NCT04403763

Study ID: 2011-101-013

Title: A First-in-Human, Phase 1/2, Dose-ascending, Multicenter, Masked, Randomized, Vehicle-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AGN-241622 in Healthy Participants and Participants with Presbyopia (Stage 1 and Stage 2) and Efficacy in Participants with Presbyopia (Stage 2)

Protocol Date: March 25, 2020

Title Page

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Protocol Number: 2011-101-013

Compound: AGN-241622

Study Phase: Phase 1/2

Short Title: Phase 1/2 study of AGN-241622 in healthy participants and participants with presbyopia

Sponsor Name and Legal Registered Address:

Allergan Sales, LLC
5 Giralda Farms
Madison, NJ 07940
USA

Regulatory Agency Identifier Number(s): IND 139578

Emergency Telephone Number: Refer to the study contacts page

SAE Reporting Fax Number/Email:

Business Unit	Email	Phone	Fax
Allergan	IR-Clinical-SAE@allergan.com	Not applicable	+1-714-796-9504 Backup: +1-714-246-5295

Sponsor Signatory:

[redacted]
Vice President, Clinical Development - Ophthalmology

[redacted]
Vice President, Clinical Pharmacology

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	28 October 2019

Amendment 1

Overall Rationale for the Amendment:

The overall rationale for Amendment 1 is to include modifications based on FDA feedback and minor clarifications. Minor editorial and document formatting revisions have not been summarized. The following is a summary of the changes that were made to each section of the protocol, and a brief rationale for these changes.

Section # and Name	Description of Change	Brief Rationale
Global	Pupil diameter assessment wording edited to state that pupil diameter will be assessed in mesopic conditions during Stage 1.	Light condition was added for clarification.
Global Synopsis, Overall Design Figure 1-1, Study Schema Section 2.1, Study Rationale Section 2.3, Benefit/Risk Assessment Section 4.1, Overall Design Section 4.2, Scientific Rationale for Study Design Section 6.3, Measures to Minimize Bias: Randomization and Masking Section 7.1, Discontinuation of Study Intervention Section 7.1.1, Study Termination Section 9.6, Data Monitoring Committee (DMC)	Wording edited to clarify that after each cohort is complete, an independent DMC will review unmasked safety and plasma PK data, along with target engagement and efficacy data if necessary (and applicable), to recommend if it is acceptable to proceed to the next planned cohort. Globally, description of DMC review data changed from masked to unmasked for the study. Wording added to state that the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort. Wording modified to state that nonclinical studies have been completed and support the safe use of AGN-241622 ophthalmic solution in human eyes. AGN-241622 ophthalmic solution is expected to be safe in healthy participants as well as participants with presbyopia. Wording edited to state: In addition, each cohort will not proceed until the preceding cohort(s) has been: 1) reviewed and deemed safe by a DMC, and 2) a positive response is received from the FDA. Wording modified to state: The DMC and FDA may recommend modifications to the protocol including discontinuation of study intervention and study upon review of safety data.	Per FDA feedback and for clarification.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1, Schedule of Activities (SoA) – Stage 1 Section 1.3.2, Schedule of Activities (SoA) – Stage 2a Section 1.3.3.1, Schedule of Activities (SoA) – Stage 2b (Cohort 7) Section 1.3.3.2, Schedule of Activities (SoA) – Stage 2b (Cohort 8) Global	Wording added that study assessments should be conducted in the sequence as listed in the SoA. Hour 0 definitions listed for the different stages, as applicable. Wording added to clarify that Pre-Hour 0 assessments are assessments listed prior to study intervention dosing (e.g., laboratory assessments, PK, IWRS) and should be conducted before Hour 0. For Stage 1, wording added that all ophthalmic assessments are to be done in both eyes. More details can be found in the notes section. For Stages 2a and 2b, wording added that all ophthalmic assessments are to be done in both eyes except for the shaded timepoints. More details can be found in the notes section. For Stage 2, physical examination assessment added to Day 30/EOS Visits and weight assessment added to Day 14 Visit at Hr 0. Wording changed to clarify that height and weight are a part of physical examination during all stages, and that height will only be assessed at screening.	For clarification.
Section 5.2.1, Stage 1 (Exclusion Criteria) Section 5.2.2, Stages 2a and 2b (Exclusion Criteria) Section 6.5.1, Prohibited Interventions Section 6.5.2, Permitted Interventions	For Stage 1, Exclusion Criterion 2.01 deleted and Exclusion Criterion 2.02 modified. For Stages 2a and 2b, combined and modified Exclusion Criteria 2.01 and 2.02. Section 6.5.1 modified for consistency against above updates and clarification. Section 6.5.2 modified for consistency against above updates and clarification.	Wording modified for more conservative approach. Safety and PK data would be reviewed from Stages 1 and 2a to look at potential interactions.
Section 8.5.1, Blood PK Sampling Procedure	Wording modified to state: Study center staff will send plasma samples to the bioanalytical laboratory or the central laboratory for storage after the last collection on Day 1 (for Stage 1) and after the last collection on Days 1 and 14 (for Stage 2). On the day of shipment, the sponsor and the specified laboratory will be notified by email as to the time and method of shipment.	For clarity.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A First-in-Human, Phase 1/2, Dose-ascending, Multicenter, Masked, Randomized, Vehicle-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AGN-241622 in Healthy Participants and Participants with Presbyopia (Stage 1 and Stage 2) and Efficacy in Participants with Presbyopia (Stage 2)

Short Title: Phase 1/2 study of AGN-241622 in healthy participants and participants with presbyopia

Rationale:

The objective of this study is to evaluate the safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 ophthalmic solution for the first time in human participants. Nonclinical studies have been completed and support the safe use of AGN-241622 ophthalmic solution in human eyes at the dose strengths of [redacted] selected for this study. These dose strengths of AGN-241622 ophthalmic solution are expected to be safe in healthy participants as well as participants with presbyopia. Stage 1 of this study will evaluate safety, tolerability, pharmacokinetics, and the target receptor engagement of AGN-241622 after a single unilateral dose in healthy participants (Cohorts 1 to 3). Stage 2a will evaluate safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 ophthalmic solution after repeat bilateral administration in participants with presbyopia (Cohorts 4 to 6). Stage 2b will evaluate safety, tolerability, and efficacy of AGN-241622 ophthalmic solution compared with an active comparator (pilocarpine HCl [redacted] 1.25% ophthalmic solution) after repeat bilateral administration in participants with presbyopia in Cohort 7; and safety, tolerability, tear pharmacokinetics, and efficacy of AGN-241622 ophthalmic solution after repeat bilateral administration in participants with presbyopia who wear contact lenses in Cohort 8. Together, the results from Stages 1 and 2 of this study will help characterize the safety, tolerability, pharmacokinetics, and efficacy profile of AGN-241622 and support the further development of AGN-241622 as a noninvasive, reversible, pharmacologic treatment for presbyopia.

Objectives and Measures

	Objectives	Measures
Stage 1	Primary • To evaluate the safety and tolerability of AGN-241622 administered once, unilaterally in healthy participants	• AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy
	Secondary • To evaluate the systemic and local pharmacokinetics of AGN-241622 administered once unilaterally in healthy participants • To evaluate the target receptor engagement of AGN-241622 as compared with vehicle administered once, unilaterally in healthy participants	• Plasma and tear concentrations and PK parameters of AGN-241622, including but not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, CL/F (plasma only), and V_z/F (plasma only) • Pupil diameter measurement (mesopic)
Stage 2a	Primary • To evaluate the safety and tolerability of AGN-241622 after repeat bilateral administration in participants with presbyopia	• AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy • Contrast sensitivity • Photopic and mesopic high contrast CDVA binocularly • Manifest refraction (mesopic and photopic) • Dilated funduscopic examination
	Secondary • To evaluate the systemic and local pharmacokinetics of AGN-241622 after repeat bilateral administration in participants with presbyopia	• Plasma and tear concentrations and PK parameters of AGN-241622, including but not limited to: $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, CL/F (plasma only), and V_z/F (plasma only)

	Objectives	Measures
Stage 2a (Continued)	• To evaluate efficacy of AGN-241622 compared with vehicle after repeat bilateral administration in participants with presbyopia	• Mesopic and photopic high contrast, binocular and monocular DCNVA • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO Questionnaires (NVPTQ, PICQ, Single-item PGIC, Single-item PGIS) • Bulbar conjunctival hyperemia
Stage 2b	• To evaluate safety, tolerability, and efficacy of AGN-241622 compared with pilocarpine HCl [redacted] 1.25% after repeat bilateral administration in participants with presbyopia in Cohort 7	Safety and Tolerability: • AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy • Contrast sensitivity • Photopic and mesopic high contrast CDVA binocularly • Manifest refraction (mesopic and photopic) • Dilated funduscopic examination Efficacy: • Mesopic and photopic high contrast, binocular and monocular DCNVA • Mesopic and photopic high contrast, binocular and monocular DCIVA • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO Questionnaires (NVPTQ, e-NVPTQ [iPhone/iPod], PICQ, Single-item PGIC, Single-item PGIS) • Bulbar conjunctival hyperemia

Objectives	Measures
• To evaluate safety, tolerability, tear pharmacokinetics, and efficacy of AGN-241622 after repeat bilateral administration in participants with presbyopia who wear contact lenses in Cohort 8	Safety and Tolerability: • AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy • Contrast sensitivity • Photopic and mesopic high contrast CDVA binocularly • Manifest refraction (mesopic and photopic) • Dilated funduscopic examination Tear Pharmacokinetics: • Tear concentrations and PK parameters of AGN-241622, including but not limited to: $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$ Efficacy: • Mesopic and photopic high contrast, binocular and monocular DCNVA • Mesopic and photopic high contrast, binocular and monocular DCIVA • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO Questionnaires (NVPTQ, e-NVPTQ [iPhone/iPod], PICQ, Single-item PGIC, Single-item PGIS) • Bulbar conjunctival hyperemia

Overall Design

This is a multicenter, randomized, double-masked (except Cohort 7), Phase 1/2 study in healthy participants and participants with presbyopia. This study will be conducted in 3 stages (Stage 1, Stage 2a, and Stage 2b). In Stage 1, healthy participants will be randomized to participate in single-ascending dose cohorts (Cohorts 1 to 3) to evaluate safety, tolerability, pharmacokinetics, and target engagement of AGN-241622. In each cohort in Stage 1, approximately 12 participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle. Participants randomized to receive active intervention will be administered a single drop of AGN-241622 at dose strengths ranging from [redacted] in the left eye. Each participant will be admitted to the study center on the evening before dosing (Day -1). Participants will receive their single dose in the morning of Day 1 and, after a full day of assessments, stay overnight and continue further safety and PK assessments on the next day (EOS Visit). After each cohort is complete, an independent DMC will review unmasked safety and plasma PK data, along with target engagement and efficacy data if necessary (and applicable), to recommend if it is

acceptable to proceed to the next planned cohort. The DMC may also recommend modifying the proposed dose strength (e.g., de-escalate to a lower dose strength), repeat the current dose strength, modify the cohort size, or stop the study. In addition, the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort. Once Cohort 2 of Stage 1 is complete, in addition to making a recommendation on whether to initiate the final cohort of Stage 1 (Cohort 3), the DMC will also make a recommendation on whether to start Stage 2 (Cohort 4) in parallel.

In Stage 2, participants with presbyopia will be selected to participate in the study. Stage 2 will be further divided into Stages 2a (Cohorts 4 to 6) and 2b (Cohorts 7 and 8). Cohorts 4 to 6 (Stage 2a) will be multiple ascending dose cohorts in which participants will be randomized to receive either AGN-241622 at dose strengths ranging from [redacted] or vehicle once daily in both eyes for 14 days. In each cohort in Stage 2a, approximately 12 participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle in order to evaluate safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 (see Figure 1-1 of Section 1.2). As in Stage 1, the DMC may recommend modifying the proposed dose strength (e.g., de-escalate to a lower dose strength), repeat the current dose strength, modify the cohort size, or stop the study. After Cohort 6 has completed, the DMC will also recommend the dose strength to be tested in Stage 2b.

Cohort 7 is a single-masked, active comparator cohort in which approximately 60 participants with presbyopia will be randomized in a 1:1 ratio to receive either pilocarpine HCl [redacted] 1.25% ophthalmic solution or AGN-241622 ophthalmic solution administered at the dose strength recommended by the DMC once daily in both eyes for 14 days. Safety, tolerability, and efficacy of AGN-241622 compared with pilocarpine HCl ([redacted]) 1.25% will be assessed after repeat bilateral topical ocular administration. Cohort 8 is an exploratory cohort in which approximately 12 participants with presbyopia who wear contact lenses will be randomized in a 3:1 ratio to receive either AGN-241622 administered at the dose strength recommended by the DMC or vehicle once daily in both eyes for 14 days. Safety, tolerability, tear pharmacokinetics, and efficacy of AGN-241622 administered at the dose strength recommended by the DMC compared with vehicle will be assessed after repeat bilateral administration.

In all cohorts of Stage 2, participants will receive their first dose in the clinic on Day 1, and stay in the clinic for safety, PK (except Cohort 7), and efficacy evaluations for approximately 10 hours postdose. For Stage 2a, participants will then return for dosing once daily and assessments from Day 2 to Day 7. For Stage 2b, on Days 3 and 7, participants will return to the clinic for dosing and assessments; on Days 1 and 3, participants will also receive multidose bottles for single unit of use for at-home dosing on Days 2, 4, 5, and 6. For participants in both Stages 2a and 2b, they will then receive multidose bottles on Day 7 for single unit of use for at-home dosing from Days 8 to 13 and will return to the clinic on Day 14 for dosing as well as safety, tolerability, PK (except Cohort 7), and efficacy evaluations for approximately 10 hours postdose. On Day 30, participants will return for a safety follow-up and EOS Visit.

The study will be conducted in the United States.

Disclosure Statement: This is a parallel group treatment study (Stage 1 [Cohorts 1 to 3]: single ascending dose; Stage 2a [Cohorts 4 to 6]: multiple ascending dose; and Stage 2b

[Cohorts 7 and 8]: multiple dose) with 2 arms per cohort that is double-masked (participant, investigator, and study site staff), except Cohort 7 which is single-masked (participant).

Number of Participants:

In each cohort in Stage 1(Cohorts 1, 2, and 3), approximately 12 healthy participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle.

In each cohort in Stage 2a (Cohorts 4, 5, and 6), approximately 12 participants with presbyopia will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle.

In Cohort 7 of Stage 2b, approximately 60 participants with presbyopia will be randomized in a 1:1 ratio to receive either AGN-241622 ophthalmic solution or pilocarpine HCl [redacted]) 1.25% ophthalmic solution.

In Cohort 8 of Stage 2b, approximately 12 participants with presbyopia who wear contact lenses will be randomized in a 3:1 ratio to receive either AGN-241622 ophthalmic solution or vehicle.

Participants who prematurely discontinue from the study may be replaced at the discretion of the sponsor.

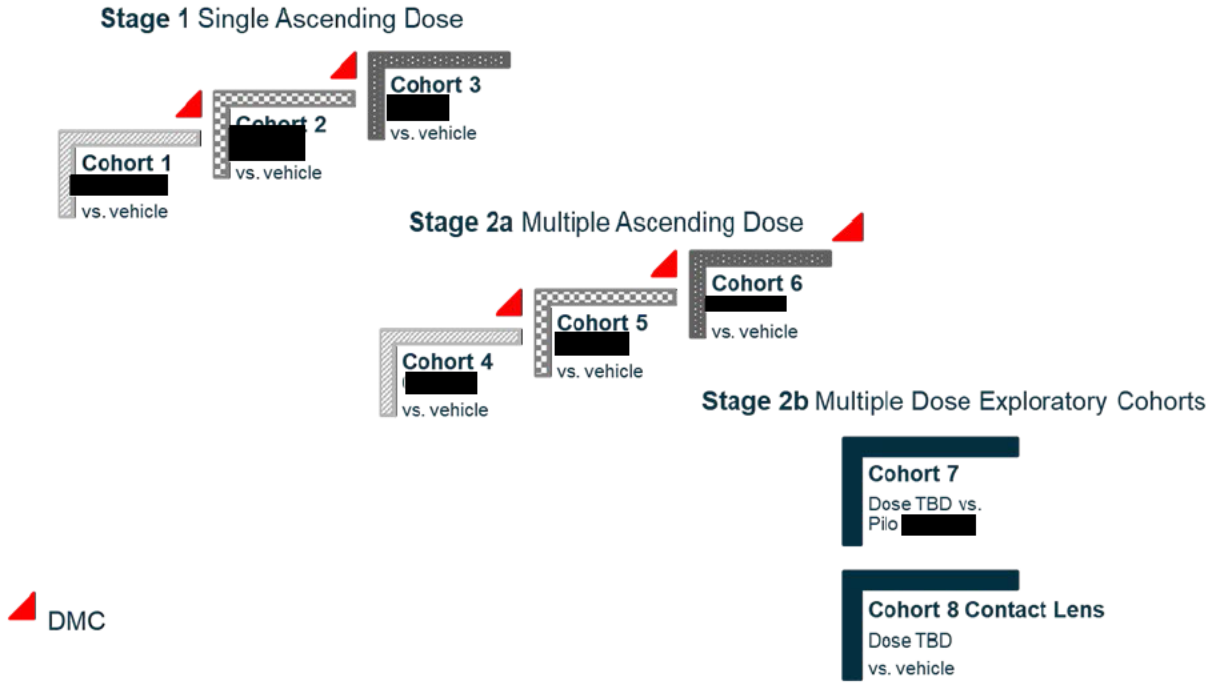
Intervention Groups and Duration: The study duration is approximately 20 days for Stage 1 (including 18 days for screening, 1 day for study intervention, and the EOS Visit on Day 2); and approximately 60 days each for Stages 2a and 2b (including 30 days for screening, 14 days for study intervention, and the EOS Visit on Day 30).

