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Study ID: 150998-006

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

Protocol Amendment 4 Date: 10 April 2018

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Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

SEQUOIA STUDY

Protocol Number: 150998-006 Amendment 4

EudraCT Number: 2014-004580-20

Phase: 3

Name of Investigational Product: Abicipar Pegol (AGN-150998)

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

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

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

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

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

Investigator Printed Name

Signature

Date

Approval Date: 10-Apr-2018

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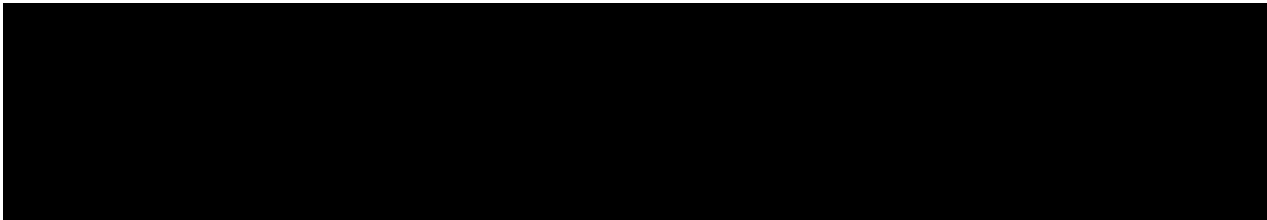
Protocol Summary

Study Compound: Abicipar pegol (hereafter referred to as abicipar)

Phase: 3

Study Objective:

To assess the safety and efficacy of abicipar compared with ranibizumab in treatment-naïve patients with neovascular age-related macular degeneration (AMD)



Study Design



Duration: 104 weeks participation for each patient following randomization

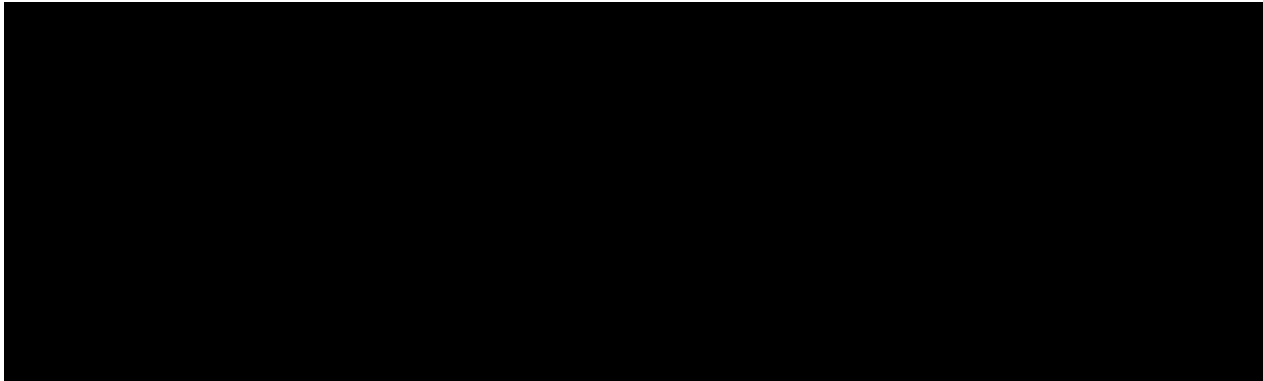
Study Treatment Groups and Dosage/Dose Regimen:

- Treatment group 2Q8: 2 mg abicipar administered at baseline (day 1) and weeks 4 and 8, followed by doses at 8-week intervals through week 96
- Treatment group 2Q12: 2 mg abicipar administered at baseline (day 1), and weeks 4 and 12, followed by doses at 12-week intervals through week 96

Controls:

- Treatment group rQ4: 0.5 mg ranibizumab administered every 4 weeks through week 96

The treating investigator will administer the masked² study medication by intravitreal injection into the study eye at the assigned visits.



¹ Defined as a loss of fewer than 15 letters in best-corrected visual acuity [BCVA] compared to baseline using the Early Treatment Diabetic Retinopathy Study [ETDRS] method [hereafter referred to as letters]

² To maintain masking, patients randomized to abicipar will receive a sham injection during the study visits when they are not scheduled to receive their assigned study medication. For the sham injections, the study eye of each patient will be prepared using a standard protocol as if they were to receive an intravitreal injection as defined in the procedure manual. For the sham injection, the treating investigator will press the blunt end of the syringe against the eye, mimicking an intravitreal injection.

Visit Schedule: Patients will have visits at screening, baseline (day 1), and every 4 weeks until week 104/early exit. For patients at selected sites who will have pharmacokinetic (PK) blood sampling, there will be additional visits 2 days after the baseline (day 1) and week 24, 48, and 96 visits.

Study Population Characteristics

Number of Patients: Approximately 900 patients will be enrolled at an estimated 200 sites in order to have 720 patients (240 per treatment group) complete the 52 week follow-up visit allowing for an early-discontinuation rate of approximately 20%.

Condition/Disease: Treatment-naïve patients with neovascular AMD

Key Inclusion Criteria: One eye will be selected and treated as the study eye. [REDACTED]

General Inclusion Criterion:

- Male or female patients, 50 years of age or older at the time of informed consent

Key Ocular Inclusion Criteria (study eye):

- BCVA ≤ 73 and ≥ 24 letters (20/40 to 20/320 Snellen equivalents, respectively) at screening and baseline (day 1, prior to treatment) visits

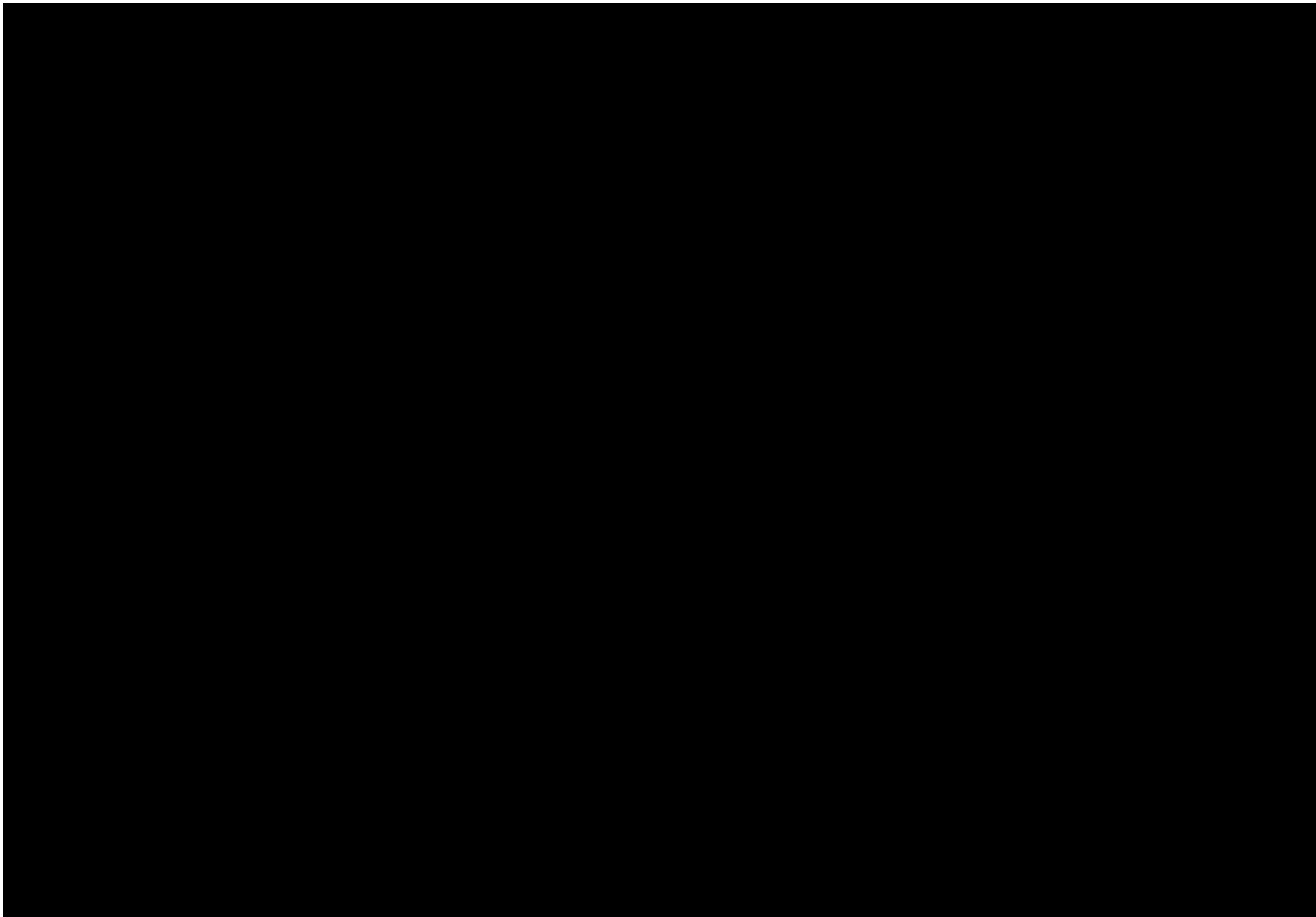
Ocular Inclusion Criterion (Non-study Eye):

- BCVA of 34 letters (Snellen equivalent 20/200) or better at baseline (day 1), prior to treatment

Key Ocular Exclusion Criteria (Either Eye)

Key Ocular Exclusion Criteria (Study Eye):

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- [Redacted]
- Cataract or refractive surgery [Redacted] within the last 3 months prior to baseline (day 1)

Response Measures

Efficacy: BCVA assessed by the ETDRS letters
CRT assessed with spectral-domain optical coherence tomography (SD-OCT) and quantified by the central reading center

[Redacted]

Masked safety data will be reviewed throughout the study by Allergan. An external independent Data and Safety Monitoring Committee (DSMC) will review selected unmasked data for safety assessment. The review frequency, criteria, and the process for making recommendations will be defined in the charter.

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General Statistical Methods and Types of Analyses: The primary analysis will occur when all patients have completed the week 52 visit or exited early and the final analysis will occur when all patients have completed the week 104 visit or exited earlier from the study. Three populations will be used for the analyses; intent-to-treat (ITT), per-protocol (PP), and safety.

The primary efficacy endpoint will be the proportion of patients with stable vision (ie, patients who lose fewer than 15 letters in BCVA from baseline) at week 52. This statistical analysis will use the PP population. The difference in the proportions between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% confidence interval for non-inferiority testing will be constructed based on Cochran-Mantel-Haenszel (CMH) method with the baseline BCVA stratification factor (≤ 55 ETDRS letters versus > 55 ETDRS letters). The non-inferiority test will be performed at week 52 with a non-inferiority margin of 10%. A gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level, first testing abicipar 2Q8 against ranibizumab followed by the comparison between abicipar 2Q12 and ranibizumab.

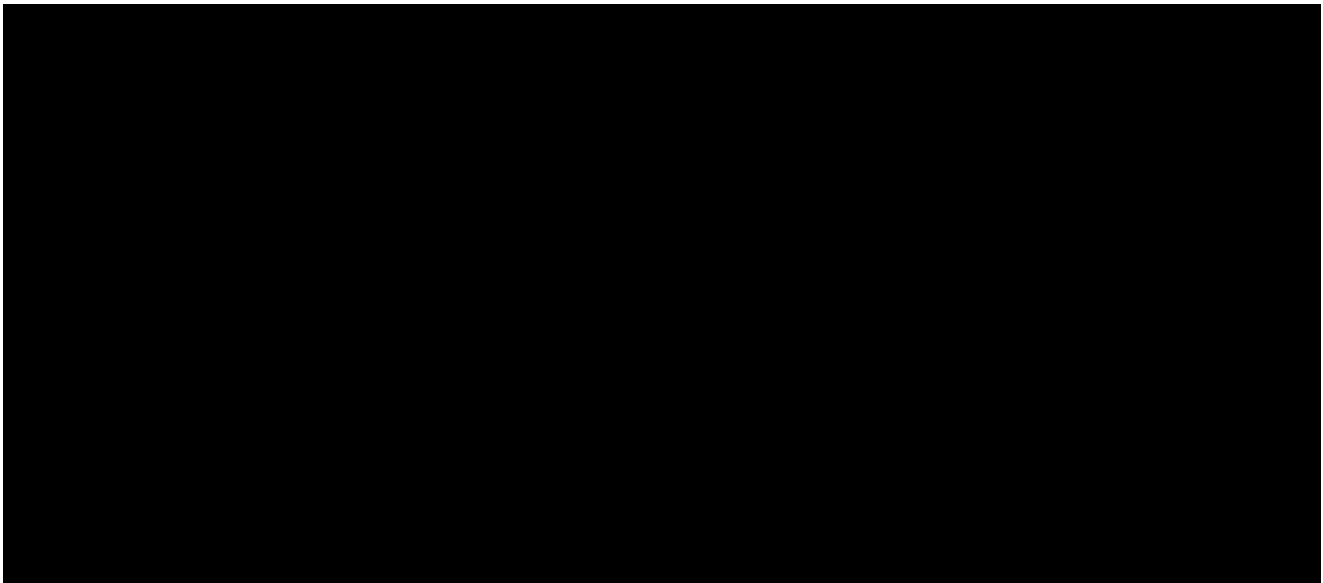
Missing values will be imputed using the last observation carried forward (LOCF) method. Sensitivity analyses of handling missing data will be performed using multiple imputation.

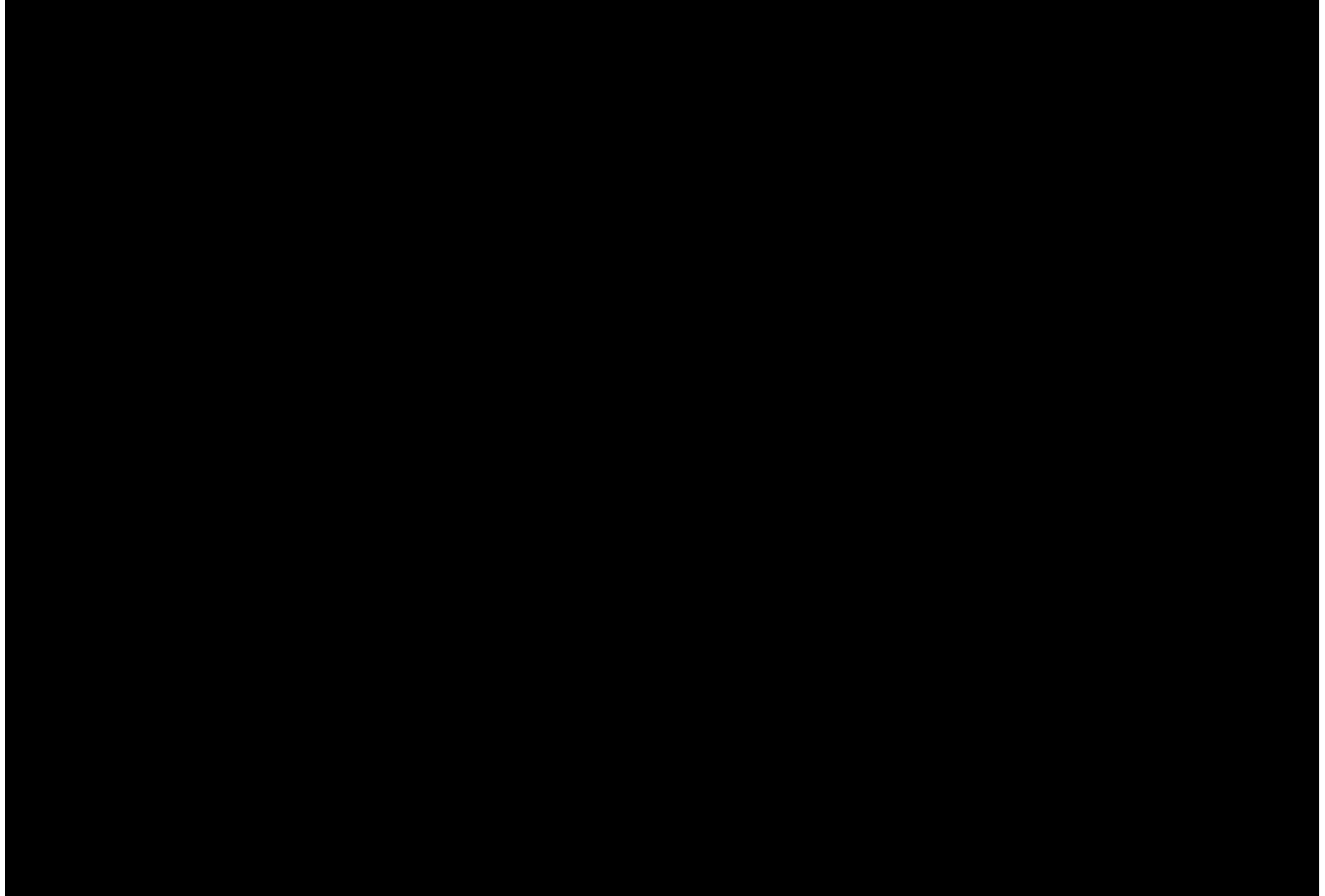
The non-inferiority comparisons will also be performed in the ITT population as a sensitivity analysis to confirm the primary analysis.

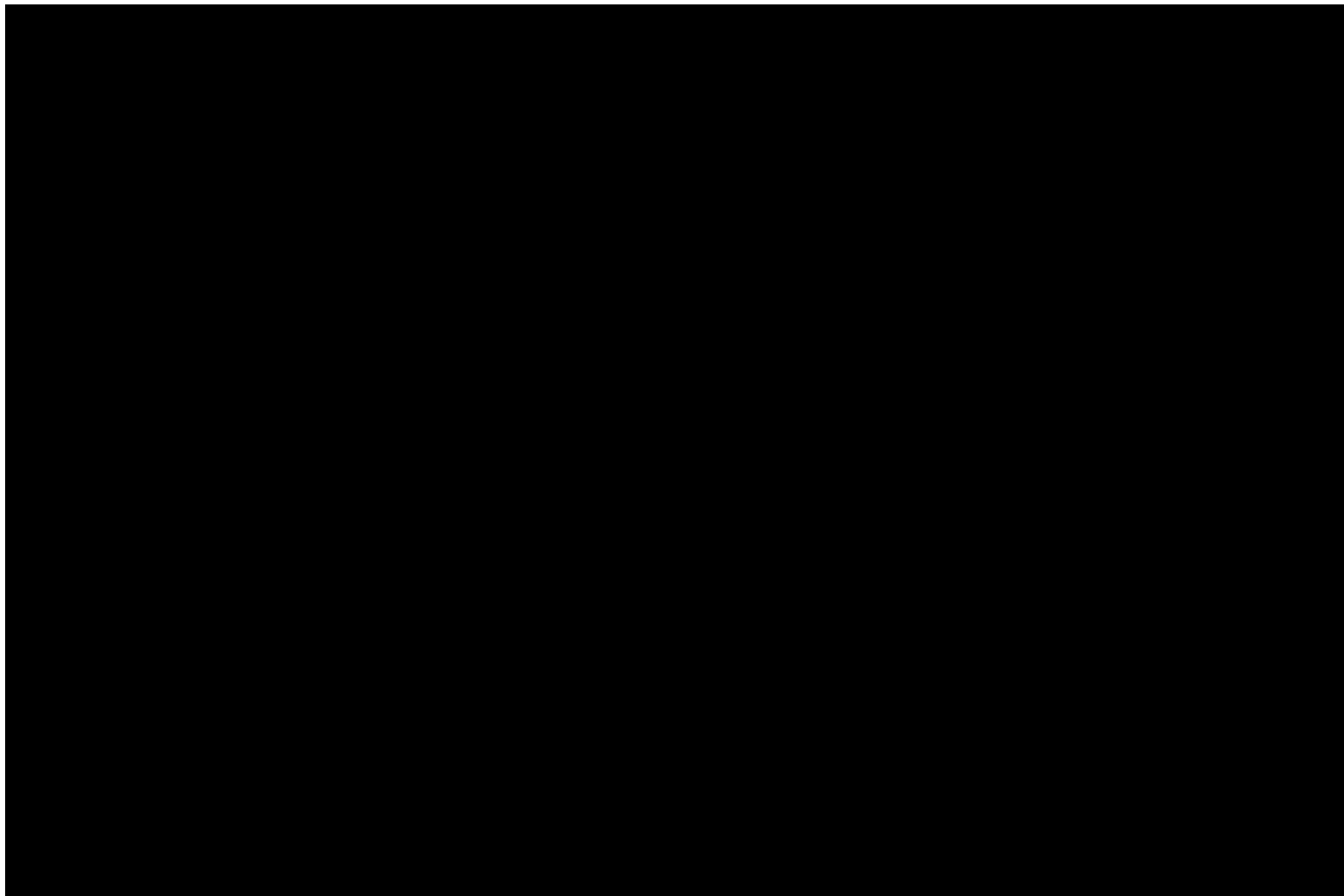
The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. The proportion of patients reporting each treatment emergent adverse event will be summarized by primary system organ class and preferred term for each treatment group.

