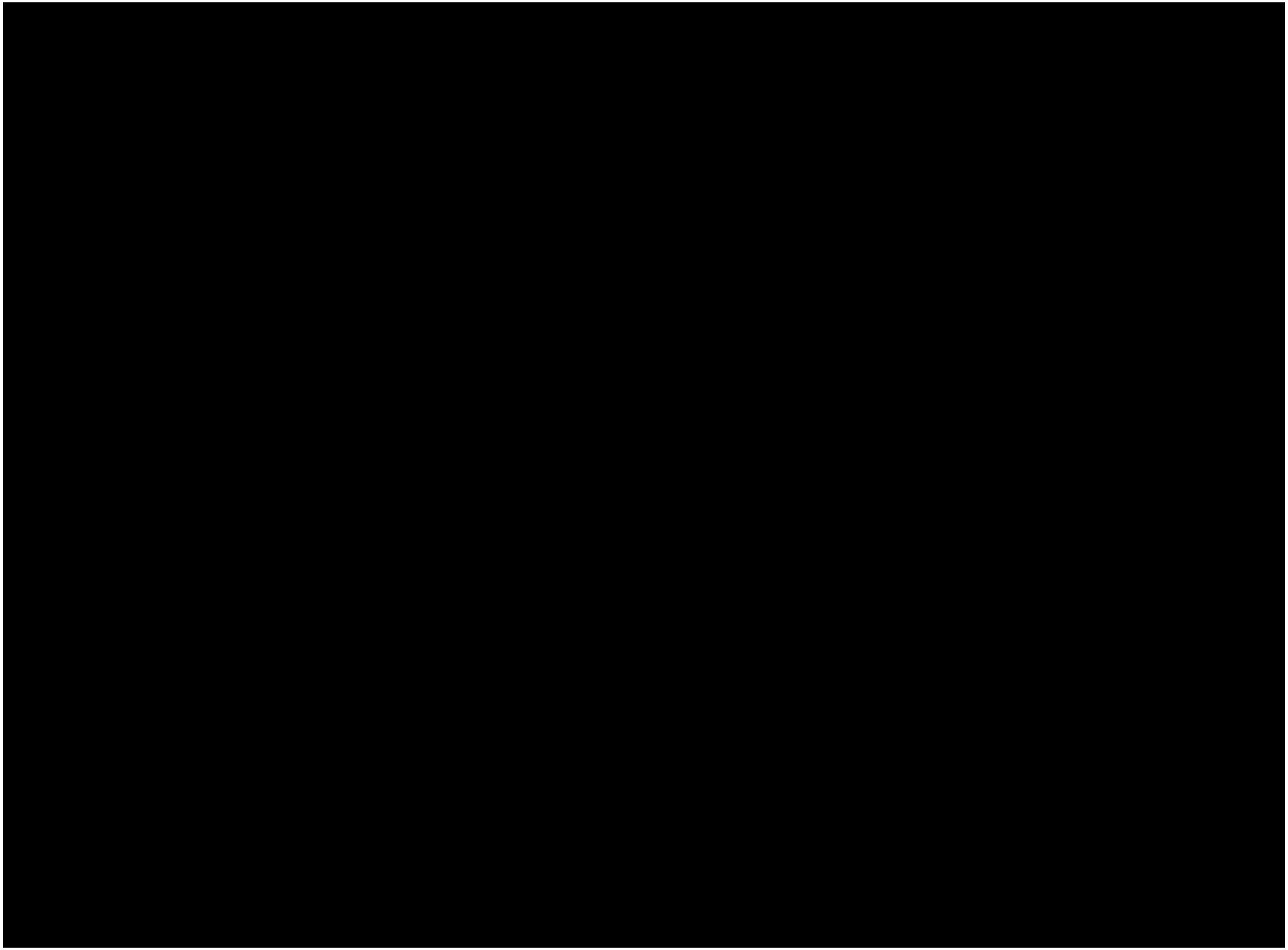
The study consists of 4 parallel groups and 5 sequences of 2-day dosing periods within each group (see Figure 1). Each dosing period is separated by a washout of 14 ± 7 days and each sequence is tested 8 times resulting in 40 patients per group.

The sample size is deemed appropriate to build a response surface model that assesses the efficacy profile of the combination relative to monotherapies.

Approval Date: 04-Apr-2016



Approval Date: 04-Apr-2016



Approval Date: 04-Apr-2016

Approval Date: 04-Apr-2016

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 (Radhakrishnan and Charman, 2007; Ostrin and Glasser, 2004). 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 diopters at age 25 (100 mm), and plateaus at 0.5 to 1 diopter 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, problems focusing on small objects and/or fine print, and are usually first noticed between the ages of 40 and 50 (Radhakrishnan and Charman, 2007; Ostrin and Glasser, 2004).

Traditional nonsurgical methods of refractive correction for presbyopia include the use of dedicated reading spectacles, bifocal, or varifocal spectacles, monovision contact lenses 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 non-distorted vision. For these reasons, older people are more than twice as likely to fall when wearing multi-focal spectacles (Lord et al, 2002; Johnson et al, 2007). 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® corneal inlay for the improvement of near vision in presbyopic eyes.

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). Of these, the KAMRA is the only FDA approved treatment for presbyopic eyes. For each of the existing technologies, visual quality is reduced at one or more viewing distances and each strategy comes with its own unique safety risks. For example, zonal bifocals (eg, zonal reading glasses, contacts) suffer from

Approval Date: 04-Apr-2016

optical aberrations, and multifocal optics reduce image quality uniformly at all viewing distances. Thus there remains a need for a non-invasive, reversible pharmacological treatment for presbyopia.

Allergan is developing a noninvasive, reversible pharmacological treatment for presbyopia based upon concurrent administration of pilocarpine hydrochloride (AGN-190584) and oxymetazoline hydrochloride (AGN-199201) ophthalmic solutions.

Pilocarpine ophthalmic solutions (1.0% to 4.0%, 1 drop administered to both eyes 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, prevention of postoperative elevated IOP associated with laser surgery, and for induction of miosis (new drug application [NDA] 200-890, pilocarpine hydrochloride ophthalmic solution package insert).

Pilocarpine is a muscarinic receptor agonist that mimics the actions of the parasympathetic neurotransmitter, acetylcholine, on smooth muscle. This causes 2 effects which 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 strength of the ciliary muscle contraction (Tsai and Forbes, 2009). 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 hydrochloride (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 the relief of redness of the eye due to minor eye irritations. It is also available as an OTC nasal spray under the brand name Afrin® at a concentration of 0.05% for topical (intranasal) administration for temporary relief of nasal congestion, sinus congestion and pressure, and to shrink swollen nasal membranes.

Approval Date: 04-Apr-2016

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 non-selective 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-HT_1) receptor agonist. Oxymetazoline was shown to be a full (or partial) agonist of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors and a weak agonist of the 5-HT_{1C} receptor (Schoeffter and Hoyer, 1991). 5-HT_1 receptor agonists are also known to have vasoconstrictive properties (Hoyer et al, 1994). 5-HT_1 receptors are mostly expressed in the central nervous system and some peripheral nerves. Activation of central 5-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 (Yu et al, 2004; Prow et al, 1996; Fanciullacci et al, 1995). A population of 5-HT_{1A} receptors are present in the rabbit and human ciliary processes (Chidlow et al, 1995; Yang and Latt, 1998) suggesting that oxymetazoline could also directly affect lens accommodation.

Alpha$_1$ agonists are frequently co-administered with local anesthetics in order 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 which could improve its tolerability, and could enhance pilocarpine's 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. These data suggest that oxymetazoline is not indicated as a monotherapy for the treatment of presbyopia at concentrations at or below 0.025% as it may slightly dilate the pupil. 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 two double-blind, randomized clinical trials. They attributed the lack of intraocular findings to the poor ocular penetration of oxymetazoline following topical ocular

Approval Date: 04-Apr-2016

administration. Consistent with the results reported by Samson and colleagues, Allergan Study 199201-007 found that oxymetazoline 0.125% monotherapy slightly dilated the pupil.

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. Finally, oxymetazoline's serotonin (5-HT1) receptor agonism may work synergistically with pilocarpine to improve uncorrected near visual acuity (UNVA) in younger presbyopia patients who still retain the ability to accommodate to near visual tasks.

1.2 Preclinical Summary

Besides the abundance of scientific literature available on similar products containing the two 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 (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 twice daily.

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 the Phase 2b study described herein to the unfixed formulation used previously in Phase 2a Study 199201-007. Dutch belted rabbits were administered a single bilateral dose of

Approval Date: 04-Apr-2016

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, 1 or 2 times/day for 14 consecutive days (Study No. TX14097). Right eyes were dosed 1 time/day and left eyes were dosed 2 times/day. 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 twice per day. 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.

The accommodative apparatus of nonhuman primates is similar to that of humans, ie, the accommodative amplitude in primates declines with age on a comparable relative time course (Kaufman et al, 1982; Bito et al, 1982). In a preclinical model to study the effect of oxymetazoline on the accommodative and miotic profile of pilocarpine in young adult monkey eyes, ophthalmic application of pilocarpine 0.5% caused a decrease in pupil size and an increase in accommodative amplitude. Coadministration or pre-administration with topical ophthalmic oxymetazoline 0.1% delayed the time to maximal accommodative response induced by pilocarpine. These preclinical findings are consistent with the hypothesis that oxymetazoline may reduce the incidence or severity of temporal or supraorbital headache by slowing the rate of pilocarpine-induced contraction of the ciliary muscle, and thus support clinical testing of this hypothesis.

Approval Date: 04-Apr-2016

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. 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 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%) monotherapy, pilocarpine (1.0%) monotherapy, or concurrent dosing of both in patients with presbyopia in a multicenter, double-masked, randomized, vehicle-controlled study. 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 once daily for 3 days, and after a 5-day washout period, twice daily for 3 days. All dosing was performed by trained personnel in the clinic. The primary efficacy variable was a UNVA response at visit 3. An UNVA responder was defined as a patient with at least a 2 line improvement in mesopic, high contrast, UNVA from baseline (hour 0 of visit 1) at a majority (at least 3) of time points postdose in the nondominant eye.

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

Approval Date: 04-Apr-2016

(oxymetazoline (0.125%)/ pilocarpine (1.0%) dosed in both eyes). In each group, patients were evenly distributed among the 4 strata of iris color and age. Sixty-three patients (96.9%, 63/65) completed the study. One patient in Group 2 and one patient in Group 4 discontinued 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 time points postdose in the nondominant eye following both once daily (QD) and twice daily (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 time points postdose in the nondominant eye following QD dosing and was numerically superior following BID dosing. Across all time points and visits, the mean change from baseline in lines of UNVA numerically favored the combination groups over pilocarpine monotherapy at later time points 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% vs. 11.8%) and BID (12.5% vs. 0%) dosing regimens, and in younger patients (ie, the 40 to 47 age cohort per the pre-specified 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 age cohort per the prespecified cutoff) the difference was less pronounced between combination 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 or modulation of the pharmacokinetics of pilocarpine providing a benefit over pilocarpine monotherapy for the treatment of presbyopia.

Approval Date: 04-Apr-2016

Oxymetazoline monotherapy, pilocarpine monotherapy, and concurrent dosing of pilocarpine and oxymetazoline in one or both eyes 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" which 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 program is to develop a fixed-dose combination of pilocarpine and oxymetazoline for the treatment of presbyopia. To date, preclinical studies in rabbits and non-human primates, 4 pilot clinical studies conducted by AltaVista Instituto del Investigation Medica at the clinic of Dr. Juan Carlos Abad, and Allergan study 199201-007 support the combination of pilocarpine and oxymetazoline for the treatment for presbyopia. These studies are summarized in the sections below.

1.4 Rationale for Study Design

Allergan Study 199201-007 achieved proof-of-concept for the current approach of treating presbyopia with a combination of oxymetazoline and pilocarpine ophthalmic solutions. This phase 2 clinical study is a systematic dose-response study designed to identify the optimum concentrations of oxymetazoline HCl (0.0125%, 0.05%, or 0.125%) and pilocarpine HCl (0.5%, 1%, or 1.5%) ophthalmic solutions dosed in combination for the improvement of UNVA in patients with presbyopia.

The results from Study 199201-007 suggest that pilocarpine improves UNVA in patients with presbyopia by decreasing pupil diameter which increases depth of focus. Oxymetazoline may further modulate the miotic effect of pilocarpine on UNVA by increasing both accommodation and duration. Study 199201-009 was designed to have more sensitivity to change in oxymetazoline concentration (ie, within patient comparison) than pilocarpine concentration (ie, between patient comparison). Secondarily, the current study brackets the concentration of pilocarpine used in 199201-007, the higher concentration of pilocarpine in the current study may result in a greater discontinuation rate. Thus, pilocarpine was selected as a between-patient variable to minimize any potential impact of patient discontinuation.

This study was designed to dose in the nondominant eye of younger presbyopic patients based on the results of 199201-007, as the greatest improvements in UNVA were seen with these two conditions. Due to the large number of comparisons when crossing over two drugs

Approval Date: 04-Apr-2016

each with 3 concentrations as well as monotherapies, it is not practical to use fixed combinations for all dose combinations in the current study. A fixed combination of pilocarpine 1% and oxymetazoline 0.125% was selected as the only fixed combination to enable bridging between the fixed combination used in this study and the unfixed combination used in this study and 199201-007.

Rationale for Dose Range

Oxymetazoline HCl has been marketed as an OTC medication for more than 3 decades in an intranasal spray containing 0.05% oxymetazoline HCl (under the brand name Afrin), and for over 2 decades in an eye drop solution containing 0.025% oxymetazoline HCl (under the brand names Visine LR and Ocuclear). 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 plasma maximal concentration (C_{max}) of 0.245 ng/mL and area under the 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 signs, electrocardiograms (ECGs), or IOP during the study.

The 0.125% dose of oxymetazoline used in Study 199201-007 resulted in a lower dose by weight (approximately 0.1 mg/dose) when compared to Afrin (0.3 mg/dose), based on the smaller ophthalmic dosing volume (35 µL). Results from Study 199201-007 showed that oxymetazoline monotherapy, pilocarpine monotherapy, and concurrent dosing of pilocarpine and oxymetazoline in one or both eyes were all safe and well tolerated. No meaningful differences were found between groups in discontinuation rate or in the incidence or severity of adverse events, with the exception of "eyelid retraction" which occurred most frequently in the oxymetazoline monotherapy group. No meaningful differences were found among groups in VAS scores for temporal or supraorbital headache. It may require a larger sample size and/or higher dose strengths of pilocarpine 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.

In the AltaVista studies, no systemic or ocular adverse events were observed in 15 patients who were exposed to up to 3 drops of ophthalmic oxymetazoline within a 15-minute time period at concentrations up to 0.125%. Additionally, a nonclinical toxicology study demonstrated the safety of ophthalmic oxymetazoline at concentrations up to 0.25% when

Approval Date: 04-Apr-2016

administered BID for 28 days in combination with pilocarpine 1.0%. A nonclinical pharmacokinetic study evaluating the unfixed vs. fixed combination formulations demonstrated that pilocarpine absorption into the iris-ciliary body was slightly lower following administration of the fixed combination. This reduction in exposure was primarily driven by lower tissue concentrations at latter timepoints in the timecourse, potentially affecting clinical duration of action. Therefore, to achieve similar pilocarpine exposure in the target tissue, this study will evaluate a maximum pilocarpine dose of 1.5%.

Results from Study 199201-007 demonstrated that the combination of pilocarpine and oxymetazoline in the nondominant eye increased the peak effect and increased the duration of effect on UNVA in comparison to pilocarpine alone in the nondominant eye. The combination of pilocarpine and oxymetazoline dosed only in the nondominant eye demonstrated greater improvements in uncorrected near vision than oxymetazoline or pilocarpine alone dosed in only one eye or the combination dosed bilaterally. For both QD and BID dosing regimens, concurrent dosing of pilocarpine and oxymetazoline in either the nondominant eye (Group 3) or bilaterally (Group 4) showed consistent improvement over both oxymetazoline monotherapy (Group 1) and pilocarpine monotherapy (Group 2) in the percentage of patients achieving at least a 2 or 3 line improvement in mesopic, high-contrast, binocular UNVA at a majority of timepoints postdose. The effect of pilocarpine alone was found to mostly return to a baseline level 6 hours after administration, while the combination showed a continued effect 6 to 8 hours after administration. Oxymetazoline monotherapy was found to have little effect on UNVA. Thus, Study 199201-007 replicated the findings reported by AltaVista.

Approval Date: 04-Apr-2016

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To identify the optimum concentrations of AGN-199201 (and AGN-190584 when dosed in combination once a day for the improvement of UNVA in patients with presbyopia

2.2 Clinical Hypotheses

At least one concurrently dosed combination of AGN-199201 and AGN-190584 will:

1. demonstrate a significant improvement in UNVA over monotherapy with AGN-199201 and monotherapy with AGN-190584 when they are dosed at the same concentrations as the combination

2. produce safety and tolerability findings no worse than cumulative findings with AGN-199201 monotherapy and AGN-190584 monotherapy when they are dosed at the same concentrations as the combination

3. Study Design

This study is a phase 2, multicenter, double-masked, parallel-group, randomized sequence, dose response, vehicle-controlled study in patients with presbyopia. Four groups (see Table 1) of different concentrations of AGN-190584 [redacted] will be used to compare unfixed combinations with AGN-199201 [redacted] and a fixed combination of AGN-190584 [redacted]) and AGN-199201 [redacted]) solutions dosed in the nondominant eye during 5 dosing periods. For all 4 treatment groups, each dosing period will be once daily for 2 consecutive days, followed by a 7 to 21 day washout before the next 2-day dosing period, until exit after the fifth 2-day dosing period. The study duration will be 39 to 112 days per patient.