Study Interventions by Study Stage and Cohort			
Stage 1	**Single Ascending Dose in Healthy Participants**		
	Cohort 1 AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle	Cohort 2 AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle	Cohort 3 AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle
Stage 2a	**Multiple Ascending Dose in Participants with Presbyopia**		
	Cohort 4 AGN-241622 [redacted] QD × 14 days both eyes 9 Active; 3 Vehicle	Cohort 5 AGN-241622 [redacted] QD × 14 days both eyes 9 Active; 3 Vehicle	Cohort 6 AGN-241622 [redacted] QD × 14 days both eyes 9 Active; 3 Vehicle
Stage 2b	**Multiple-Dose Exploratory Cohorts in Participants with Presbyopia**		
	Cohort 7 AGN-241622 (dose strength TBD) versus pilocarpine HCl [redacted]) 1.25% QD × 14 days both eyes 60 (30 per treatment arm)	Cohort 8 AGN-241622 (dose strength TBD) (in participants who wear contact lenses) QD × 14 days both eyes 9 Active; 3 Vehicle	

Data Monitoring Committee: Yes

1.2. Schema

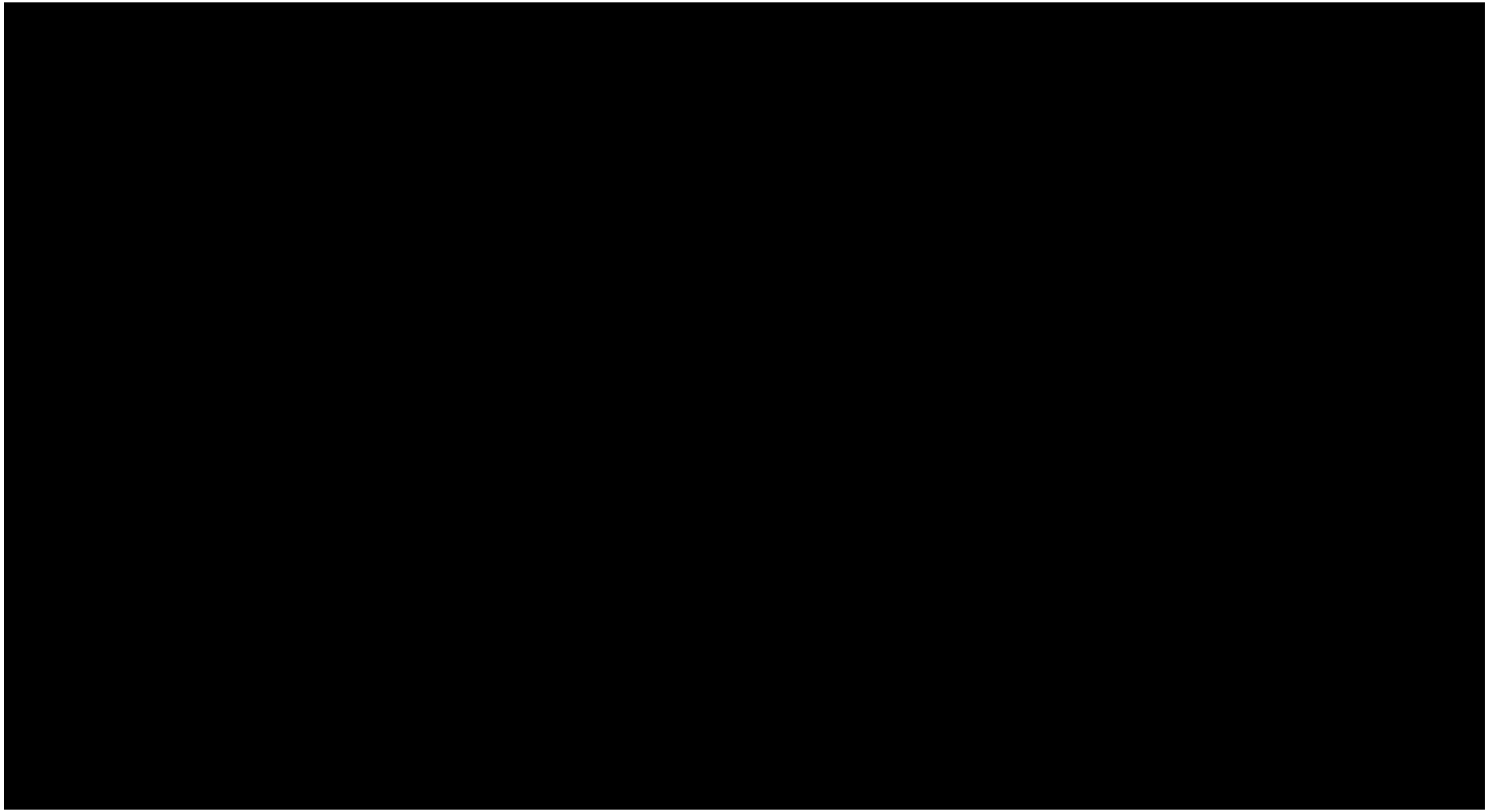
Figure 1-1 Study Schema



The DMC will review available unmasked safety and plasma PK data, along with target engagement and efficacy data if necessary (and applicable), from each completed cohort to recommend if it is acceptable to proceed to the next planned cohort, modify the proposed dose strength (e.g., de-escalate to a lower dose strength), repeat the current dose strength, modify the cohort size, or stop the study. In addition, the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort.

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities (SoA) – Stage 1



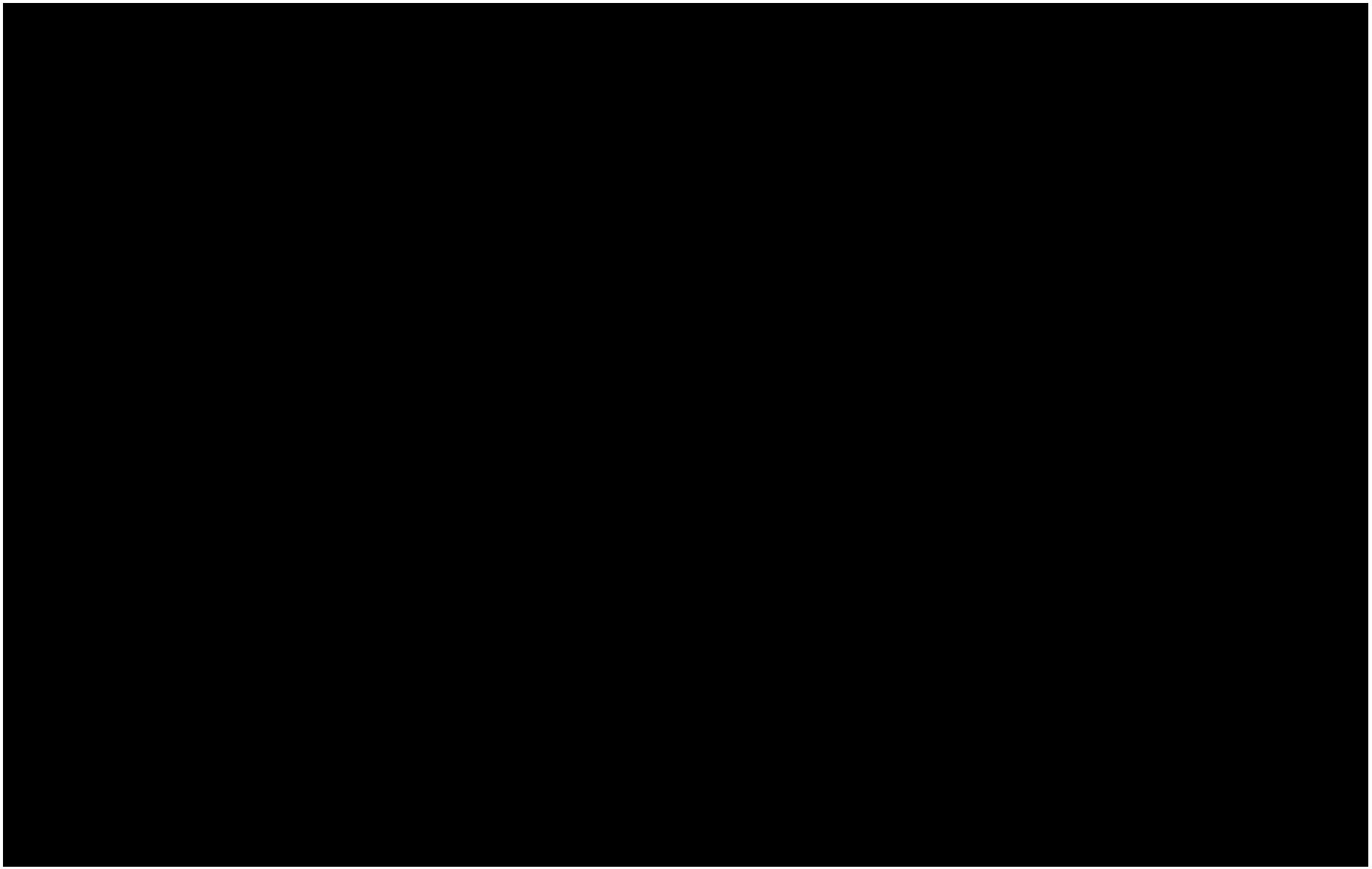


Table 1-2 Schedule of Visits and Procedures: Screening to Day 7 (Stage 2a)

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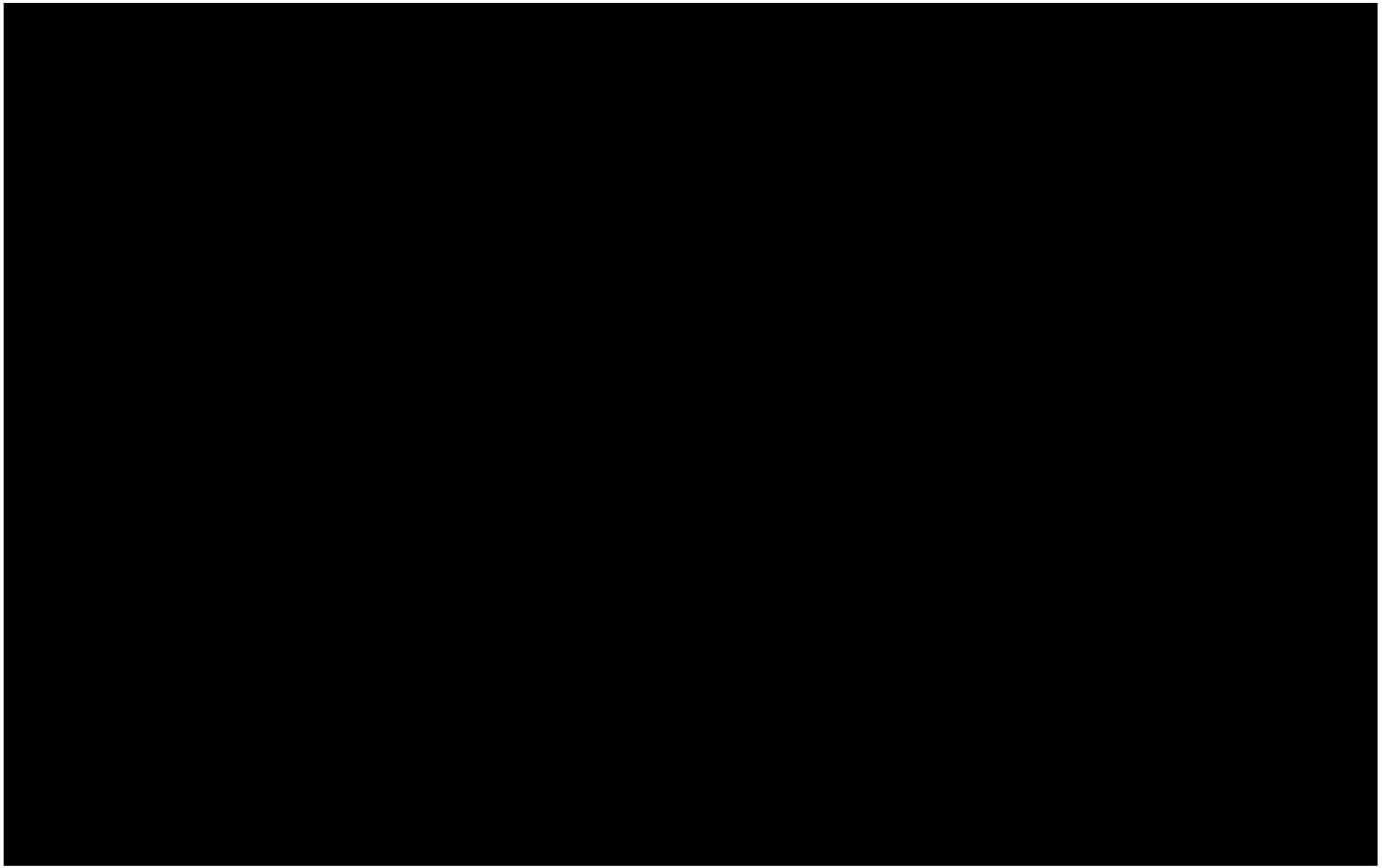