Sample Size Calculation: A sample size of 240 patients in each treatment group will provide approximately 95% power with a 2-sided alpha level of 0.05 to demonstrate non-inferiority of an abicipar group versus the ranibizumab group for stable vision (ie, patients who lose fewer than 15 letters in BCVA from baseline) at week 52, with a non-inferiority margin of 10%. This calculation is based on the assumption of a 90% response rate for both groups.

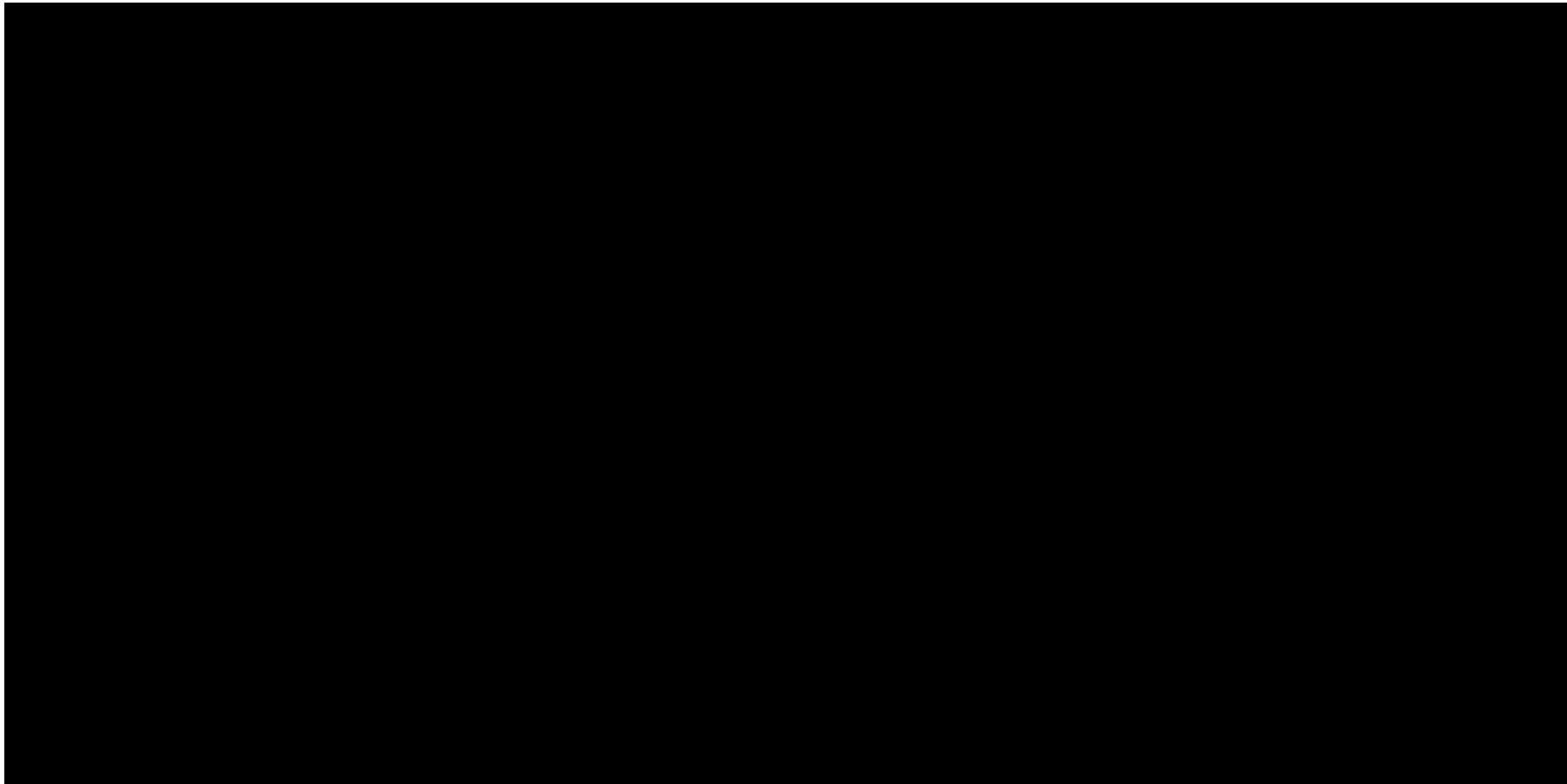
With an anticipated dropout rate of approximately 20% during a 52 week period, a total of 900 patients will be enrolled so that approximately 720 patients (240 per group) will complete the 52 week follow-up as required for the primary endpoint evaluation.







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1. Background and Clinical Rationale

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the United States (US) and other Western countries (Rein et al, 2009). AMD is a macular disorder characterized by drusen deposits, retinal pigment epithelium abnormalities, geographic atrophy, and neovascular maculopathy (Pieramici et al, 2006). The advanced stages of AMD, which are associated with severe loss of vision, consist of either choroidal neovascularization (neovascular or exudative AMD) or central geographic atrophy (non-exudative AMD). The majority of severe vision loss due to advanced AMD is attributable to the development of choroidal neovascularization (CNV) (Ferris, 1983; Sommer et al, 1991). Neovascular AMD is characterized by the growth of choroidal vessels into the subretinal space. These newly formed vessels have a tendency to leak blood and fluid, causing retinal edema which is accompanied by symptoms of metamorphopsia. The new vessels are accompanied by proliferation of fibrous tissue, and the continued growth of this lesion into the macula results in progressive, severe, and irreversible central vision loss (Shah and Del Priore, 2007; Shah and Del Priore, 2009). Without treatment, neovascular AMD results in severe visual impairment with an average loss of around 4 lines of visual acuity within 2 years of disease onset (Blinder et al, 2003; Wong et al, 2008).

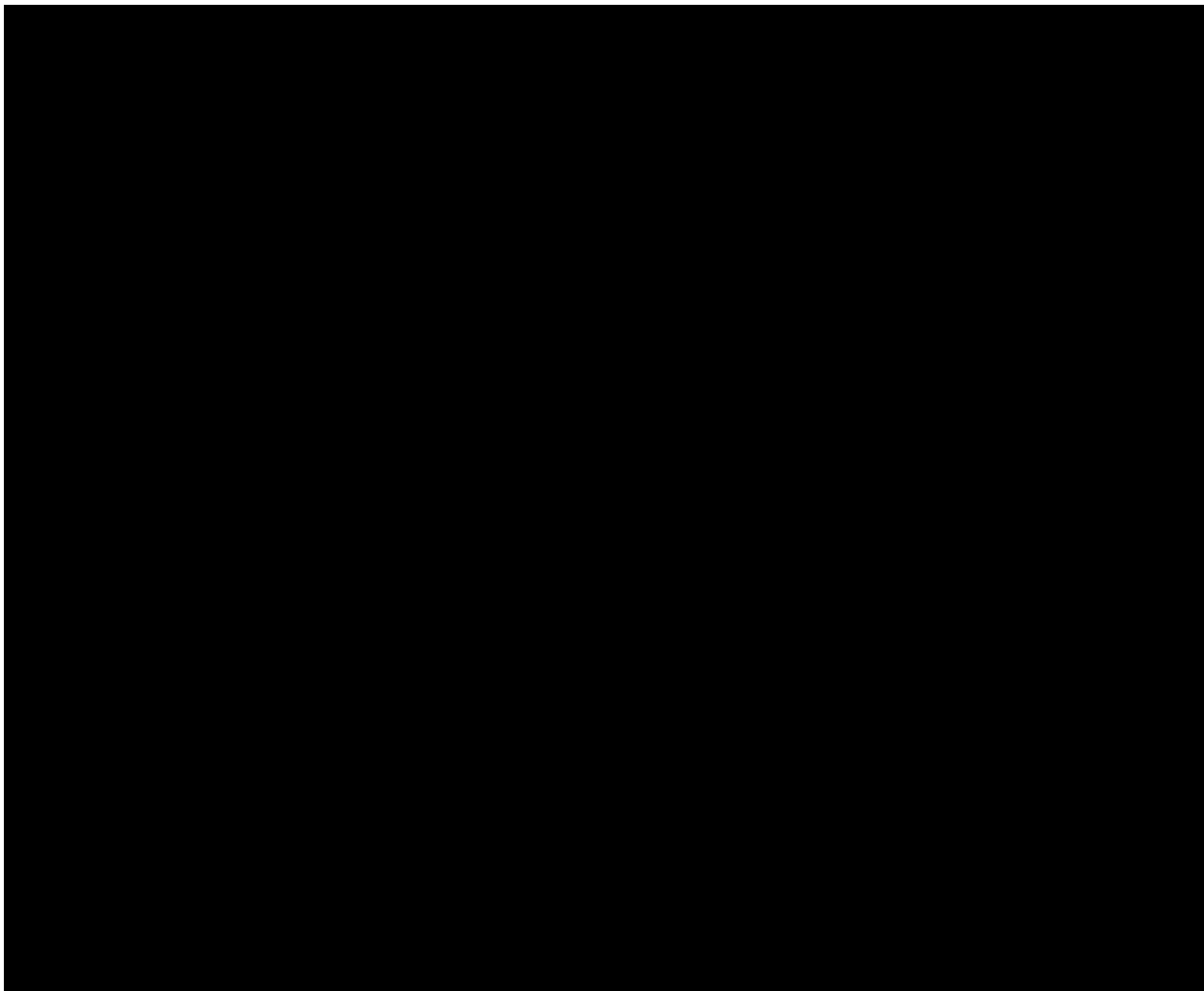
Vascular endothelial growth factor-A (VEGF-A) is implicated in the development and maintenance of the neovascularization that is characteristic of the neovascular form of AMD (Ding et al, 2009). Studies have shown elevated VEGF-A levels in areas of laser-induced CNV in primates, and clinically in patients with AMD. VEGF-A is a potent mitogen for endothelial cells, which causes increased vascular permeability and promotes leukocyte-induced damage to retinal endothelial cells (Grisanti and Tatar, 2008). Degenerated tissues produce and release VEGF-A which binds to specific receptors located on the endothelial cells of nearby pre-existing blood vessels. These endothelial cells then proliferate and migrate out through the diseased tissue. Pericytes, smooth muscle-like cells, provide structural support to these newly-formed blood vessel loops and blood flow begins in these vessels. Thus, VEGF-A serves as a rate-limiting step in angiogenesis (Ciulla and Rosenfeld, 2009). It also increases vascular permeability by leukocyte-mediated endothelial cell injury, formation of fenestrae, and the dissolution of tight junctions. This leads to intraretinal fluid accumulation and subsequent distortion of the macula, resulting in decreased visual acuity. As a result, VEGF-A has been the target of most anti-VEGF treatments (Cheung et al, 2013).

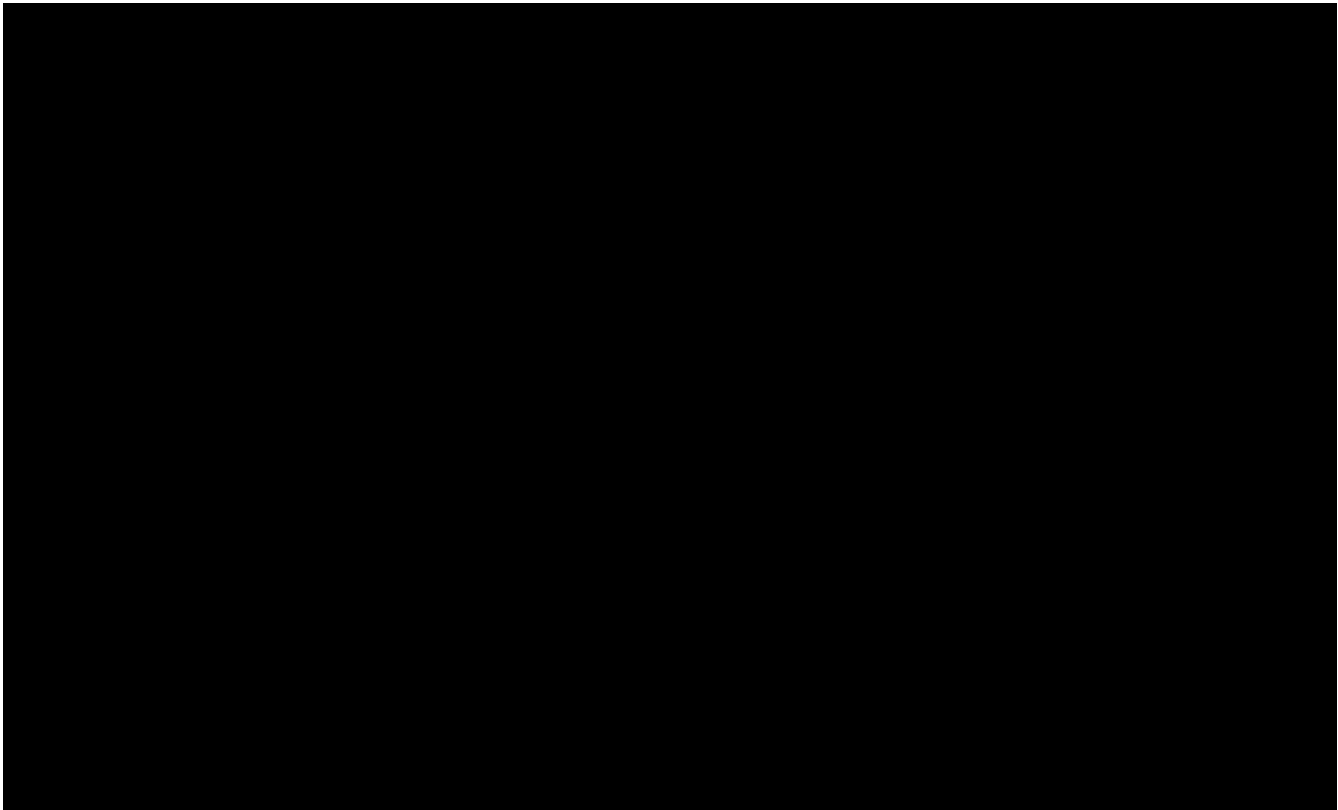
The discovery of VEGF-A's role in the pathogenesis of neovascular ocular disease provided a strong rationale for the development of highly-specific and targeted anti-VEGF-based

therapies (Ciulla and Rosenfeld, 2009). Three anti-VEGF agents, pegaptanib sodium, ranibizumab, and aflibercept are currently approved in many countries for the treatment of neovascular AMD. In addition, off-label use of a fourth anti-VEGF agent, bevacizumab, as a treatment option for neovascular AMD has become common worldwide. These agents are delivered to the vitreal cavity by intravitreal injection.

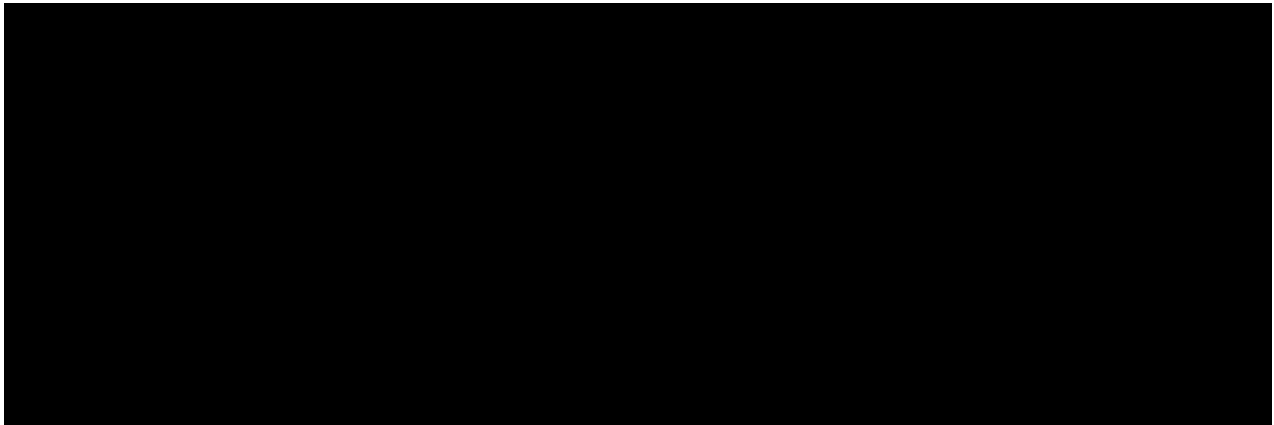
One drawback of these treatments is the need to frequently administer intravitreal injections. It would be highly desirable to develop an agent that requires less frequent injections. Not only would this remove a significant treatment burden on patients and their healthcare providers, it would decrease the risk of complications associated with frequent intravitreal injections.

Abicipar pegol (hereafter referred to as abicipar) was in-licensed from Molecular Partners (MP). The drug substance (abicipar-1) was evaluated in 2 phase 1 studies; one in patients with neovascular AMD, and one in patients with diabetic macular edema.





These data support the proposed dosing regimens of both abicipar treatment arms in the phase 3 study. These abicipar treatment regimens afford the possibility to reduce the treatment burden of the number of intravitreal injections (8 or 6 abicipar intravitreal injections in Year 1 for the 2Q8 and 2Q12 abicipar arms, respectively, versus 13 for the ranibizumab arm), while maintaining the efficacy of an anti-VEGF therapy, including 3 initial doses followed by 8- or 12-week dosing intervals to assess the efficacy and safety of abicipar in a phase 3 study.



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For further information, please refer to the Investigator's Brochure for abicipar.