Following a screening visit (days -18 to -1) patients will be randomized at a baseline visit (visit 1) in a 1:1:1:1 ratio (stratified by the UNVA at baseline of ≤ 20/80 and > 20/80) to 1 of the following treatment groups (also summarized in Table 1):

- Group 1: AGN-199201 [redacted] and AGN-190584 vehicle 0%
- Group 2: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]
- Group 3: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]
- Group 4: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]

Approval Date: 04-Apr-2016

All patients will receive the fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] ophthalmic solutions within one of the 5 dosing periods. Vehicles for AGN-190584, AGN-199201, and the fixed combination ophthalmic solutions all have the same formulation.

Study medication will be administered once daily in each eye during office visits at hour 0 (8 AM ± 1 hour) for 2 consecutive days during each dosing period. Dosing periods will be separated by a washout period of 14 ± 7 days. Eyes receiving both AGN-199201 and AGN-190584 are to receive a single drop of AGN-199201, followed approximately 5 to 7 minutes later by a single drop of AGN-190584. Eyes receiving the fixed combination of AGN-190584 [redacted] and AGN-199201 [redacted]) are to receive a single drop of the fixed combination drug, followed approximately 5 to 7 minutes later by a single drop of vehicle. Eyes receiving vehicle alone are to receive 2 drops of vehicle, separated by approximately 5 to 7 minutes. The study design is depicted in Figure 1.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 160 patients (40 per group) will be enrolled at approximately 15 US sites. Approximately 35 patients per group are expected to complete the study based on an anticipated dropout rate of 12.5% (5 dropped patients per group).

4.2 Study Population Characteristics

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

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, ≥ 40 and < 51 years of age

[redacted]

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

Approval Date: 04-Apr-2016

[redacted]

Approval Date: 04-Apr-2016

4.4 Exclusion Criteria

The following are 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 which are likely to interfere with visual acuity
5. History of cataract surgery, phakic intraocular lens (PIOL surgery), corneal inlay surgery, or any intraocular surgery.

[redacted]

10. Diagnosis of any type of glaucoma or ocular hypertension

[redacted]

Approval Date: 04-Apr-2016

Systemic:

[redacted]

Approval Date: 04-Apr-2016

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

The concurrent use of non-ocular medications that do not have a substantial effect on the pupil, accommodative properties, or retinal function of the eye is 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.

4.5.2 Prohibited Medications/Treatments

Use of ocular medication(s) other than study medications administered to conduct study procedures (see Sections 6.3 and 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 from 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 is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

Approval Date: 04-Apr-2016

5. Study Treatments

5.1 Study Treatments and Formulations

AGN-199201 [redacted]

AGN-190584 [redacted]

The fixed combination (AGN-199201 [redacted] w/v and AGN-190584 [redacted]

5.2 Control Treatments

The vehicles of AGN-199201, AGN-190584, [redacted]

5.3 Methods for Masking

Study medication will be administered to each randomized patient at each dosing period by qualified site personnel. 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 ratio into 1 of 4 treatment groups:

- Group 1: AGN-199201 [redacted] and AGN-190584 vehicle (0%)
- Group 2: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]
- Group 3: AGN-199201 ([redacted] and AGN-190584 ophthalmic solution [redacted]

Approval Date: 04-Apr-2016

- Group 4: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]

All patients will receive the fixed combination of AGN-190584 ophthalmic solution [redacted] and AGN-199201 ophthalmic solution [redacted] within one of the 5 dosing periods. The order of the dosing sequence in each group is shown in Table 3.

Patients will be stratified by UNVA at baseline of ≤ 20/80 and > 20/80. For determination of stratification group assignment for each patient, sites will be required to enter the UNVA at baseline 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 2 strata as described in Section 5.4, and they will be assigned to 1 of the 4 treatment groups, in a masked fashion 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 2 medication kit numbers (one for nondominant eye and one for dominant eye) 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 medication kit number, study number, and dominant or nondominant eye. Each medication kit (carton) will contain 2 multidose bottles of study treatment; 1 bottle will be labeled with an 'X' and 1 bottle will be labeled with a 'Y'. The study treatment in each bottle will be administered in sequence (a single drop from bottle X first, followed 5 to 7 minutes later by a single drop from bottle Y). The IxRS will provide the site with the specific medication kit number(s) for each randomized patient at the time of randomization (day 1 of the first dosing period) and on day 1 of each subsequent dosing period. Sites will assign study medication kits according to the IxRS instructions. Sites will receive the IxRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Approval Date: 04-Apr-2016

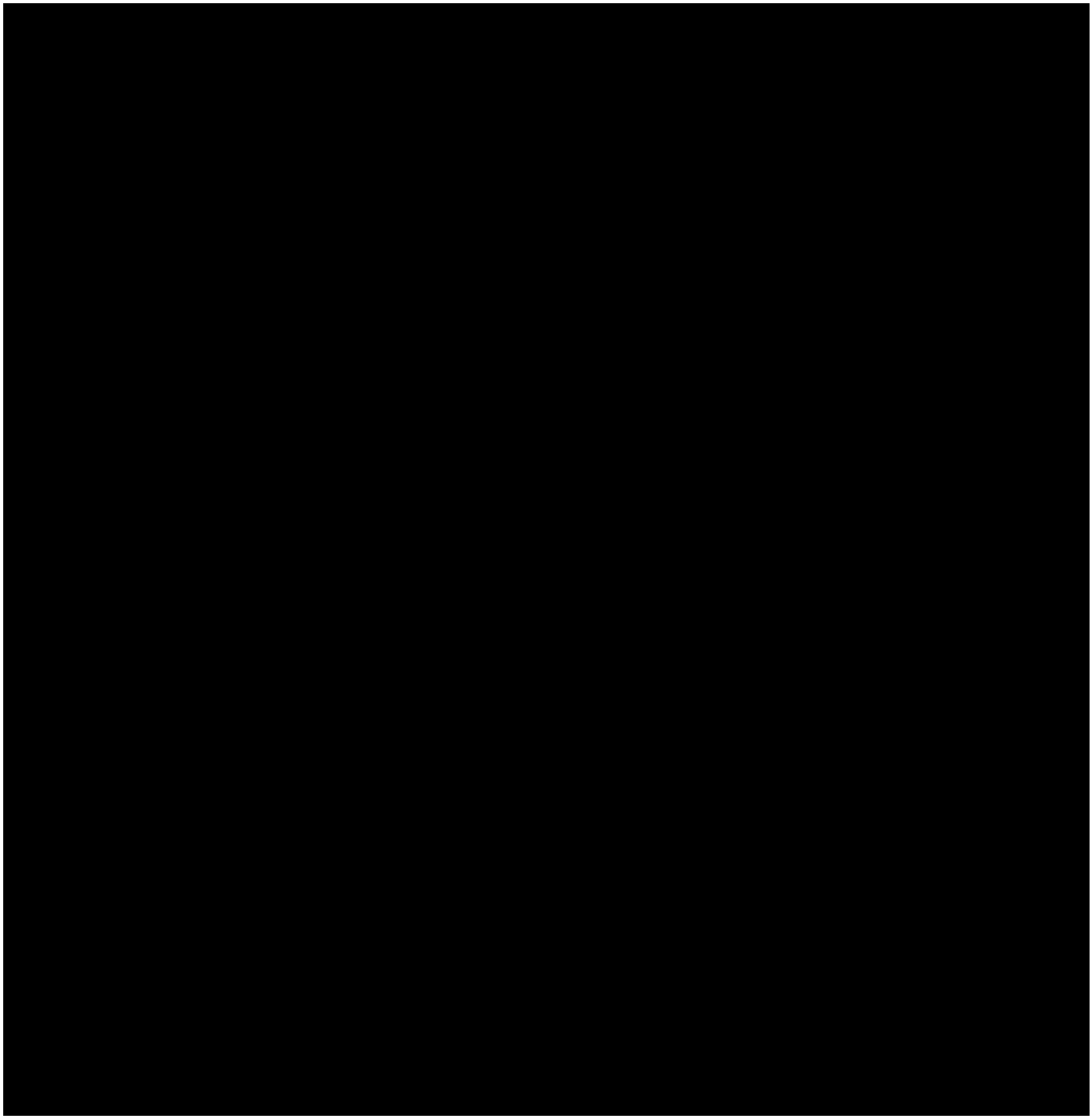
5.6 Treatment Regimen and Dosing

This study is a controlled comparison of the unfixed combinations of AGN-199201 (and AGN-190584 ophthalmic solution, and the fixed combination of AGN-190584 and AGN-199201 dosed in the nondominant eye. The dosing sequence of the nondominant eye in each group is shown in Table 3.

Study medication or vehicle will be administered once daily in each eye during office visits by designated site personnel at hour 0 (8 AM ± 1 hour) for 2 consecutive days during each dosing period. Dosing periods will be separated by a washout period of 14 ± 7 days.

Eyes receiving both AGN-190584 and AGN-199201 are to receive a single drop of AGN-199201 followed approximately 5 to 7 minutes later by a single drop of AGN-190584 (Eyes receiving the fixed combination of AGN-190584 (and AGN-199201 (are to receive a single drop of the fixed combination drug (followed approximately 5 to 7 minutes later by a single drop of vehicle Eyes receiving vehicle alone are to receive a single drop of vehicle (followed approximately 5 to 7 minutes later by a single drop of vehicle

Approval Date: 04-Apr-2016



Approval Date: 04-Apr-2016

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).

5.8 Treatment Administration

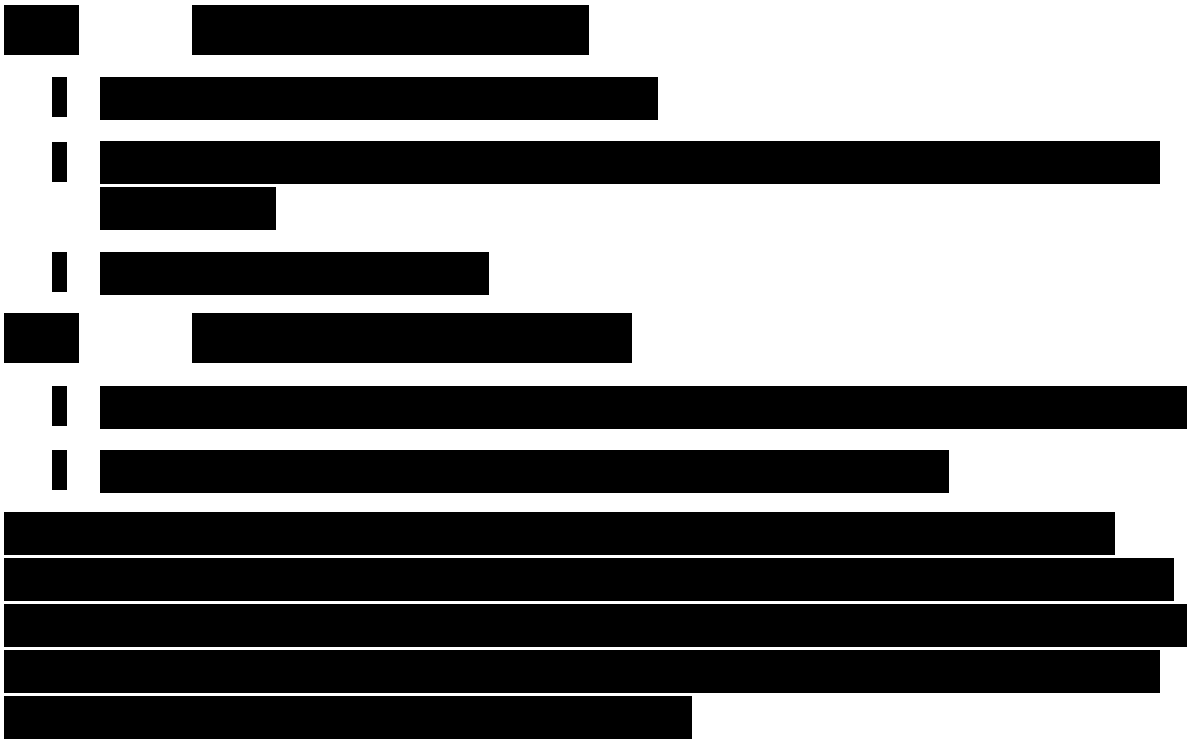
Study medication or vehicle will be administered to each randomized patient once daily in each eye during office visits at hour 0 (8 AM ± 1 hour) for 2 consecutive days during each dosing period by site personnel not otherwise involved in measuring safety, tolerability, or efficacy parameters. See Sections 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 is mesopic, high contrast UNVA.



Approval Date: 04-Apr-2016

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Approval Date: 04-Apr-2016

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Approval Date: 04-Apr-2016

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6.5 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 is 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 is defined as all randomized patients with a baseline and at least 1 post baseline assessment of mesopic, high contrast, UNVA and will be analyzed as randomized. The efficacy variables will be analyzed using the mITT population.

The per protocol (PP) population is defined as all randomized patients who have no significant protocol deviations that affect the primary efficacy variable and complete all study visits. The PP population will be determined prior to database lock. The primary efficacy variable will also be analyzed using the PP population on an as-treated basis.

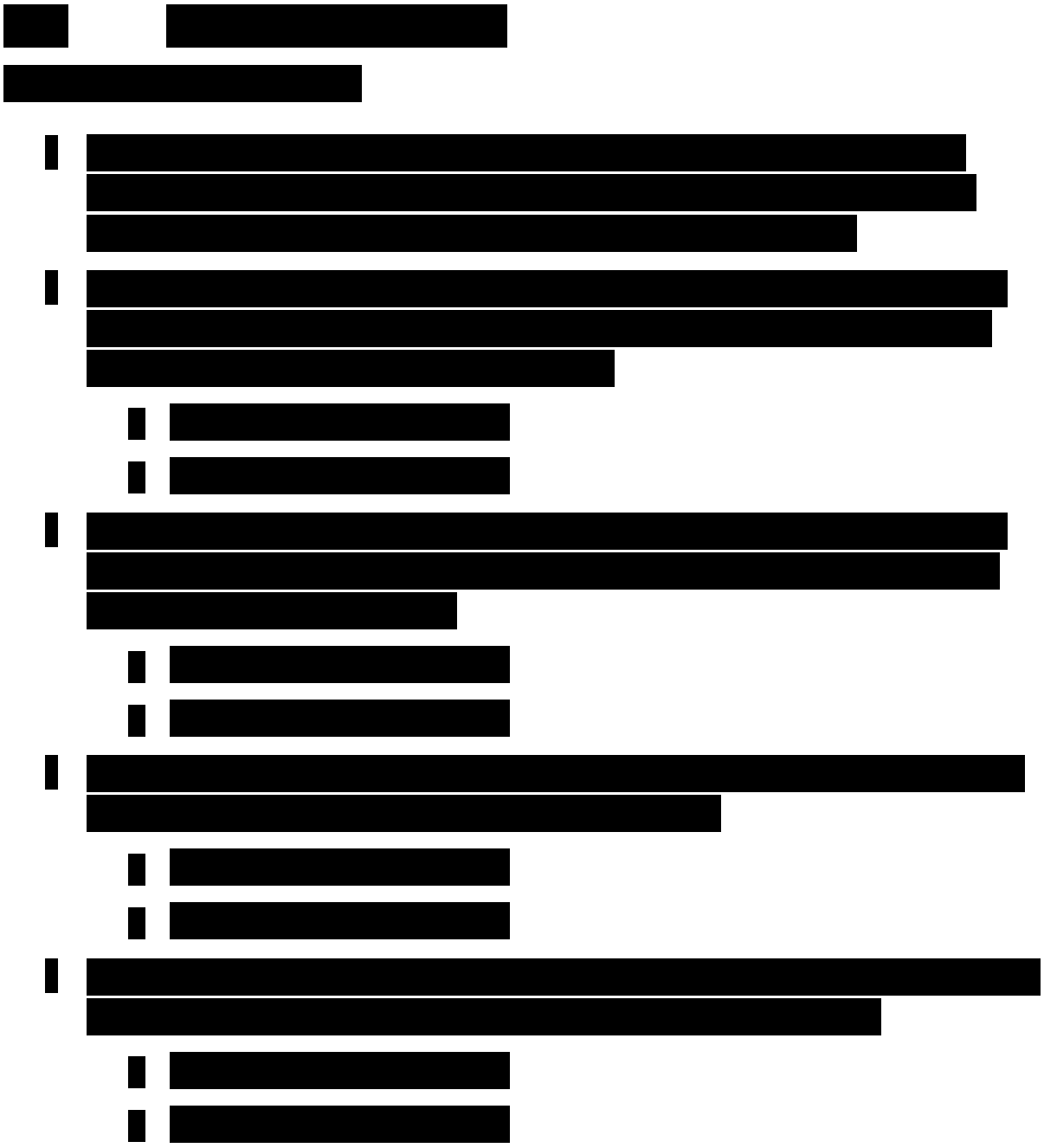
The safety population is defined as all patients who received at least 1 dose of study treatment and will be analyzed as treated. All safety measures will be analyzed using the safety population.

Approval Date: 04-Apr-2016

7.2 Collection and Derivation of Primary and Other Efficacy Assessments

7.2.1 Primary Efficacy Variable

The primary efficacy variable is the weighted average change from baseline in UNVA letter in the nondominant eye over 2-day periods between hour 1 and hour 10. Baseline will be the hour 0 measure for each dosing period.



Approval Date: 04-Apr-2016

[redacted]

7.3 Hypothesis and Methods of Analysis

In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using mixed model, analysis of variance (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 Pearson's chi-square test, Fisher's exact test, or Cochran-Mantel-Haenszel (CMH) test.