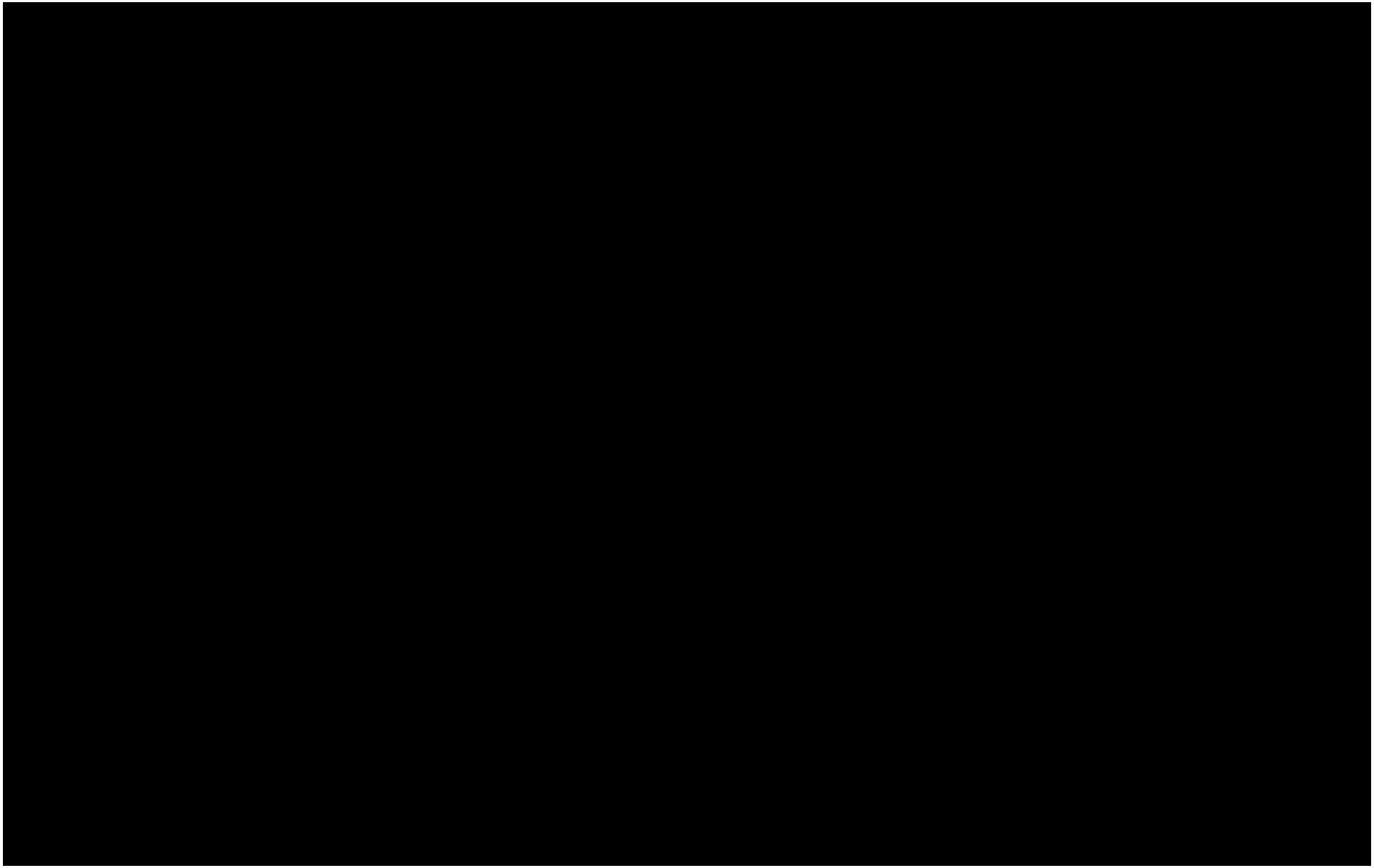
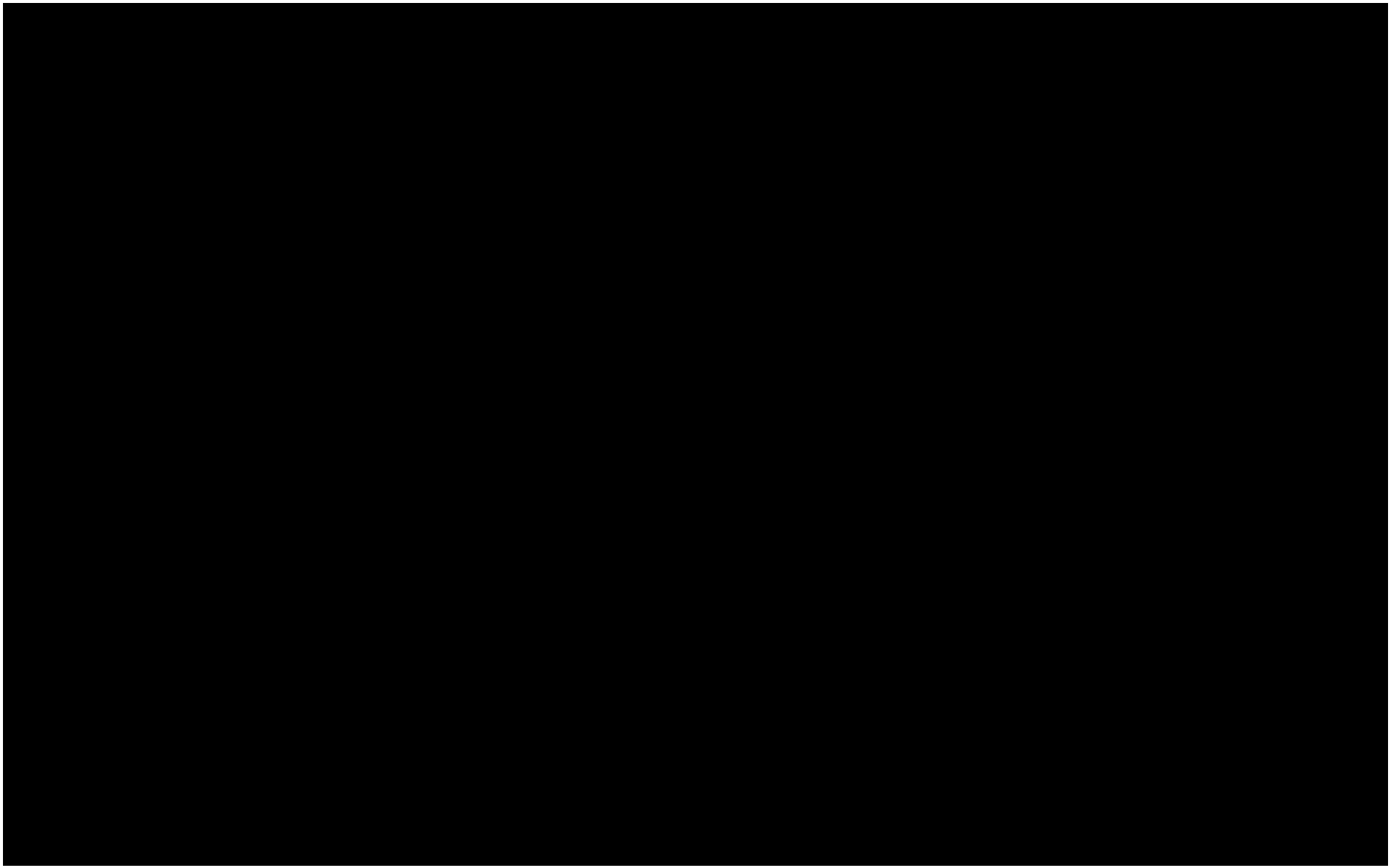
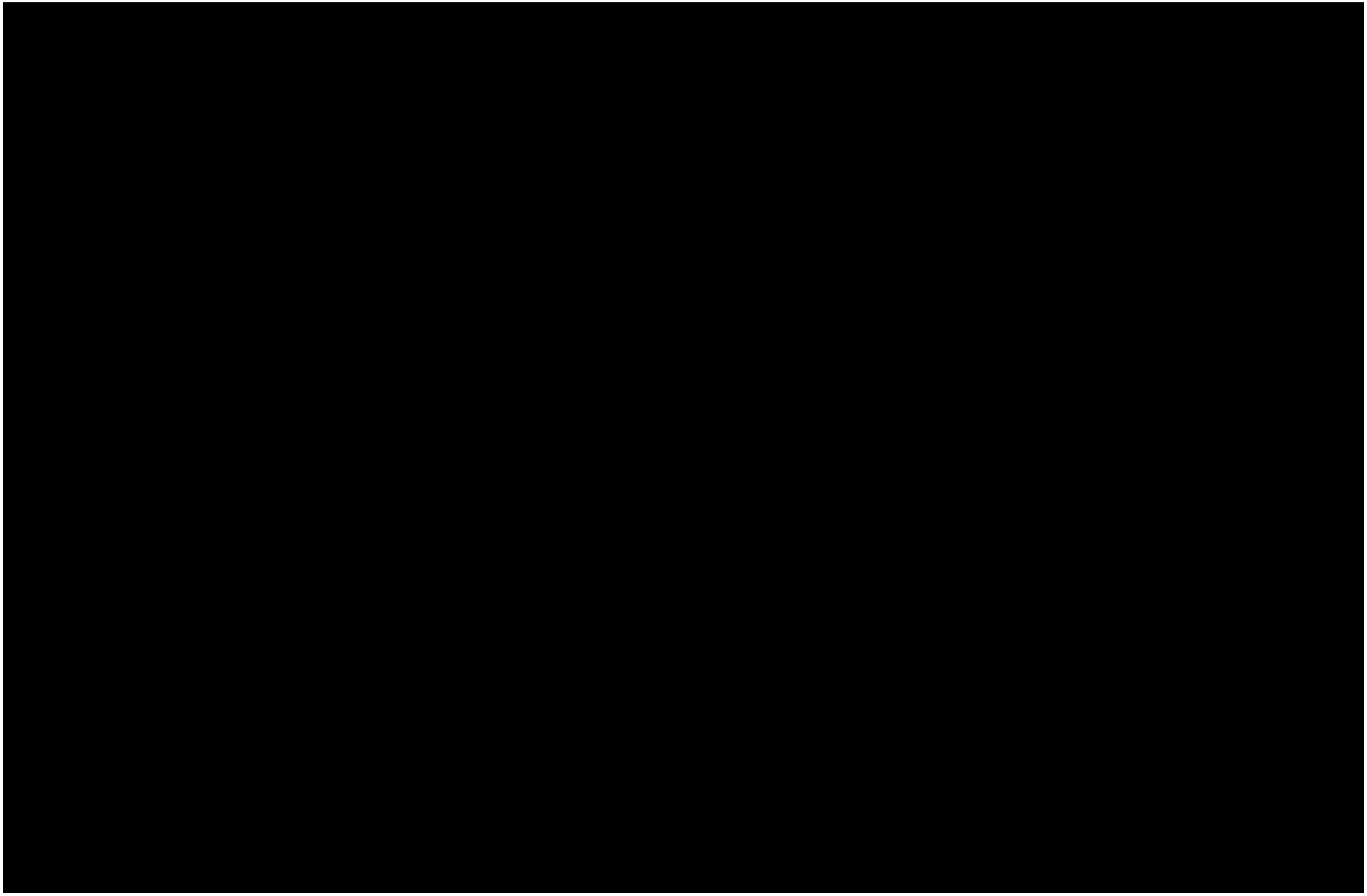
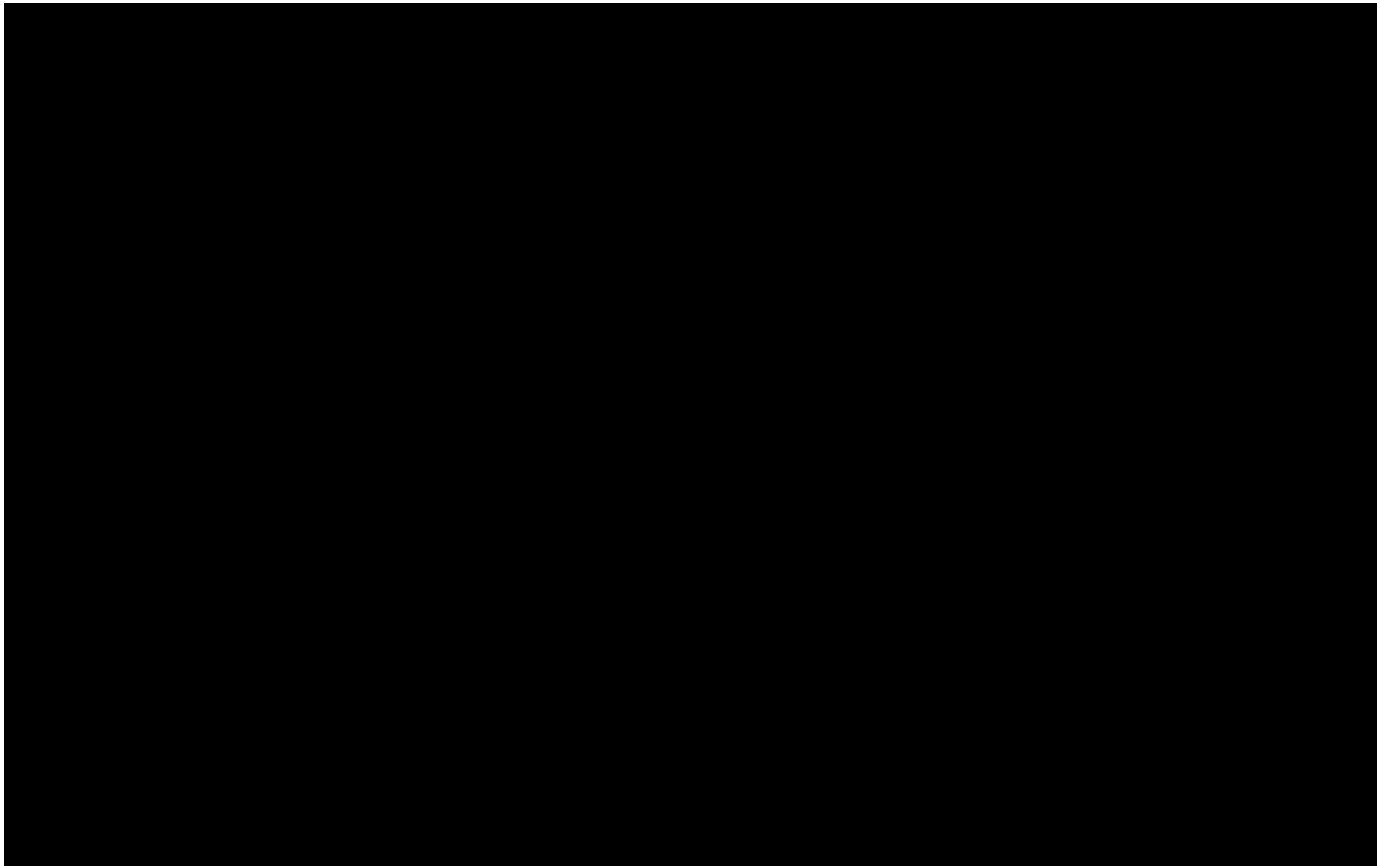


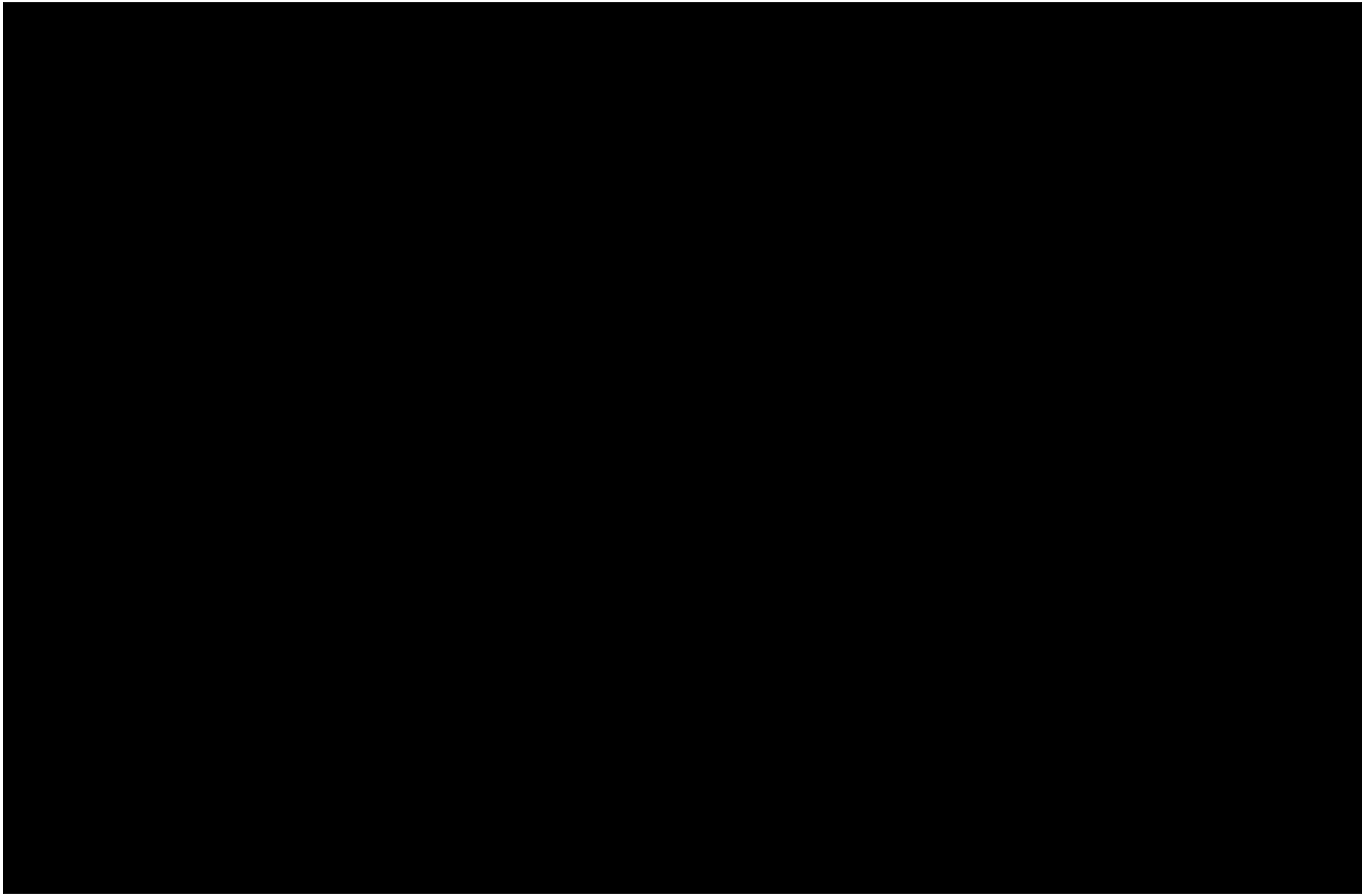
Table 1-3 Schedule of Visits and Procedures: Day 14 to Day 30/End-of-Study (Stage 2a)