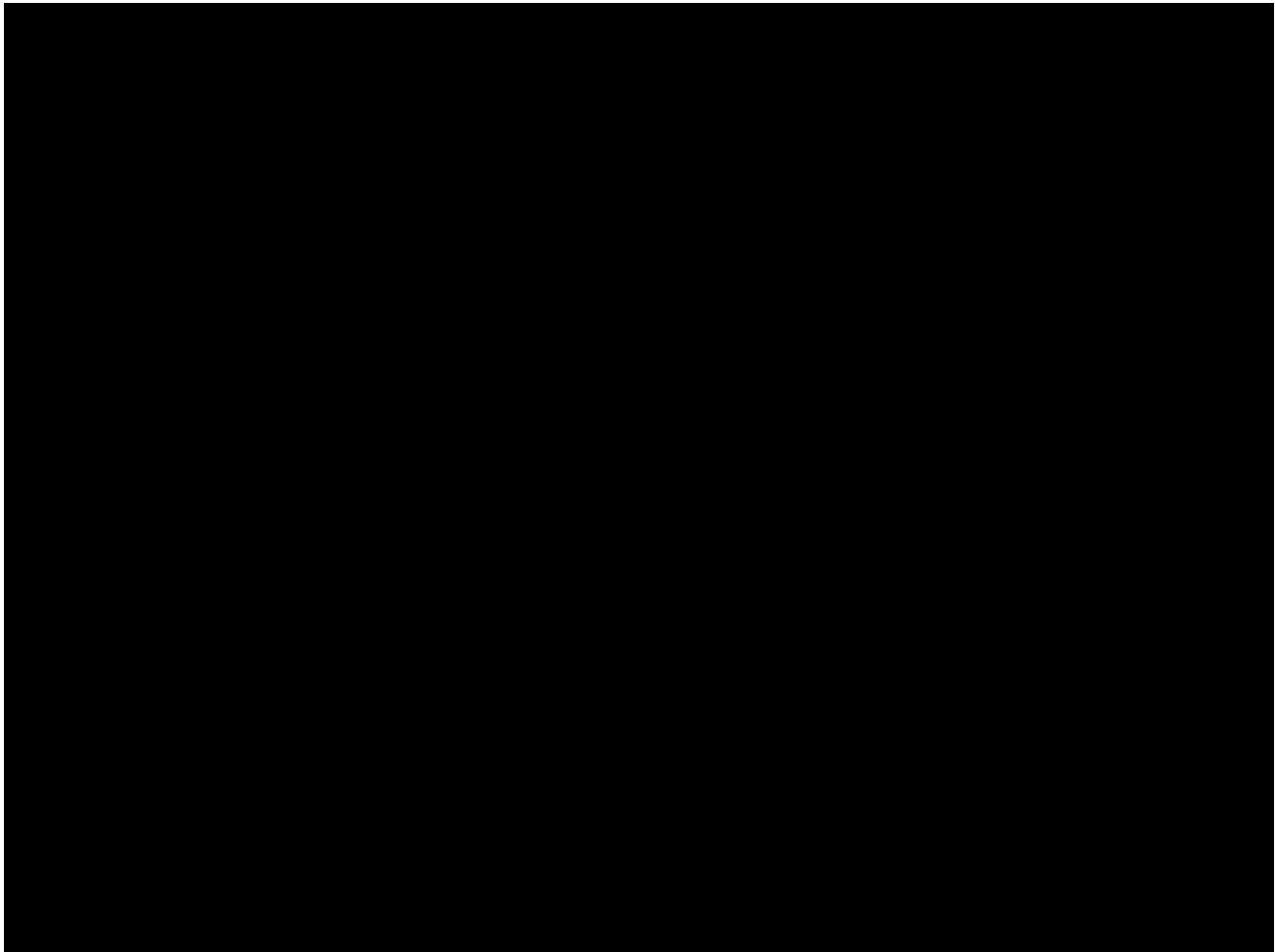
The purpose of this study is to evaluate the safety and efficacy of abicipar (2 mg), compared to 0.5 mg ranibizumab in treatment-naïve patients with neovascular AMD.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To assess the safety and efficacy of abicipar compared with ranibizumab in treatment-naïve patients with neovascular AMD

2.2 Clinical Hypotheses



³ Defined as a loss of fewer than 15 letters in best-corrected visual acuity [BCVA] compared to baseline using the Early Treatment Diabetic Retinopathy Study [ETDRS] method [hereafter referred to as letters]

[REDACTED]

3.1 Data and Safety Monitoring Committee

Masked safety data will be continually monitored throughout the study by Allergan to identify new safety signals for risk mitigation. In addition, an external independent Data and Safety Monitoring Committee (DSMC) will review selected unmasked data for safety assessment. The review frequency, criteria, and the process for making recommendations will be defined in the charter.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 900 patients will be enrolled at an estimated 200 sites in order to have 720 patients (240 per treatment group) complete the 52 week follow-up visit allowing for an early-discontinuation rate of approximately 20%.

4.2 Study Population Characteristics

Treatment-naïve patients with neovascular AMD will be enrolled in the study.

Only one eye will be selected as the study eye for the duration of the study. [REDACTED]

[REDACTED]

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4.3 Inclusion Criteria

The following are requirements for entry into the study:

General Inclusion Criteria

1. Male or female patients, 50 years of age or older at the time of informed consent
2. Patient has completed/signed an informed consent prior to conduct of any study-related procedures or examinations, is able to follow study instructions, and is likely to complete all required visits
3. Patient has provided, at screening, written documentation in accordance with the relevant country and local privacy requirements (eg, Written Authorization for Use and Release of Health and Research Study Information and written Data Protection consent, as required by regional health authorities)

Ocular Inclusion Criteria (Study Eye)

[Redacted text block]

[Redacted text block]

6. BCVA \leq 73 and \geq 24 letters (20/40 to 20/320 Snellen equivalents, respectively) at screening and at baseline (day 1, prior to treatment) visits

[Redacted text block]

Ocular Inclusion Criteria (Non-study Eye)

8. BCVA of 34 letters (Snellen equivalent 20/200) or better at baseline (day 1), prior to treatment

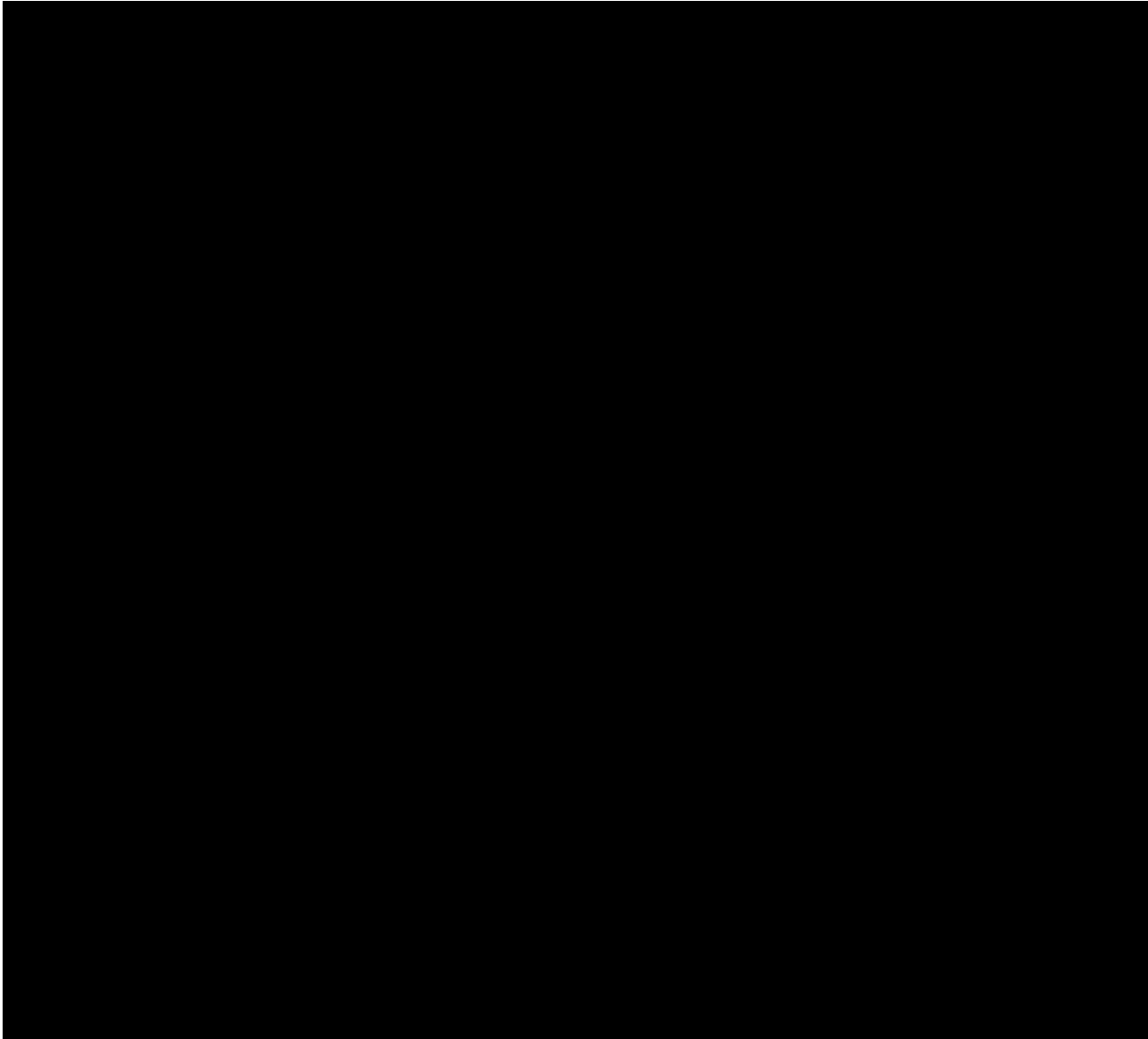
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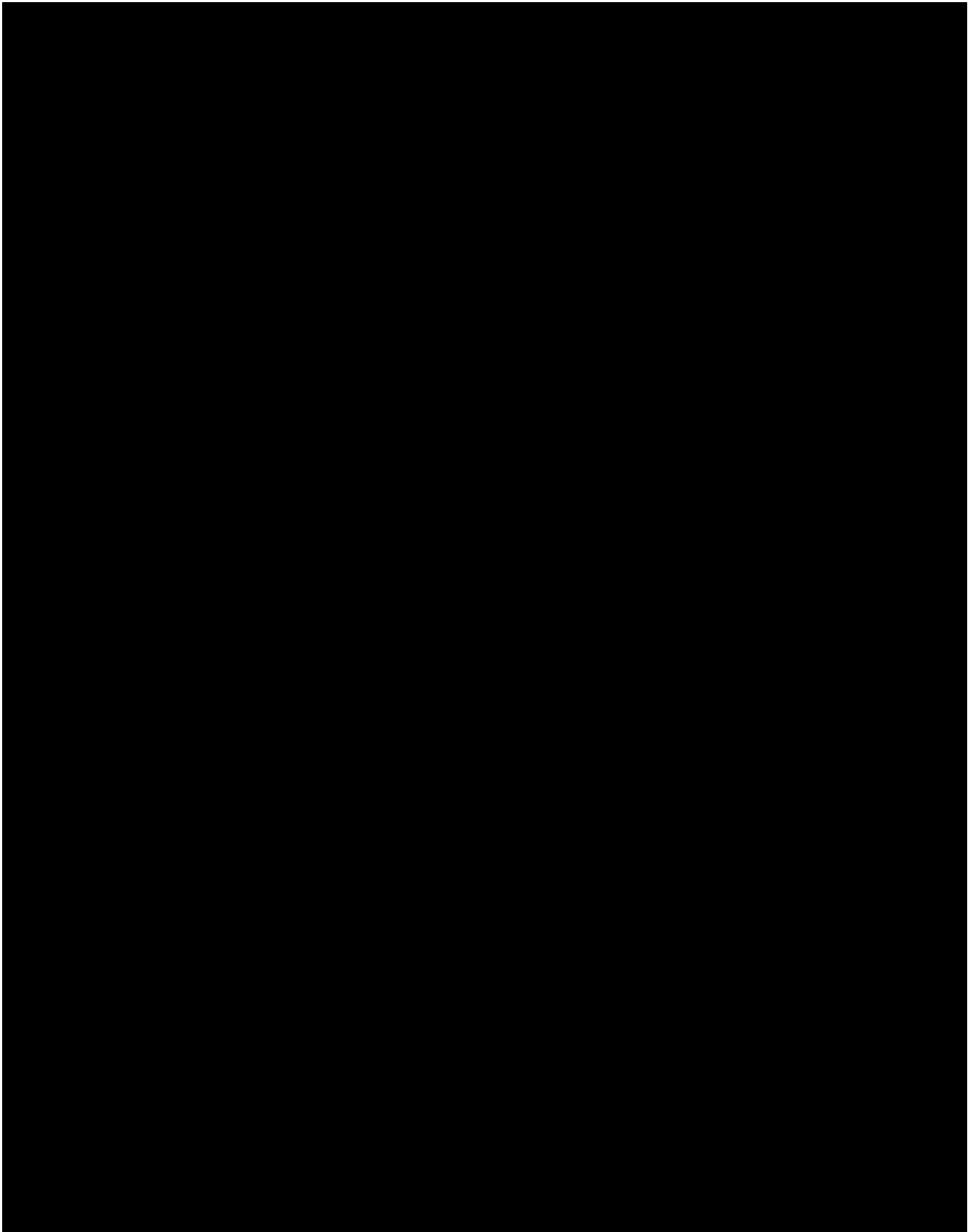
4.4 Exclusion Criteria

Patients must have NONE of the following criteria in order to be considered eligible to participate in the study:

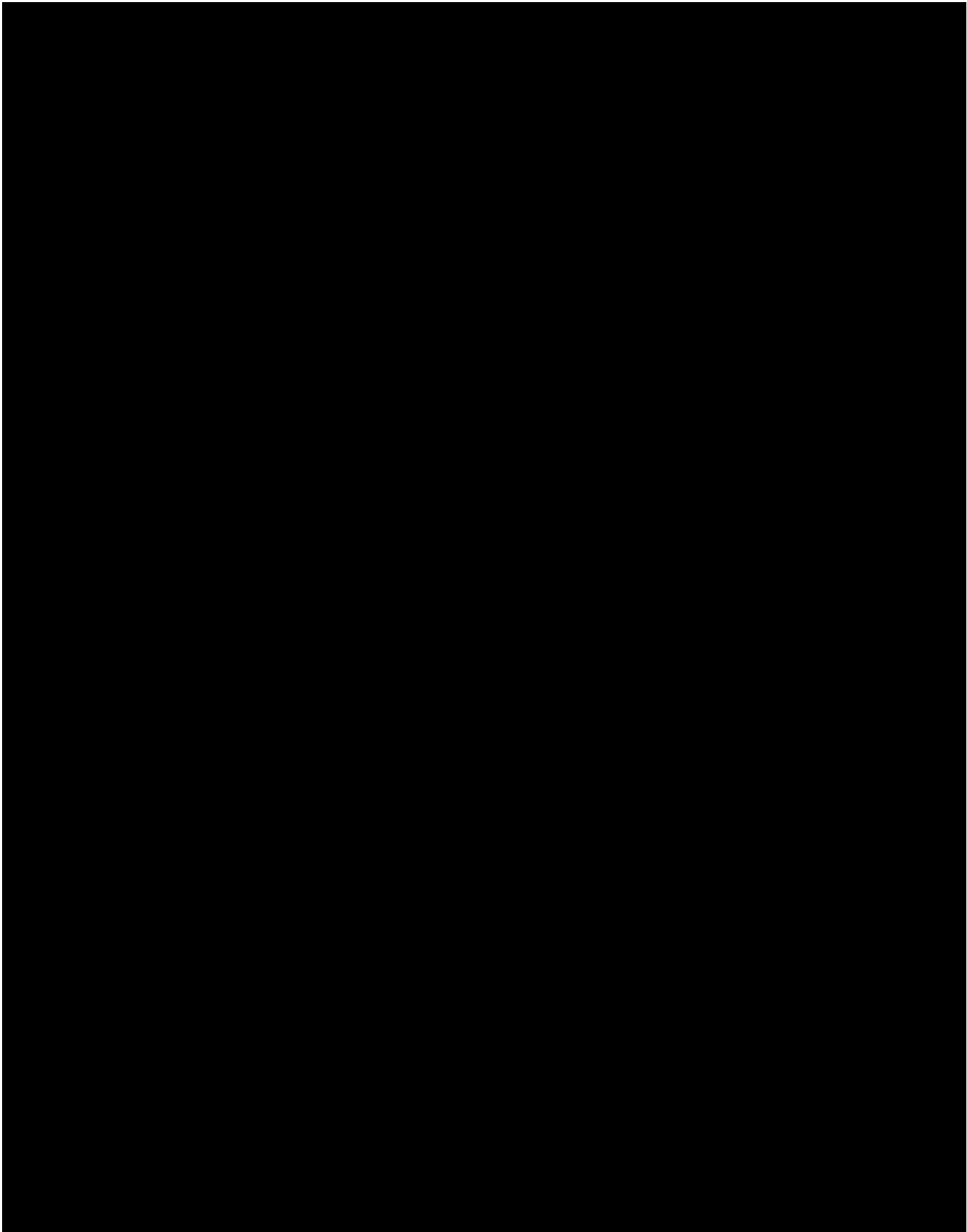
General Exclusion Criteria

1. Females who are pregnant, nursing, planning a pregnancy during the study, or who are of childbearing potential and not using a reliable method of contraception (Section 4.5.1.1) and/or not willing to use a reliable method of contraception during their participation in the study. A pregnancy test administered to women of childbearing potential at the baseline visit (day 1, prior to treatment) must be negative for the patient to receive study medication





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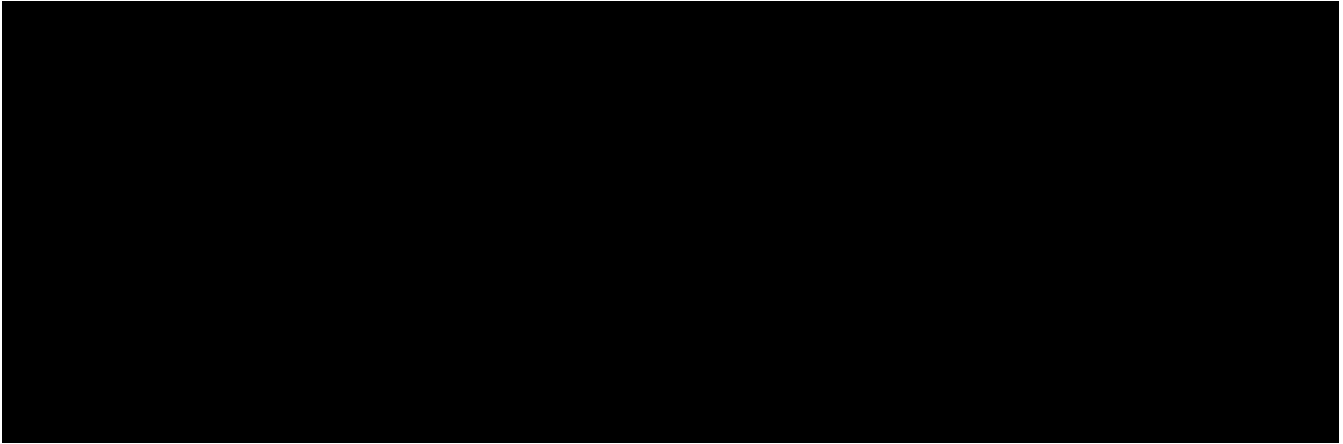
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4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at any time at the discretion of the investigator. All medications should be recorded in the electronic case report form (eCRF). If the permissibility of a specific medication/treatment is in question, please contact Allergan.



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

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (eg, have undergone 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: hormonal contraceptives (ie, oral, patch, injection, implant or vaginal contraceptive ring), intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or sexual abstinence. For male patients who participate in the study, condoms should be used as method of contraception.