There will be no adjustment of type I error rate for the multiple tests. A 2-sided test with a p-value ≤ 0.05 will be considered statistically significant.

There will be no imputation of missing data for the all analysis.

7.3.1 Primary Efficacy Analyses

For the primary efficacy analysis, the weighted average change from baseline will be analyzed using a mixed model with treatment group, dosing period, baseline UNVA, and iris color as fixed effects.

[redacted]

Approval Date: 04-Apr-2016

[redacted]

7.4 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy variable by UNVA at baseline (UNVA ≤ 20/80 or > 20/80), iris color (brown or not brown), gender, race, and ethnicity.

7.5 Sample Size Calculation

The study consists of 4 parallel groups and 5 sequences of 2-day dosing periods within each group (see Figure 1). Each dosing period is separated by a washout of 14 ± 7 days and each sequence is tested 8 times resulting in 40 patients per group.

The sample size is deemed appropriate to build a response surface model that assesses the efficacy profile of the combination relative to monotherapies.

7.6 Interim Analyses

There will be no interim analyses.

8. Study Visit Schedule and Procedures

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

Approval Date: 04-Apr-2016

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 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

Each dosing period will be separated by a washout of 14 ± 7 days.

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.

Approval Date: 04-Apr-2016

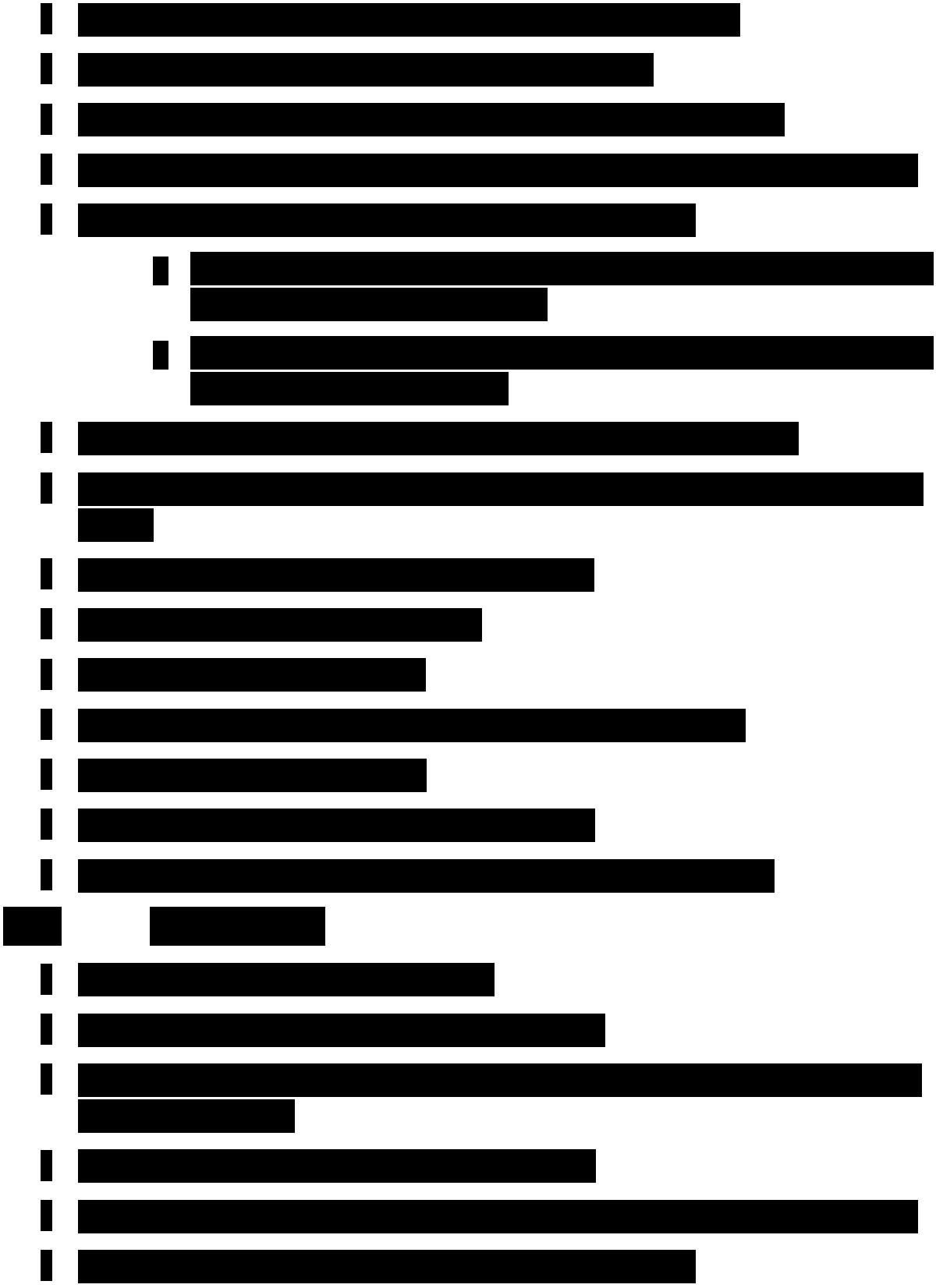
[redacted]

The following section provides a list of procedures for each scheduled visit. All ophthalmic procedures should be performed for each eye, unless otherwise noted. Additional information on the examination procedures, equipment, and techniques for the measures listed in this section is presented in Section 6.3.

[redacted]

Approval Date: 04-Apr-2016

Approval Date: 04-Apr-2016



Approval Date: 04-Apr-2016

[redacted]

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 spectacles are worn for vision correction, patients should remember to bring the spectacles 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.

Approval Date: 04-Apr-2016

- 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 4.5.2).

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 used any concomitant medications or had any procedures performed since the previous visit.

All doses of study medication will be administered by study personnel, therefore patient compliance with the study medication regime will not be monitored.

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 the sponsor and will be clearly documented on the appropriate case report form.

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.

Approval Date: 04-Apr-2016

If the patient withdraws prior to completing the study, the procedures outlined for the visit 2/study exit should be performed at the last visit attended (see Section 8.4.3).

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 9.5).

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 case report form. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

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

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

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

Adverse events will be assessed, documented, and recorded in the electronic case report form (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,

Approval Date: 04-Apr-2016

non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or 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.

Approval Date: 04-Apr-2016

9.1.4 Relationship to Study Drug or Study Procedure

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

9.2 Procedures for Reporting Adverse Events

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

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

9.3 Procedures for Reporting a Serious Adverse Event

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

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

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any

Approval Date: 04-Apr-2016

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 logging 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.

Approval Date: 04-Apr-2016

10. Administrative Items

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

10.1 Protection of Human Patients

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

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

10.1.2 Compliance With IRB or IEC Regulations

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

10.1.3 Compliance With Good Clinical Practice

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

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

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

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards

Approval Date: 04-Apr-2016

to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

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

10.3.1 Patient Privacy

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

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

10.4 Documentation

10.4.1 Source Documents

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

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

- Patient's name.
- Patient's contact information.

Approval Date: 04-Apr-2016

- 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, time of day, and protocol designated hours for all patient visits/timepoints.
- 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, results of urine pregnancy tests).
- Patient medical, surgical, and ophthalmic histories (including demographics); screening ophthalmological assessments; and for females, documentation of non-childbearing potential or results of pregnancy test.
- 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.

Approval Date: 04-Apr-2016

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

10.4.3 Study Summary

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

10.4.4 Retention of Documentation

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

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

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

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

10.4.4.1 Study Site

The study site should retain the essential documents to be kept at the study site, such as source documents, contracts, informed consent form, protocol, records on control of the investigational product, or other study-related documents until either item 1 or 2 listed below, whichever is later. However, when the sponsor requires that these documents are to be

Approval Date: 04-Apr-2016

retained for longer period, the study site should discuss it with Allergan about the period and method of preservation. The record retainer designated for each record should be responsible for the preservation.

1. The date of approval for manufacturing and marketing applications of the relevant investigational products (in case of discontinuing its development, until at least 3 years after the date of development discontinuation).

2. The day at least 3 years after the date of the termination or completion of the clinical study.

The study site and the record retainer should take measures in such a way that these records are not lost or abandoned during the designated period of preservation and that they are presented upon request.

10.4.4.2 Institutional Review Board (IRB)

The IRB should retain all relevant records such as standard operating procedures (SOPs), membership lists (including qualifications of the members), submitted documents, minutes of meetings, and correspondence until either item 1 or 2 listed below, whichever is later.

1. The date of approval for manufacturing and marketing applications of the relevant investigational products (in case of discontinuing its development, until at least 3 years after the date of development discontinuation).

2. The day at least 3 years after the date of the termination or completion of the clinical study.

When the study site or the sponsor requests the SOPs and membership lists, the IRB should comply with the request.

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 multi-dose bottles of study treatment; one bottle will be labeled with an [redacted] and one bottle will be labeled with a

Approval Date: 04-Apr-2016

[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 multi-dose 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 designee for destruction.

10.6 Monitoring by the Sponsor

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

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

10.7 Publications

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

Approval Date: 04-Apr-2016

10.8 Coordinating Investigator

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

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Approval Date: 04-Apr-2016

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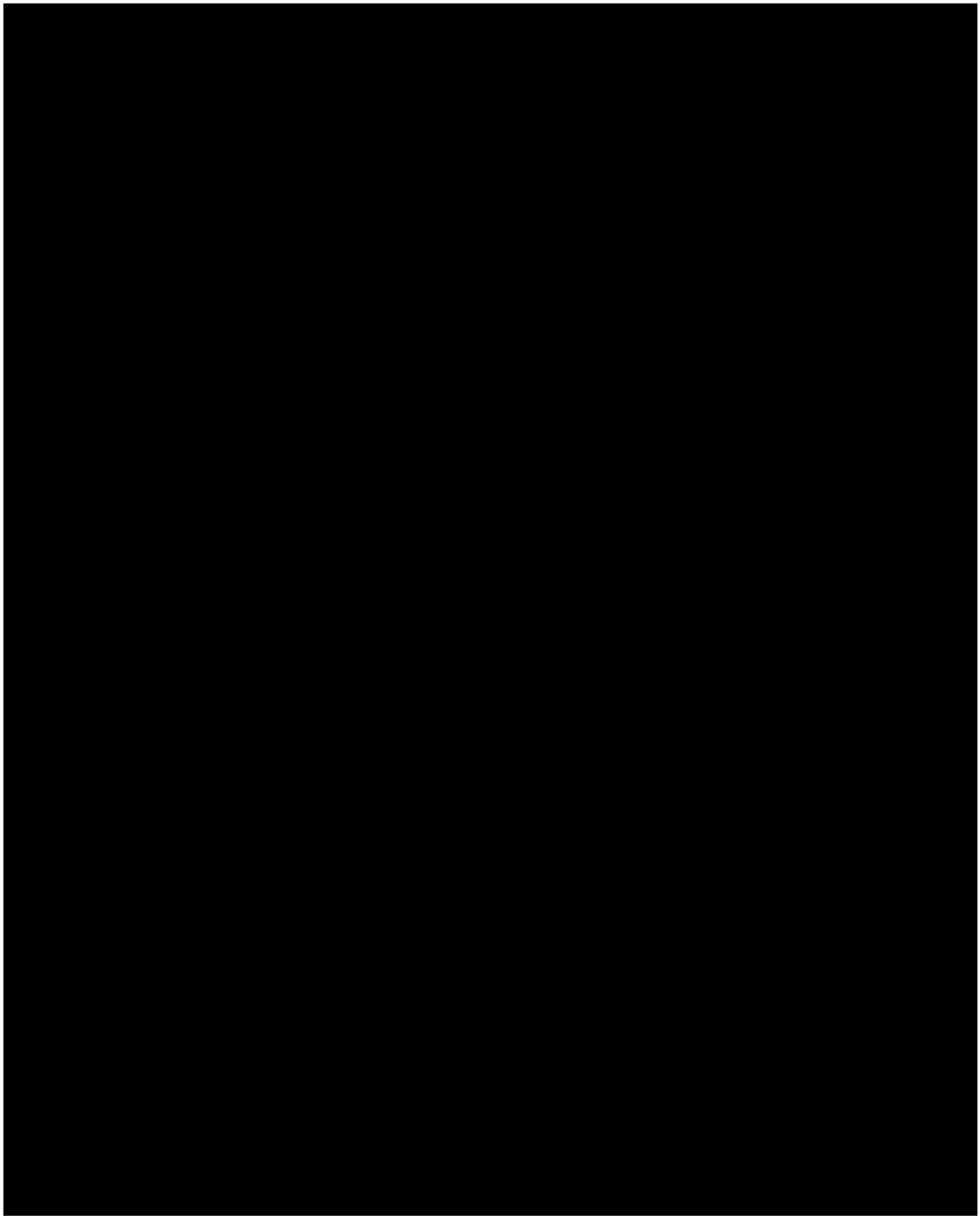
Approval Date: 04-Apr-2016

12. Attachments



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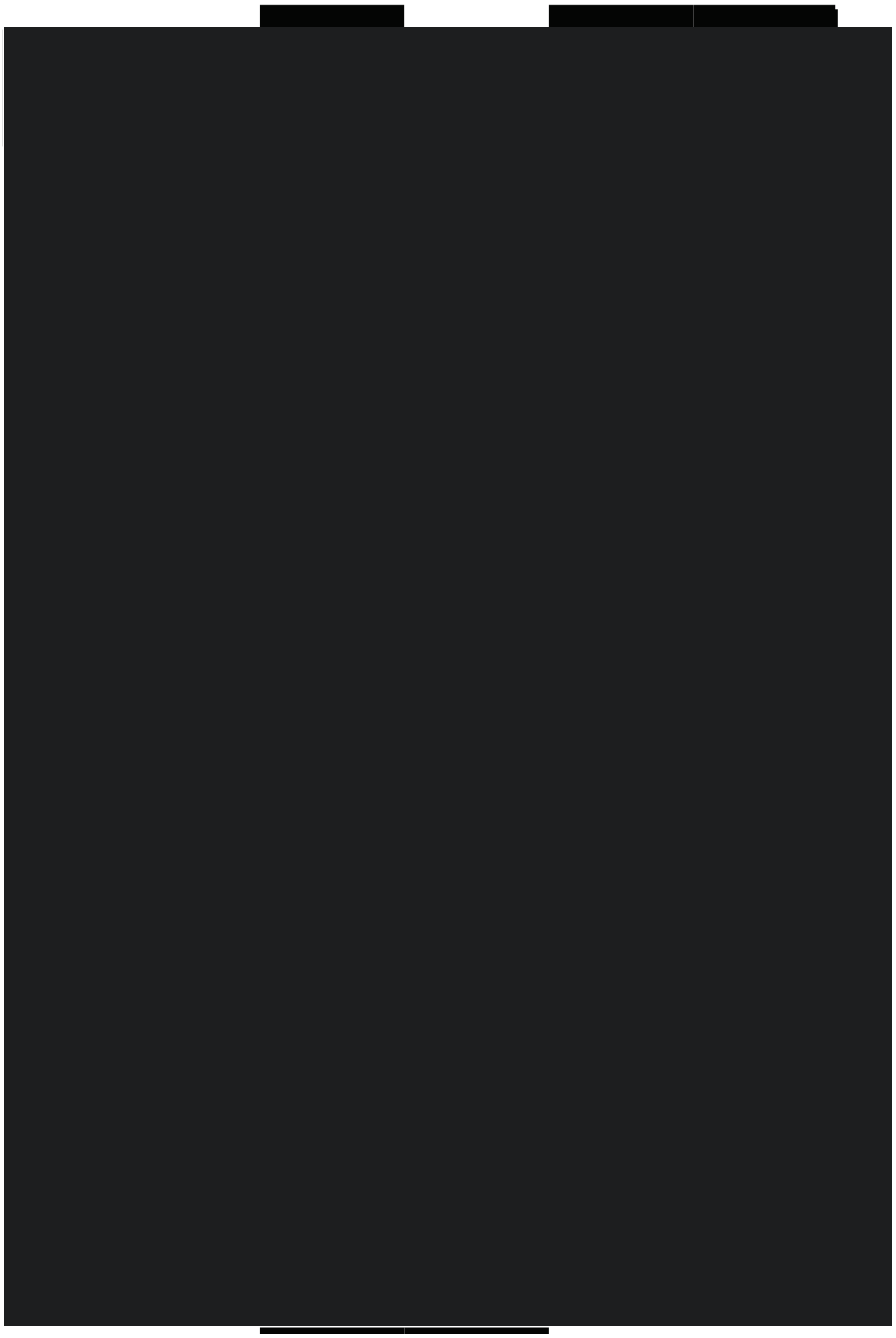