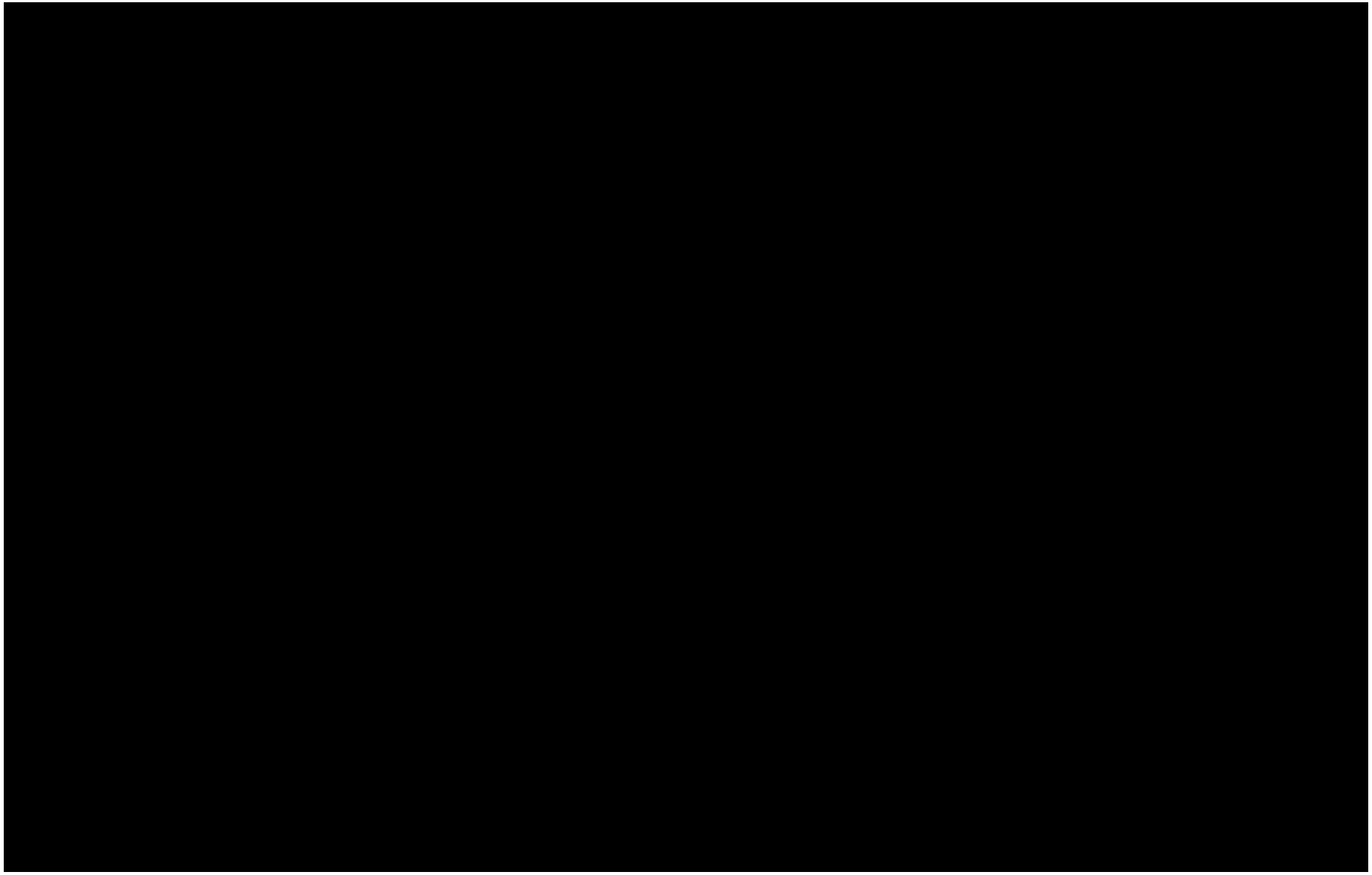


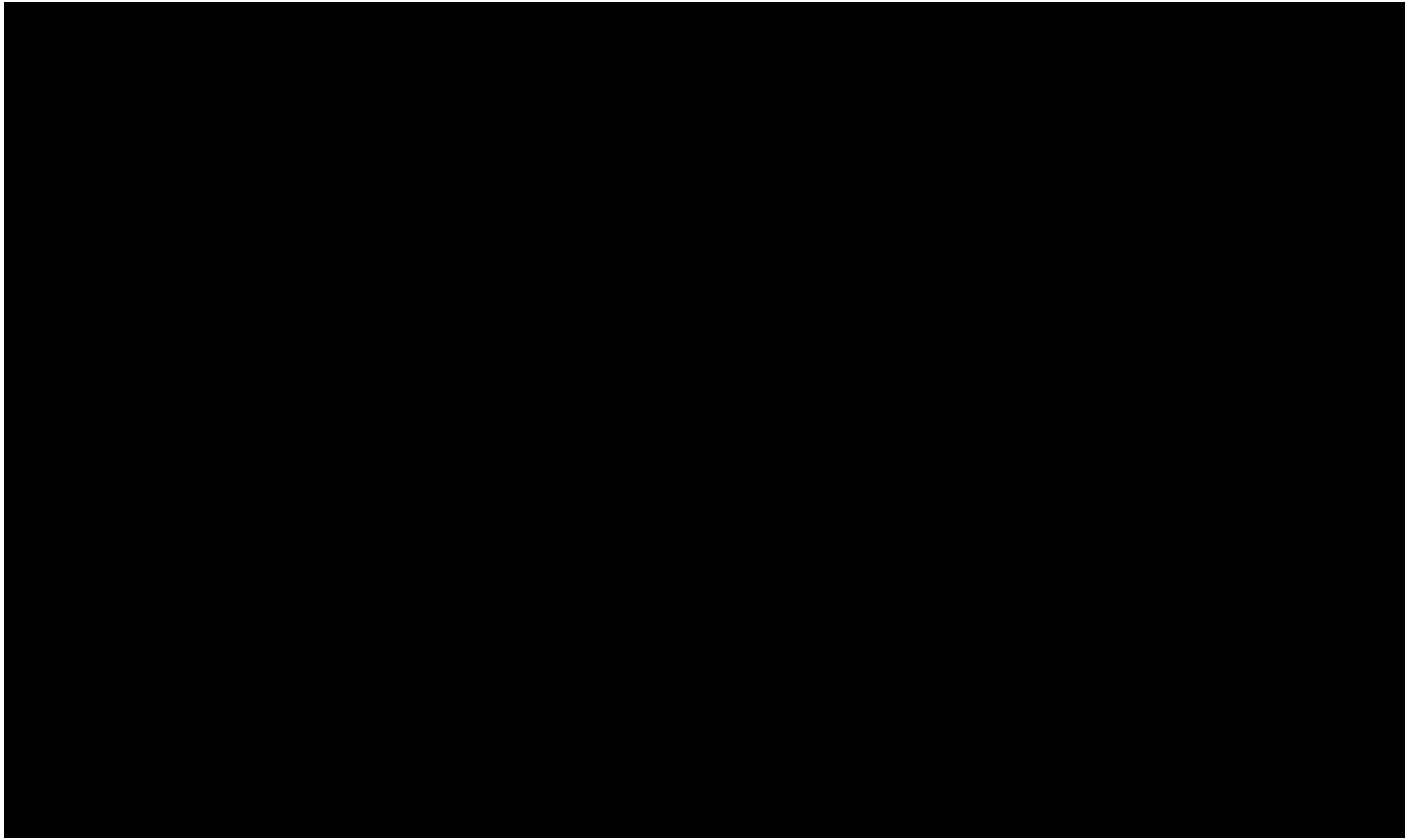


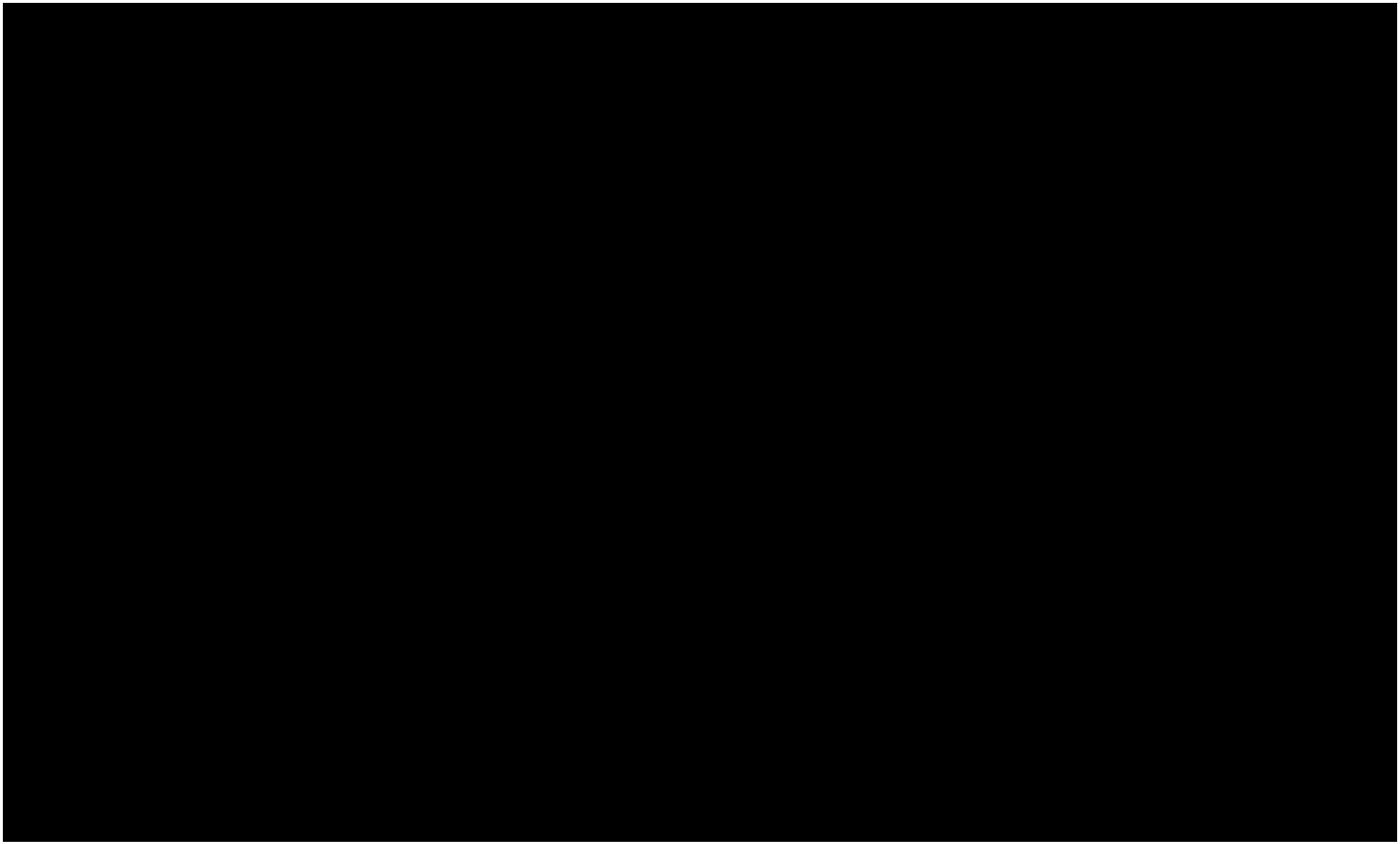


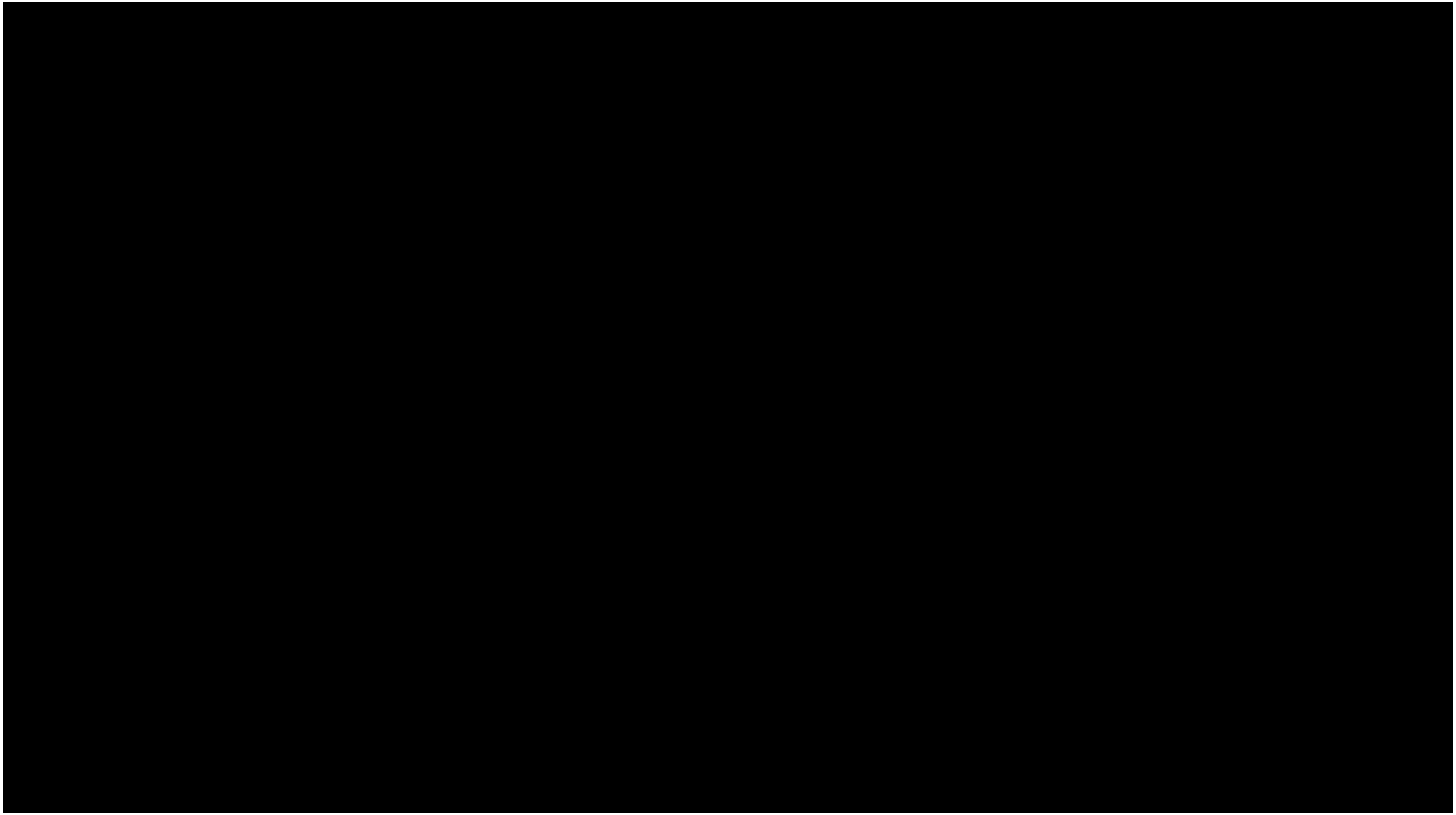
1.3.3. Schedule of Activities (SoA) – Stage 2b