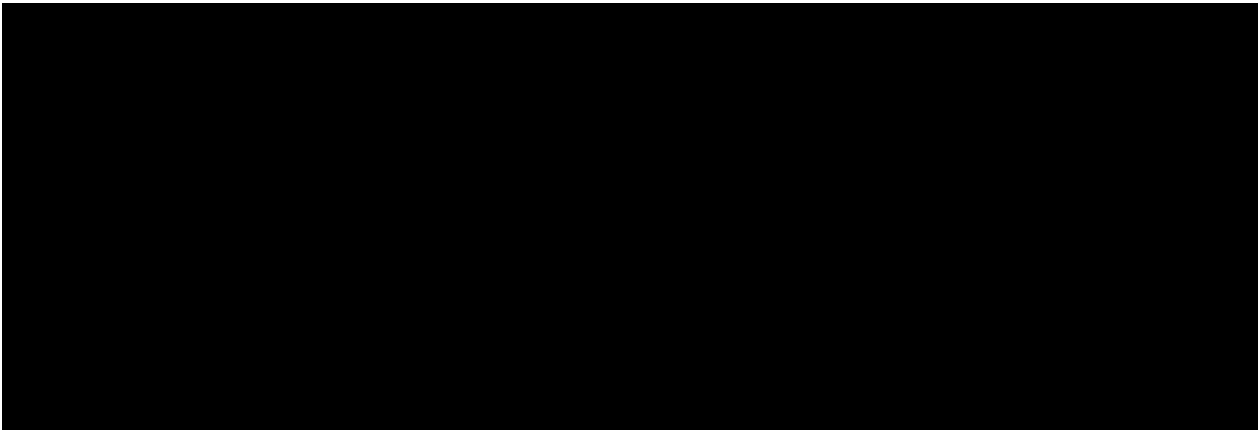
The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

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 being treated with an investigational drug (abicipar) or approved control (ranibizumab), 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.

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

4.5.2 Prohibited Medications/Treatments

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



4.5.3 Escape Medications

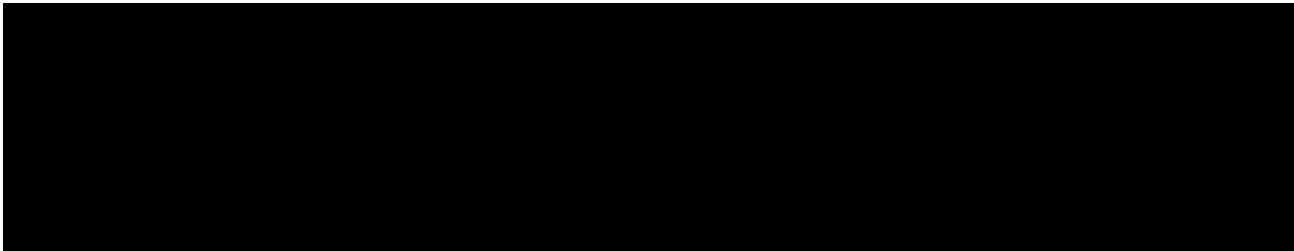
Patients who meet the escape criteria (see Section 5.6.2) may escape to standard of care. Standard of care is defined as the preferred anti-VEGF intravitreal treatment per the site’s practice.

4.5.4 Special Diet or Activities

None

5. Study Treatments

5.1 Study Treatments and Formulations



5.2 Control Treatment

The control treatment, 0.5 mg ranibizumab (Lucentis), will be provided (for the study eye only).

5.3 Methods for Masking

The following individuals or roles will be masked to study medication for the duration of the study:

- Patients
- All site personnel responsible for performing BCVA and CRT
- Assessing investigator responsible for all assessments except the post-injection assessment
- Central reading center personnel involved in the assessment of images

Ranibizumab (Lucentis[®]) will be provided and masked by packaging the commercial supplies inside of an outer carton which looks identical to the packaging of abicipar. The injecting ophthalmologist and any assistants who prepare the material for injection (or sham treatment) will be unmasked to treatment. To maintain masking, patients randomized to abicipar will receive a sham injection during the study visits when they are not scheduled to receive their assigned study medication; see Section 5.6.

In an effort to avoid bias, staff members who are made aware of the study treatment of an individual patient shall not continue to collect efficacy variables (BCVA and CRT) for that patient.

For more details, refer to the procedure manual.

5.4 Treatment Allocation Ratio and Stratification

Patients will be randomized [REDACTED] to 3 treatment groups (2Q8, 2Q12, and rQ4). [REDACTED]

[REDACTED]

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]

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.

An automated interactive voice response system/interactive web response system (IVRS/IWRS) will be used to manage the randomization and treatment assignment based on a central randomization scheme prepared by Allergan Biostatistics. The randomization scheme will be based on region.

Study medication will be labeled with medication kit numbers. At the time of randomization, the IVRS/IWRS will provide the site with the specific medication kit number for each randomized patient. Sites will receive the IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents. A list of patients assigned to abicipar groups will be provided to the bioanalytical laboratories to facilitate analysis of serum samples.

5.6 Treatment Regimen and Dosing

- Treatment group 2Q8: [REDACTED]

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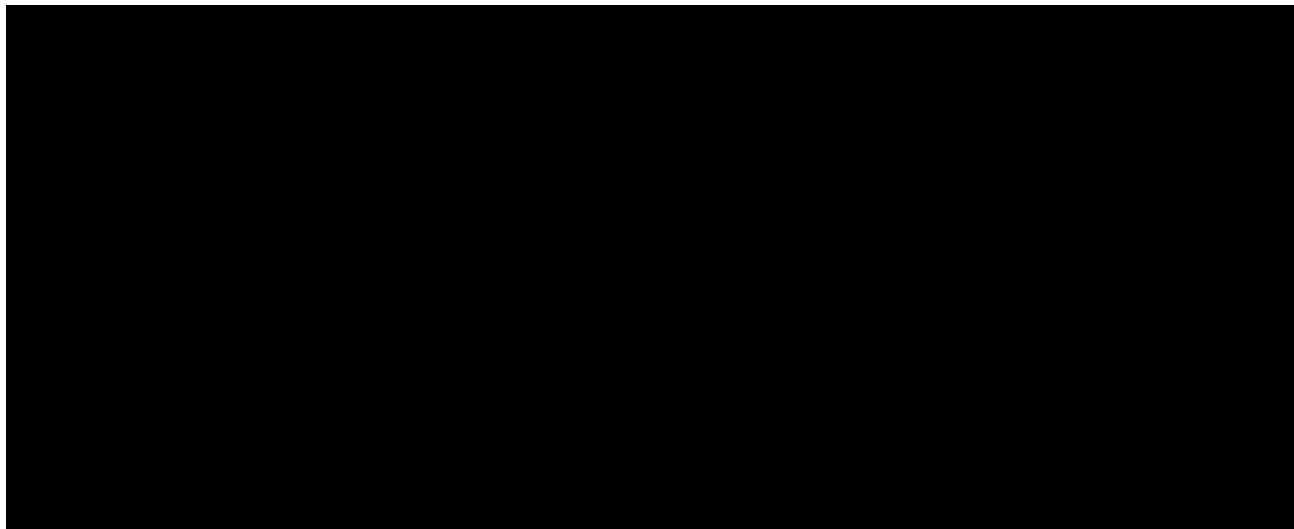
- Treatment group 2Q12: [REDACTED]
- Treatment group rQ4: 0.5 mg ranibizumab administered every 4 weeks from baseline (day 1) through week 96

Masked study treatment will be administered into the study eye by intravitreal injection (or sham treatment). One eye will be assigned as the study eye for the duration of the study. To maintain masking, patients randomized to abicipar will receive a sham injection during the study visits when they are not scheduled to receive their assigned study medication. For the sham injections, the study eye of each patient will be prepared using a standard protocol as if they were to receive an intravitreal injection as defined in the procedure manual. For the sham injection, the treating investigator will press the blunt end of the needleless syringe against the eye, mimicking an intravitreal injection.

5.6.1 Treatment Regimen Adjustments

If the study eye develops a treatment-related adverse event at any time during the study, treatment dose may be temporarily held and the reason for dose holding will be recorded on the eCRF.

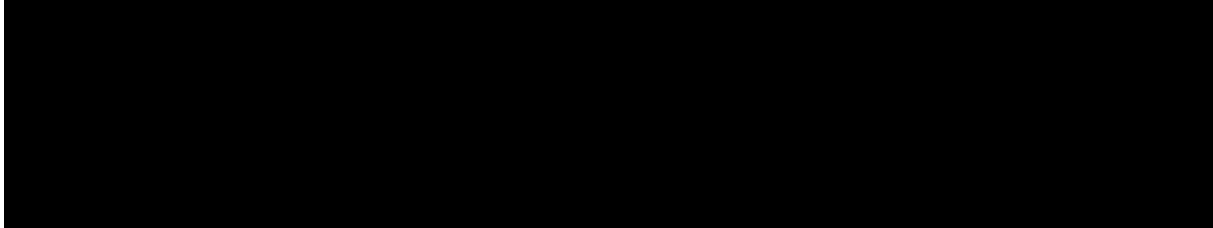
The treatment regimen will be adjusted based on the following criteria:



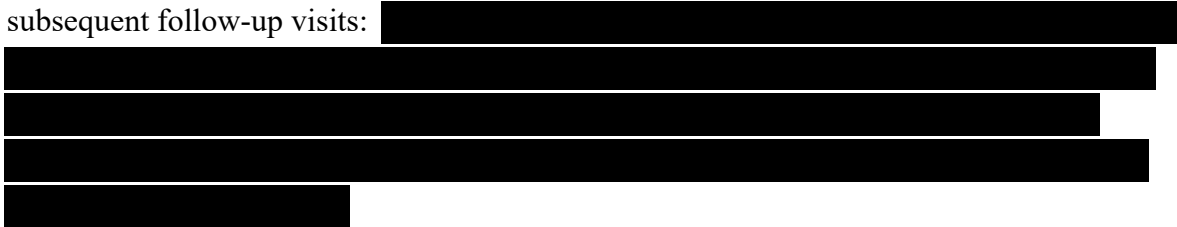
The investigator may hold or discontinue study treatment for other safety reasons at his/her discretion.

5.6.2 Escape to Standard of Care

During the first 52 weeks of the study, if a patient has met the following criteria, he/she will be qualified to escape to standard of care:



Patients who escape to standard of care will be required to complete the study exit procedures indicated at the week 104/early exit visit and will be reevaluated at the subsequent follow-up visits:



5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients enrolled into the clinical study, at no cost to the patient, in accordance with the conditions specified on the study medication kit label and in the procedure manual. Only assigned individuals authorized by the investigator may have access to study medication.

5.8 Preparation of Study Medications/Treatments

Abicipar should be prepared in a hospital pharmacy or by an investigator or trained assistant in the clinic using aseptic technique. The instructions for preparation of the individual doses are provided in the procedure manual.

Ranibizumab should be prepared per the Lucentis prescribing information.

5.9 Treatment Administration

Abicipar and ranibizumab will be administered by intravitreal injection as specified in the procedure manual. The injection volume is 0.05 mL (50 µL).

Prior to study treatment administration, the study eye of each patient will be prepared using the standard protocol as described in the procedure manual.

6. Response Measures and Summary of Data Collection Methods

Details of measures and data collection methods are outlined in the procedure manual.

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

- BCVA assessed using the ETDRS letters ([Age-Related Eye Disease Study \[AREDS\] Research Group, 2001](#))

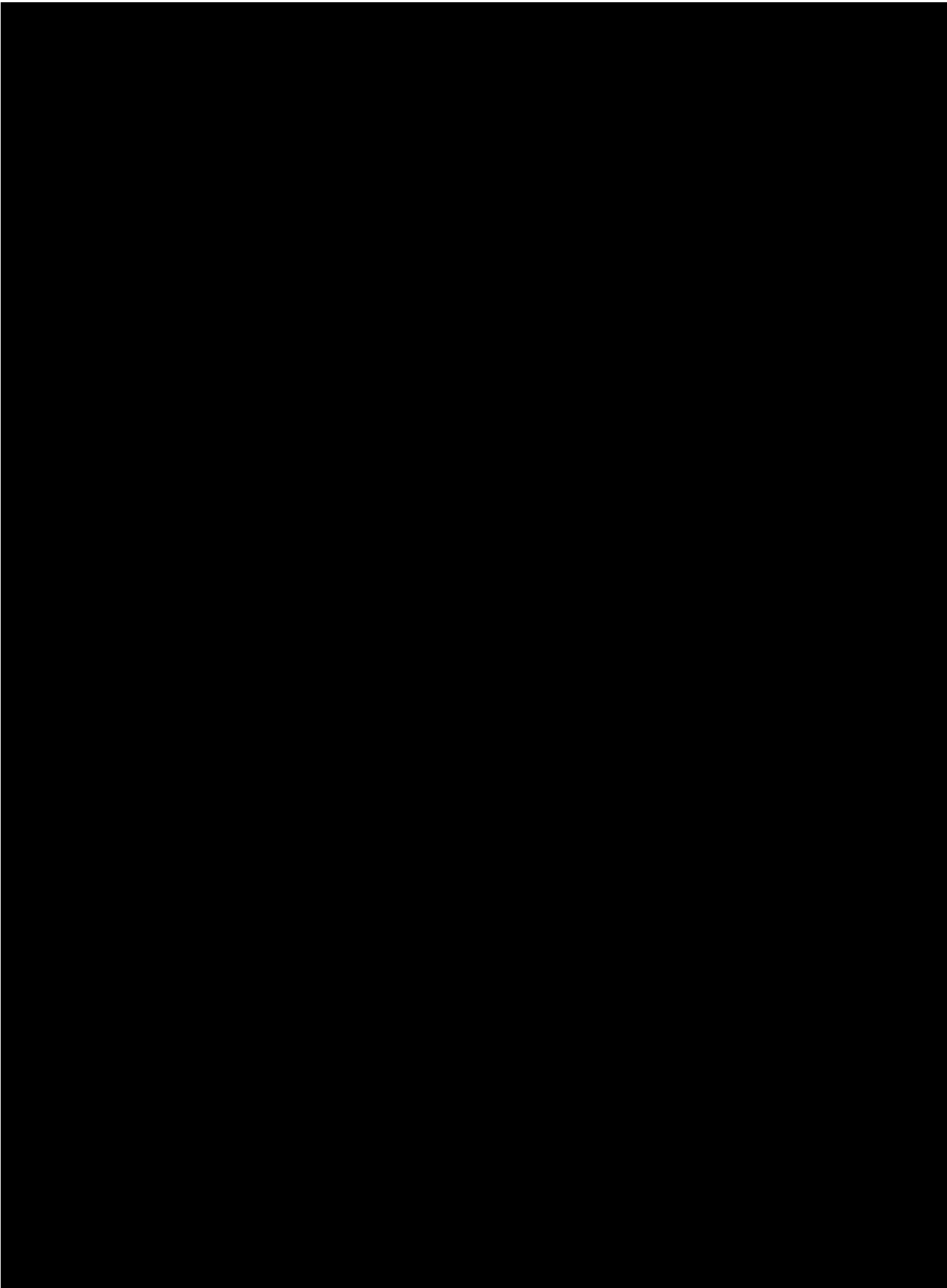
6.1.2 Secondary Efficacy Measures

- BCVA assessed using the ETDRS letters
- CRT assessed with spectral-domain optical coherence tomography (SD-OCT) and quantified by the central reading center
- National Eye Institute Visual Functioning Questionnaire-25 Item (NEI-VFQ-25) composite score

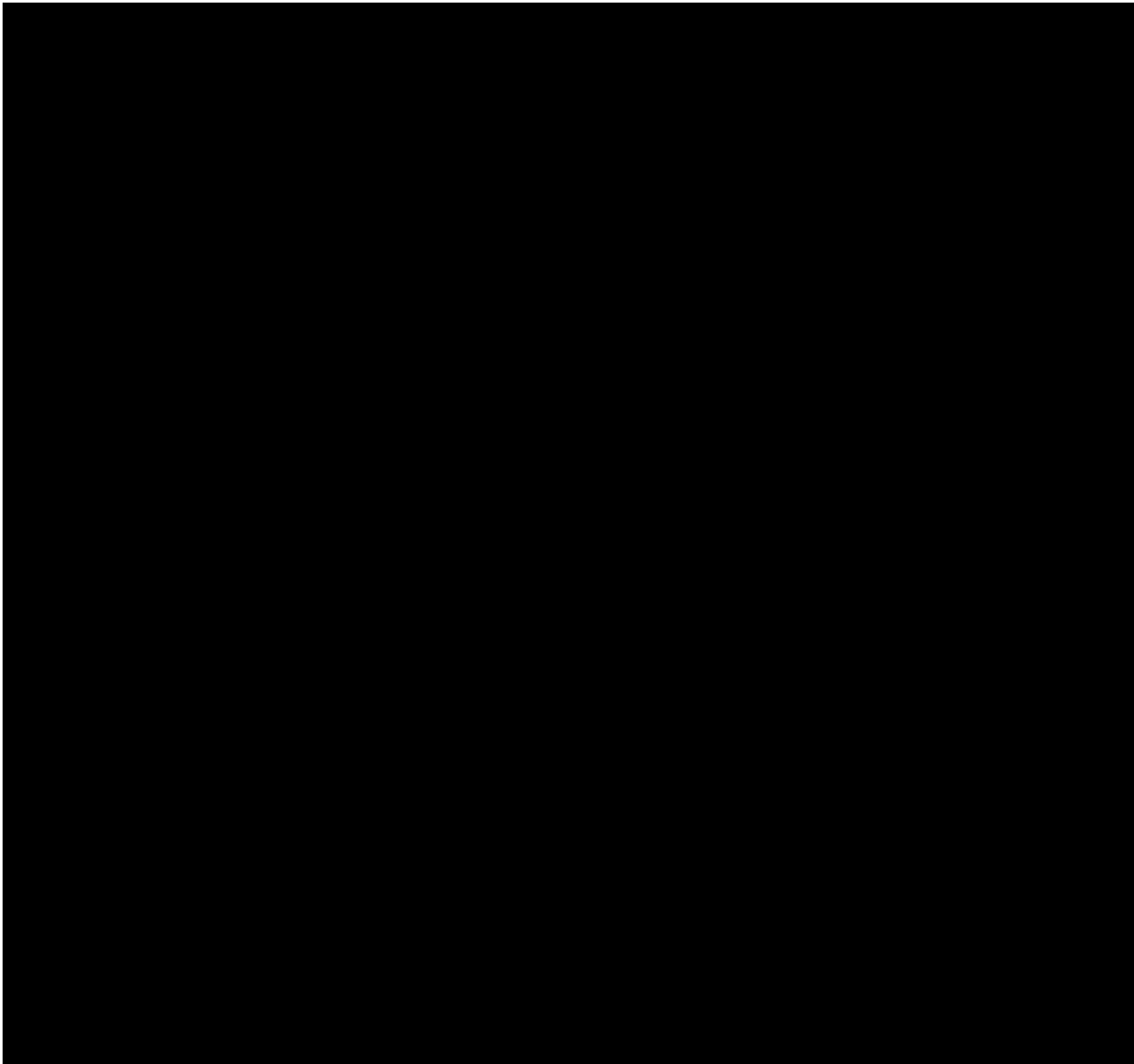
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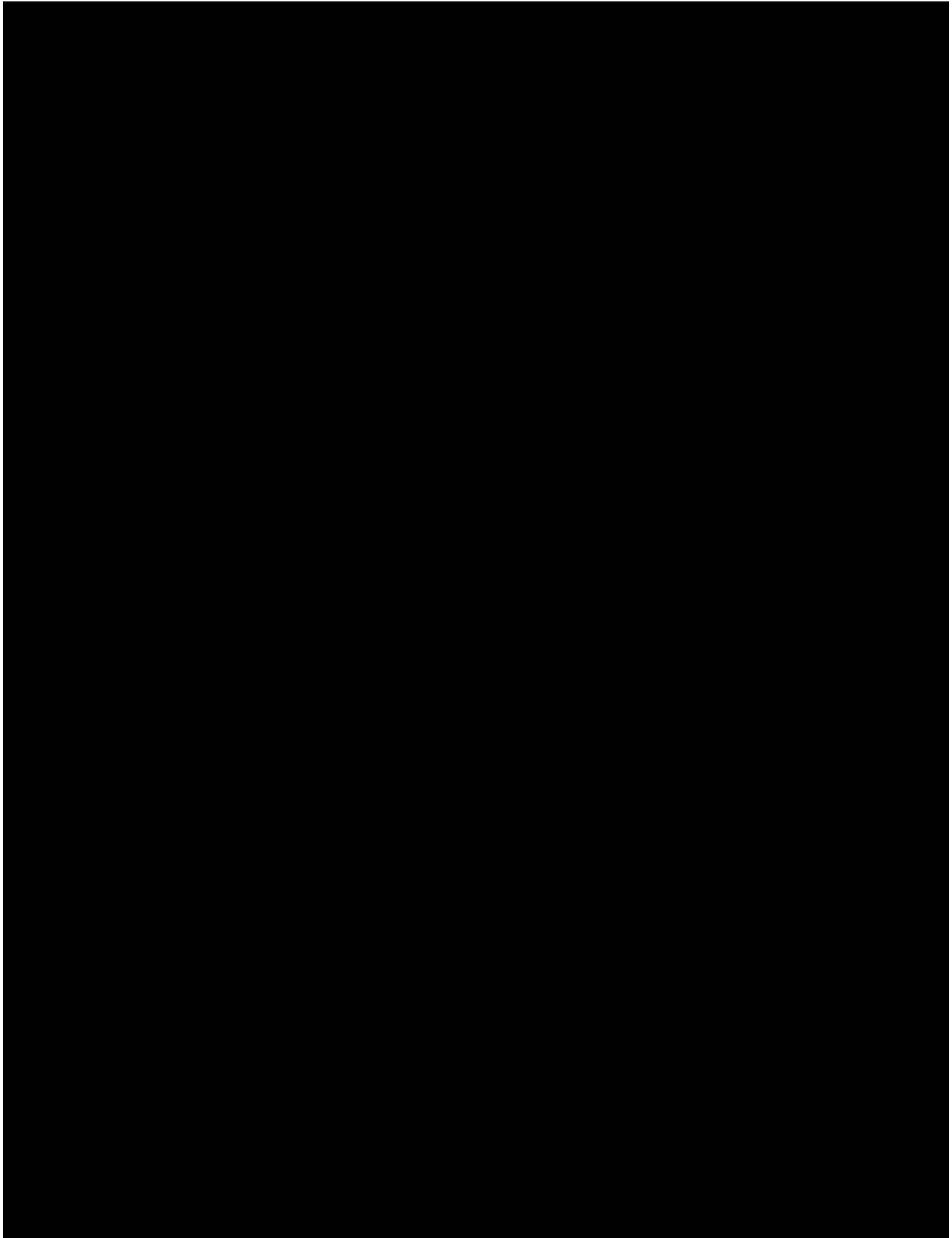
6.4.2 Efficacy