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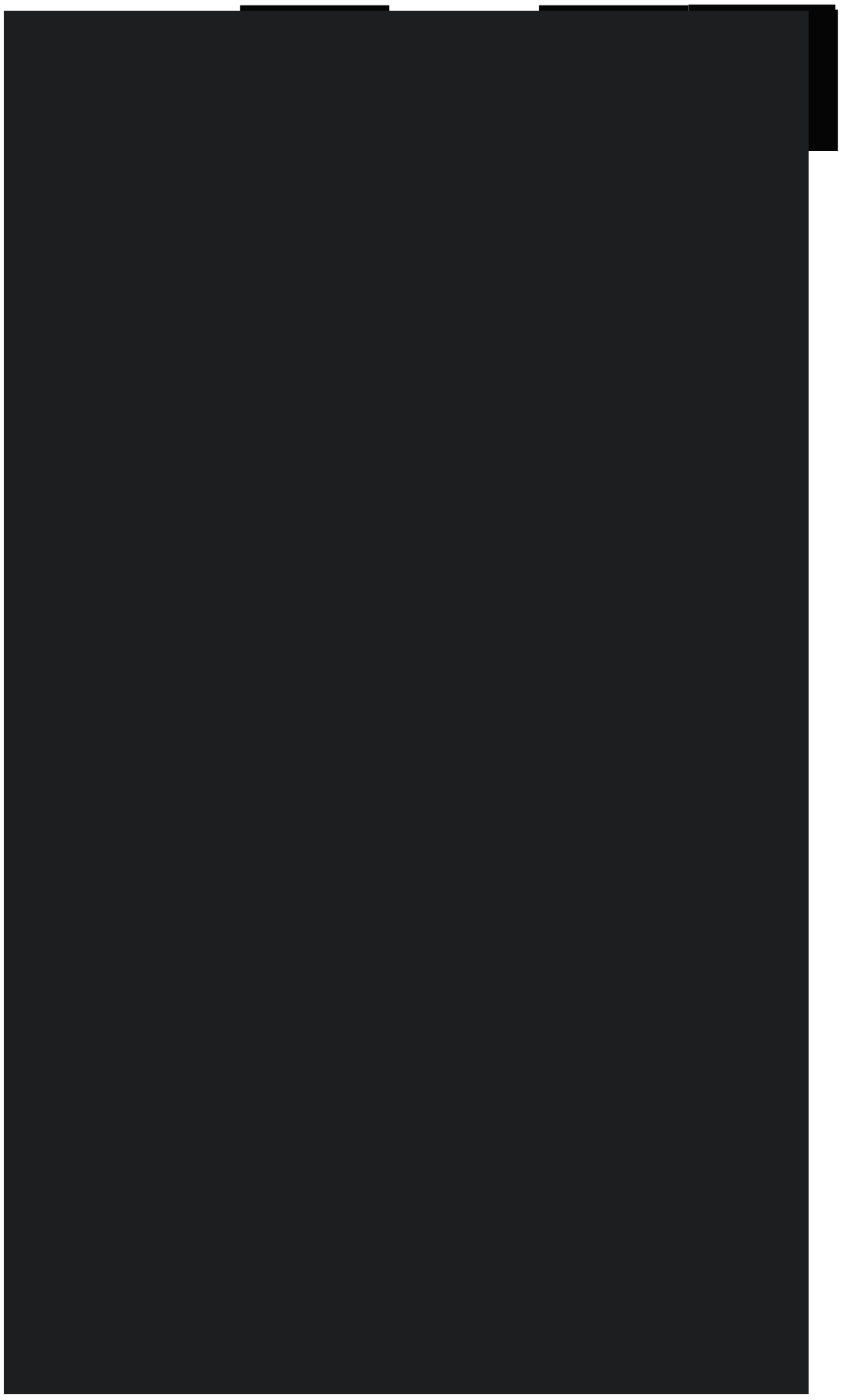

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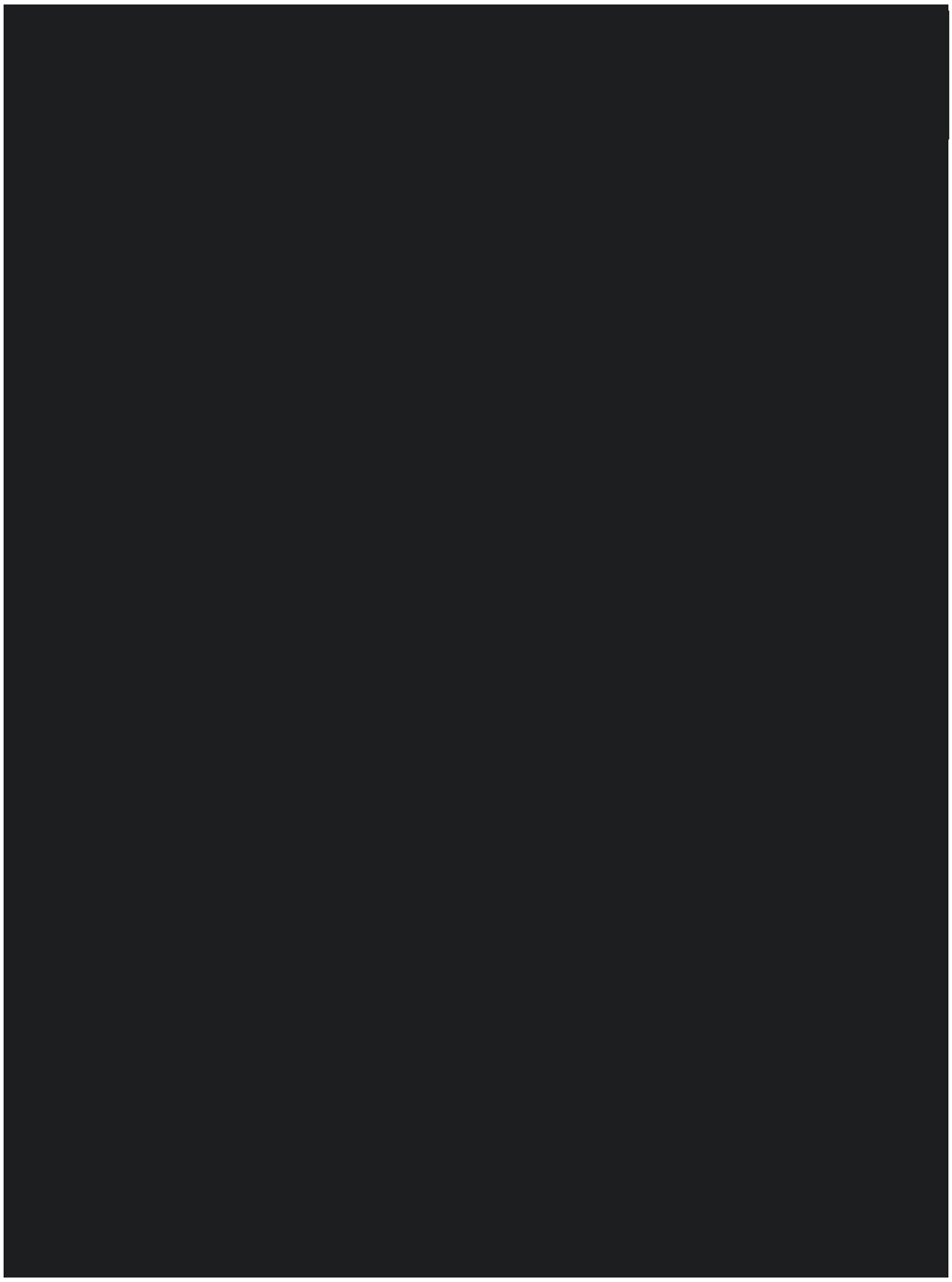

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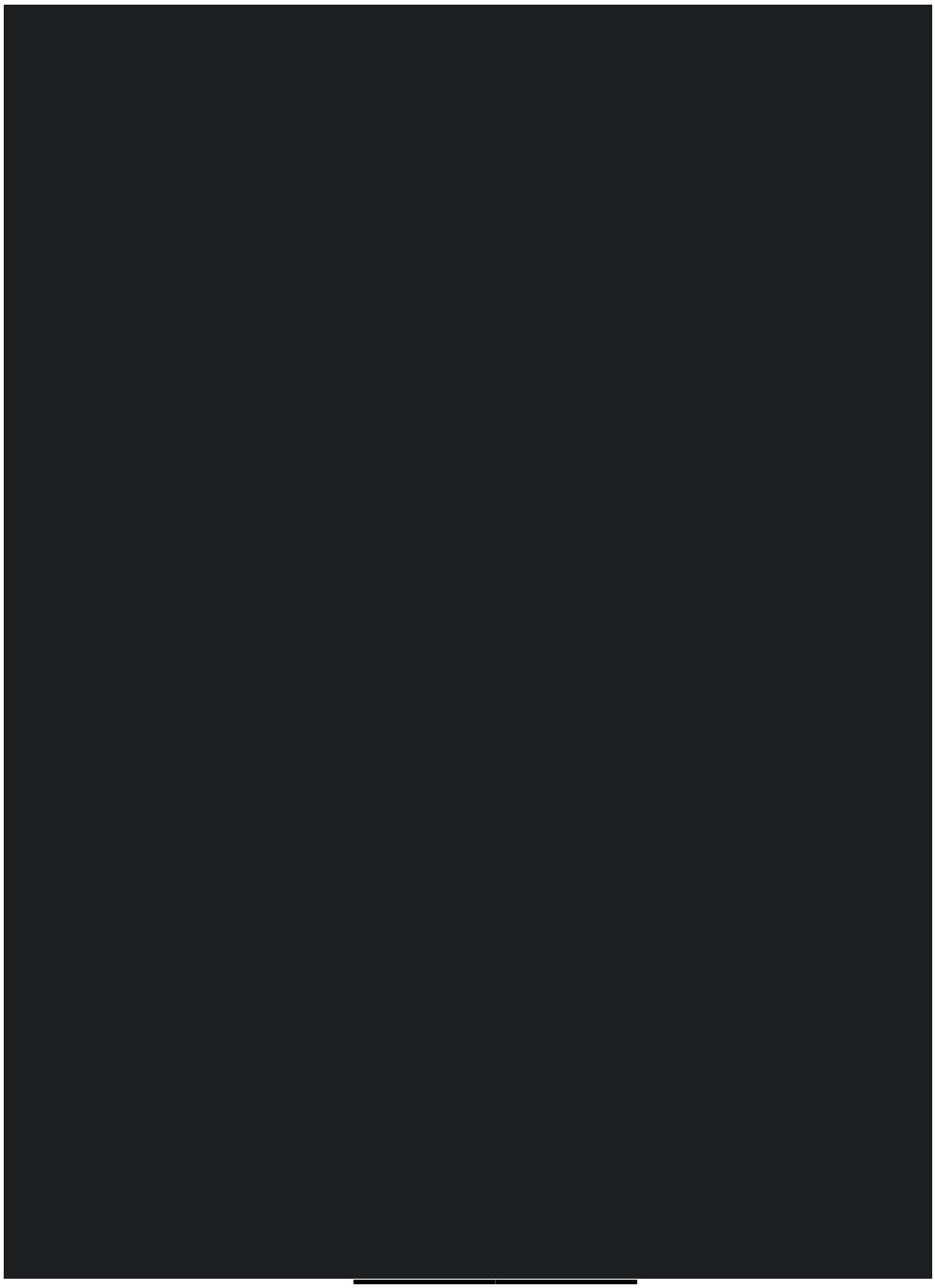

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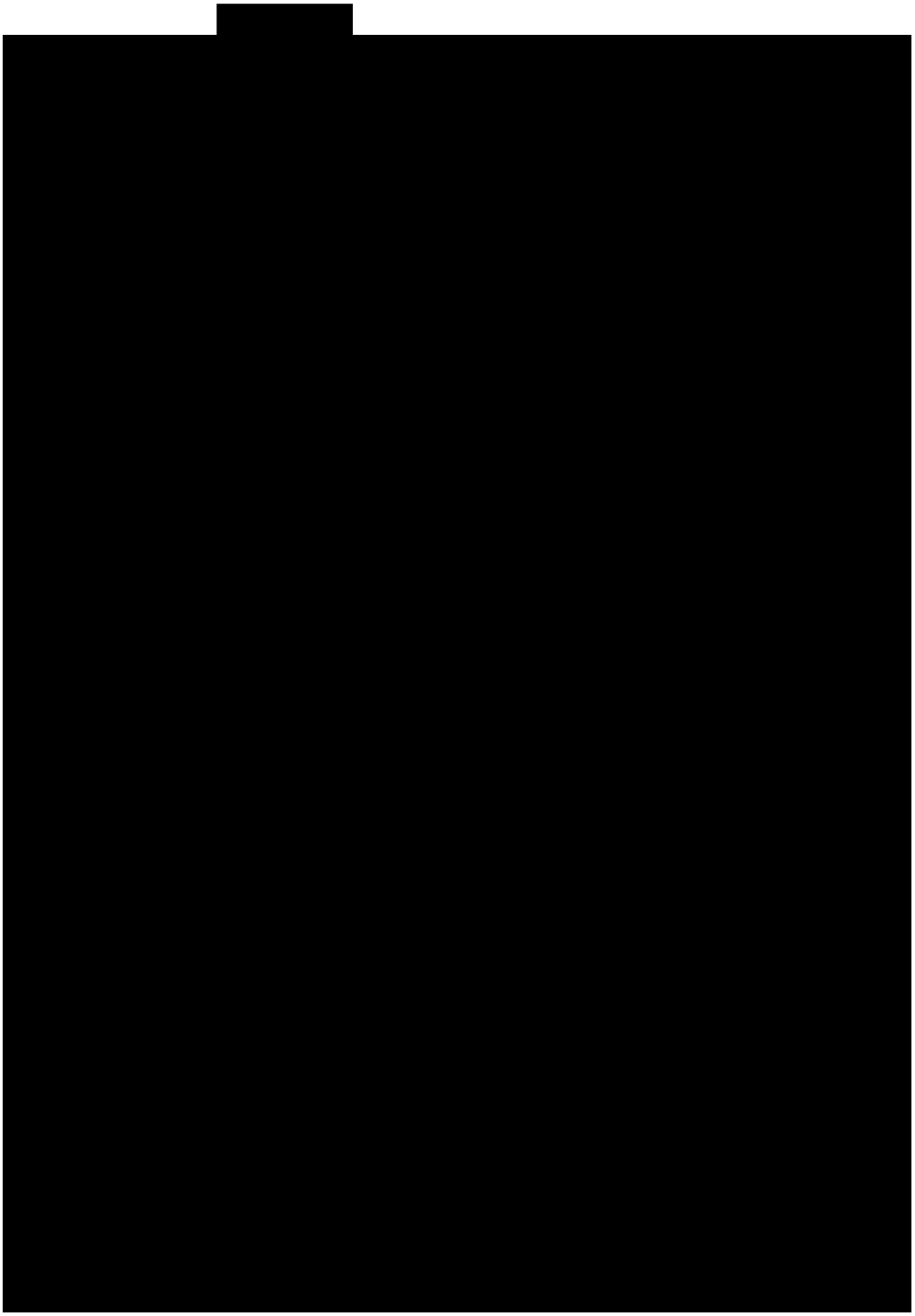

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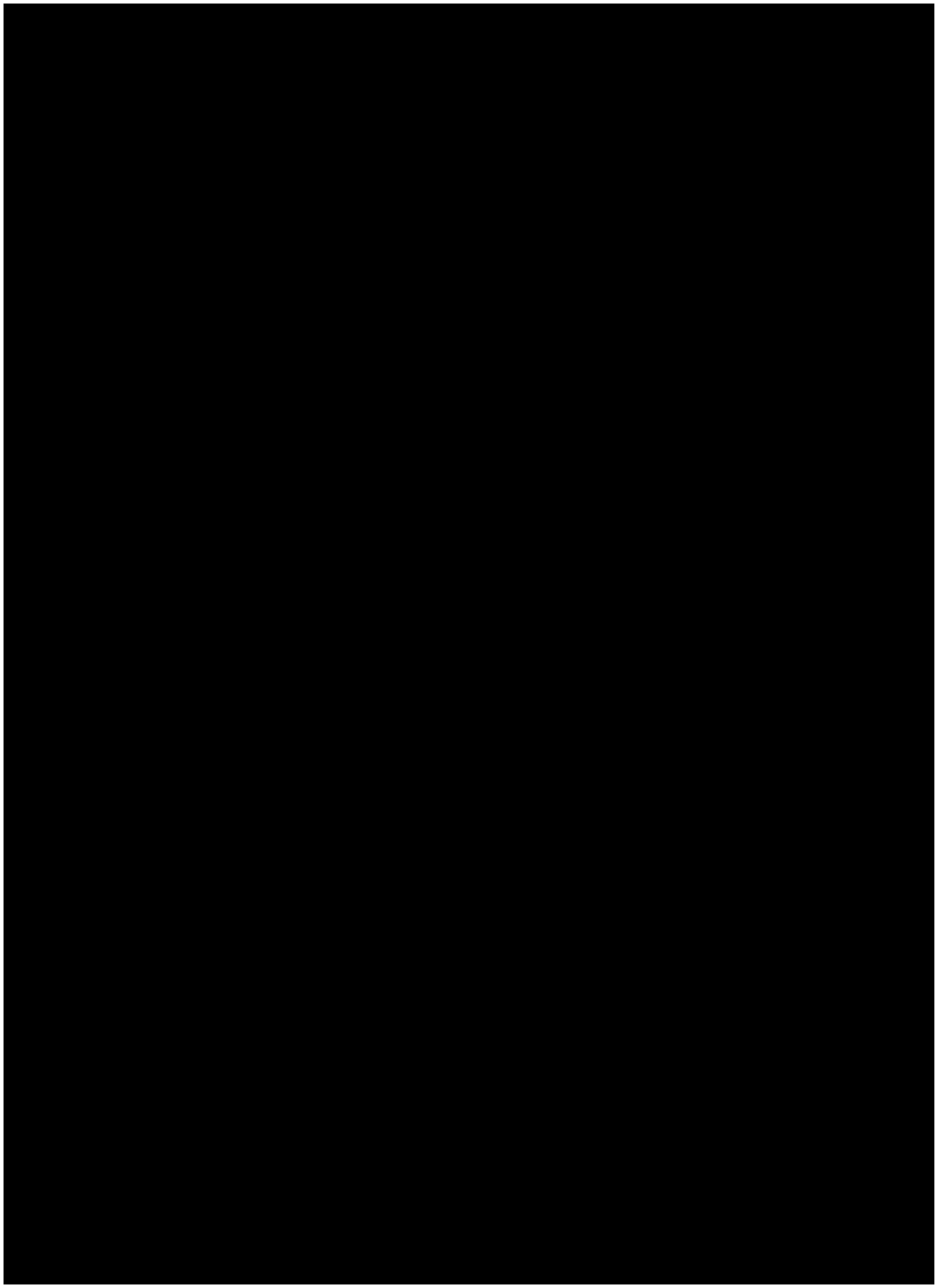