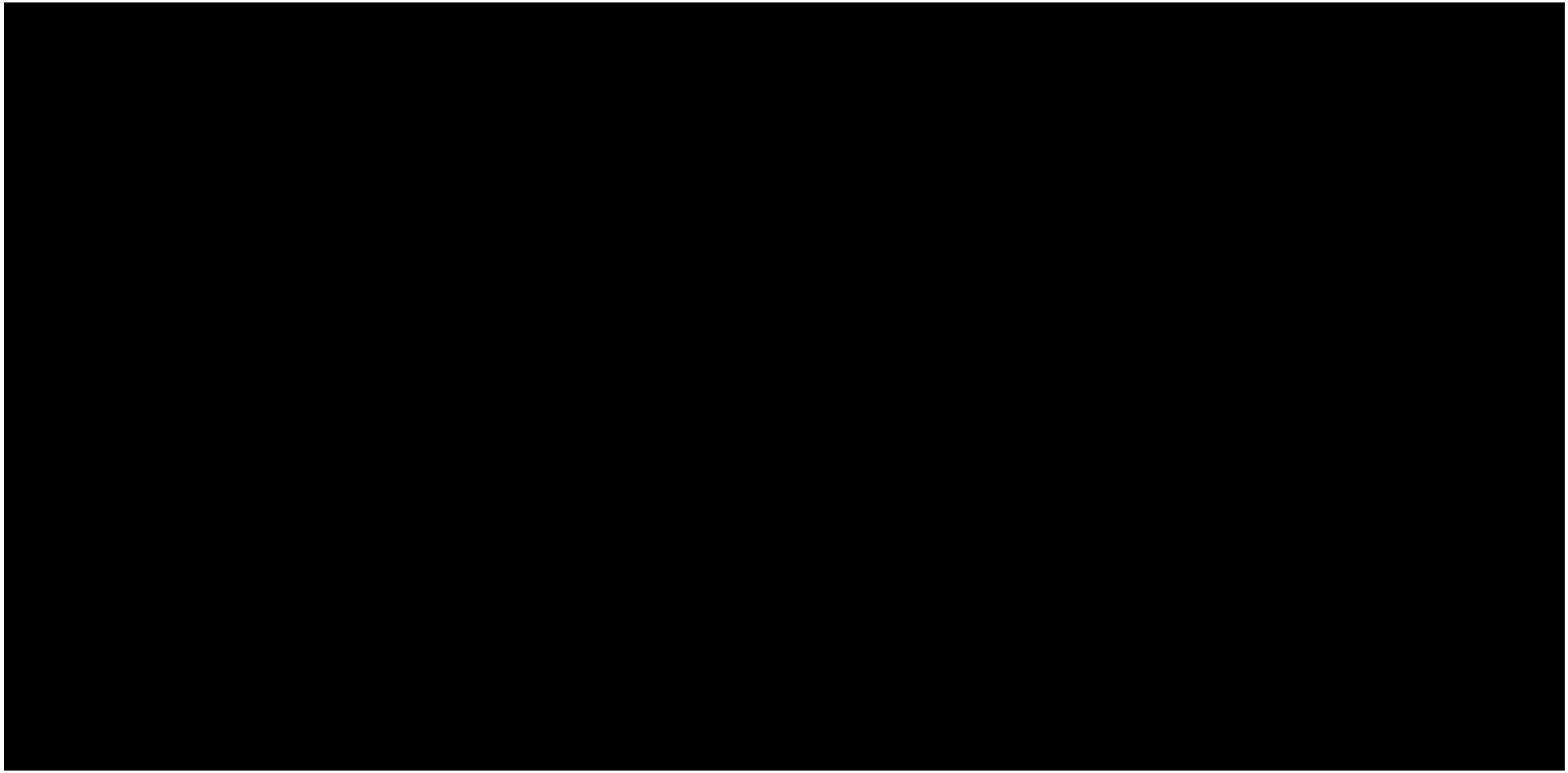


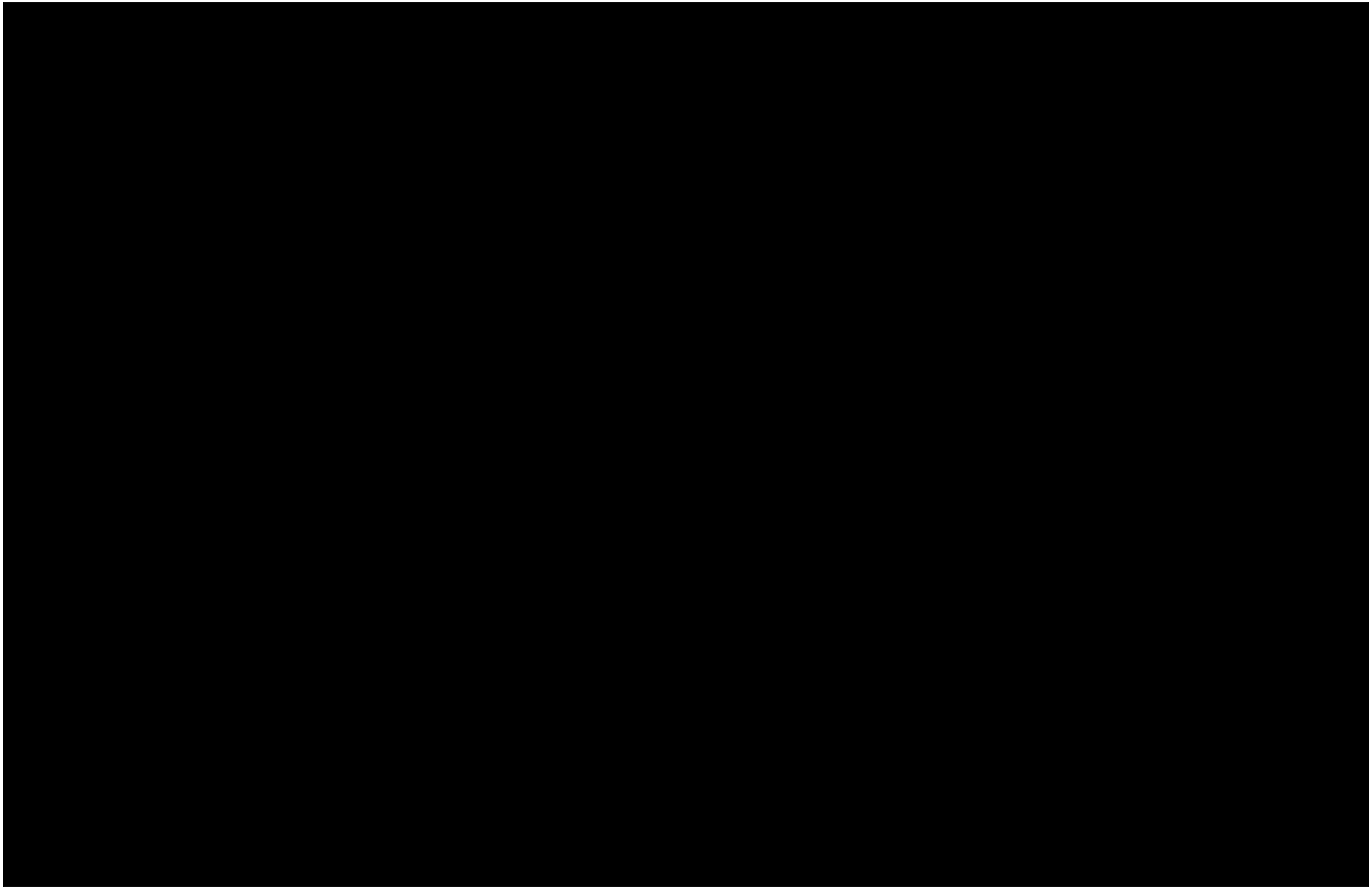




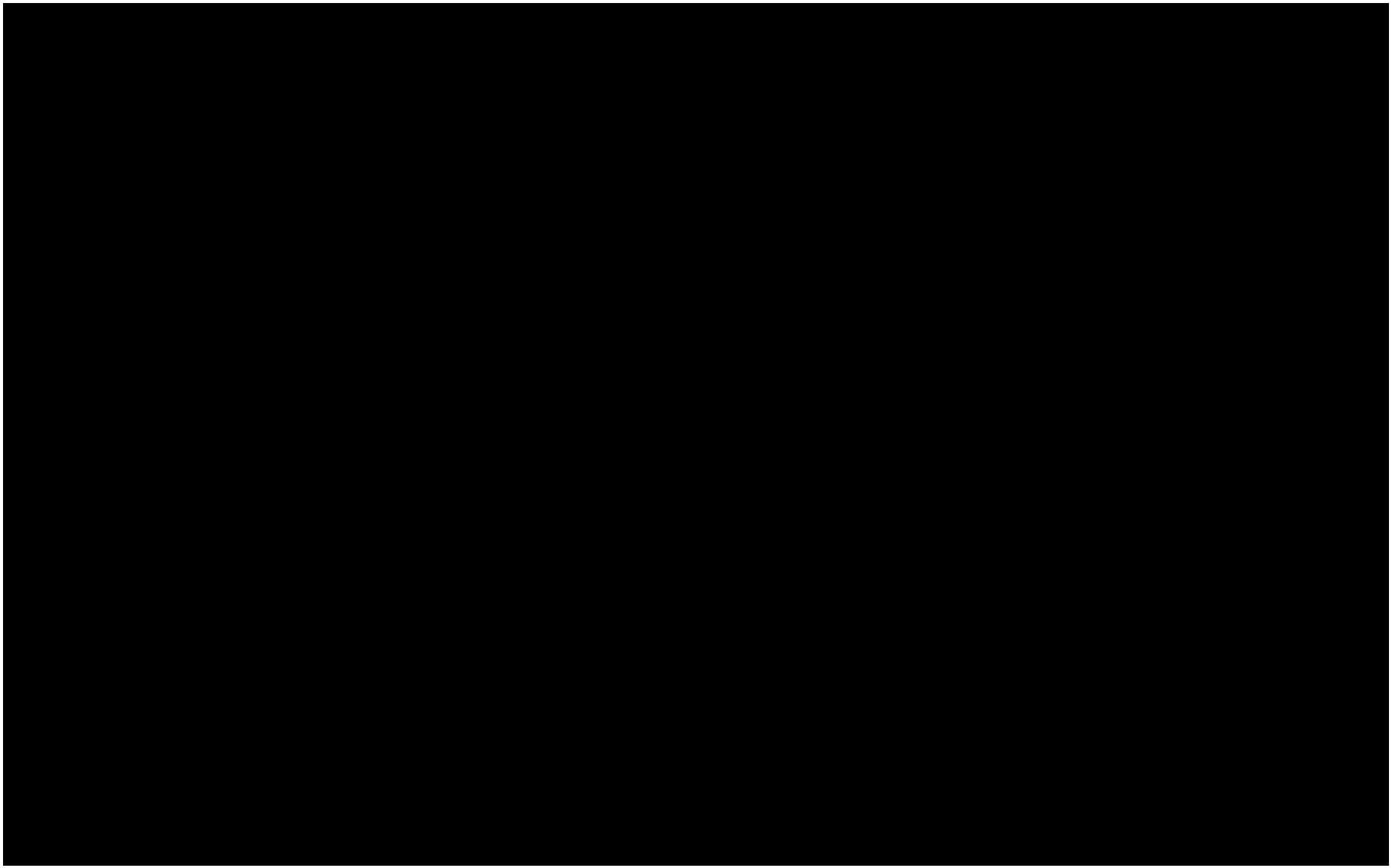


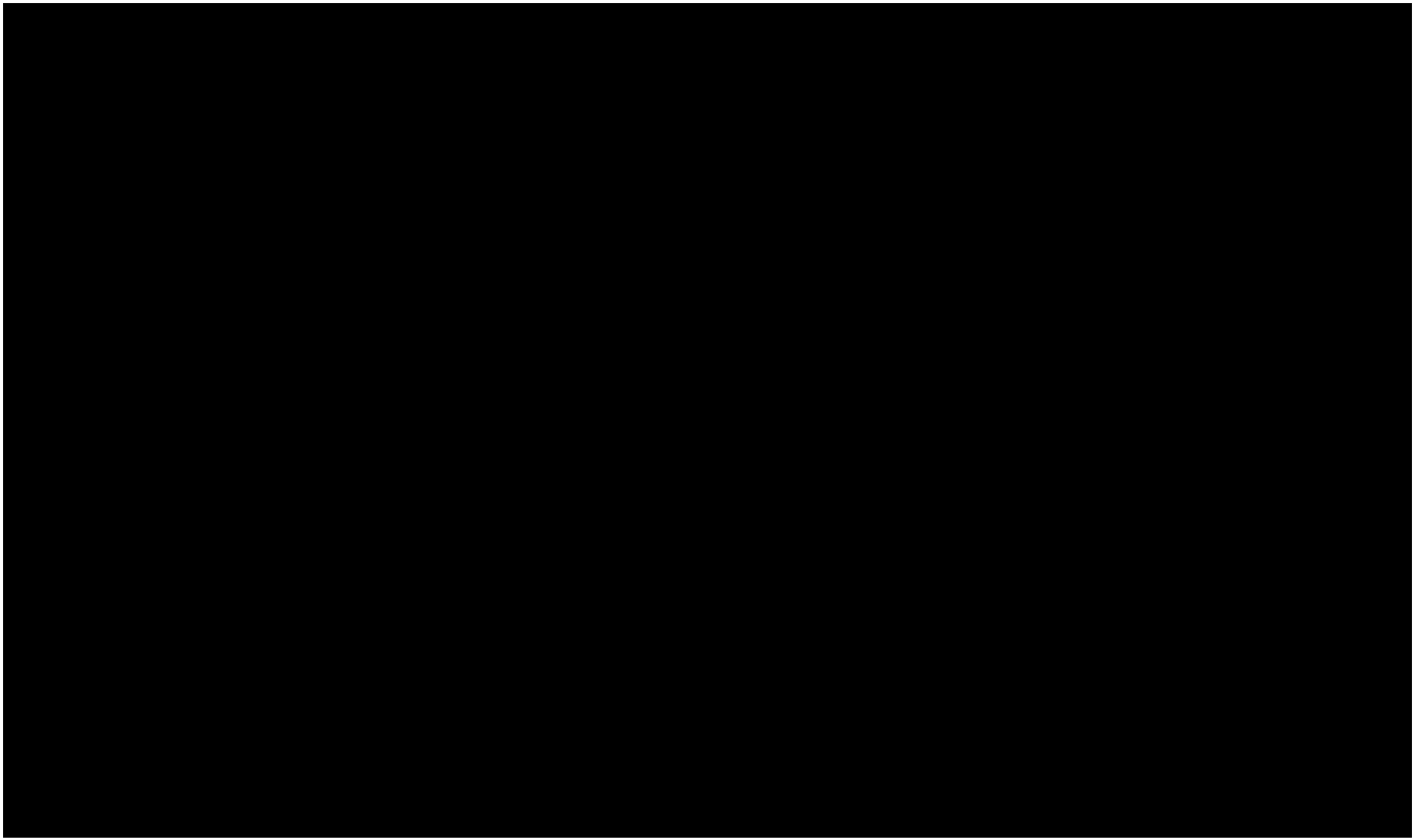






1.3.3.2. Stage 2b (Cohort 8)





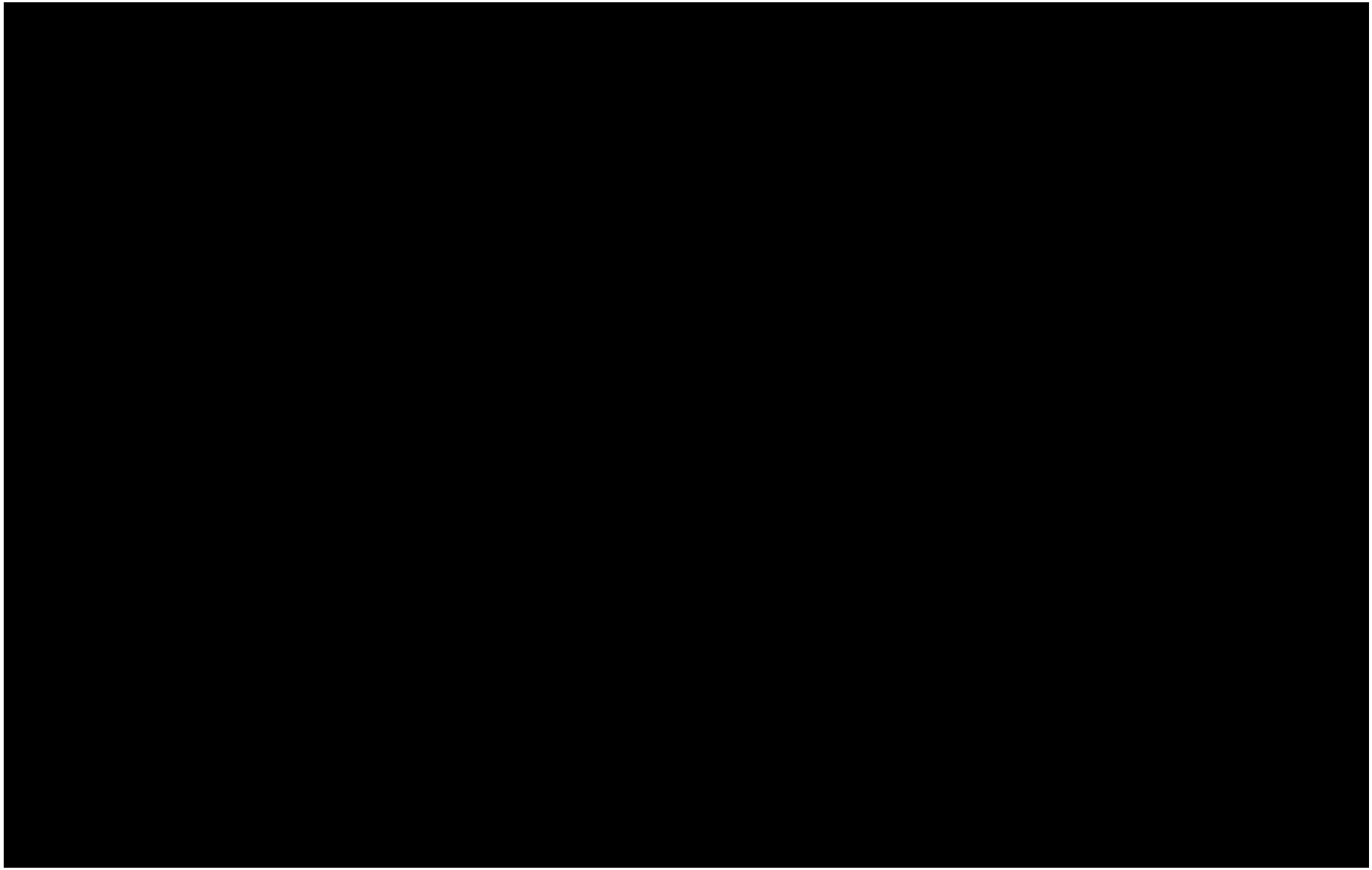
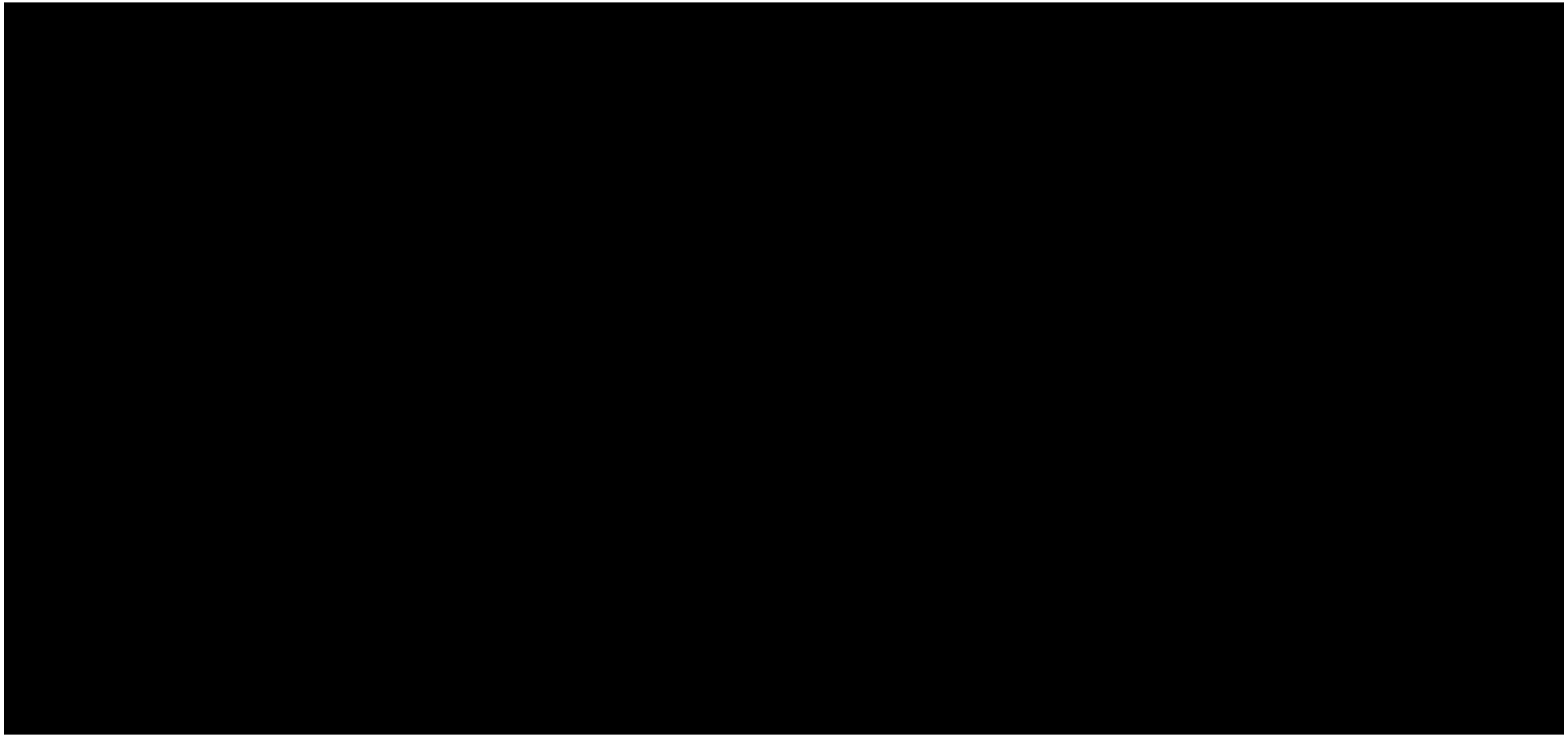
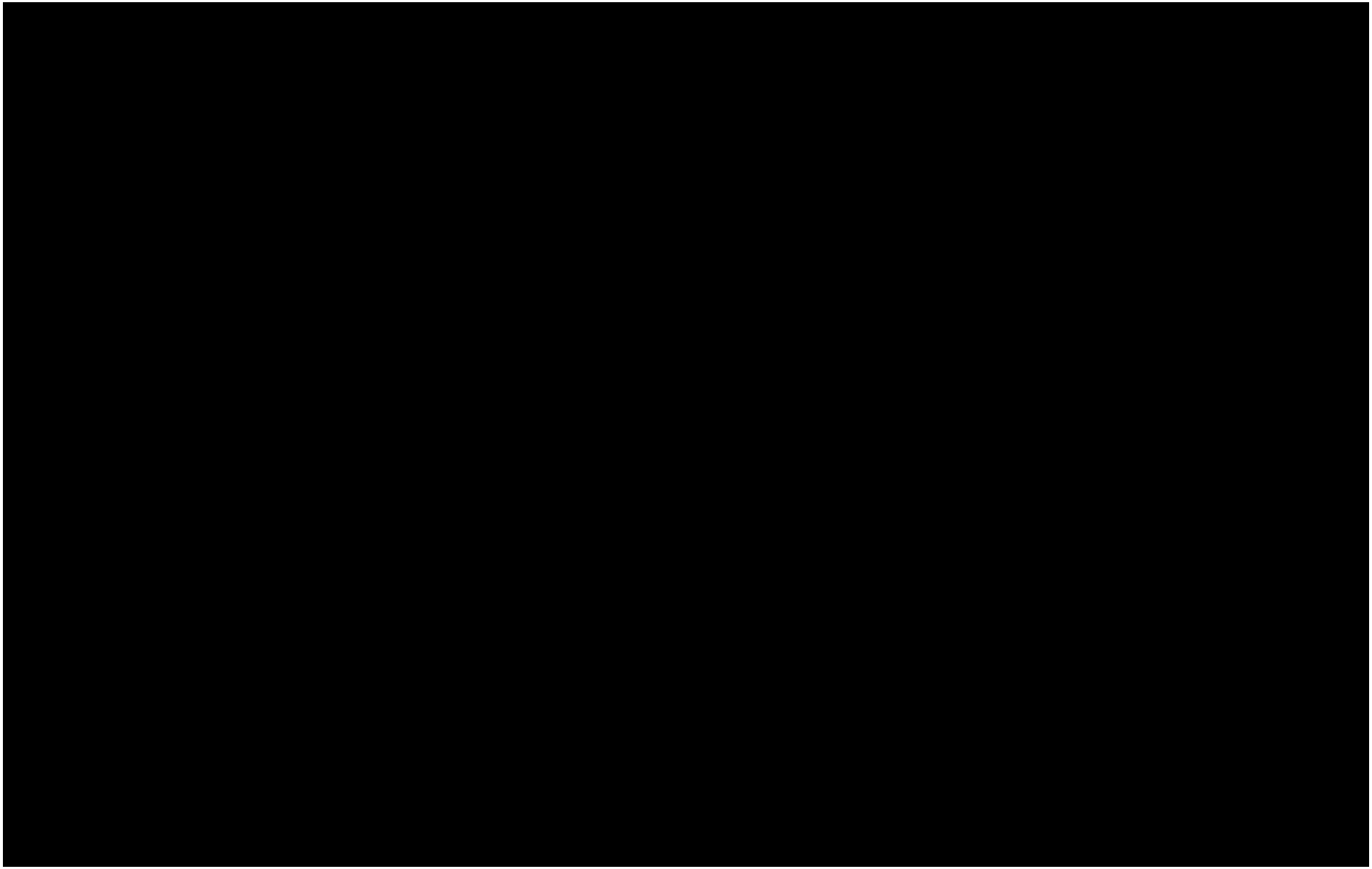


Table 1-7 Schedule of Visits and Procedures: Day 14 to Day 30/End-of-Study (Stage 2b; Cohort 8)





2. Introduction

Allergan is investigating AGN-241622 ophthalmic solution as a noninvasive, reversible, pharmacologic treatment for presbyopia, a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age.

2.1. Study Rationale

The objective of this study is to evaluate the safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 ophthalmic solution for the first time in human participants. Nonclinical studies have been completed and support the safe use of AGN-241622 ophthalmic solution in human eyes. AGN-241622 ophthalmic solution is expected to be safe in healthy participants as well as participants with presbyopia. Stage 1 of this study will evaluate safety, tolerability, pharmacokinetics, and the target receptor engagement of AGN-241622 after a single unilateral dose in healthy participants (Cohorts 1 to 3). Stage 2a will evaluate safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 ophthalmic solution after 14 days of dosing in participants with presbyopia (Cohorts 4 to 6). Stage 2b will evaluate safety, tolerability, and efficacy of AGN-241622 ophthalmic solution compared with an active comparator (pilocarpine HCl [redacted] 1.25% ophthalmic solution) after 14 days of dosing in participants with presbyopia in Cohort 7; and safety, tolerability, tear pharmacokinetics, and efficacy of AGN-241622 ophthalmic solution after 14 days of dosing in participants with presbyopia who wear contact lenses in Cohort 8. Together, the results from Stages 1 and 2 of this study will help characterize the safety, tolerability, pharmacokinetics, and efficacy profile of AGN-241622 and support the further development of AGN-241622 as a noninvasive, reversible, pharmacologic treatment for presbyopia.

2.2. Background

The impairment of near vision is common among older adults. In 2005, 1.044 billion people globally were estimated to have presbyopia, and prevalence is expected to increase to 1.782 billion by 2050 (Holden 2008). Both nonsurgical and surgical methods for the correction of presbyopia are available. Traditional nonsurgical methods of refractive correction for presbyopia include the use of dedicated reading spectacles, bifocal or varifocal spectacles, and monovision or multifocal contact lenses. A number of surgical techniques are also used for the treatment of presbyopia, which include monovision PRK or LASIK, conductive keratoplasty, intraocular lenses, and corneal inlays. However, for each of the existing technologies mentioned above, visual quality is reduced at 1 or more viewing distances, and each comes with its own unique safety risks and associated complications. For example, bifocals and progressive lenses (e.g., reading glasses, contacts) produce optical aberrations and can increase the risk of falls (Johnson 2007; Lord 2002). Multifocal optics reduce image quality uniformly at all viewing distances. For surgical technologies, surgical risks, the need for repositioning and explantation, or regression of effect have limited their widespread adoption (Moshirfar 2017; Ruiz 2009; Tomita 2015). Thus, there remains a need for a noninvasive, reversible, pharmacologic treatment for presbyopia.

2.2.1. AGN-241622

2.2.1.1. Pharmacology

AGN-241622 is a potent, pan-agonist at the α2-adrenergic receptor that has been shown to elicit a miotic response in a rabbit nonclinical model for presbyopia. In vitro, binding and enzyme uptake assays indicate that AGN-241622 has greater selectivity for α2- relative to α1-adrenergic receptors. Ocular administration of AGN-241622 to Dutch-belted rabbits reduced pupil diameter in a dose-dependent manner, with effects maintained for ≥ 6 hours. Several α2-adrenergic receptor agonists such as brimonidine and oxymetazoline have been shown to be safe and effective in humans and are currently marketed for indications such as glaucoma and rosacea, respectively. AGN-241622 is expected to exert its effect of improving near vision by inhibiting the iris dilator muscle, thereby decreasing pupil size and increasing depth of focus. Studies have shown that reducing pupil size can improve near vision and reading speed, and that α-adrenergic receptor agonists such as brimonidine are able to reduce pupil size in humans after topical ocular instillation. For AGN-241622, nonclinical studies have shown that it has the potential to be more potent, have a longer lasting effect, and because of its low melanin binding properties, have a more consistent effect than brimonidine across patients with varying iris colors.

2.2.1.2. Pharmacokinetics

The ocular exposure of [redacted] AGN-241622 ophthalmic solutions was characterized in rabbits. Following single topical ocular administration of [redacted] AGN-241622 ophthalmic solution to rabbit eyes, AGN-241622 concentrations in ocular tissues, including cornea, conjunctiva, and tears, were sustained above the anticipated efficacious levels [redacted] for at least 6 hours postdose (Report 1421-P01-057).

Systemic exposure after topical ocular administration was evaluated in rabbits and dogs. In rabbits, systemic exposure after daily topical ocular administration of [redacted] AGN-241622 for 28 days was minimal. The increases in mean C_{max} and AUC values were generally less than dose proportional. Exposure to AGN-241622 was higher following multiple doses; however, concentration values were generally below the limit of quantitation (BLQ) by 24 hours postdose on Days 1 and 28, suggesting no accumulation of AGN-241622 in plasma after multiple doses in rabbits. In dogs, systemic exposure after daily topical ocular administration of [redacted] for 28 days was also minimal. Exposure increased with the increase in dose level from [redacted] and the increases in mean C_{max} and AUC_{0-t} values were generally dose proportional. No accumulation of AGN-241622 was observed after multiple doses in dogs. No gender differences in systemic exposure were observed in rabbits or dogs.

2.2.1.3. Toxicology