6.4.2.1 Best-corrected Visual Acuity

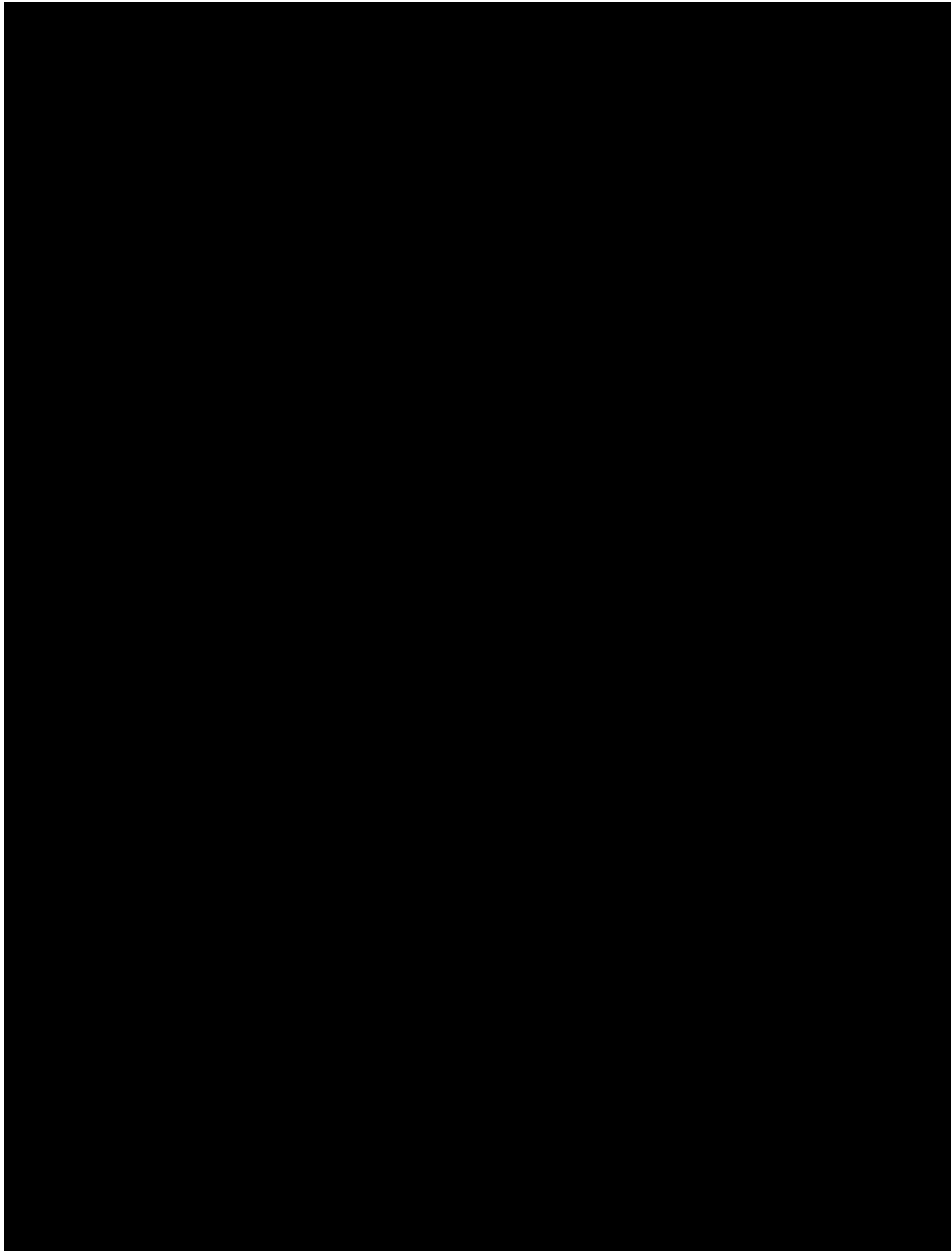
BCVA will be quantified using the ETDRS method ([AREDS Research Group, 2001](#)).

BCVA testing should precede any examination requiring contact with the study eye. BCVA should be performed following manifest refraction and completed according to the procedures outlined in the procedure manual. [REDACTED]

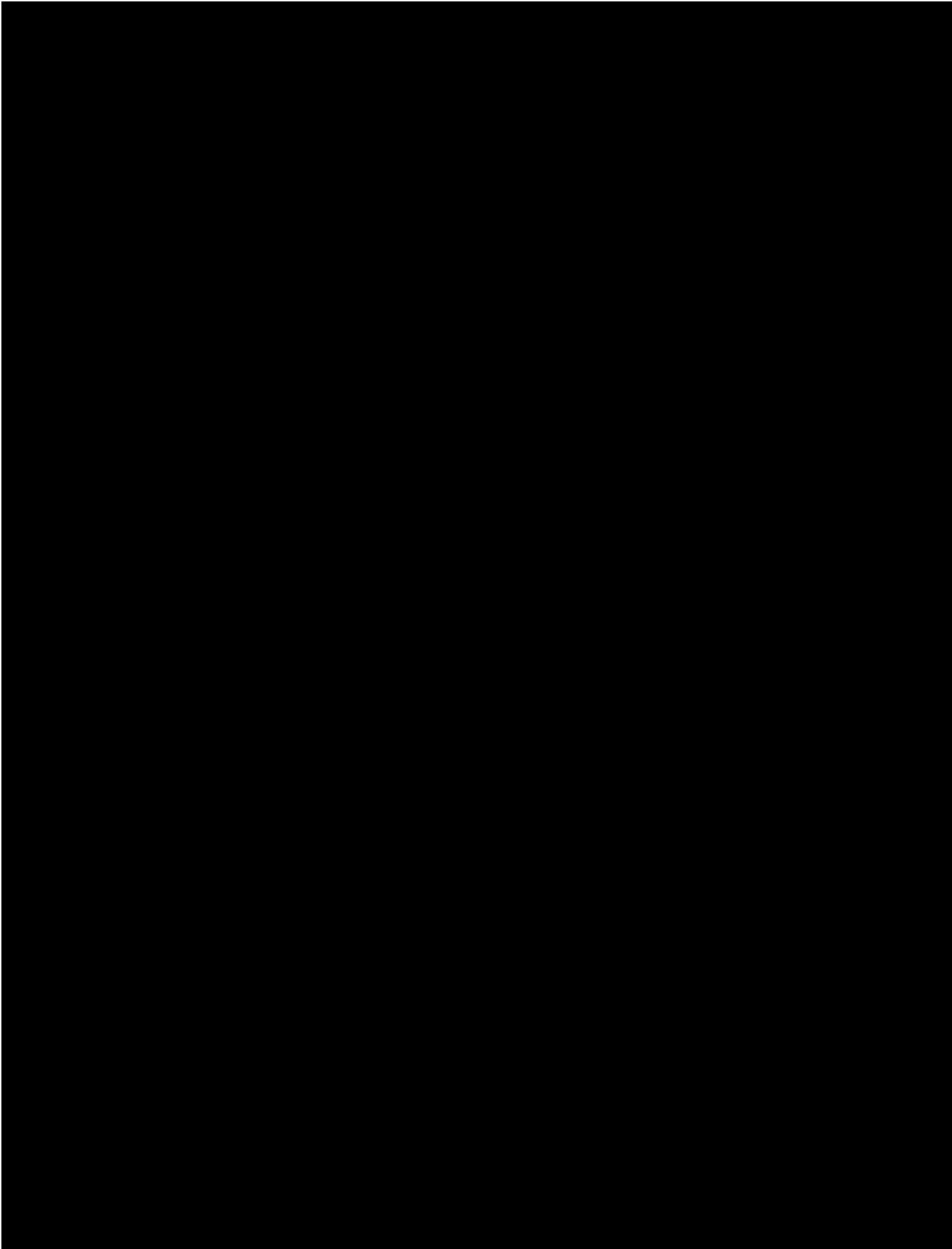
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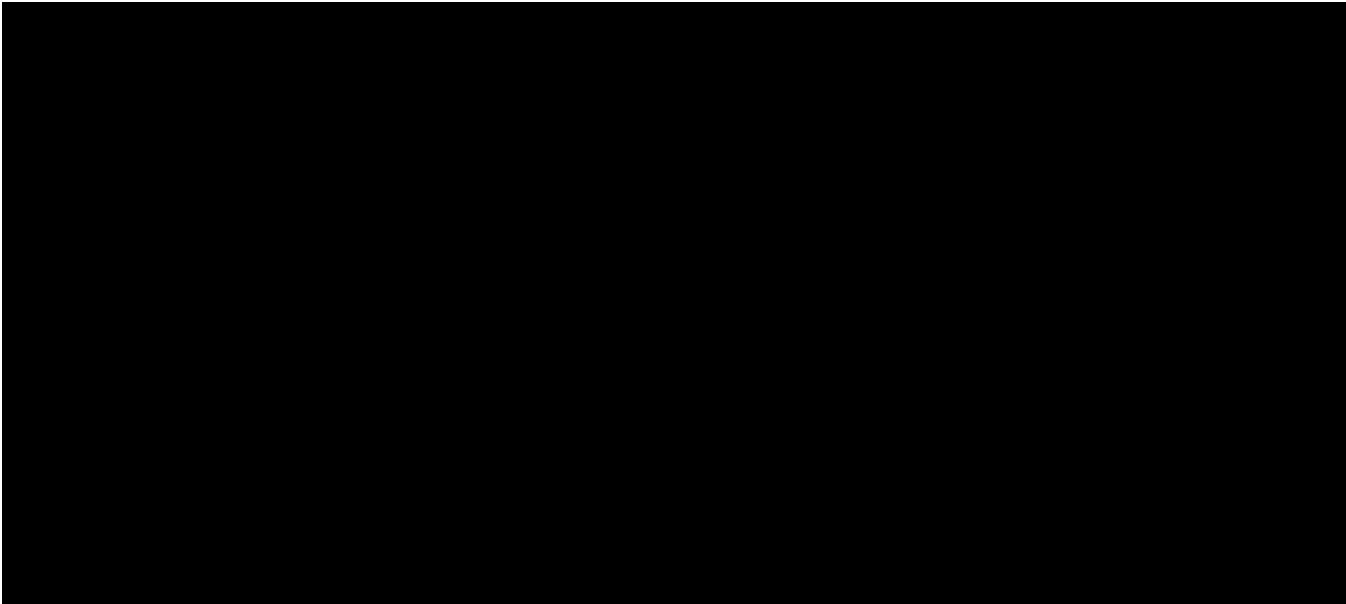
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6.4.3.6 Best-corrected Visual Acuity

All BCVA measures will be used as safety measures to evaluate vision loss over time. BCVA is also used as a measure of efficacy as described in Section [6.4.2.1](#).

6.4.3.7 Pregnancy Test

Females of childbearing potential will have a pregnancy test (urine or serum) performed as indicated in [Table 1](#).

6.4.3.8 Adverse Events

All adverse events will be monitored and reported on an adverse event eCRF, including onset, seriousness, severity, action taken, and relationship to study drug. If adverse events occur, the first concern will be the safety of the study patient.

6.5 Other Study Supplies

Allergan will make provisions (directly or indirectly) to supply the study sites with pregnancy test kits, ETDRS supplies (if needed), study medications, intravitreal injection supplies, PK blood sampling kits, and immunogenicity (anti-drug antibody) blood sampling kits. Details are provided in the procedure manual.

Tubes for collection of blood and urine samples will be provided by a central laboratory.

6.6 Summary of Methods of Data Collection

Clinical data will be entered into an eCRF. Data entered into the eCRF will correspond to and be supported by source documentation maintained at the site.

7. Statistical Procedures

There will be two database locks. The primary analysis will occur when all patients have completed the week 52 visit, or exited earlier. The final analysis will occur when all patients have completed week 104 visit or exited early from the study. The details of all analyses will be provided in the analysis plan which will be finalized before database lock for the primary analysis at week 52.

7.1 Analysis Populations

The following 3 populations will be used for statistical analysis: intent-to-treat (ITT), per-protocol (PP), and safety.

The ITT population will include all randomized patients. The ITT population will be used for all efficacy analyses. The PP population will include all randomized and treated patients who do not have protocol deviations that impact the primary efficacy variable. The PP population will be used for analyses of primary and key secondary efficacy variables. The safety population will include all treated patients.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

Efficacy measures will be based on BCVA and CRT measured in the study eye. [REDACTED]
[REDACTED] Missing data will be imputed with values using last observation carried forward (LOCF) methods for the primary and secondary analyses.

7.2.1 Primary Efficacy Variables

- Proportion of patients with stable vision (ie, patients who lose fewer than 15 letters in BCVA) from baseline at week 52

7.2.2 Secondary Efficacy Variables

- Mean change from baseline in BCVA at week 52
- Mean change from baseline in CRT as assessed with SD-OCT and quantified by the central reading center at week 52
- Proportion of patients with a gain of 15 or more ETDRS letters in BCVA from baseline at week 52
- Mean change from baseline in NEI-VFQ-25 composite score at week 52

7.3 Methods of Analysis

7.3.1 Primary Efficacy Analyses

The primary efficacy endpoint will be the proportion of patients with stable vision (ie, patients who lose fewer than 15 letters in BCVA from baseline) at week 52. The difference in the proportion between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% confidence interval (CI) for non-inferiority testing will be constructed based on Cochran-Mantel-Haenszel (CMH) method with the baseline BCVA stratification factor (≤ 55 ETDRS letters versus > 55 ETDRS letters). The non-inferiority test will be performed at week 52 using the PP population and with a non-inferiority margin of 10%. If the lower limit of 95.1% CI of difference in proportion of response (abicipar minus ranibizumab) is $\geq -10\%$, non-inferiority of abicipar to ranibizumab will be established.

[REDACTED]

[REDACTED]

The non-inferiority comparisons will also be performed in the ITT population as a sensitivity analysis to confirm the primary analysis.

Sensitivity analyses of handling missing data will be performed using multiple imputation.

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7.3.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be performed at week 52 for variables listed in Section 7.2.2 using the ITT and PP populations.

For the key secondary efficacy endpoint (mean change from baseline in BCVA at week 52), the statistical analysis for the non-inferiority test will be based on the PP population [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] The difference in mean change from baseline in BCVA between each abicipar arm and ranibizumab (abicipar group minus ranibizumab group) and the corresponding 2-sided 95.1% CI will be calculated based on the MMRM model. The non-inferiority test will be performed using a non-inferiority margin of 5 letters. Non-inferiority of abicipar is established if the lower limit of the CI is > - 5.0 letters. The same [REDACTED] model will be applied to the ITT population and the lower limit of the CI will be compared to the 5-letter margin for non-inferiority testing and to zero for superiority testing.

As a sensitivity analysis, mean change in BCVA will be analyzed using an analysis of covariance (ANCOVA) model, which includes the treatment group, baseline CRT (≤ 400 or > 400 microns), and lesion type of choroidal neovascularization (predominantly classic versus minimally classic or occult) as fixed effects and baseline BCVA as a covariate.

For the analysis of secondary efficacy variables, change from baseline in CRT and change from baseline in NEI-VFQ-25 composite scores, similar analysis procedure will be used as outlined for BCVA above for superiority testing using the ITT population.

For the secondary efficacy endpoint, proportion of patients with a gain of 15 or more letters, a similar analysis procedure will be used as outlined for the primary efficacy variable of stable vision for superiority testing using the ITT population.

7.3.3 Secondary Efficacy Analyses for US FDA

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]. If non-inferiority of both abicipar arms is established for the primary efficacy endpoint of stable vision, testing for the mean

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change from baseline in BCVA at week 52 will be performed following the same sequence as defined above. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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7.4 Sample Size Calculation

For the primary efficacy endpoint of stable vision (ie, patients who lose fewer than 15 letters in BCVA from baseline) at week 52, a sample size of 240 patients in each treatment group will provide approximately 95% power with a 2-sided alpha level of 0.05 to demonstrate non-inferiority of an abicipar group versus ranibizumab with a non-inferiority margin of 10%. This calculation is based on the assumption of a 90% response rate for both groups.