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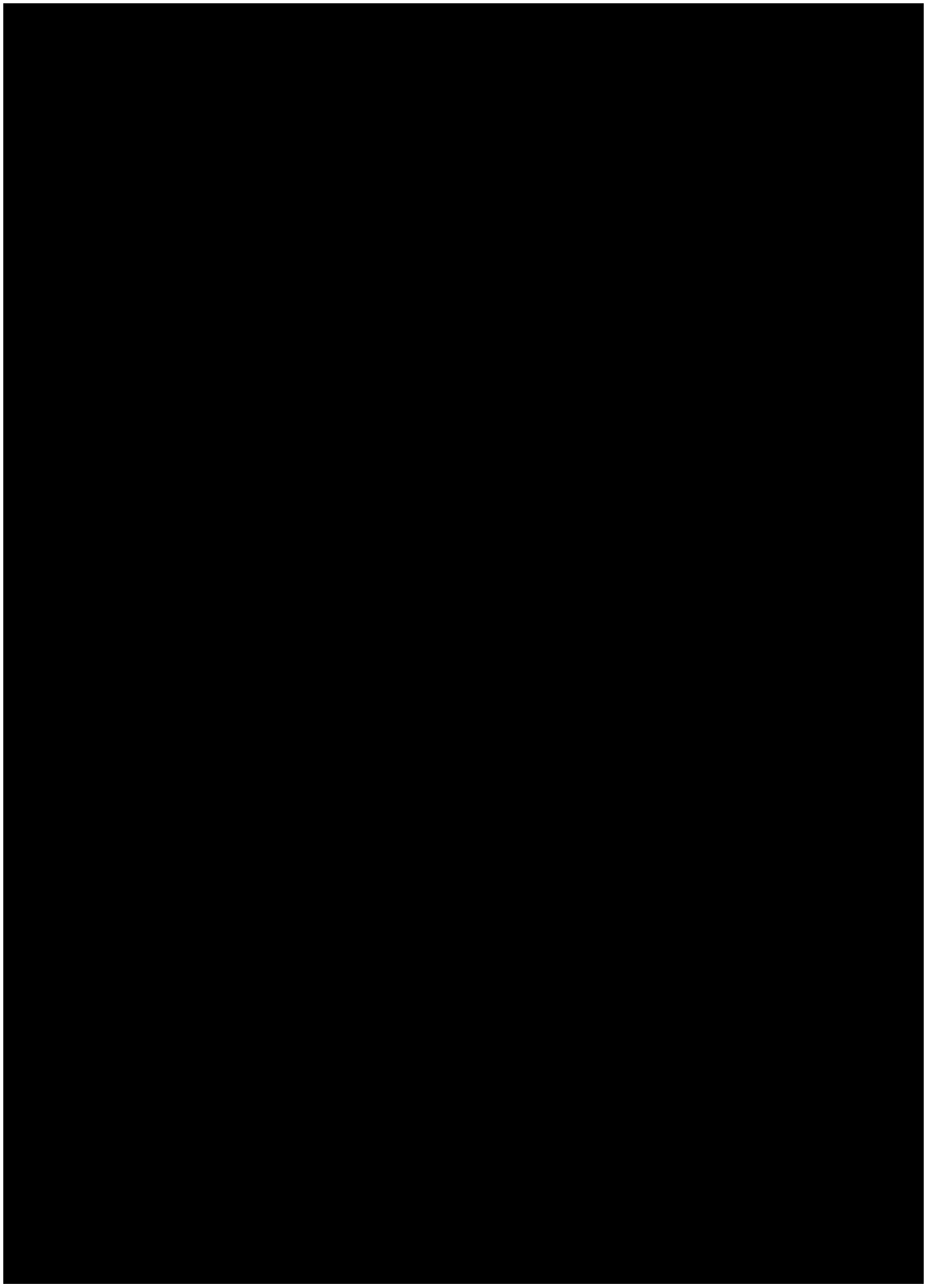

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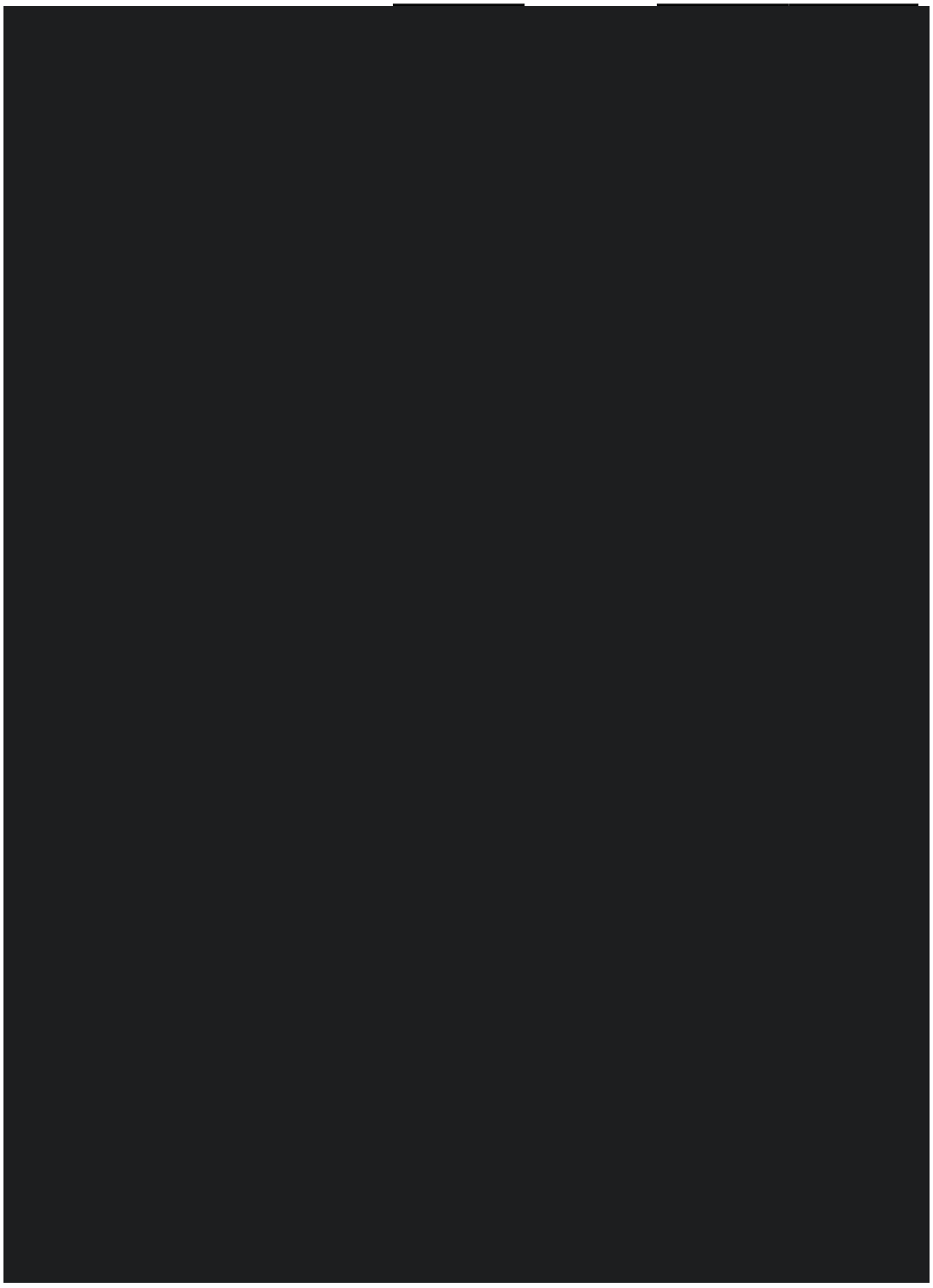

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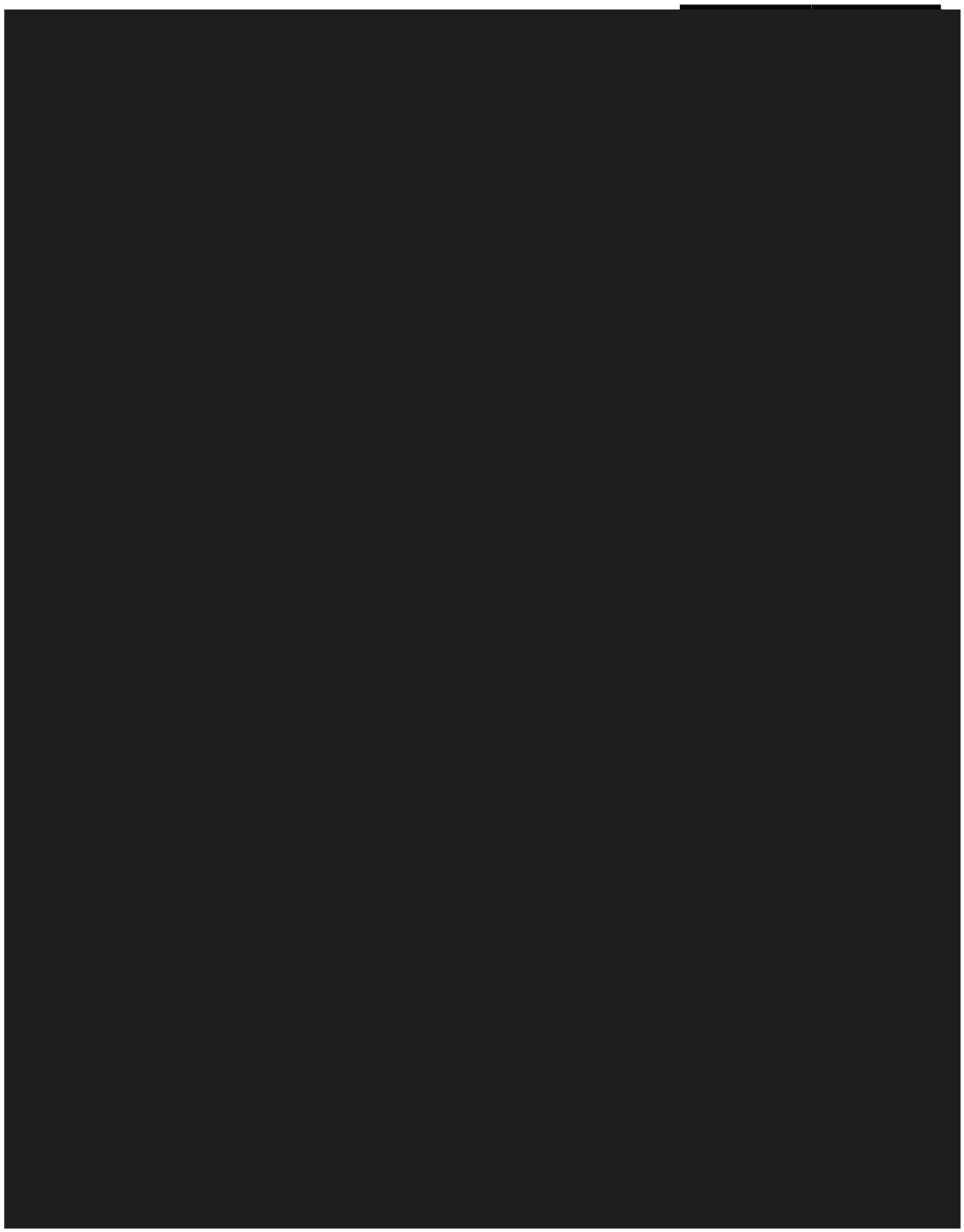

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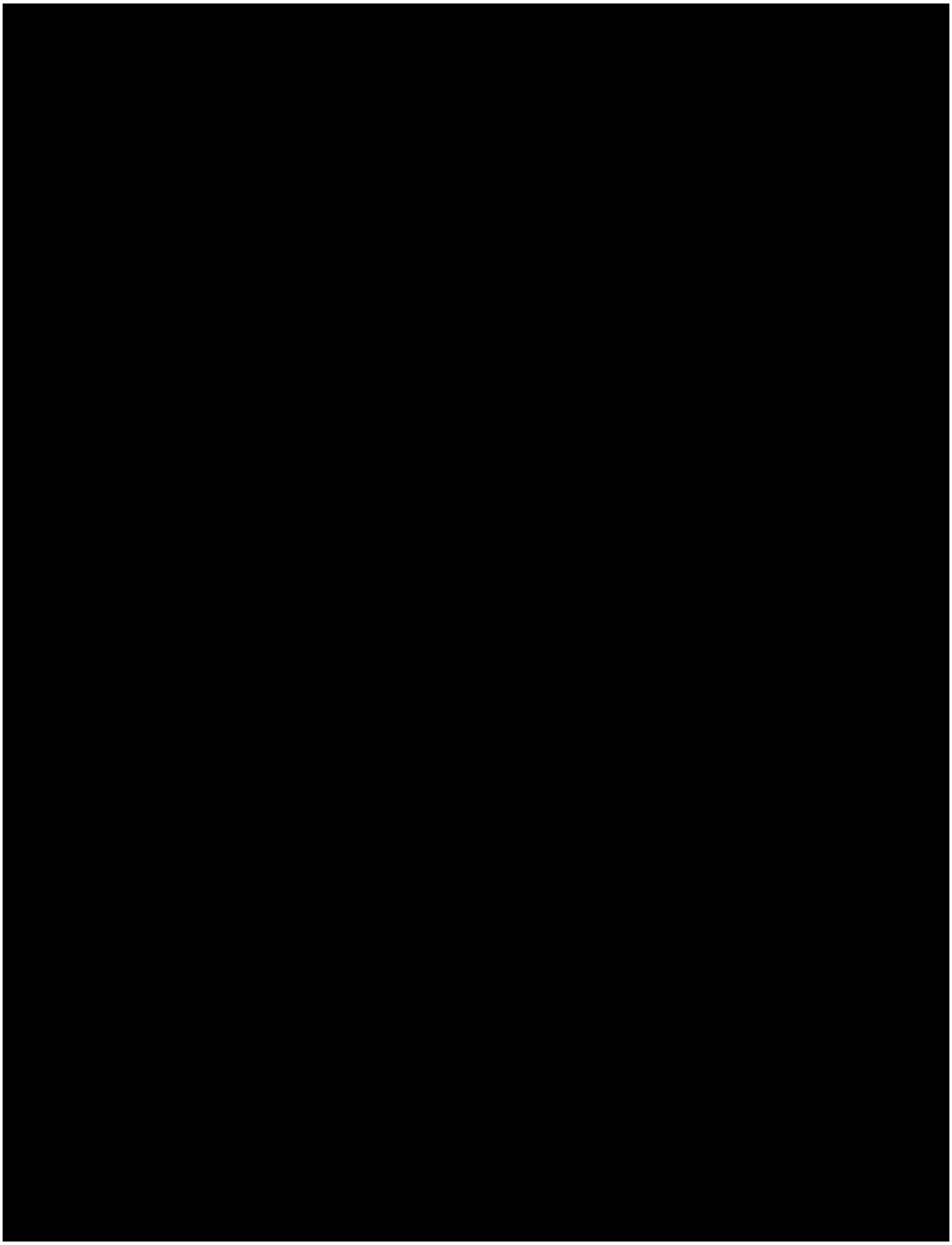

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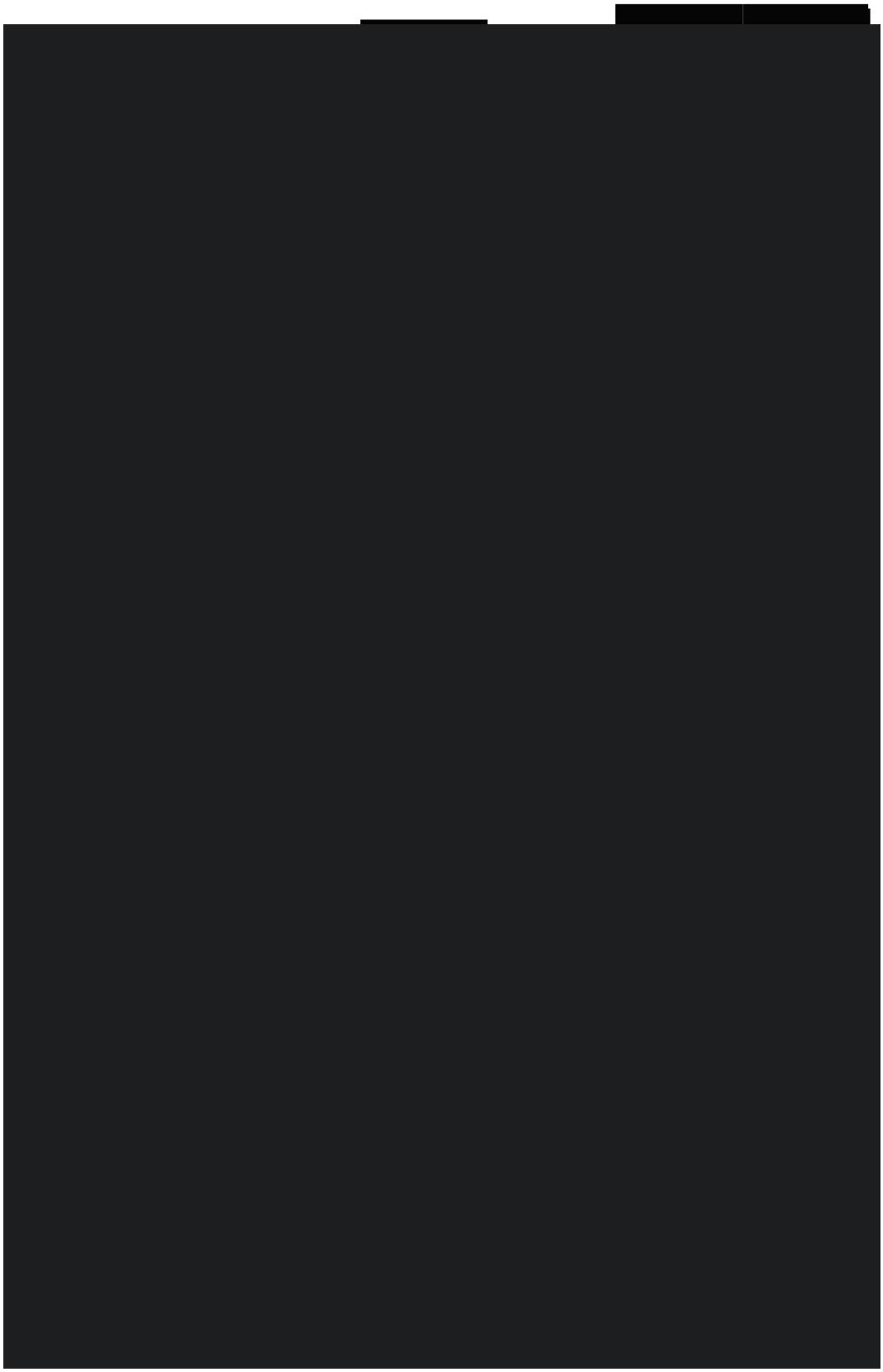