Ocular and systemic toxicity of AGN-241622 was evaluated in rats, rabbits, and dogs. In the GLP-compliant rat toxicology study, male and female Sprague Dawley rats received daily dorsal subcutaneous injections of [redacted] mg/kg/day for 28 days. Marked reduced body weight growth and low food consumption were observed in animals administered ≥ [redacted] mg/kg/day. However, tolerance to these effects gradually developed during the dosing phase, with robust recovery during the 2-week recovery phase. Consequently, the body weight and food consumption effects were considered nonadverse. However, due to the large difference in body

weight during the dosing phase, the dose of [redacted]/kg/day was considered minimally tolerated. Effects noted in clinical observations, functional observational battery, and clinical and anatomical pathology were related to expected pharmacology of an α2-adrenergic receptor agonist, were reversible, and were considered nonadverse. For these reasons, the NOAEL for this study was [redacted]/kg/day and this dose has a [redacted] margin of safety over the predicted human exposure at the proposed starting clinical dose.

Respiratory function was assessed in male Sprague Dawley rats administered a single subcutaneous dose of [redacted] mg/kg AGN-241622. All dose levels of AGN-241622 lowered respiration rate (as much as -17%) and minute volume (as much as -26%), consistent with the expected pharmacologic activity of an α2-adrenergic receptor agonist, with the primary effects occurring between approximately 1 and 3.5 hours postdose. The changes were not considered adverse and did not display strict dose dependency. However, because the effects observed in this study were present at all doses, they will still be monitored closely in this clinical study. The NOAEL for this study was the top dose of [redacted] mg/kg, providing a [redacted] margin of safety over the predicted human exposure at the proposed starting clinical dose.

In the GLP-compliant dog toxicology study, male and female beagles were administered [redacted] AGN-241622 once daily to the left eye via topical instillation for 28 days, followed by a 2-week recovery phase. AGN-241622 was tolerated up to [redacted] mg/left eye/day). AGN-241622-related findings at this dose level were generally limited to vomitus, thin appearance (1 animal), pupil constriction or dilation, red palpebral conjunctiva, and ocular discharge. AGN-241622-related clinical observations for animals administered [redacted] included adverse body weight loss, thin appearance, and inappetence, which ultimately required sacrifice for 2 females. Due to the mild severity of findings and the lack of impact on the health and well-being of animals administered [redacted] AGN-241622, effects at this dose were considered nonadverse. Therefore, the NOAEL for this study was [redacted] AGN-241622 ([redacted] mg/left eye/day), and this dose has a 34-fold margin of safety over the predicted human exposure at the proposed starting clinical dose.

In the GLP-compliant safety pharmacology study in dogs, 4 male beagles were topically administered [redacted] of AGN-241622 as a single drop (approximate dose volume of 35 µL/drop) to the left eye in a Latin-square dosing design on Days 1, 5, 9, and 13, with cardiovascular telemetry data recorded. AGN-241622 had no effect on mortality, clinical observations, body weight, body temperature, or activity at any dose level. No qualitative ECG abnormalities were noted. A dose of [redacted] increased PR interval (up to 13 msec; +12%), but this finding was likely secondary to lower heart rate values observed with a similar time course, consistent with the expected pharmacology of an α2-adrenergic receptor agonist. QT interval also lengthened as a result of lower heart rate, but no test article related effect on heart rate corrected QTc interval was noted. QRS duration was unaffected by AGN-241622. A dose of [redacted] caused increased diastolic arterial pressure by up to 10 mm Hg (+13%), and decreased arterial pulse pressure, by as much as -14 mm Hg (-21%), was noted at all dose levels. Cardiac contractility, as assessed by left ventricular dP/dtmax values, was decreased by as much as [redacted] Hg/sec (-25%) following administration of [redacted] No changes in systolic, mean arterial, or left ventricular end diastolic pressures were attributed to AGN-241622. Furthermore, no effects were observed at the lowest dose of [redacted] except for a minimal and transient decrease (up to 6%) in arterial pulse pressure. The NOAEL for this study was the top

dose of [redacted] once daily, providing a 79-fold margin of safety over the predicted human exposure at the proposed starting clinical dose.

In the GLP-compliant rabbit toxicology study, male and female New Zealand white rabbits were administered [redacted] AGN-241622 once daily to the left eye via topical instillation at an approximate dose volume of [redacted] dose for 28 days, followed by a 2-week recovery phase. AGN-241622-related clinical observations included urogenital swelling and pupil constriction in left (dosed) eyes of animals administered [redacted] AGN-241622 and pupil dilation in left (dosed) eyes of animals administered [redacted] AGN-241622. These effects were transient and exhibited evidence of reversibility during the recovery phase. Due to the mild severity of findings and the lack of impact on the health and wellbeing of animals administered [redacted] AGN-241622, effects for this dose were considered nonadverse. Therefore, the NOAEL for this study was [redacted] AGN-241622 [redacted] mg/left eye/day), and this dose has a [redacted] margin of safety over the predicted human exposure at the proposed starting clinical dose.

Overall, ocular administration of AGN-241622 at relevant clinical concentrations is well tolerated and did not result in adverse changes. Observed systemic effects of AGN-241622 are known pharmacologic effects of α2-receptor agonists that are transient and reversible, and will be monitored in this study.

More detailed information regarding nonclinical findings, chemistry, and pharmacology of AGN-241622 is provided in the AGN-241622 investigator's brochure.

2.2.2. Pilocarpine HCl [redacted]

2.2.2.1. Pharmacology

Pilocarpine HCl is a muscarinic receptor agonist that mimics the actions of the parasympathetic neurotransmitter, acetylcholine, on smooth muscle. This causes two effects that enhance near vision: 1) constriction of the iris sphincter muscle, resulting in pupil constriction (miosis), and 2) contraction of the ciliary muscle, resulting in central lens steepening and lens accommodation (focusing from distance to near) (García-Lázaro 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 1975).