With an anticipated dropout rate of approximately 20% during a 52 week period, a total of 900 patients will be enrolled so that approximately 720 patients (240 per group) will complete the 52 week follow-up as required for the primary endpoint evaluation.

7.5 Interim Analyses

No interim analyses are planned for this study. However, an external independent DSMC will assess the safety during the study. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

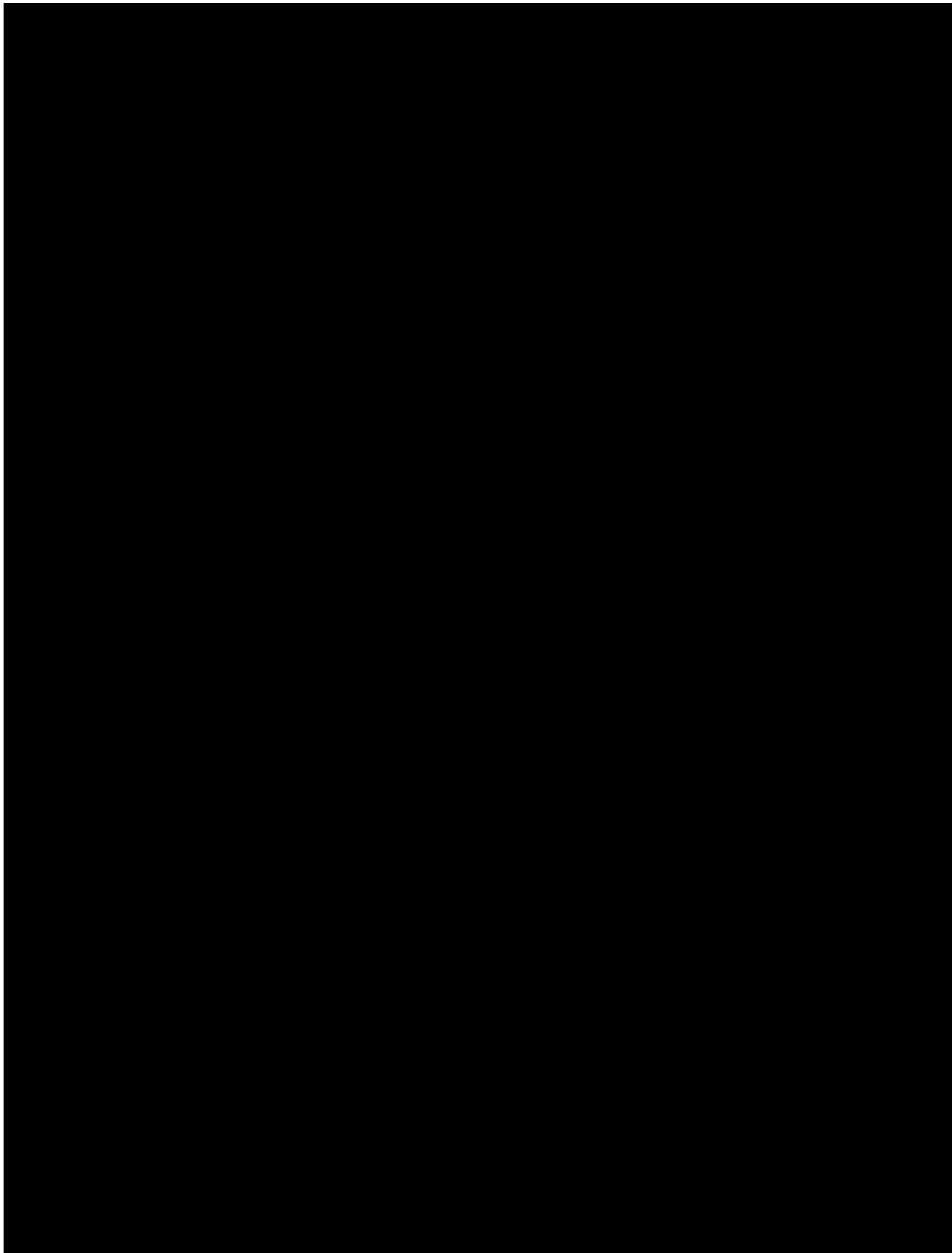
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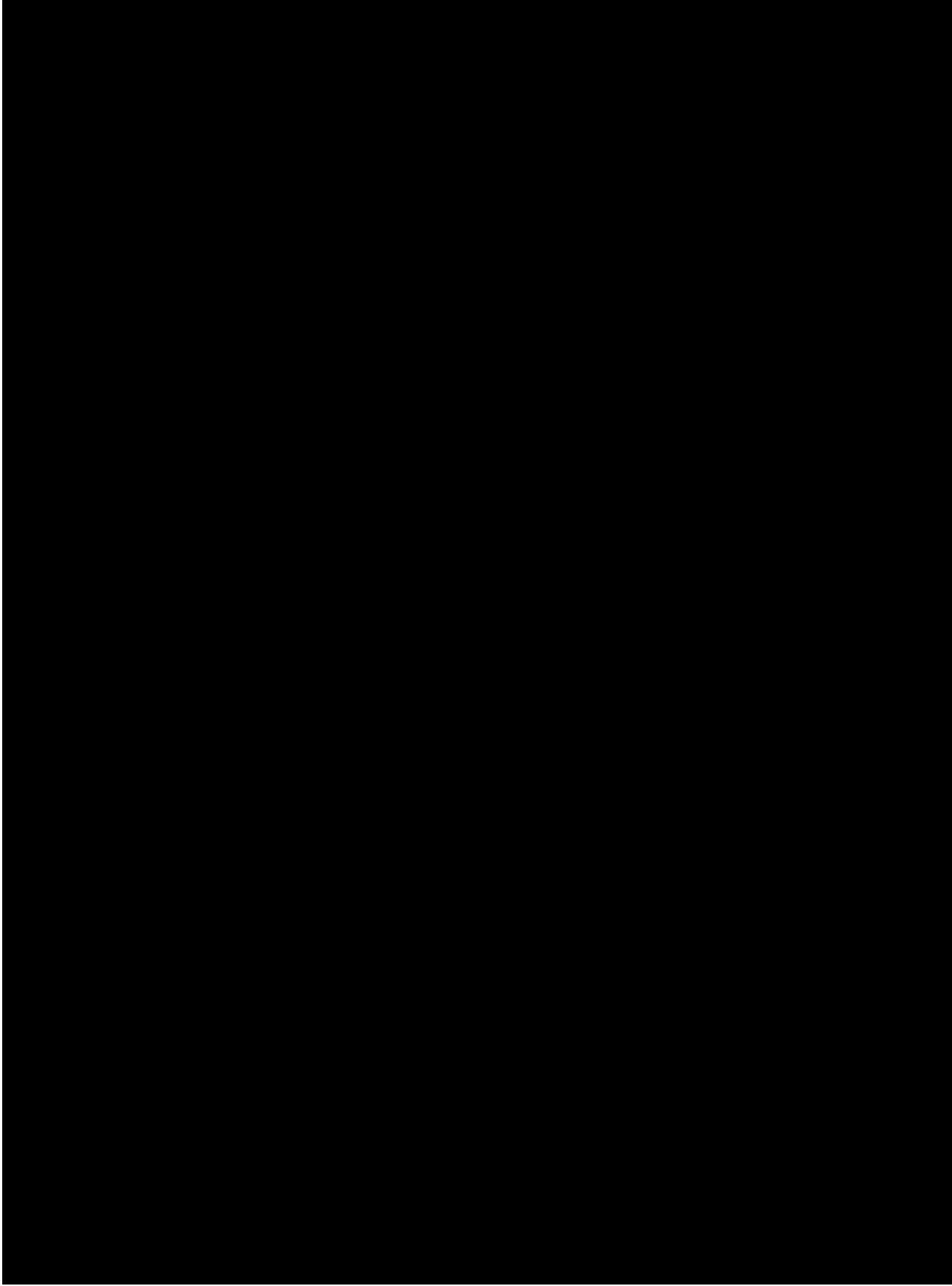
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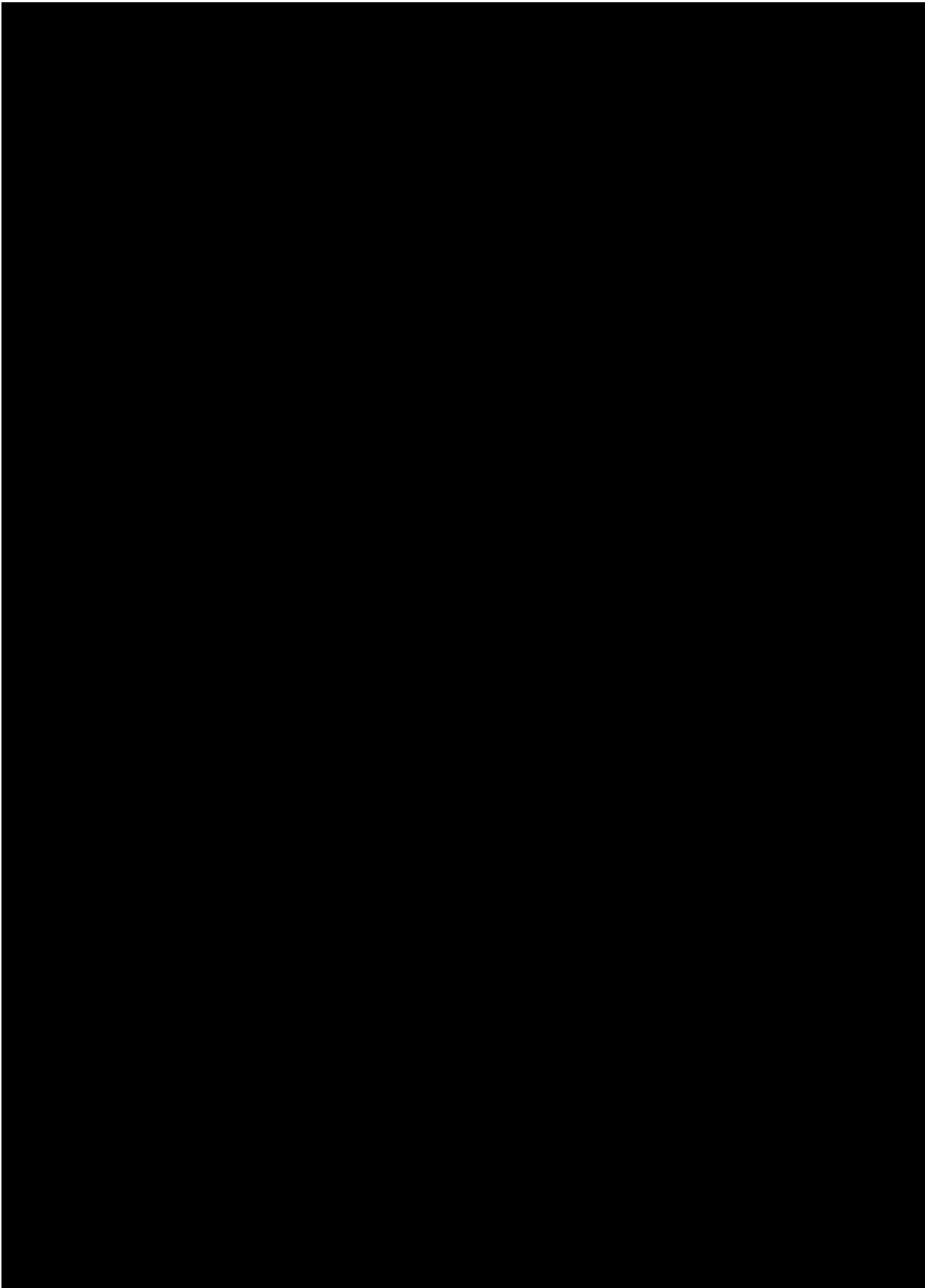
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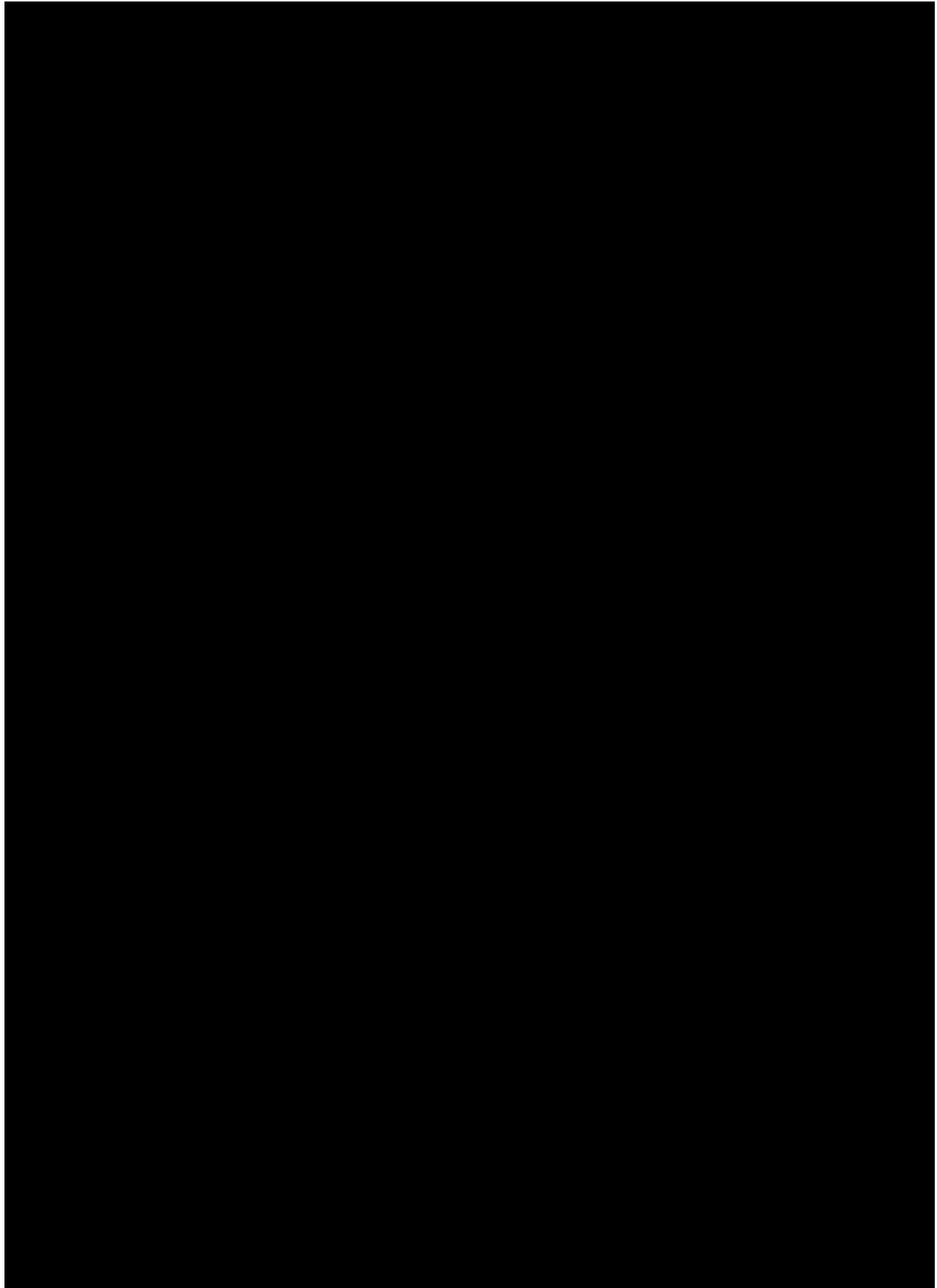
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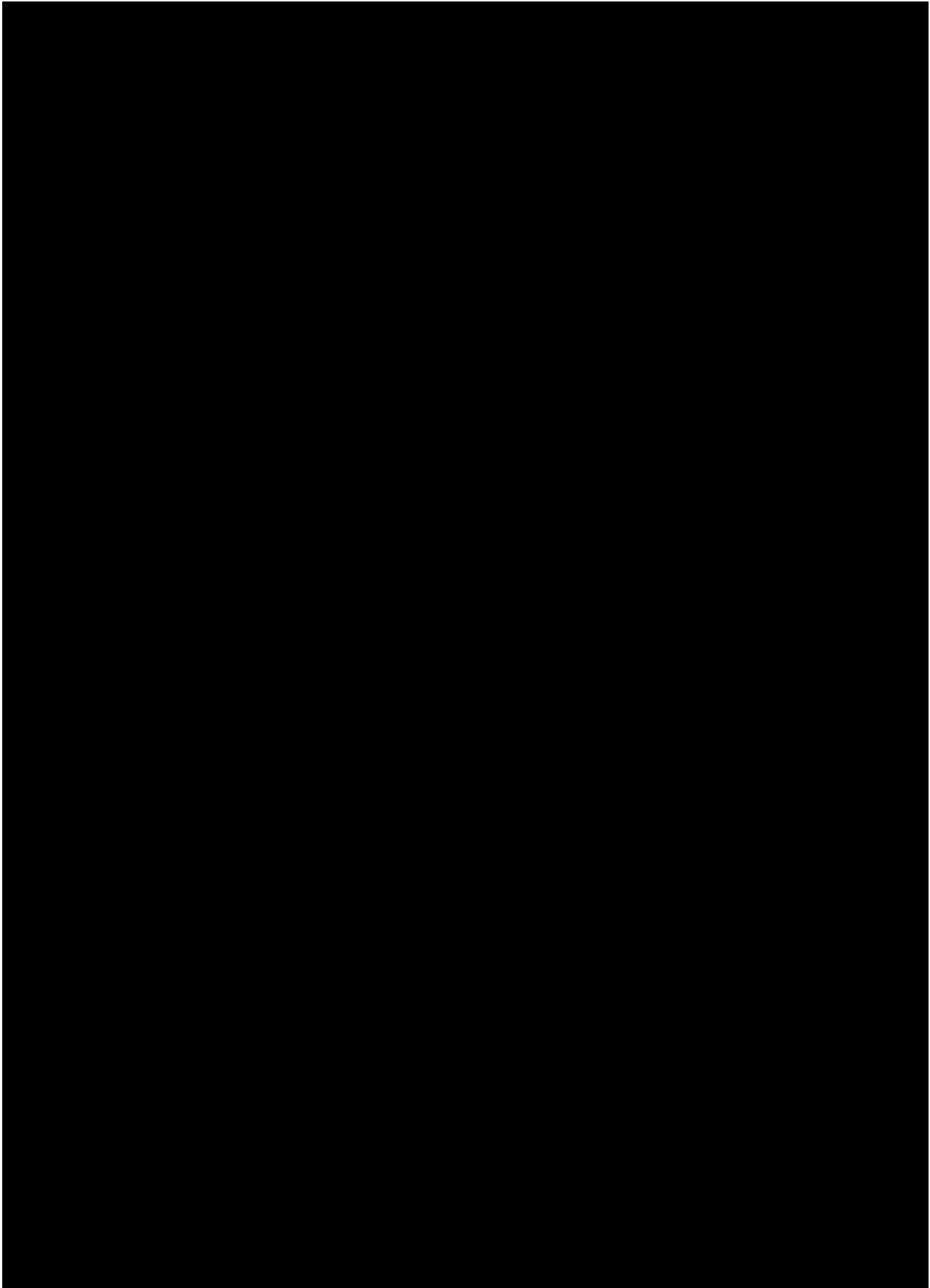