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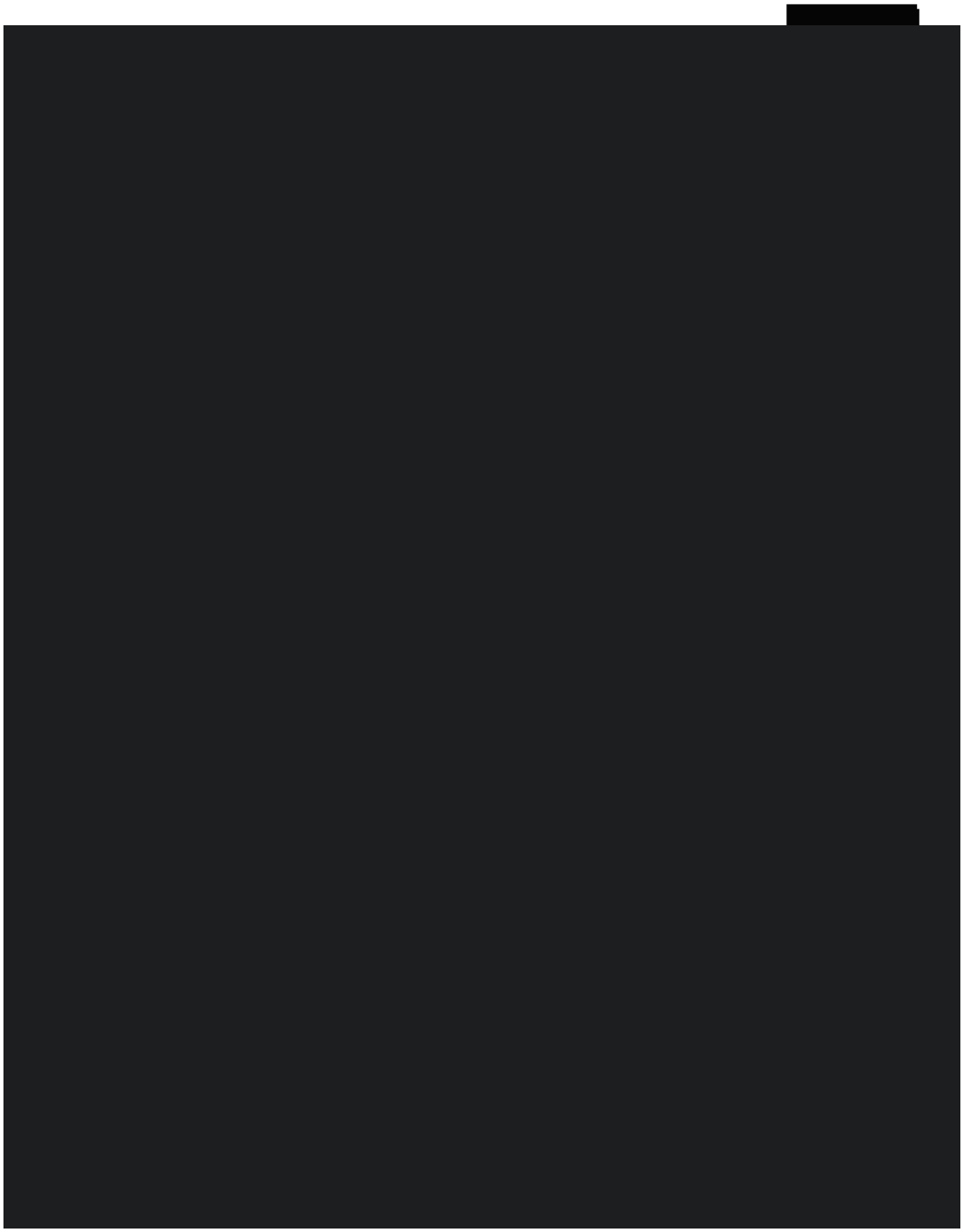

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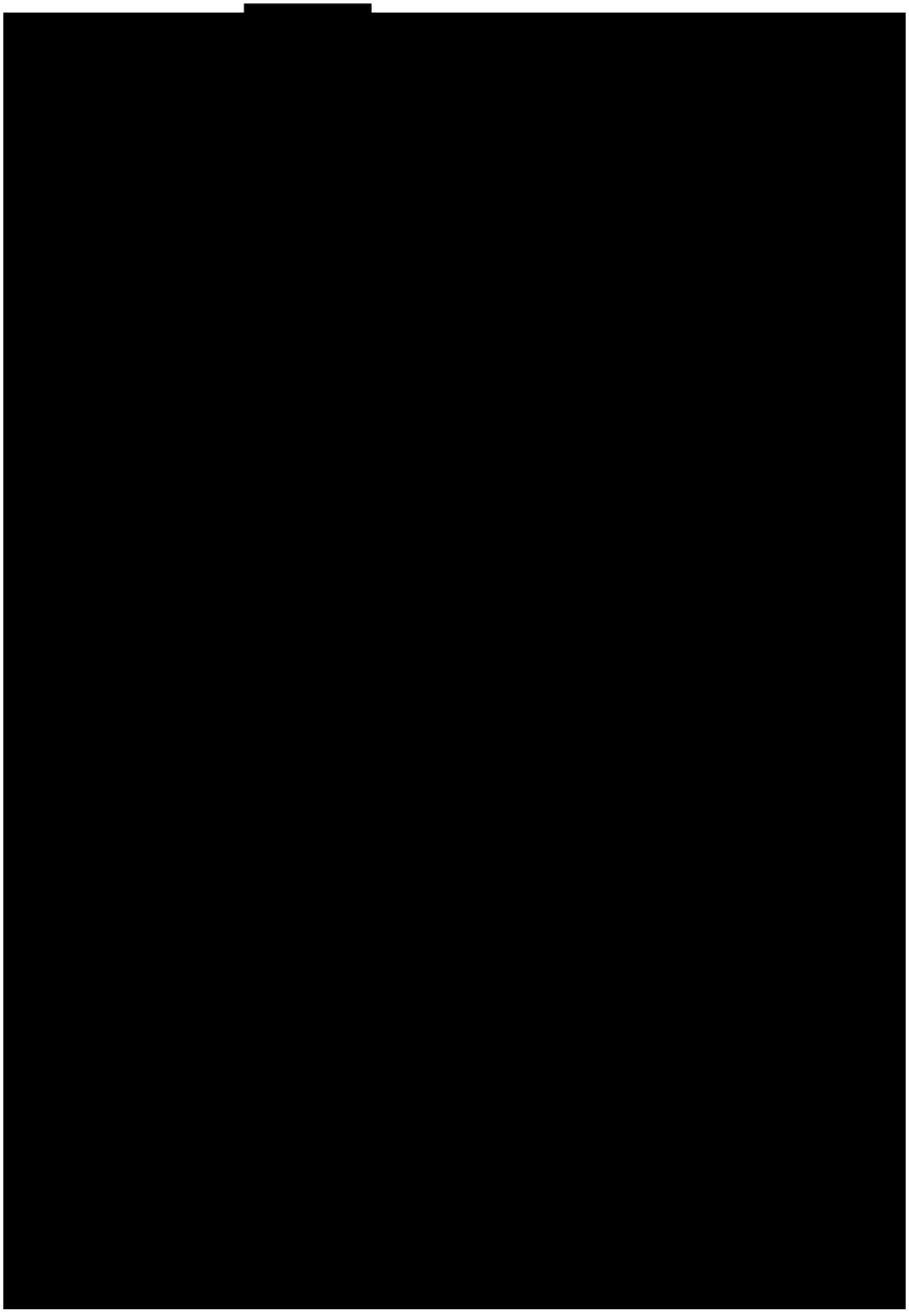

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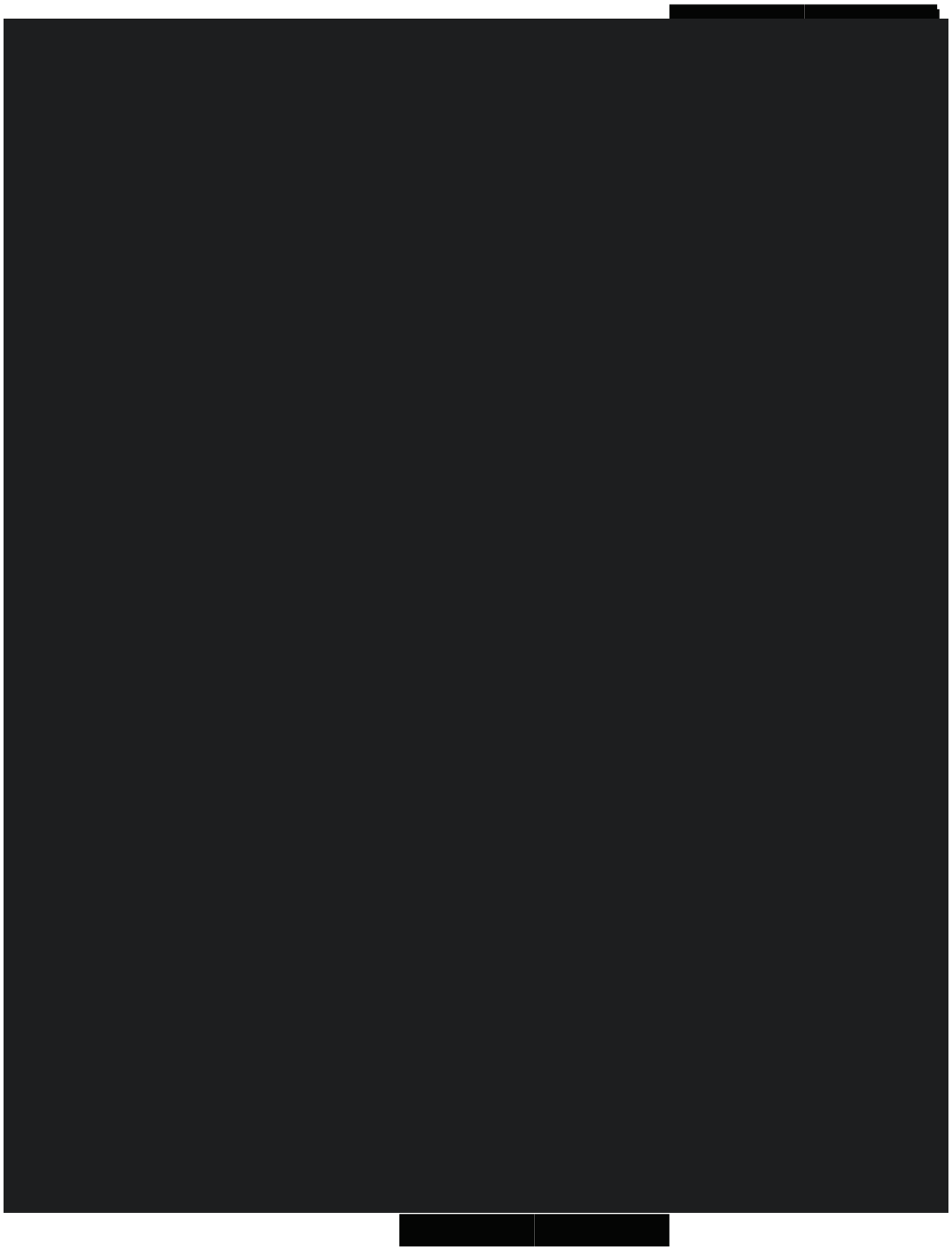

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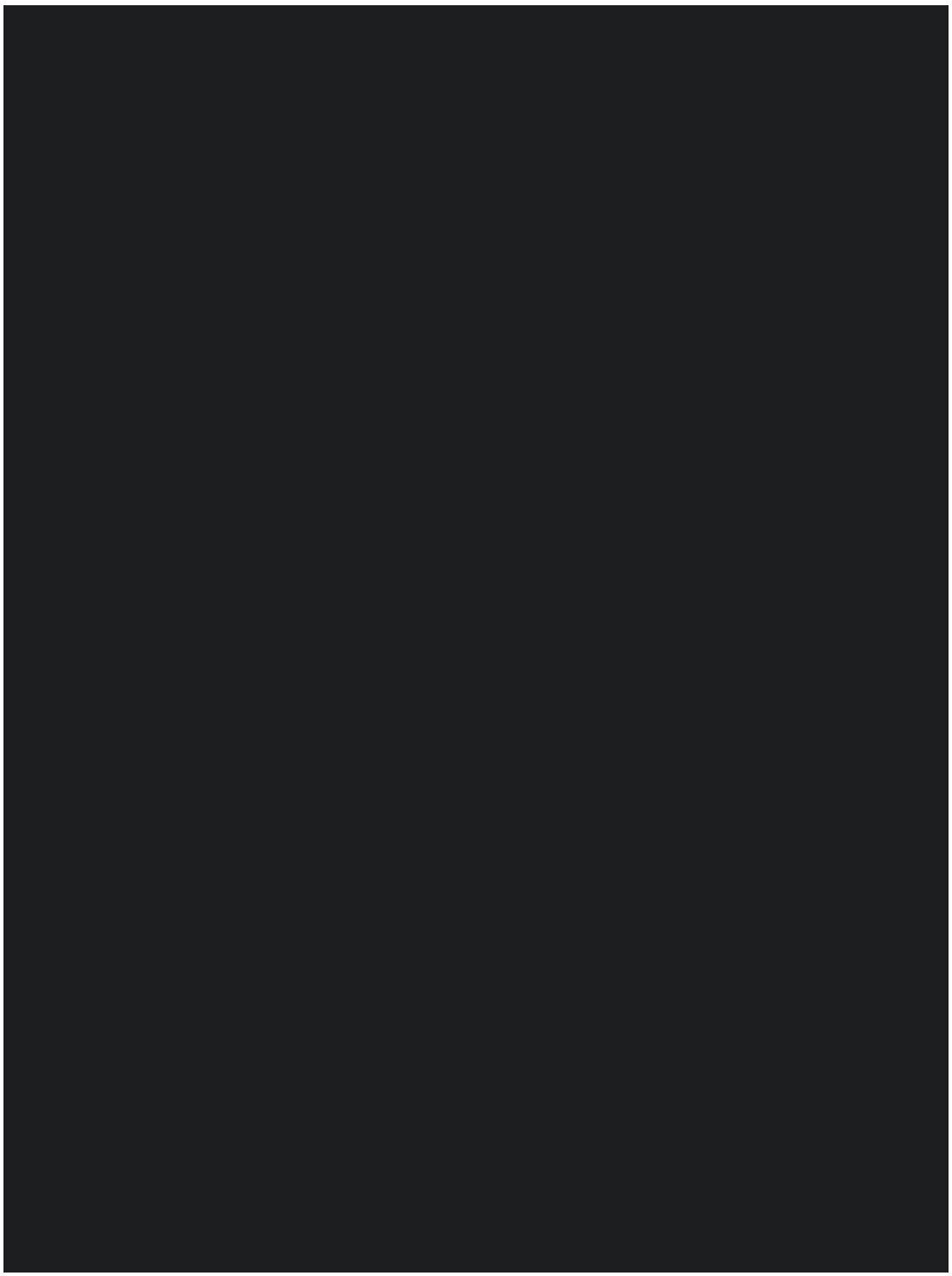