2.2.2.2. Clinical Studies and Postmarket Experience

Pilocarpine HCl ophthalmic solutions are currently used for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension, management of acute-angle closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and induction of miosis (Pilocarpine HCl ophthalmic solution package insert 2011). Currently, the use of pilocarpine HCl ophthalmic solution is limited by the commonly experienced AE of temporal and periorbital headache (i.e., brow ache), which is believed to be due to the rapidity of the ciliary muscle contraction (Tsai 2009). However, Allergan has established an acceptable safety profile of [redacted] in 3 Phase 2 clinical studies (Studies 199201-007, 199201-009, 199201-010, and IND 122483) [redacted] As a result, discontinuation rates for all Phase 2 clinical studies

were generally low and safety parameters were not clinically significant between participants who received [redacted] compared with participants who received vehicle or a combination therapy. The majority of AEs reported in any treatment group were mild to moderate in intensity.

Efficacy measures for the Phase 2 clinical studies included mesopic uncorrected near visual acuity line and letter improvement. Of the various concentrations of [redacted] evaluated, near vision was most improved compared with vehicle under mesopic and photopic conditions at the 1.0% and 1.5% pilocarpine HCl concentrations, respectively. Pilocarpine HCl [redacted]) 1.25% has been selected for further development for presbyopia in Phase 3 and is also the dose selected as an active comparator in this study.

More detailed information regarding clinical safety findings, clinical efficacy findings, chemistry, and pharmacology is provided in the pilocarpine HCl investigator's brochure.

2.3. Benefit/Risk Assessment

Based on the pharmacology of the 2 interventions (AGN-241622 and pilocarpine HCl [redacted] 1.25%) and the nonclinical data, it is reasonable to expect that either or both may reduce pupil diameter after topical ocular administration in both healthy participants and participants with presbyopia, and potentially improve near vision in participants with presbyopia. Clinical data generated for pilocarpine HCl ([redacted]) 1.25% in participants with presbyopia supports this hypothesis. While there are no clinical data on AGN-241622 ophthalmic solution to date, topical ocular administration of similar compounds in the same class have resulted in reduced pupil size and improved near vision in humans with presbyopia.

Based on existing toxicology data, no risks of particular severity or seriousness are anticipated with topical ophthalmic administration of AGN-241622 or pilocarpine HCl [redacted] 1.25%.

In the most recent clinical experience with pilocarpine HCl ophthalmic solution, pilocarpine HCl was dosed topically with oxymetazoline (Oxy) in different dose combinations and TEAEs were reported by 28.6% (8/28) of participants in the vehicle group, 40.0% (12/30) of participants in the Oxy 0.0125%/pilocarpine (Pilo) 0.5% OU group, 50.0% (15/30) of participants in the Oxy 0.05%/Pilo 1.0% OU group, 46.9% (15/32) of participants in the Oxy 0.125%/Pilo 1.5% OU group, and 32.3% (10/31) of participants in the Oxy 0.125%/Pilo 1.5% nondominant (ND) group. The majority of AEs were ocular, mild in intensity, and related to treatment. The most frequently reported TEAEs were headache, instillation site pain, and vision blurred. All TEAEs were deemed by the investigator to be mild or moderate in intensity; none were reported as severe. No participant died or experienced a serious TEAE. Discontinuations due to AEs were reported by 1 participant (moderate headache) in the Oxy 0.125%/Pilo 1.5% OU group and 1 participant (mild heart rate increased and insomnia) in the Oxy 0.125%/Pilo 1.5% ND group. No clinically meaningful findings emerged from assessments of mesopic, high contrast uncorrected distance visual acuity, vital signs, macroscopic hyperemia assessment, temporal and supraorbital headaches, or IOP. One participant in the Oxy 0.125%/Pilo 1.5% OU group and 1 participant in the Oxy 0.125%/Pilo 1.5% ND group had clinically significant slit lamp biomicroscopy findings (conjunctival hemorrhage, eyelid edema, and conjunctival hyperemia). No other slit lamp biomicroscopy findings occurred. Finally, the study intervention tolerability

and drop comfort assessments indicated that the majority of participants in all treatment groups found the study intervention to be tolerable.

There is no clinical experience with AGN-241622. The dose escalation design, coupled with DMC review of safety data in between cohorts, is expected to minimize risk to participants in the study. In addition, the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AGN-241622 and pilocarpine HCl ([redacted]) 1.25% may be found in the respective investigator's brochures.

3. Objectives and Measures

	Objectives	Measures
Stage 1	Primary • To evaluate the safety and tolerability of AGN-241622 administered once, unilaterally in healthy participants	• AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy
	Secondary • To evaluate the systemic and local pharmacokinetics of AGN-241622 administered once unilaterally in healthy participants • To evaluate the target receptor engagement of AGN-241622 as compared with vehicle administered once, unilaterally in healthy participants	• Plasma and tear concentrations and PK parameters of AGN-241622, including but not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, CL/F (plasma only), and V_z/F (plasma only) • Pupil diameter measurement (mesopic)
Stage 2a	Primary • To evaluate the safety and tolerability of AGN-241622 after repeat bilateral administration in participants with presbyopia	• AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy • Contrast sensitivity • Photopic and mesopic high contrast CDVA binocularly • Manifest refraction (mesopic and photopic) • Dilated funduscopic examination
	Secondary • To evaluate the systemic and local pharmacokinetics of AGN-241622 after repeat bilateral administration in participants with presbyopia	• Plasma and tear concentrations and PK parameters of AGN-241622, including but not limited to: $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, CL/F (plasma only), and V_z/F (plasma only)

	Objectives	Measures
Stage 2a (Continued)	• To evaluate efficacy of AGN-241622 compared with vehicle after repeat bilateral administration in participants with presbyopia	• Mesopic and photopic high contrast, binocular and monocular DCNVA • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO Questionnaires (NVPTQ, PICQ, Single-item PGIC, Single-item PGIS) • Bulbar conjunctival hyperemia
Stage 2b	• To evaluate safety, tolerability, and efficacy of AGN-241622 compared with pilocarpine HCl [redacted] 1.25% after repeat bilateral administration in participants with presbyopia in Cohort 7	Safety and Tolerability: • AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy • Contrast sensitivity • Photopic and mesopic high contrast CDVA binocularly • Manifest refraction (mesopic and photopic) • Dilated funduscopic examination Efficacy: • Mesopic and photopic high contrast, binocular and monocular DCNVA • Mesopic and photopic high contrast, binocular and monocular DCIVA • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO Questionnaires (NVPTQ, e-NVPTQ [iPhone/iPod], PICQ, Single-item PGIC, Single-item PGIS) • Bulbar conjunctival hyperemia

Objectives	Measures
• To evaluate safety, tolerability, tear pharmacokinetics, and efficacy of AGN-241622 after repeat bilateral administration in participants with presbyopia who wear contact lenses in Cohort 8	Safety and Tolerability: • AEs • Vital signs • 12-lead ECG • Clinical laboratory assessments • Study intervention tolerability and drop comfort assessments • IOP • Slit lamp biomicroscopy • Contrast sensitivity • Photopic and mesopic high contrast CDVA binocularly • Manifest refraction (mesopic and photopic) • Dilated funduscopic examination Tear Pharmacokinetics: • Tear concentrations and PK parameters of AGN-241622, including but not limited to: $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$ Efficacy: • Mesopic and photopic high contrast, binocular and monocular DCNVA • Mesopic and photopic high contrast, binocular and monocular DCIVA • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO Questionnaires (NVPTQ, e-NVPTQ [iPhone/iPod], PICQ, Single-item PGIC, Single-item PGIS) • Bulbar conjunctival hyperemia

4. Study Design

4.1. Overall Design

This is a multicenter, randomized, double-masked (except Cohort 7), Phase 1/2 study in healthy participants and participants with presbyopia. This study will be conducted in 3 stages (Stage 1, Stage 2a, and Stage 2b). In Stage 1, healthy participants will be randomized to participate in single-ascending dose cohorts (Cohorts 1 to 3) to evaluate safety, tolerability, pharmacokinetics, and target engagement of AGN-241622. In each cohort in Stage 1, approximately 12 participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle. Participants randomized to receive active intervention will be administered a single drop of AGN-241622 at dose strengths ranging from [redacted] in the left eye. Each participant will be admitted to the study center on the evening before dosing (Day -1). Participants will receive their single dose in the morning of Day 1 and, after a full day of assessments, stay overnight and continue further safety and PK assessments on the next day (EOS Visit). After each cohort is complete, an independent DMC will review unmasked safety and plasma PK data, along with target engagement and efficacy data if necessary (and applicable), to recommend if it is acceptable to proceed to the next planned cohort. The DMC may also recommend modifying the proposed dose strength (e.g., de-escalate to a lower dose strength), repeat the current dose strength, modify the cohort size, or stop the study. In addition, the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort. Once Cohort 2 of Stage 1 is complete, in addition to making a recommendation on whether to initiate the final cohort of Stage 1 (Cohort 3), the DMC will also make a recommendation on whether to start Stage 2 (Cohort 4) in parallel.

In Stage 2, participants with presbyopia will be selected to participate in the study. Stage 2 will be further divided into Stages 2a (Cohorts 4 to 6) and 2b (Cohorts 7 and 8). Cohorts 4 to 6 (Stage 2a) will be multiple ascending dose cohorts in which participants will be randomized to receive either AGN-241622 at dose strengths ranging from [redacted] or vehicle once daily in both eyes for 14 days. In each cohort in Stage 2a, approximately 12 participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle in order to evaluate safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 (Figure 1-1). As in Stage 1, the DMC may recommend modifying the proposed dose strength (e.g., de-escalate to a lower dose strength), repeat the current dose strength, modify the cohort size, or stop the study. After Cohort 6 has completed, the DMC will also recommend the dose strength to be tested in Stage 2b.

Cohort 7 is a single-masked, active comparator cohort in which approximately 60 participants with presbyopia will be randomized in a 1:1 ratio to receive either pilocarpine HCl [redacted] 1.25% ophthalmic solution or AGN-241622 ophthalmic solution administered at the dose strength recommended by the DMC once daily in both eyes for 14 days. Safety, tolerability, and efficacy of AGN-241622 compared with pilocarpine HCl ([redacted]) 1.25% will be assessed after repeat bilateral topical ocular administration. Cohort 8 is an exploratory cohort in which approximately 12 participants with presbyopia who wear contact lenses will be randomized in a 3:1 ratio to receive either AGN-241622 administered at the dose strength recommended by the DMC or vehicle once daily in both eyes for 14 days. Safety, tolerability, tear pharmacokinetics, and efficacy of AGN-241622 administered at the dose strength

recommended by the DMC compared with vehicle will be assessed after repeat bilateral administration.

In all cohorts of Stage 2, participants will receive their first dose in the clinic on Day 1, and stay in the clinic for safety, PK (except Cohort 7), and efficacy evaluations for approximately 10 hours postdose. For Stage 2a, participants will then return for dosing once daily and assessments from Day 2 to Day 7. For Stage 2b, on Days 3 and 7, participants will return to the clinic for dosing and assessments; on Days 1 and 3, participants will also receive multidose bottles for single unit of use for at-home dosing on Days 2, 4, 5, and 6. For participants in both Stages 2a and 2b, they will then receive multidose bottles on Day 7 for single unit of use for at-home dosing from Days 8 to 13 and will return to the clinic on Day 14 for dosing as well as safety, tolerability, PK (except Cohort 7), and efficacy evaluations for approximately 10 hours postdose. On Day 30, participants will return for a safety follow-up and EOS Visit.

The study will be conducted in the United States.

Participants who prematurely discontinue from the study may be replaced at the discretion of the sponsor.

Study interventions by study stage and cohort are summarized in Table 4-1.

Table 4-1 Study Interventions by Study Stage and Cohort

Study Interventions by Study Stage and Cohort			
Stage 1	**Single Ascending Doses in Healthy Participants**		
	Cohort 1 AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle	Cohort 2 AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle	Cohort 3 AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle
Stage 2a	**Multiple Ascending Dose in Participants with Presbyopia**		
	Cohort 4 AGN-241622 [redacted] QD × 14 days both eyes 9 Active; 3 Vehicle	Cohort 5 AGN-241622 [redacted] QD × 14 days both eyes 9 Active; 3 Vehicle	Cohort 6 AGN-241622 [redacted] QD × 14 days both eyes 9 Active; 3 Vehicle
Stage 2b	**Multiple-Dose Exploratory Cohorts in Participants with Presbyopia**		
	Cohort 7 AGN-241622 (dose strength TBD) versus pilocarpine HCl [redacted] 1.25% QD × 14 days both eyes 60 (30 per treatment arm)	Cohort 8 AGN-241622 (dose strength TBD) (in participants who wear contact lenses) QD × 14 days both eyes 9 Active; 3 Vehicle	

4.1.1. Clinical Hypotheses

Stage 1

- A single dose of AGN-241622 ophthalmic solution dosed unilaterally will demonstrate an acceptable safety and tolerability profile in healthy participants.
- A single dose of AGN-241622 ophthalmic solution dosed unilaterally will result in systemic exposure in healthy participants with sufficient safety margins to nonclinical safety studies.
- A single dose of AGN-241622 ophthalmic solution dosed unilaterally will demonstrate a decrease in pupil diameter in healthy participants as compared with vehicle.

Stage 2a

- Repeat doses of AGN-241622 ophthalmic solution dosed bilaterally for 14 days will demonstrate an acceptable safety and tolerability profile in participants with presbyopia.
- Repeat doses of AGN-241622 ophthalmic solution dosed bilaterally for 14 days will result in systemic exposure in participants with presbyopia with sufficient safety margins (see Table 4-2).
- Repeat doses of AGN-241622 ophthalmic solution dosed bilaterally for 14 days will demonstrate a numeric improvement in DCNVA compared with vehicle in participants with presbyopia.

Stage 2b

- Repeat doses of AGN-241622 ophthalmic solution dosed bilaterally for 14 days will demonstrate an acceptable safety and tolerability profile in participants with presbyopia (Cohort 7) and participants with presbyopia wearing contact lenses (Cohort 8).
- Repeat doses of AGN-241622 ophthalmic solution dosed bilaterally for 14 days will demonstrate similar improvement in DCNVA compared with pilocarpine HCl [redacted] 1.25% in participants with presbyopia (Cohort 7).

4.2. Scientific Rationale for Study Design

This study is designed as 3 distinct stages to ensure that the safety and tolerability of AGN-241622 are achieved in healthy participants in Stage 1 before participants with presbyopia are exposed and assessed for safety, tolerability, and efficacy in Stages 2a and 2b. Although α2-adrenergic receptor agonists are a class of compounds with extensive clinical experience, AGN-241622 is a new chemical entity, and the study design of this Phase 1/2 study will assess its ocular and systemic safety in an adaptive fashion. Healthy participants and participants with presbyopia will be subject to various ocular assessments such as IOP measurements, biomicroscopy, and fundus examination, while systemically they will be assessed with 12-lead ECG, vital signs measurements, and clinical laboratory assessments to ensure participant safety. In addition, each cohort will not proceed until the preceding cohort(s) has been: 1) reviewed and deemed safe by a DMC, and 2) a positive response is received from the FDA. Vehicle has been selected as a comparator for Stages 1 and 2a and 2b (Cohort 8 only) of this study as there are

currently no approved pharmacologic therapies for presbyopia. [redacted], also known as pilocarpine HCl [redacted] ophthalmic solution, is selected as an active comparator in Stage 2b Cohort 7 because it is actively under development by Allergan for the same indication of presbyopia. Testing both [redacted] and AGN-241622 in the same study will provide an exploratory head-to-head comparison of the safety and efficacy of both compounds.

4.3. Justification for Dose

In nonclinical testing, AGN-241622 was shown to be highly potent and maximally efficacious in a rabbit presbyopia model at dose strengths ranging from [redacted] Because this rabbit model has been shown to be highly translatable to humans, the same dose strengths are expected to be efficacious in participants with presbyopia. Safety margins generated from GLP-compliant nonclinical studies support the safe starting dose strength of [redacted] in humans (Table 4-2). Dose escalation of AGN-241622 in this study will be based on clinical safety and PK exposure observed during conduct of the study.

Table 4-2 Safety Margins of Starting Clinical Dose to Nonclinical NOAELs

Species	NOAEL	Systemic Safety Margin[a] (Animal/Human)	
		C_{max} (ng/mL)	AUC (ng*hr/mL)
28-day Systemic Rat Study	[redacted]	2080	1611
28-day Ocular Rabbit Study		113	123
28-day Ocular Dog Study		34	43
Rat Respiratory Safety Pharmacology Study	[redacted]	7210	6392
Dog Cardiovascular Safety Pharmacology Study		79	244

[a] Safety margins are based on comparisons of animal exposure at the NOAEL dose to predicted human exposure

* Predicted human exposure was extrapolated from the exposure in dogs in the 28-day ocular dog study based on differences in body surface area between dogs and humans.

Pilocarpine HCl [redacted] ophthalmic solution 1%, 2%, and 4% is a marketed product for the reduction of elevated IOP. Through modeling and evaluation of the Phase 2 results (Studies 199201-007, 199201-009, and 199201-010), Allergan has determined the optimal dose of [redacted] to be 1.25% for the treatment of presbyopia and this dose is being evaluated in Phase 3 studies.