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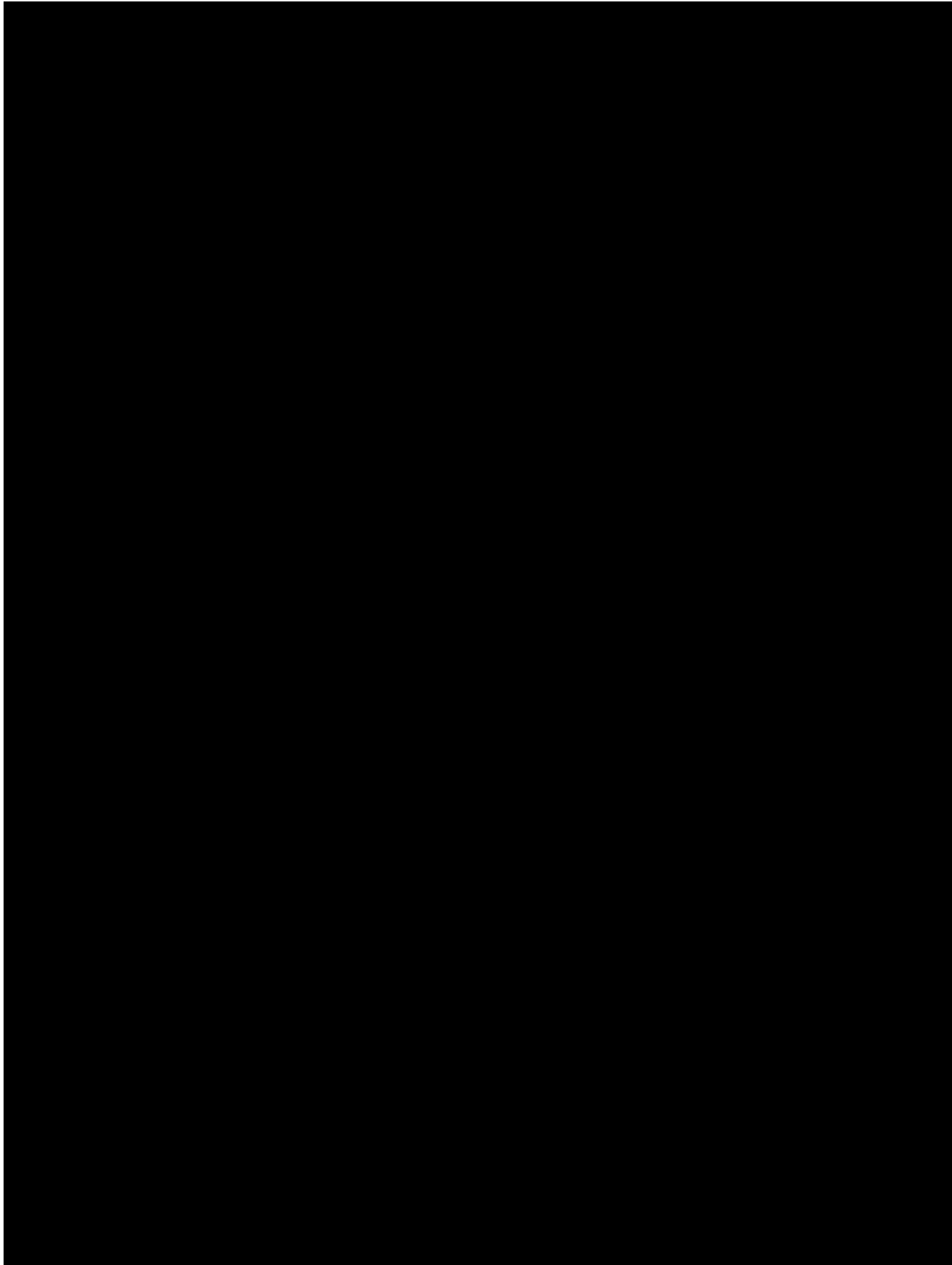
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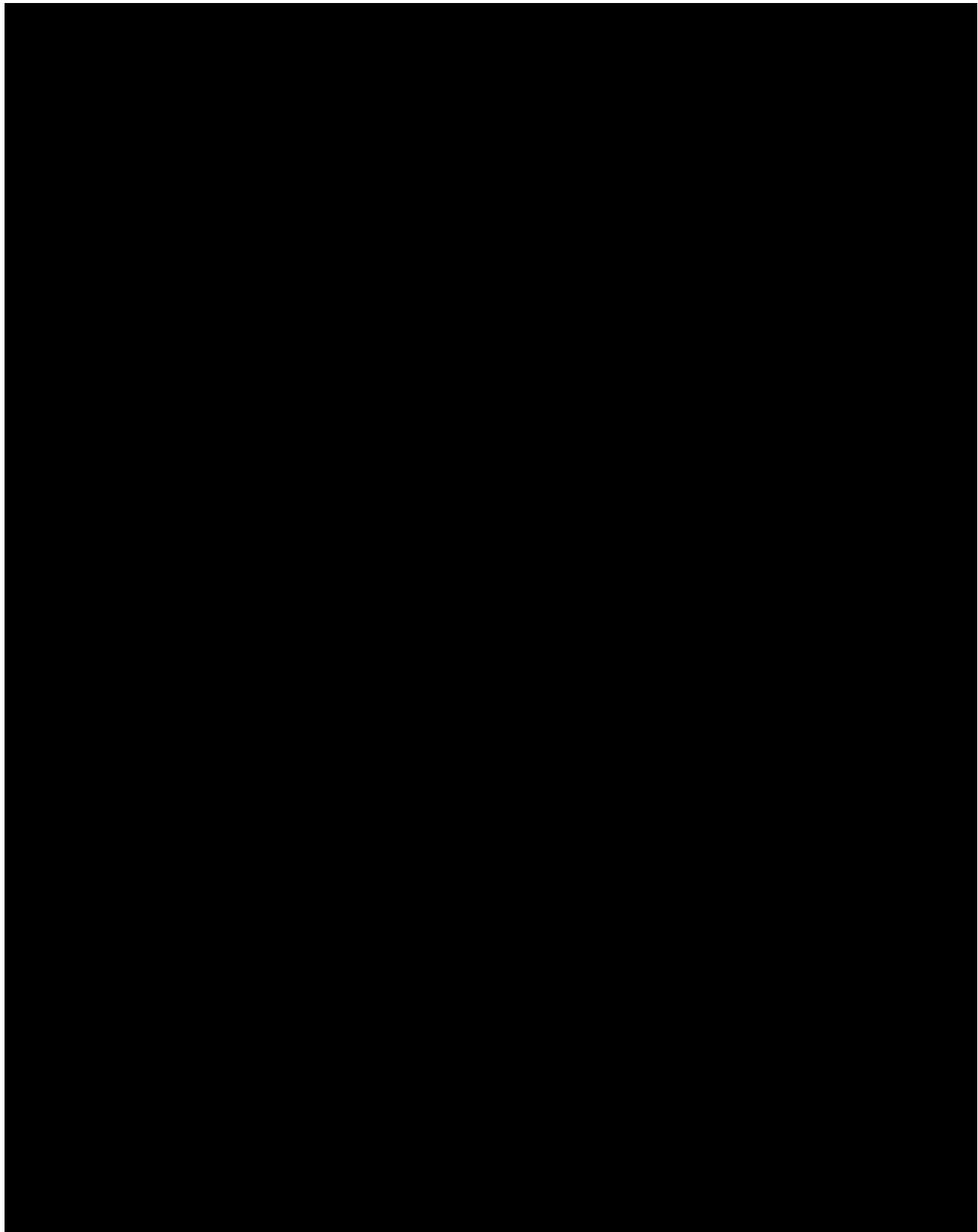
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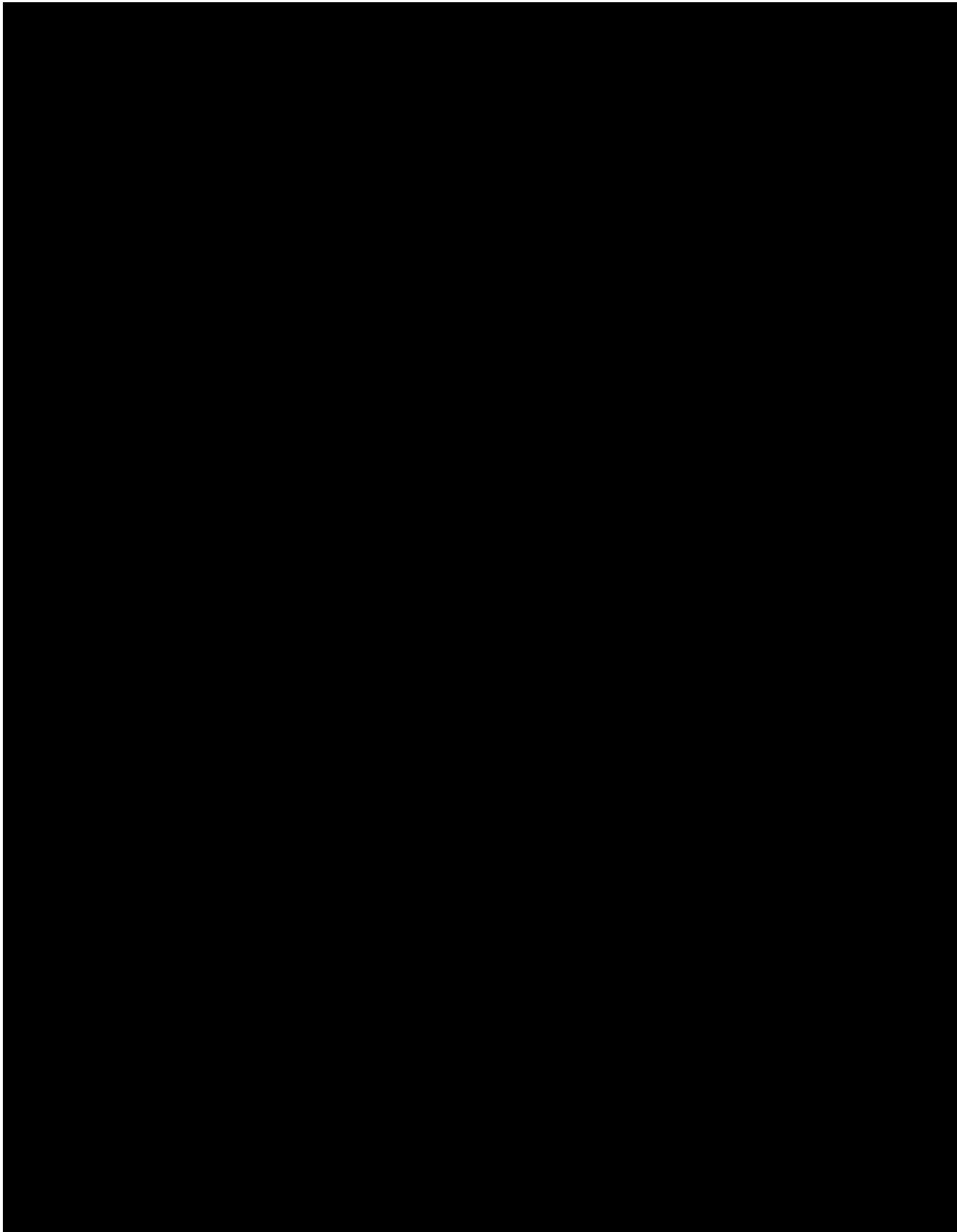
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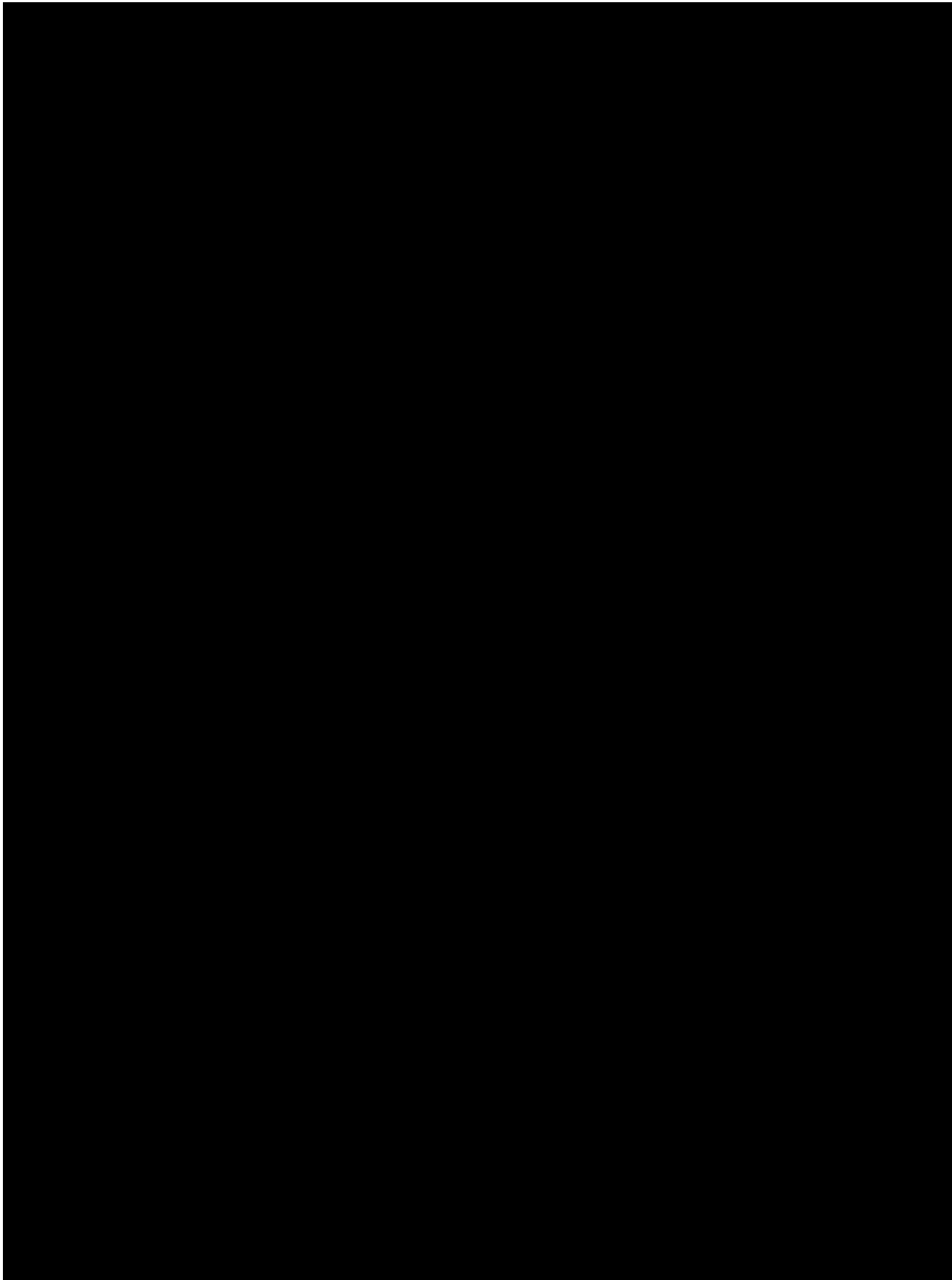
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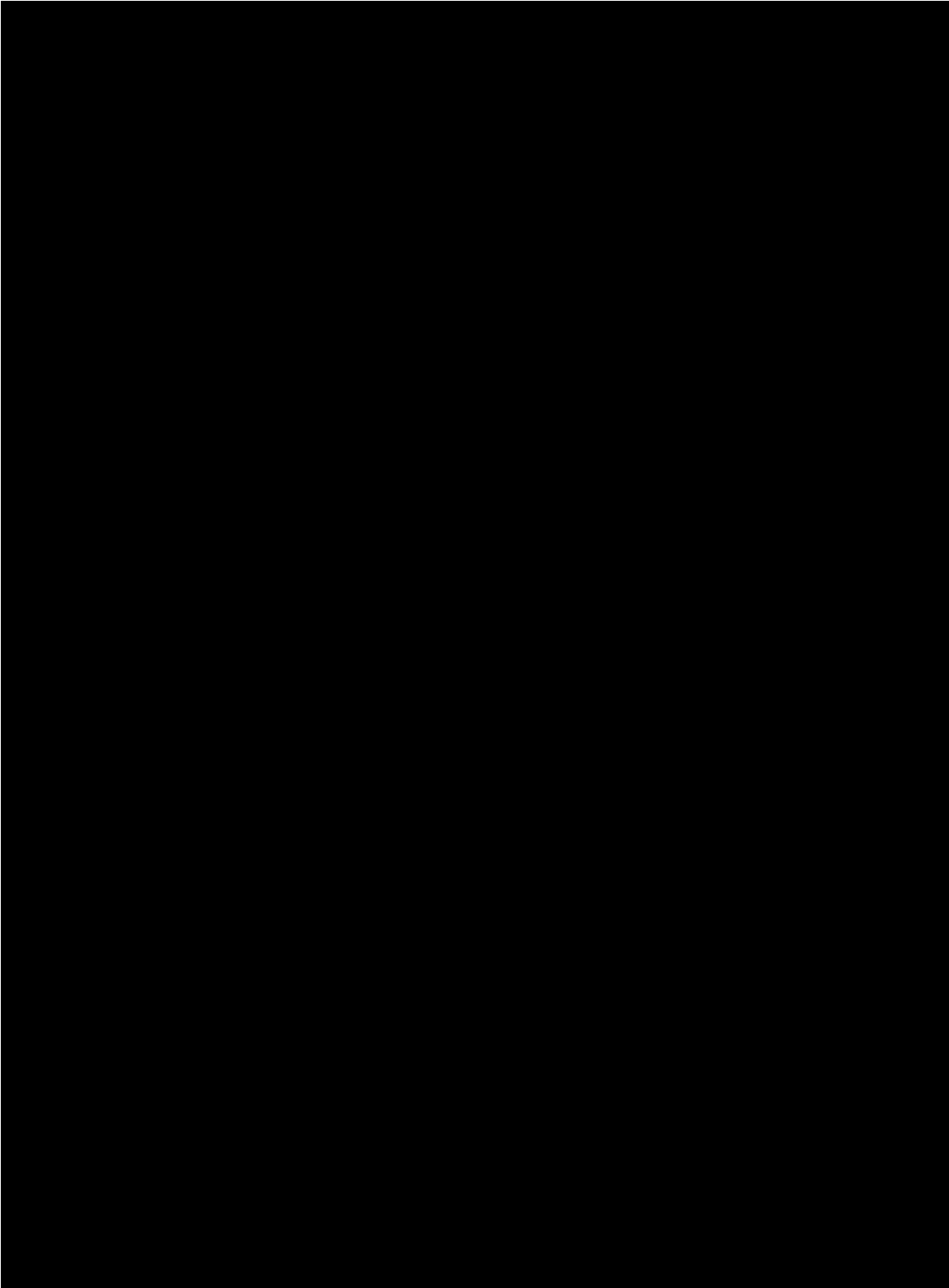
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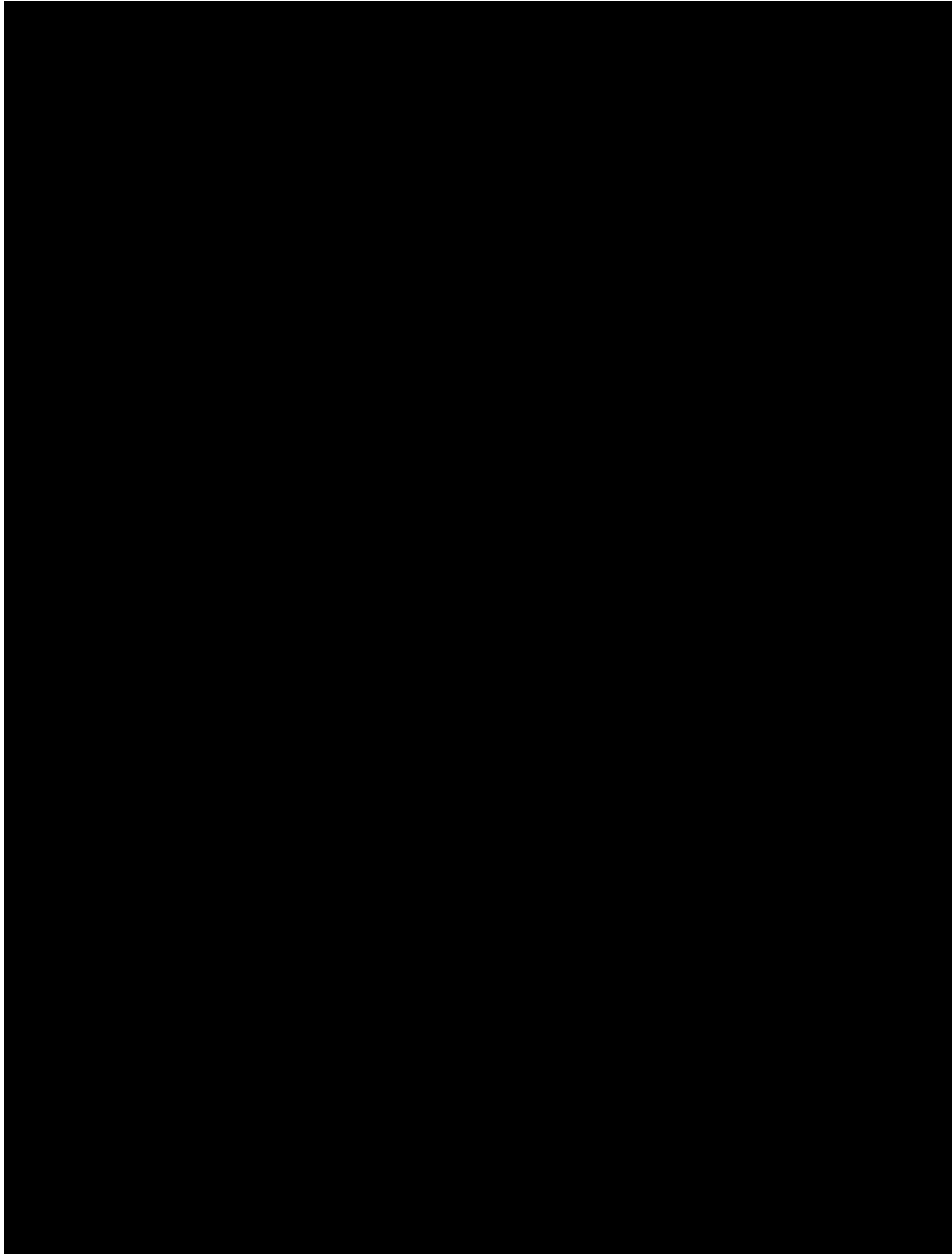
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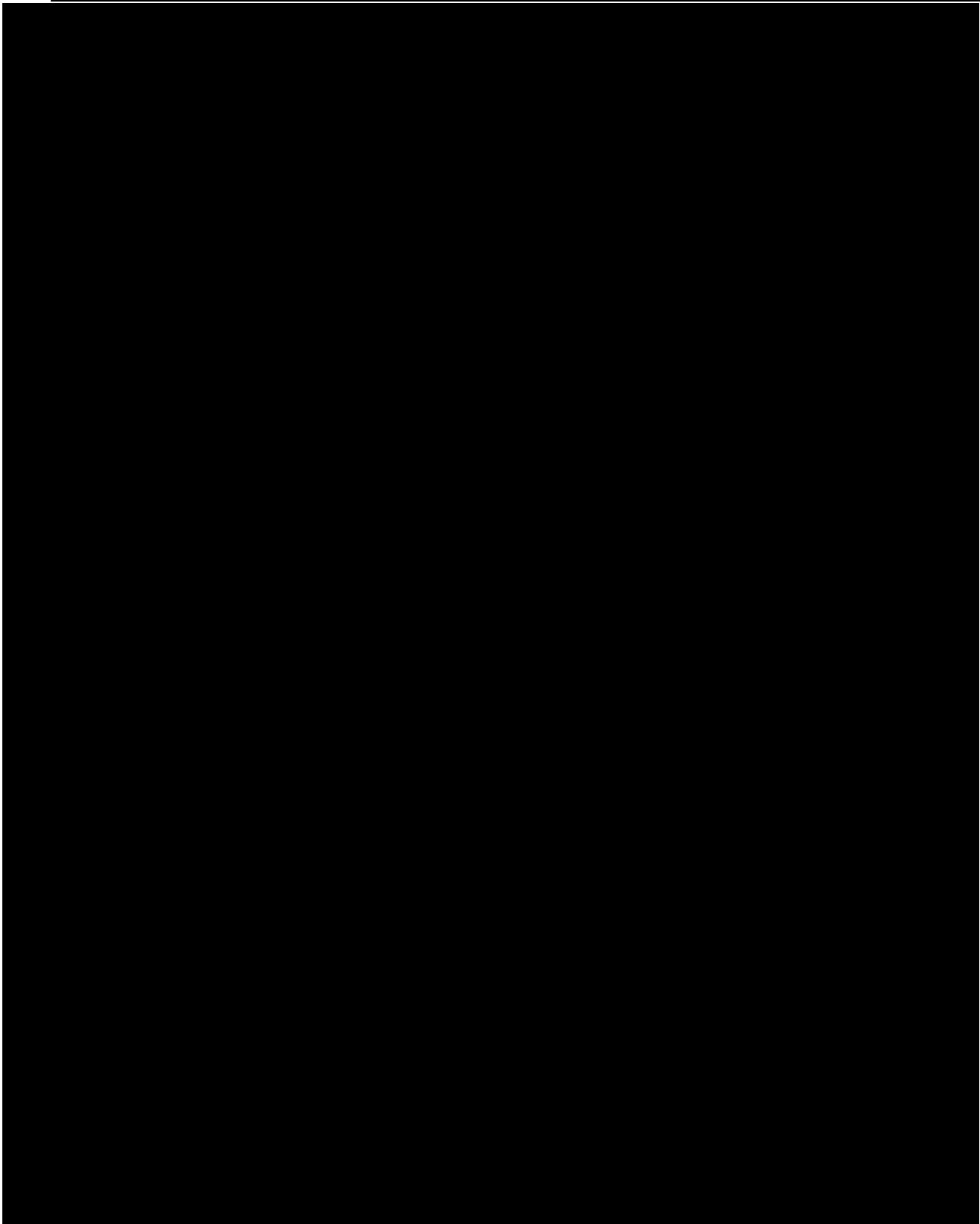
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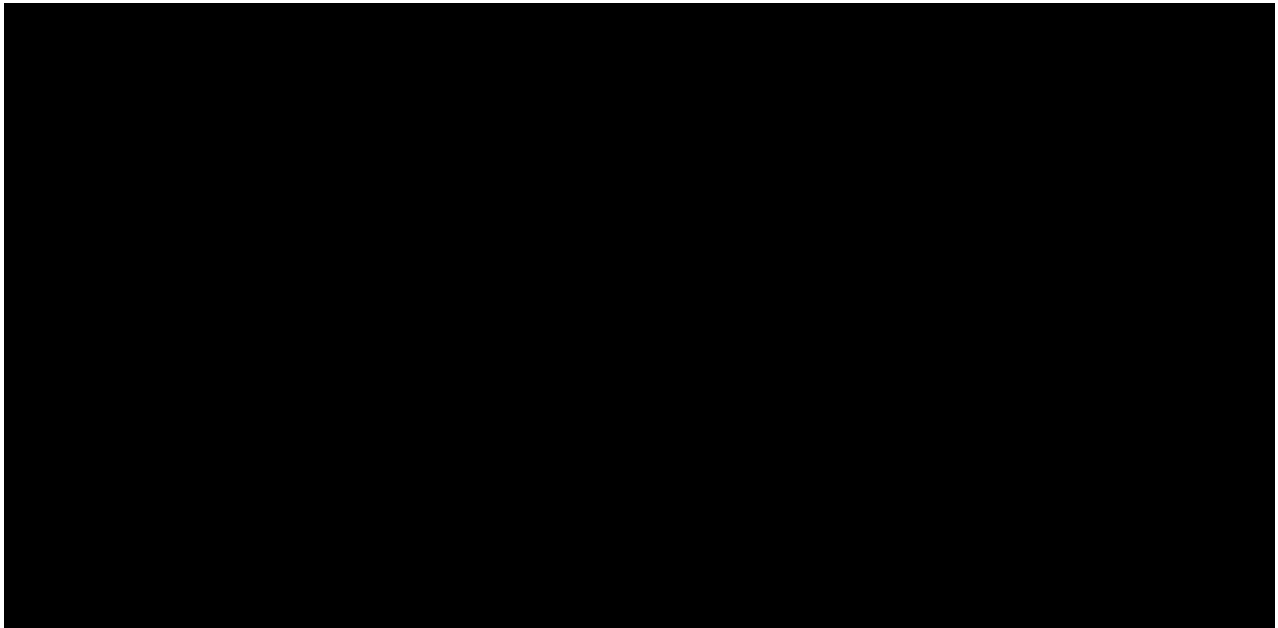
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8.4 Instructions for the Patients