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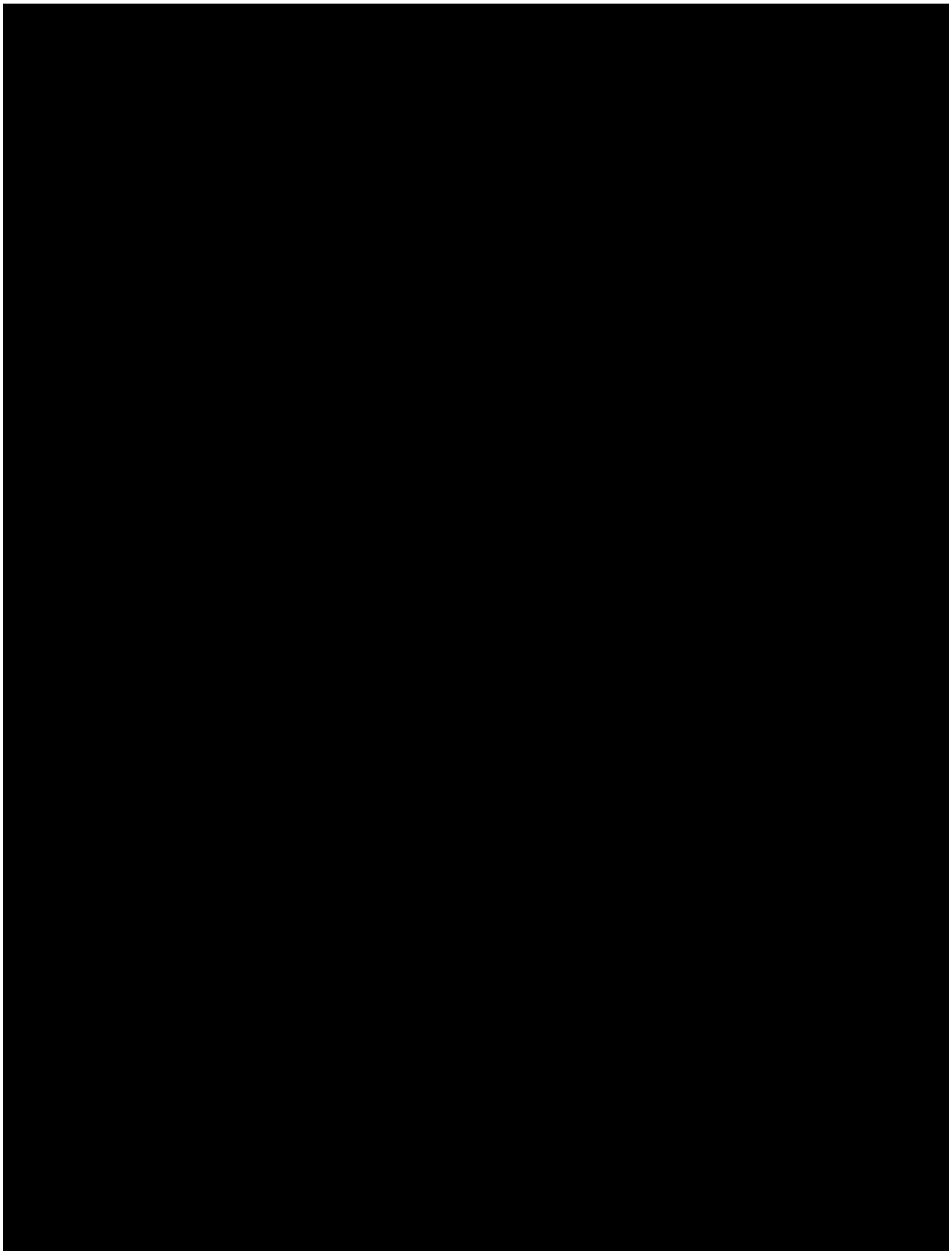

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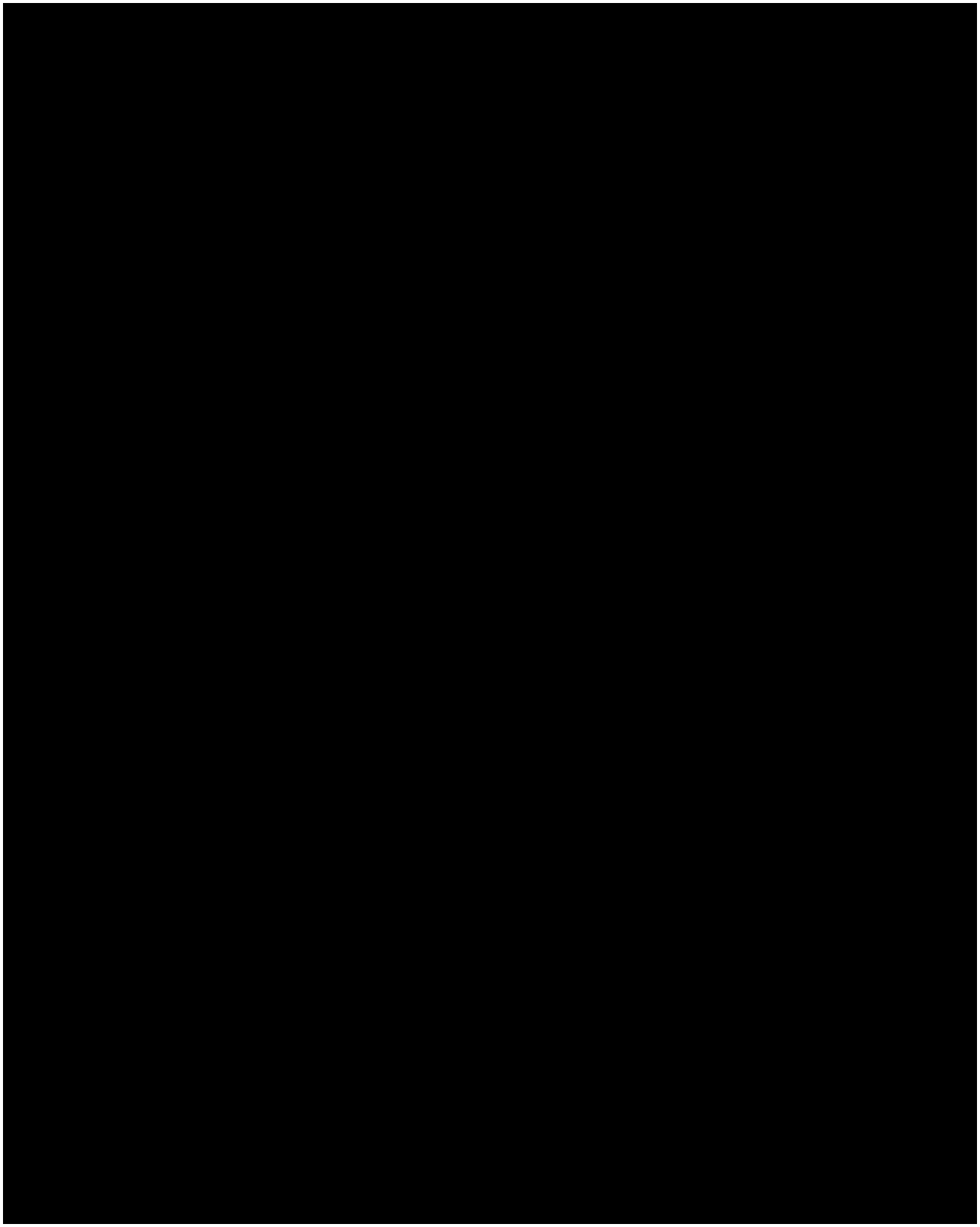

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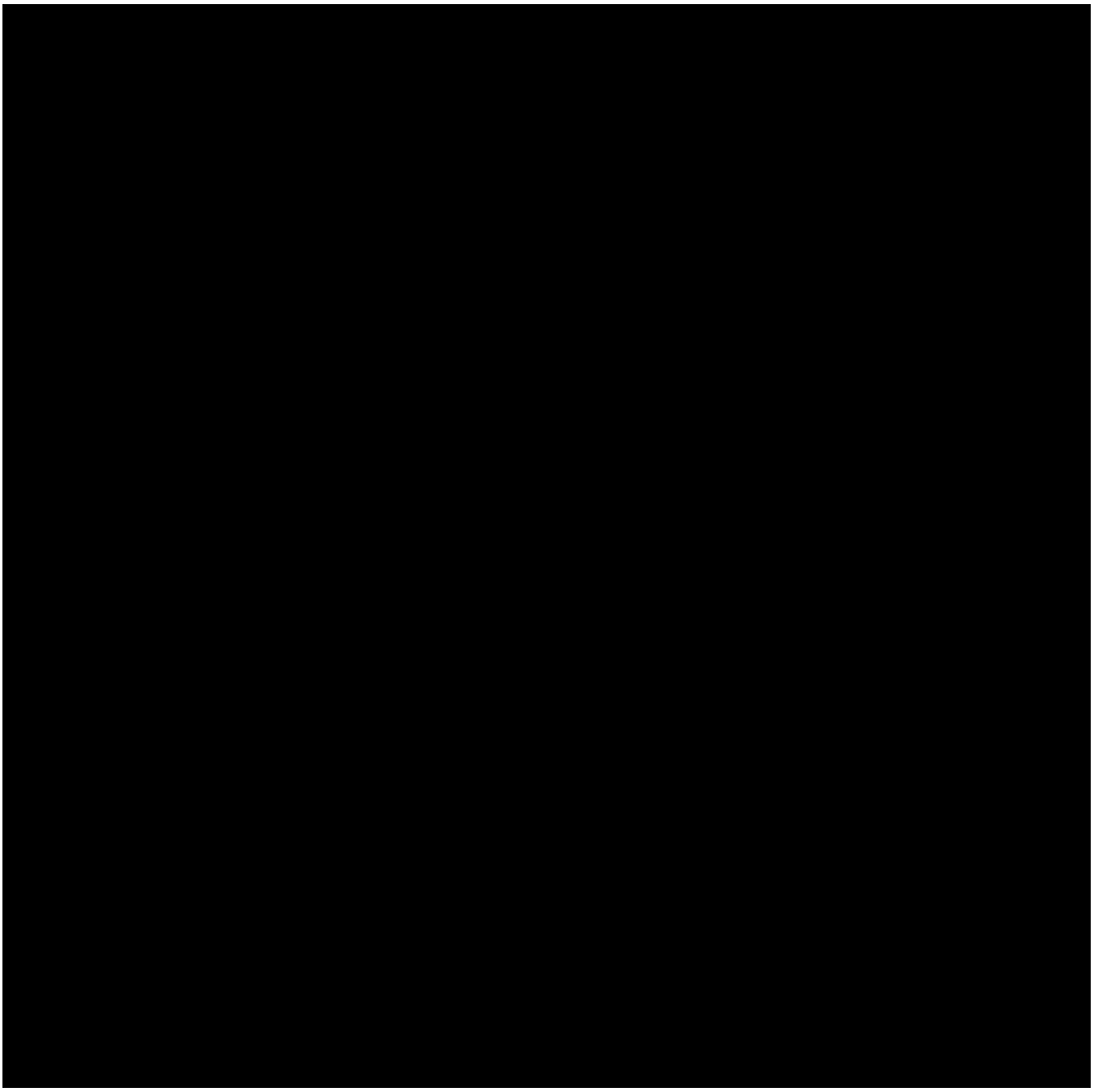

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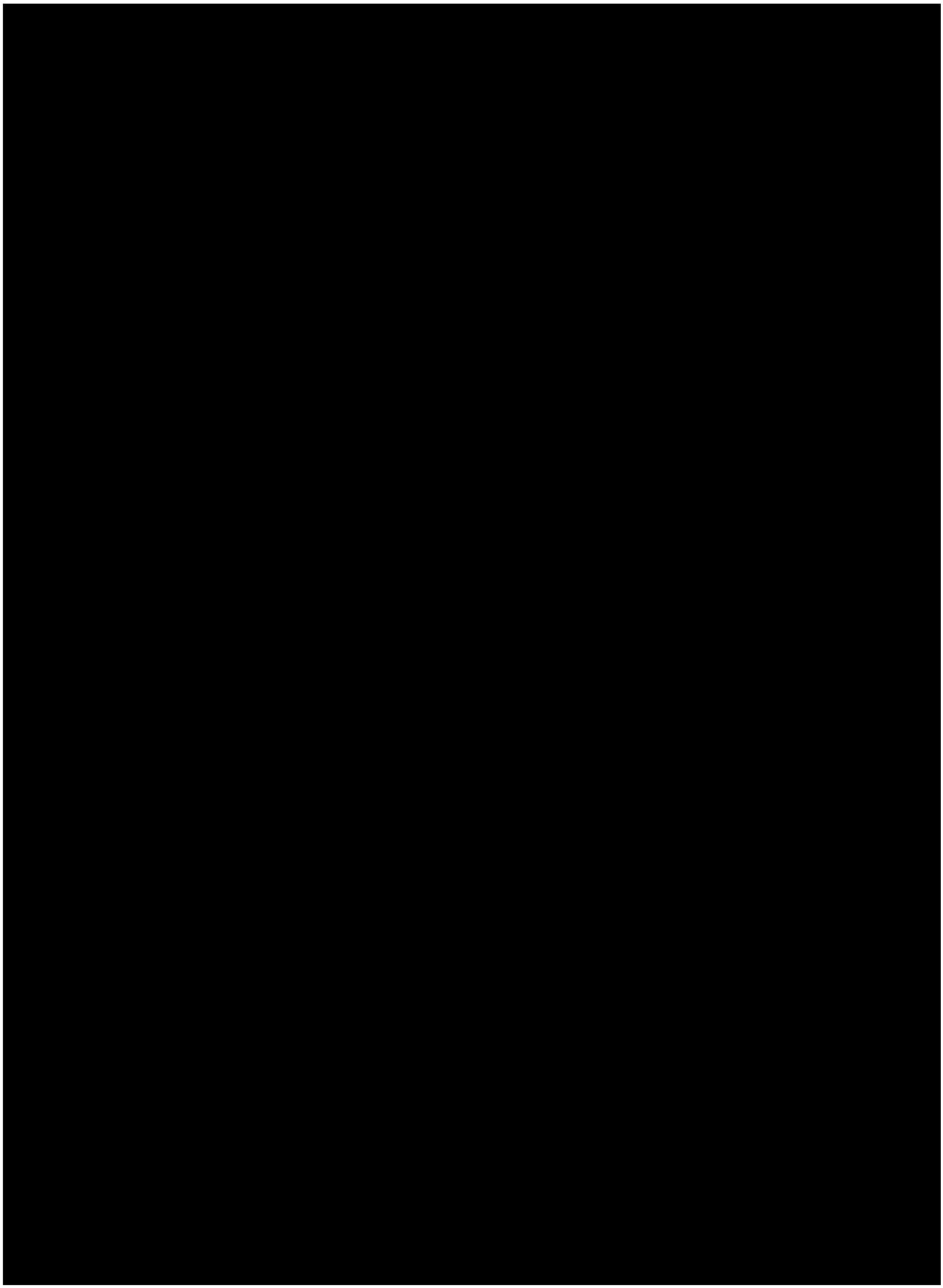

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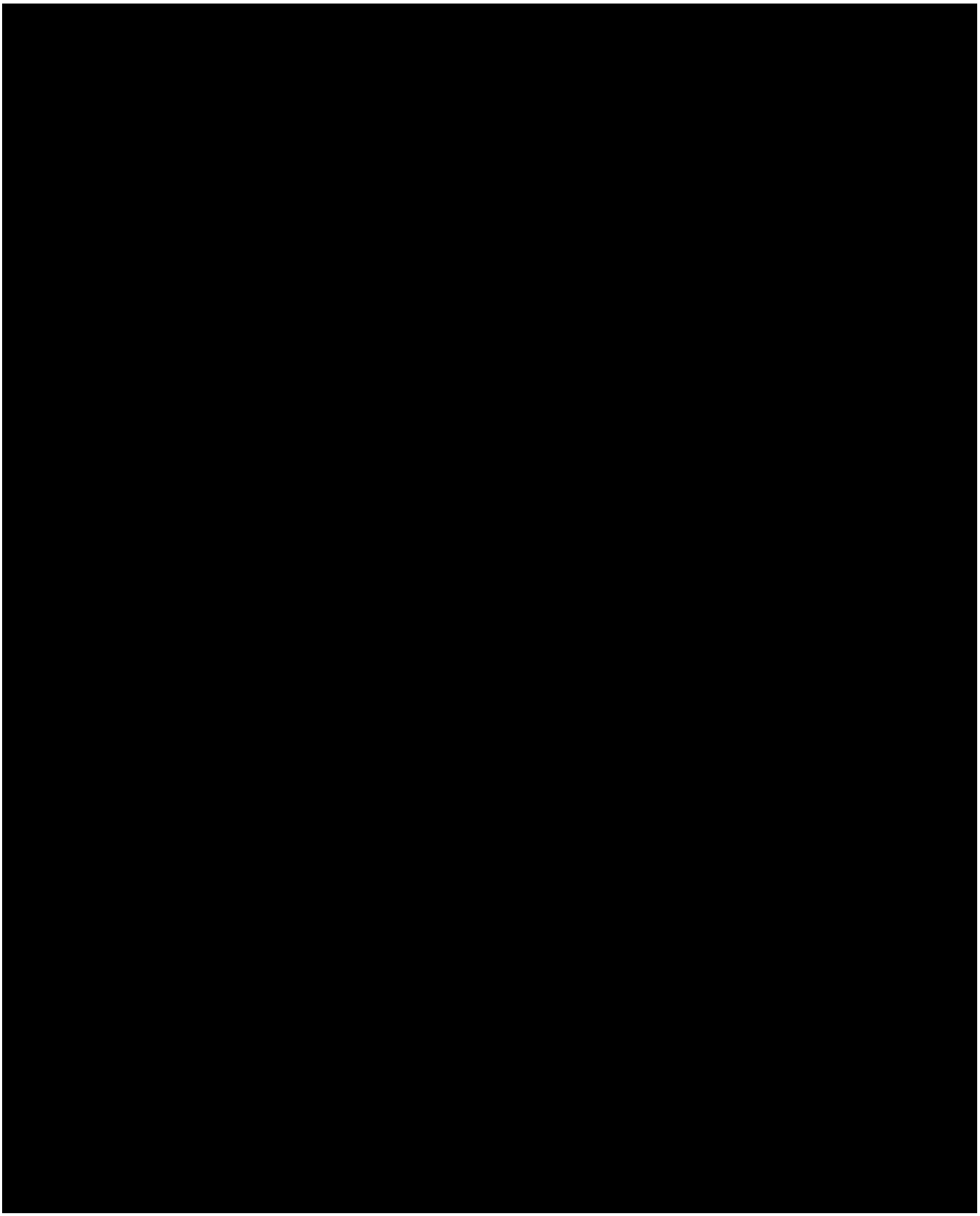