Patients are instructed that they do not need to fast before visits.

Patients are instructed to strictly follow the study visit schedule and to report all changes in condition to the investigative site.

8.5 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and well-being of patients during the study. The eCRFs should be completed for each unscheduled visit.

8.6 Compliance With Protocol

Allergan must be informed of any patients who are inadvertently enrolled despite significant deviation from protocol-specified criteria. A decision regarding the patient's continued participation will be made on a case-by-case basis.

8.7 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time. A patient's participation in the study may be terminated if it is deemed by the investigator or Allergan that it is unsafe for the patient to continue in the study.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate eCRF. Patients who discontinue early from the study will not be replaced.

Patients who discontinue early due to escape to standard of care must complete the week 104/early exit visit procedures and follow-up visits as described in Section 5.6.2.

[REDACTED]

8.8 Withdrawal Criteria

See Section 5.6.2.

8.9 Study Termination

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

9. Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject 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 neovascular AMD, including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

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

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

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

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient’s entry into the study. If it has not been documented at the time of the patient’s entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

9.1.3 Severity

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

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

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. A study procedure occurring during the screening/baseline period can include a study required diagnostic procedure.

For treatment-related adverse events, the investigator will note on the eCRF whether the event is related to the study medication, and/or the injection procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

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

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 16 weeks after the last administration 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 Sheet 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.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

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

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

10. Administrative Items

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

10.1 Protection of Study Patients

10.1.1 Compliance With Informed Consent Regulations (US 21 Code of Federal Regulations [CFR] Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative.

10.1.2 Compliance With IRB or IEC Regulations

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

10.1.3 Compliance With Good Clinical Practice

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

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

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

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

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

10.3.1 Patient Privacy

Written authorization (US sites only), data protection consent (European Union [EU] 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.

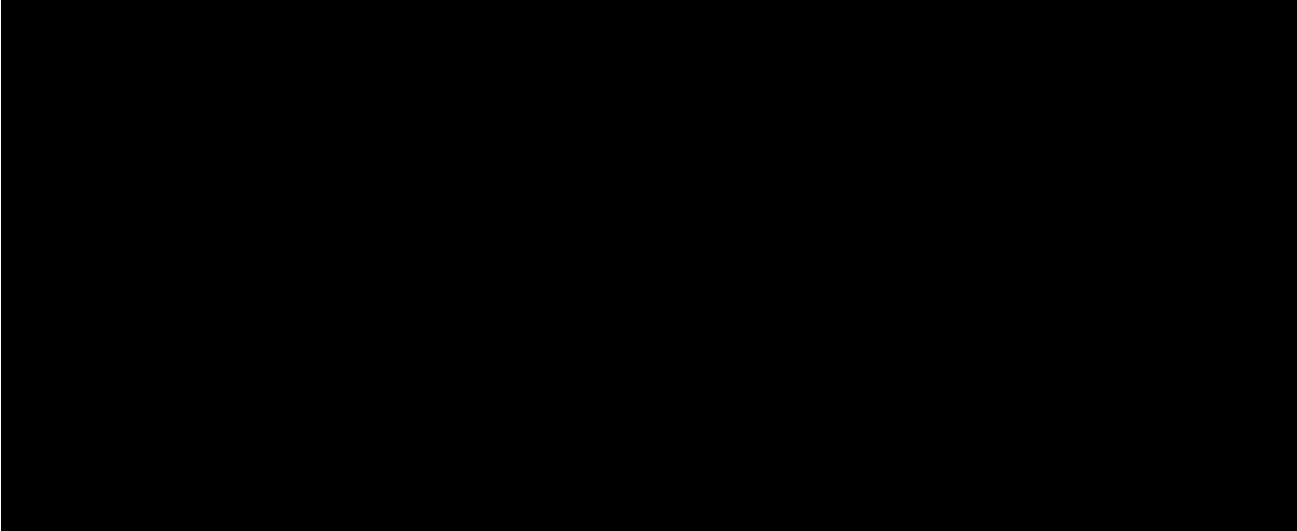

10.4 Documentation

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 CRFs serves as part of the investigator's record of a patient's study-related data.

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

- patient's name
- patient's contact information
- the date that the patient entered the study, patient number, and patient randomization (or medication kit) number
- the study title and/or the protocol number of the study and the name of Allergan
- a statement that informed consent was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- dates of all patient visits
- all concurrent medications (list all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- occurrence and status of any adverse events
- the results of pregnancy tests performed by the site
- vital signs and general physical examination findings
- copies of the laboratory reports generated by the central laboratory for the analysis of blood and urine samples
- visual acuity worksheets

- 
- procedure notes of the study medication procedure should include the following:
 - date and time the vial is removed from the refrigerator
 - date and time of the procedure
 - evaluation of the injection site
 - location of the injection to the nearest clock hour
 - complications, if any
 - the date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- 

10.4.2 Case Report Form Completion

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

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

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

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

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

10.5.1 Labeling/Packaging

Study medication will be packaged, labeled, and supplied by Allergan or an Allergan approved labeling, packaging and distribution vendor. All study medications will be supplied in identical appearing packaging, identified as an investigational compound and will be labeled with the protocol study number and medication kit number. The label will contain information per country specific regulatory requirements and may include but is not limited to storage conditions and a caution statement regarding investigational use.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, the number of units returned to the investigator by the patient, 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 only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator. A unit is defined as a single-dose vial.

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

[REDACTED]

[REDACTED] If local policy does not allow storage of used study medication vials, the site may destroy the used vials per their local policy, but must keep the kit box for the detailed inventory of the study medication.

10.6 Monitoring by the Sponsor

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

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

10.7 Handling of Biological Specimens

[REDACTED]

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Details about the handling, processing, and shipment of all biological specimens are provided in the procedure manual.

[Redacted]

10.8 Publications

[Redacted]

10.9 Coordinating Investigator

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

11. References

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12. Attachments

12.1 Glossary of Abbreviations

Term/Abbreviation	Definition
2Q8	treatment group that has 2 mg abicipar administered at baseline (day 1) and weeks 4 and 8, followed by doses at 8-week intervals through week 96
2Q12	treatment group that has 2 mg abicipar administered at baseline (day 1), and weeks 4 and 12, followed by doses at 12-week intervals through week 96
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AREDS	Age-Related Eye Disease Study
BCVA	best-corrected visual acuity
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CNV	choroidal neovascularization
CRF	case report form
CRT	central retinal thickness
eCRF	electronic case report form
DA	disc area
DSMC	Data and Safety Monitoring Committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
	
EU	European Union
GCP	Good Clinical Practices
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IVRS	interactive voice response system

Term/Abbreviation	Definition
IWRS	interactive web response system
ITT	intent-to-treat (population)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
MP	Molecular Partners
[REDACTED]	[REDACTED]
OCT	optical coherence tomography
OU	both eyes
PDT	photodynamic therapy
PEG	polyethylene glycol
PK	pharmacokinetic(s)
PP	per-protocol (population)
PPV	pars plana vitrectomy
RBC	red blood cell
REACH	Study 150998-001
RPE	retinal pigment epithelium
rQ4	control treatment group that has 0.5 mg ranibizumab administered every 4 weeks through week 96
SD-OCT	spectral-domain optical coherence tomography
SE	study eye
SEQUOIA	Study 150998-006 (current study)
TEAE	treatment-emergent adverse event
US	United States
VEGF	vascular endothelial growth factor
WBC	white blood cell
[REDACTED]	[REDACTED]

12.2 Protocol Amendment Summary Amendment 1

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

Protocol 150998-006 Amendment 1

Date of Amendment: March 2015

Amendment Summary

This summary includes changes made to Protocol 150998-006 (approved November 2014).

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 (page 2)	Added the underlined text: “The following information can be found on FDA Form 1572 and/or study contacts page and/or <u>Trial Master File</u> : 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.”	FDA Form 1572 is a US-specific document and will only be collected for US study sites. Investigator information may also be found in the trial master file.
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]

Note: Stricken text was removed and underlined text was added

12.3 Protocol Amendment Summary Amendment 2

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

Protocol 150998-006 Amendment 2

Date of Amendment: April 2016

Amendment Summary

This summary includes changes made to Protocol 150998-006 Amendment 1 (approved March 2015).

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 (page 2)	Updated title of Allergan Signatory	Administrative change
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 1	Updated to include additional support for dosing regimens used in the study	Revised language for purposes of clarification only
[REDACTED]	[REDACTED]	[REDACTED]
Section 3.1	Updated to include purpose of monitoring.	Revised language for purposes of clarification only
[REDACTED]	[REDACTED]	[REDACTED]
Section 4.5.1.1	Updated to include use of condoms as preferred method of contraception for male patients participating in the study	To specify male contraceptive measures

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 7.3.1	Added that if non-inferiority for both abicipar arms is established, that superiority testing of abicipar over ranibizumab will be performed	Updated to reflect changes to the statistical analysis plan

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
Section 7.3.3	Updated to describe additional analyses if non-inferiority for both abicipar arms is established	Updated to align with FDA's comments at the end-of-phase 2 meeting
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
Section 10.5.3	Added the following: <u>If local policy does not allow storage of used study medication vials, the site may destroy the used vials per their local policy, but must keep the kit box for the detailed inventory of the study medication.</u>	Revised language for accommodating the local policy of handling the used study medication
Section 12.1	Added abbreviations for the following: ANCOVA, PDT, and PEG	Included abbreviations that were either added or not previously defined.

Note: Stricken text was removed and underlined text was added

12.4 Protocol Amendment Summary Amendment 3

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

Protocol 150998-006 Amendment 3

Date of Amendment: February 2017

Amendment Summary

This summary includes changes made to Protocol 150998-006 Amendment 2 (approved April 2016).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
Section 10	Updated to reflect the current template language with regards to conducting the study in accordance with applicable laws and regulations.	Administrative change.

Approval Date: 10-Apr-2018

12.5 Protocol Amendment Summary Amendment 4

Title: Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration

Protocol 150998-006 Amendment 4

Date of Amendment: April 2018

Amendment Summary

This summary includes changes made to Protocol 150998-006 Amendment 3 (approved February 2017).

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]

Approval Date: 10-Apr-2018

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 10-Apr-2018

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150998-006 Protocol Amendment 4