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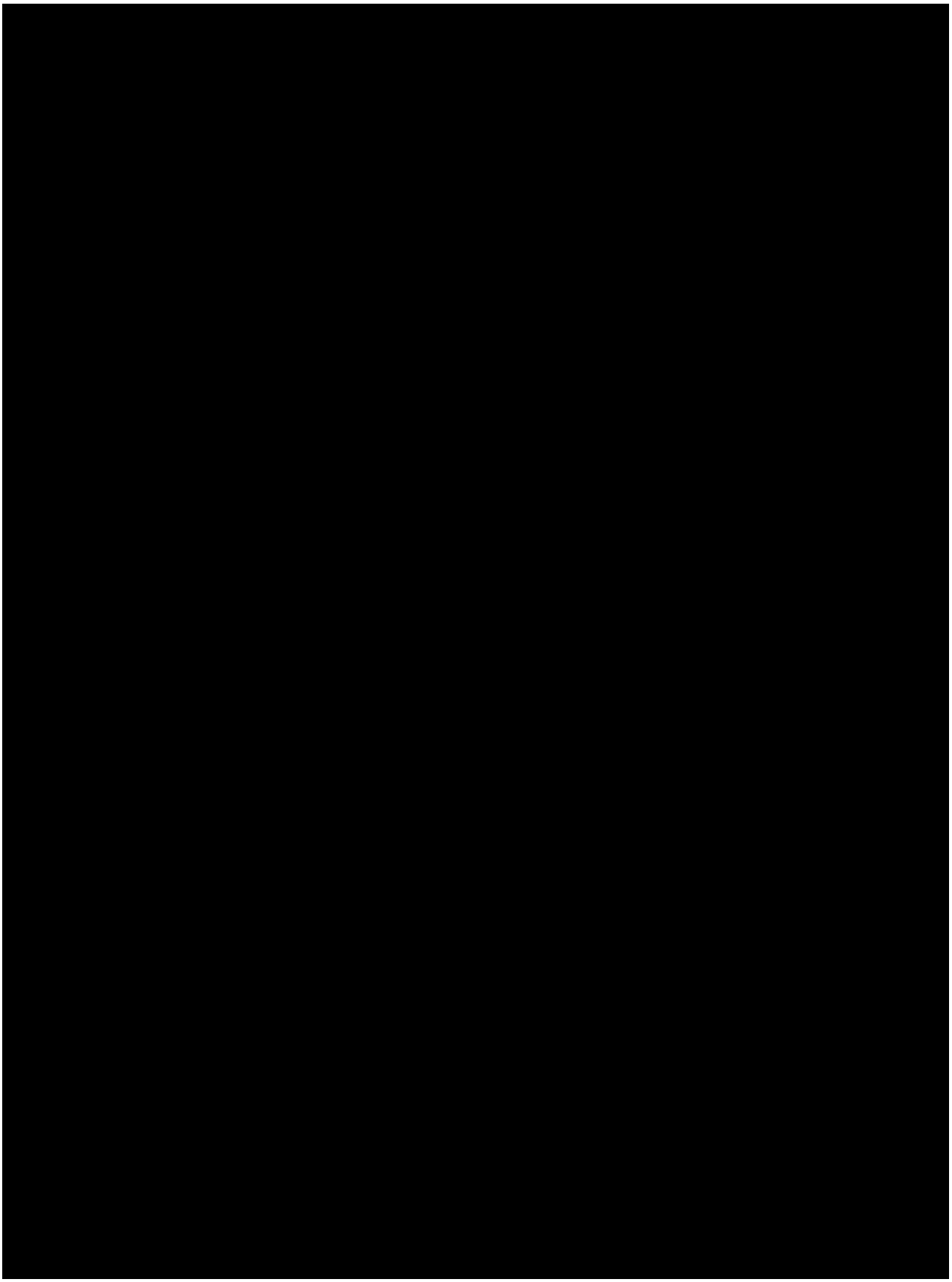
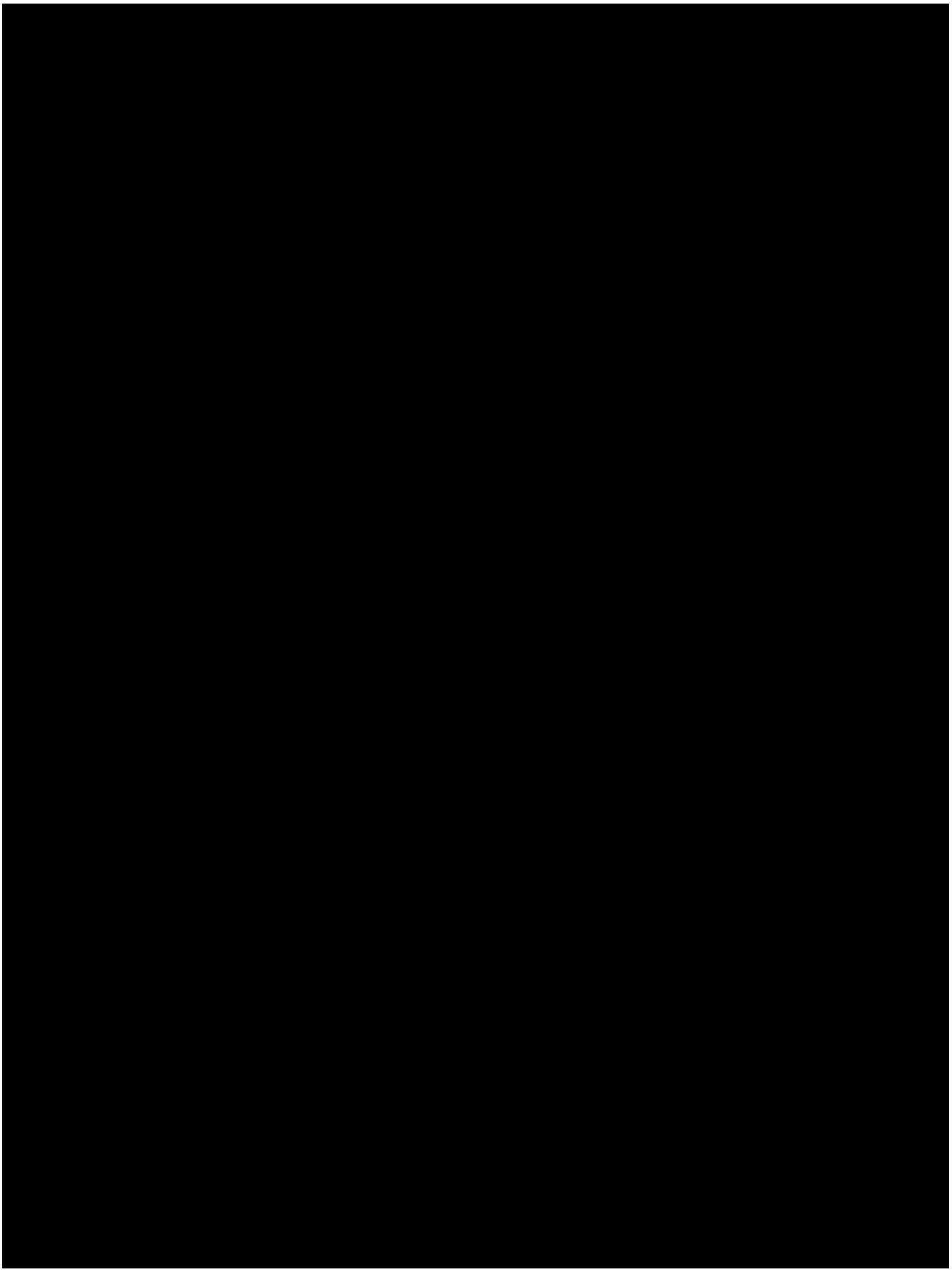


Approval Date: 04-Apr-2016



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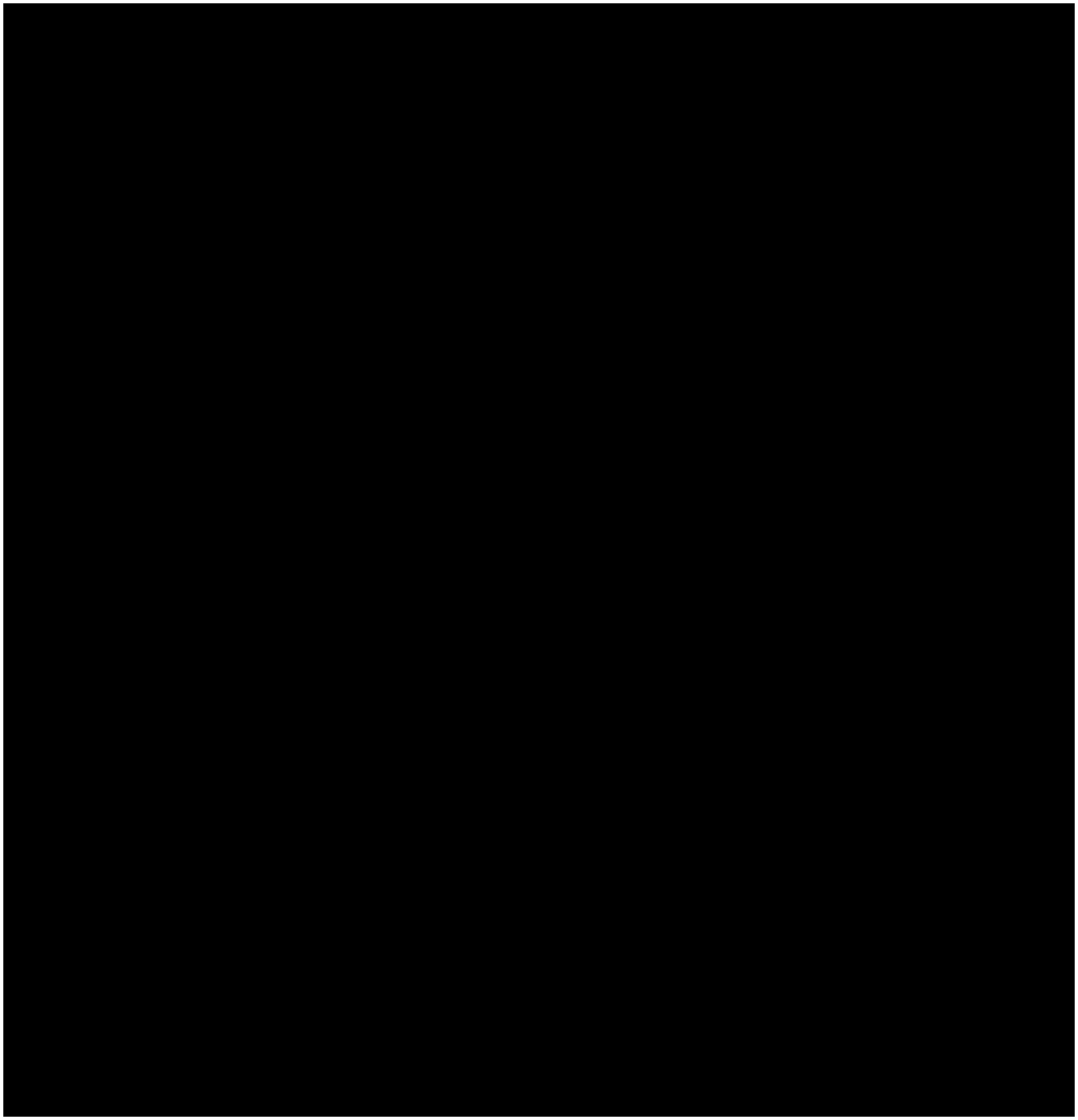

Approval Date: 04-Apr-2016

12.10 Glossary of Abbreviations

Term/Abbreviation	Definition
5-HT	serotonin
ANCOVA	analysis of covariance
AP	analysis plan
AUC_{0-12}	area under the curve from time 0 to 12 hours
BID	twice daily
bpm	beats per minute
C_{max}	maximal concentration
C/D	cup to disc
cd/m^2	candelas per square meter
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
D	diopters
DET	dry eye test
ECGs	electrocardiograms
eCRF	electronic case report form
EDC	electronic data capture
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
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NDA	new drug application

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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
OD	right eye
OS	left eye
OTC	over-the-counter
PDE5	phosphodiesterase 5
PGIC	Patient Global Impression of Change
PIOL	phakic intraocular lens
PP	per protocol
PRK	photorefractive keratectomy
PRO	patient reported outcome
QD	once daily
SOP	standard operating procedure
UDVA	uncorrected distance visual acuity
UNVA	uncorrected near visual acuity
US	United States
VAS	visual analog scale

Approval Date: 04-Apr-2016

12.11 Protocol Amendment 1 Summary

Title: A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

Protocol 199201-009 Amendment 1

Date of Amendment: October 2015

Amendment Summary

This summary includes changes made to Protocol 199201-009 (September 2015). The study duration was changed from 47 to 109 to 44 to 117 days, Table 3 was corrected to include the fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted], and measurement of the crystal lens thickness was changed to measurement of the anterior chamber depth.

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]

Approval Date: 04-Apr-2016

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Protocol [redacted]	[redacted]	[redacted]
Protocol [redacted]	[redacted]	[redacted]
Protocol Summary and Sections 7.2.1 and 7.3.1	"Average change from baseline" was revised to "weighted average change from baseline" for the primary efficacy analysis	To clarify the definition of the primary efficacy variable
Section 5.5	Study medication will be labeled with medication kit number, study number, dominant or nondominant eye, and lot number ~~all possible concentrations of AGN-199201, AGN 190584, and vehicle~~.	Text was revised to match study medication labels
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Approval Date: 04-Apr-2016

Section	Revision	Rationale
[redacted]		

Approval Date: 04-Apr-2016

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Section 7.4	Ethnicity was added to the subgroup analyses	To match the eCRF
[redacted]	[redacted]	[redacted]
Section 9.1.3	The “Not Applicable” category was deleted from the severity assessment for an adverse event	This category will not be used in this study
Section 11	Prow, 1996 was added to the reference list	Inadvertently omitted
[redacted]	[redacted]	[redacted]

Approval Date: 04-Apr-2016

12.12 Protocol Amendment 2 Summary

Title: A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

Protocol 199201-009 Amendment 2

Date of Amendment: December 2015

Amendment Summary

This summary includes changes made to Protocol 199201-009 Amendment 1 (October 2015). The Allergan Medical Safety Physician contact information was changed and "lot number" was deleted from the description on how study medication will be labeled.

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 Medical Safety Physician contact information was changed	To reflect the current physician supporting the protocol
Section 5.5	Study medication will be labeled with medication kit number, study number, and dominant or nondominant eye~~, and lot number~~.	Text was revised to match study medication labels

Approval Date: 04-Apr-2016

12.13 Protocol Amendment 3 Summary

Title: A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

Protocol 199201-009 Amendment 3

Date of Amendment: February 2016

Amendment Summary

This summary includes changes made to Protocol 199201-009 Amendment 2 (December 2015). Visit 3 of each dosing period, the OCT measure, and the electrical device PRO measure was removed from the study; the order of the Grand Seiko measurements was reversed to perform UDVA first and then UNVA; and the macroscopic hyperemia assessment was moved to be performed before the slit lamp biomicroscopy.

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, and an e-mail address was added for serious adverse event reporting	To reflect the current Therapeutic Area Head, and to facilitate serious adverse event reporting
[redacted]	[redacted]	[redacted]
Protocol	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Approval Date: 04-Apr-2016

Section	Revision	Rationale
[redacted]	[redacted]	
Section 4.5.1.1	~~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 5.5	The IxRS will provide the site with the specific medication kit number(s) for each randomized patient at the time of randomization. <u>(day 1 of the first dosing period) and on day 1 of each subsequent dosing period</u>.	For clarification
[redacted]	[redacted]	[redacted]
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]
[redacted]	[redacted]	[redacted]

Approval Date: 04-Apr-2016

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Section 7.2.1	The primary efficacy variable is the weighted average change from baseline in UNVA letter in the nondominant eye over ~~three~~ 2-day periods between hour 1 and hour 10.	To reflect the removal of visit 3
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Approval Date: 04-Apr-2016

Section	Revision	Rationale
	measurements were added at hours [redacted]	
[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 8.9	Visit 3/study exit was changed to visit 2/study exit	To reflect the removal of visit 3
Section 9.5	A section on the procedures for pregnancy follow-up and reporting was added	To be consistent with the Informed Consent Form

Approval Date: 04-Apr-2016

12.14 Protocol Amendment 4 Summary

Title: A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

Protocol 199201-009 Amendment 4

Date of Amendment: April 2016

Amendment Summary

This summary includes changes made to Protocol 199201-009 Amendment 3 (February 2016). Table 2 and relevant sections of the protocol were corrected to include a photopic pupil measurement (both eyes, distance) at screening and near manifest refraction at baseline/visit 1, and the order of the sodium fluorescein corneal staining (Oxford scale), Schirmer's tear test (with anesthesia), IOP, and gonioscopy/angle assessment was revised for optimal collection during the conduct of the study.

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]
Protocol	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Approval Date: 04-Apr-2016

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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	For clarification

Approval Date: 04-Apr-2016

Section	Revision	Rationale
	during the near-vision tasks and associated near-vision task questionnaires, but may use their glasses to fill out other study related questionnaires.	

Approval Date: 04-Apr-2016

ALLERGAN

Protocol 199201-009 Amd 4

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

Approval Date: 04-Apr-2016