4.4. End of Study Definition

The end of study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all study visits.

5. Study Population

Stage 1:

Healthy participants, 40 to 65 years of age

Stages 2a and 2b:

Participants with presbyopia, 40 to 65 years of age

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1. Stage 1

1.	**Age**
1.01	Participant must be 40 to 65 years of age inclusive, at the time of signing the informed consent
2.	**Type of Participant**
2.01	Healthy Participant
2.02	[redacted]
2.03	Be nonsmoking and a nonuser of nicotine-containing products (never smoked or used nicotine-containing products or have not smoked or used nicotine-containing products within the previous 1 year)
[redacted]	
3.	**Sex**
3.01	Male or female
4.	**Informed Consent**
4.01	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
4.02	Written informed consent from the participant has been obtained prior to any study-related procedures
4.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable

[redacted]

6.	**Other**
6.01	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

5.1.2. Stages 2a and 2b

1.	**Age**
1.01	Participant must be 40 to 65 years of age inclusive, at the time of signing the informed consent
2.	**Type of Participant and Presbyopia Characteristics**
2.01	In good general health at the Screening Visit, as determined by the investigator
2.02	[redacted]
2.03	Be nonsmoking and a nonuser of nicotine-containing products (never smoked or used nicotine-containing products or have not smoked or used nicotine-containing products within the previous 1 year)
2.04	[redacted]

[redacted]

3.	**Sex**
3.01	Male or female
4.	**Informed Consent**
4.01	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
4.02	Written informed consent from the participant has been obtained prior to any study-related procedures
4.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable
5.	[redacted]
[redacted]	[redacted]
	[redacted]

5.02	Female participants must be willing to minimize the risk of inducing pregnancy throughout the study, up through 30 days after the last dose of study intervention (refer to Appendix 7, Section 10.7)
	A female participant is eligible if at least 1 of the following conditions applies: a. She is not a female of childbearing potential as defined in Appendix 7, Section 10.7 OR b. She is a female of childbearing potential who agrees to follow the contraceptive guidance in Appendix 7, Section 10.7 throughout the study In addition, all female participants of childbearing potential must test negative for pregnancy at Screening (serum test) and on Day 1 (urine test).
6.	**Other**
6.01	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Stage 1

[redacted]

1.04	History of alcohol or other substance abuse within the previous 5 years

[redacted]

3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study

[redacted]

5.01	Females who are pregnant, nursing, or planning a pregnancy during the study. Female or males who are of childbearing potential and do not agree to use highly effective contraception during the study (refer to Appendix 7, Section 10.7)
5.02	The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study

5.2.2. Stages 2a and 2b

[redacted]

1.04	History of alcohol or other substance abuse within the previous 5 years

[redacted]

3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study

[redacted]

[redacted]

5.01	Females who are pregnant, nursing, or planning a pregnancy during the study. Female or males who are of childbearing potential and do not agree to use highly effective contraception during the study (refer to Appendix 7, Section 10.7)

[redacted]

5.3. Lifestyle Considerations

5.3.1. Habitual Distance Corrections (Stages 2a and 2b only)

Participants who wear bifocal or multifocal spectacles or contact lenses will be provided with a pair of monofocal spectacles or contact lenses (only for Cohort 8) with the same or improved distance correction (20/32 or better) as their new habitual correction. Participants whose distance habitual corrections are worse than 20/32 will also be provided with a pair of new spectacles or contact lenses (only Cohort 8) with improved distance correction (20/32 or better). Participants are required to wear the newly provided spectacles or contact lenses for at least 7 days before Day 1 and during the study, and no bifocal or multifocal or old habitual correction lenses should be used. Only monofocal spectacles or contact lenses (only for Cohort 8) can be worn between study visits and on the study visit days. Reading glasses are allowed between study visits when needed.

5.3.2. Meals and Dietary Restrictions

Participants must not take dietary supplements or other foods or beverages that may affect various drug-metabolizing enzymes and transporters (e.g., grapefruit, grapefruit juice, grapefruit-containing beverages) during the study.

5.3.3. Caffeine, Alcohol, and Tobacco

1. Participants must refrain from ingesting caffeine during the 30 minutes preceding vital signs measurements.
2. Participants must abstain from drinking alcohol from 72 hours before administration of study intervention and during the study treatment period (defined as Day 1 postdosing through Day 2 during Stage 1; defined as Day 1 postdosing through Day 14 during Stage 2).
3. Participants are nonsmoking and nonusers of nicotine-containing products (never smoked or used nicotine-containing products or have not smoked or used nicotine-containing products within the previous 1 year) at screening. Use of tobacco/nicotine products is also not allowed from the Screening Visit until after the final follow-up visit.

5.3.4. Activity

Participants must not engage in strenuous activity at any time during the study intervention period. Participants may participate in light recreational activities during the study (e.g., watching television, reading, jogging).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 6-1 Study Interventions

Study Intervention Name	AGN-241622	[redacted]	Vehicle
Type	Drug	Drug	Drug
Drug Substance	AGN-241622-2A	Pilocarpine HCl [redacted] 1.25%	Not applicable
Dosage Formulation	Topical eye drop	Topical eye drop	Topical eye drop
Identity of Formulation and Unit Dose Strengths	AGN-241622 ophthalmic solutions [redacted]	Pilocarpine HCl [redacted]) 1.25% ophthalmic solution [redacted]	AGN-241622 ophthalmic solution (placebo) [redacted])
Dosage Levels	1 drop in left eye once (Stage 1) 1 drop in each eye once daily for 14 days (Stage 2a/Stage 2b)	1 drop in each eye once daily for 14 days (Cohort 7) (Stage 2b)	1 drop in left eye once (Stage 1) 1 drop in each eye once daily for 14 days (Stage 2a/Stage2b [Cohort 8])
Route of Administration	Topical eye drop	Topical eye drop	Topical eye drop
Use	Experimental	Active-comparator	Placebo-comparator
IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in sterile, 10-mL bottles. Each bottle will be labeled as required per country requirement. An investigational caution label will appear on the individual bottle and the outer carton: Use as directed Keep Out of Reach of Children Caution: New Drug--Limited by Federal Law to	Study intervention will be provided in sterile, 5-mL bottles. Each bottle will be labeled as required per country requirement. An investigational caution label will appear on the individual bottle and the outer carton: Use as directed Keep Out of Reach of Children Caution: New Drug--Limited by Federal Law to	Study intervention will be provided in sterile, 10-mL bottles. Each bottle will be labeled as required per country requirement. An investigational caution label will appear on the individual bottle and the outer carton: Use as directed Keep Out of Reach of Children Caution: New Drug--Limited by Federal Law to

[redacted]

The study intervention will be supplied in LDPE eye dropper bottles each containing 5 or 3.5 mL of study intervention and labeled with the protocol number, kit number, volume, storage information, warning language (Caution: New Drug—Limited by Federal Law to Investigational Use. Keep Out of Reach of Children), and instructions to use as directed.

6.1.1. Instructions for Use and Administration

[redacted]

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention in the clinic (participants will administer study intervention themselves on days of at-home dosing). All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual or other specified location.
5. Participants will be instructed on the proper storage of study intervention and to keep it out of the reach of children at all times.

6.3. Measures to Minimize Bias: Randomization and Masking

All participants will be centrally assigned to study intervention using an IWRS. The cap of the number of participants can be recommended by the DMC for Cohort 7. Randomization and kit assignment will be conducted on Day 1. In Cohorts 1 to 6 and 8, participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle. In Cohort 7, participants will be assigned in a 1:1 ratio to receive pilocarpine HCl [redacted] 1.25% ophthalmic solution or AGN-241622 ophthalmic solution. Cohort 7 will be single masked, in which

participants will be masked for the study intervention assignment and site staff and the investigator will not discuss the study intervention assignment with the participants.

Before the study is initiated, login information and directions for the IWRS will be provided to each study center. Study intervention and vehicle will be dispensed at the study visits summarized in the SoA for Stages 1, 2a, and 2b (Sections 1.3.1, 1.3.2, and 1.3.3, respectively).

The identity of study intervention will be masked to the participants and study centers for Cohorts 1 to 6 and 8. The identity of study intervention will be masked to the participants only for Cohort 7. The IWRS will be programmed with mask-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unmasking of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unmasking is warranted, the investigator should make every effort to contact the sponsor prior to unmasking a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unmasked, the sponsor must be notified within 24 hours after breaking the mask. The date and reason that the mask was broken must be recorded in the source documentation.

At the end of each cohort or at ad hoc meetings, the DMC will review unmasked safety and plasma PK data, along with target engagement and efficacy data if necessary (and applicable), from each cohort and provide a recommendation on whether the study can proceed to the next cohort. In addition, the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort.

An internal independent review team (comprised of but not limited to, a medical safety physician, statistician, clinical pharmacologist, and a clinical representative) will make up the DMC for the study. The composition of the independent team will be documented in the DMC Charter, TMF, and clinical study report. The members of the independent team will be different from the study team members who manage and maintain the study conduct activities, including data collection, data clarification, analysis development, safety monitoring, study center monitoring and management.

6.4. Study Intervention Compliance

For the inpatient dosing during Stages 1 (Day 1), 2a (Days 1 to 7, and Day 14), and 2b (Days 1, 3, 7, and 14), participants will receive all doses under the direct supervision of study center personnel. Study intervention compliance will be assumed to be 100% when dosing has been recorded in the eCRF.

For home dosing during Stages 2a and 2b (Days 8 to 13), study intervention compliance will be monitored by counting the number of bottles dispensed and returned. Before dispensing new study intervention at each visit, study center personnel will make every effort to collect all unused study intervention and empty bottles.

The study center will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration for inpatient dosing.

6.5. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the participant's eCRF at each study visit along with the reason the medication is taken.

From the Screening Visit to the EOS Visit, site staff will question each participant specifically on the use of concomitant medications.

6.5.1. Prohibited Interventions

The decision to administer a prohibited medication/treatment will be made with the safety of the study participant as the primary consideration. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

For Stages 1 and 2a, use of any medication, other than the study intervention or medications administered to conduct study procedures is prohibited from the Screening Visit through study exit, except for those contraceptives listed in Table 10-2.

For Stage 2b, use of any ophthalmic medications, other than the study intervention or medications administered to conduct study procedures is prohibited from the Screening Visit through study exit.

6.5.2. Permitted Interventions

Use of the following systemic medications are permitted in Stage 2b, provided that the treatment regimen has remained stable for at least 1 month prior to Screening and is not anticipated to change during the duration of the study:

[redacted]

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of screening or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

Any medication taken during the study between the date of the first dose of study intervention and the date of the EOS Visit will be recorded in the eCRF as a concomitant medication; any medication started after the EOS Visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.6. Dose Modification

Dose modification is not applicable.

6.7. Intervention after the End of the Study

No intervention is planned following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

Reasons for discontinuation from the study intervention and/or the study may include the following:

- AE
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject
- Death
- Other

7.1. Discontinuation of Study Intervention

See the SoA (Sections 1.3.1, 1.3.2, and 1.3.3) for data to be collected at the time of early termination.

The DMC and FDA may recommend modifications to the protocol including discontinuation of study intervention upon review of safety data.

Study intervention may also be paused due to safety concerns at any time by the site investigator. The sponsor and DMC should be notified immediately if study intervention was paused.

7.1.1. Study Termination

The sponsor may stop the study (and/or the study center) for any reason with appropriate notification. The DMC and FDA may recommend study termination upon review of safety data.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- At the time of discontinuing from the study, if possible, an EOS Visit should be conducted, as shown in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3).

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, Section 10.1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Stage 1

No efficacy measures will be assessed in Stage 1. Pupil diameter (mesopic) will be assessed as a measure of target engagement.

Stages 2a and 2b

Efficacy assessments in Stages 2a and 2b are:

- Mesopic and photopic high contrast, binocular and monocular DCNVA (refer to Sections 1.3.2 and 1.3.3 for assessment timepoints)
- Mesopic and photopic high contrast, binocular and monocular DCIVA (only in Stage 2b; (refer to Section 1.3.3 for assessment timepoints)

Measurement: Visual acuity for near (40-cm), intermediate (66-cm) and distance (4-meter) targets will be measured in mesopic and photopic conditions. Mesopic condition is defined as lighting 3.2 to 3.5 candelas per square meter (cd/m^2; 10 to 11 lux) measured at the target. Photopic condition is defined as lighting $\geq$ 80 cd/m^2 (251 lux) measured at the target.

- Mesopic and photopic pupil diameter (distance and near) (refer to Sections 1.3.2 and 1.3.3 for assessment timepoints)
- Depth of focus (refer to Sections 1.3.2 and 1.3.3 for assessment timepoints)

Measurement: Depth of focus will be measured on each eye.

- Bulbar conjunctival hyperemia (refer to Sections 1.3.2 and 1.3.3 for assessment timepoints)

Measurements: Bulbar conjunctival hyperemia in each eye will be graded separately by the investigator using sponsor-provided reference photographs.

Assessment should be performed by the same evaluator whenever possible in the same facility. Illumination should be consistent throughout the study. **Note:** The bulbar conjunctival hyperemia assessment is a different assessment than the hyperemia scales described as part of the biomicroscopic examination (Appendix 8, Section 10.8).

- PRO Questionnaires (only in Stages 2a and 2b) (refer to Sections 1.3.2 and 1.3.3 for assessment timepoints)

Near Vision Presbyopia Task-based Questionnaire (NVPTQ): Comprised of 12 questions on 4 reading tasks (i.e., reading a paragraph from a book, reading excerpts from an article in a newspaper, reading a portion of a nutrition label, and reading a section from a restaurant menu).

Electronic Near Vision Presbyopia Task-based Questionnaire (e-NVPTQ) (iPhone/iPod version) (only in Stage 2b; refer to Section 1.3.3): Comprised of 5 questions on an electronic reading task (i.e., reading a text on iPhone or iPod)

Measurements (NVPTQ and e-NVPTQ):

- Participants will complete specific reading tasks under mesopic (for NVPTQ) and photopic (for e-NVPTQ) conditions without any near-vision correction.
- Participants will then answer 3 questions for each task (5 questions for e-NVPTQ), rating their vision-related reading ability and satisfaction with their vision-related reading ability.
- There is no explicit recall period used for the NVPTQ and e-NVPTQ; the intention is for participants to complete the questionnaire immediately after completing each task.

Presbyopia Impact and Coping Questionnaire (PICQ): Participants will answer 20 questions about the degree to which they were impacted by their difficulty seeing up close (e.g., found daily near vision tasks difficult, or experienced self-consciousness); or engaged in coping behaviors (e.g., changed the font size on electronic screens) during the previous 7 days.

Single-Item Patient Global Impression of Status (PGIS): Participants will answer a single question about their global impression of the status of their near-vision acuity in the past 7 days.

Single-Item Patient Global Impression of Change (PGIC): Participants will answer a single question about their global impression of change in their near-vision acuity.

Details are provided in the study procedure manual.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height (only at screening) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Physical examinations should be completed by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- Oral/axillary temperature, heart rate, respiration rate, and blood pressure will be assessed.
- Systolic and diastolic blood pressure and heart rate will be measured after participants have been at rest (seated) for at least 5 minutes in a quiet setting without distractions (e.g., television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure will be recorded in mm Hg and heart rate will be recorded in bpm.

8.2.3. Electrocardiograms

- Sites shall transmit all study-required ECGs obtained to the ECG vendor, unless otherwise specified in the study procedure manual.
- A standard 12-lead ECG that measures PR, QRS, QT, QTc, QTcB, and QTcF intervals will be performed in the supine position at the nominal times (relative to the dosing times) as outlined in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3).

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Sections 1.3.1, 1.3.2, and 1.3.3) for the timing and frequency.
- At screening, the investigator or sub-investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical safety physician.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2 must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded as an SAE or AE in the eCRF.
    - Urine dipstick kits may be used to conduct drugs-of-abuse screens and pregnancy tests and alcohol screen at the study center post-screening. Alternatively, a breathalyzer may be used for an alcohol screen.

8.2.5. Study Intervention Tolerability and Drop Comfort Assessments

The presence and severity of ocular symptoms will be elicited from the participant separately for their treated eye(s), as applicable. Symptoms including blurred vision, foreign body sensation, pain, burning/stinging, tearing, and itching will be classified using a 5-point grading scale with duration of symptoms immediately after the drop instillation of each dose of study intervention. If any other ocular symptoms are present, these will be captured.

Participants will be asked to rate the overall comfort of the eye drops using a 6-point scale (i.e., soothing, very comfortable, comfortable, uncomfortable, very uncomfortable, or intolerable) immediately after the drop instillation for the right and left eyes separately, as applicable. Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints. Details are outlined in Appendix 9, Section 10.9.

8.2.6. IOP

IOP should be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. Measurements will be taken using a Goldmann applanation tonometer affixed to a slit lamp with the participant seated. Both eyes will be tested, with the right eye preceding the left eye. Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints. Details are outlined in Appendix 11, Section 10.11.

8.2.7. Slit lamp Biomicroscopy

Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil, and sodium fluorescein corneal staining. Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints. Details are outlined in Appendix 8, Section 10.8.

8.2.8. Sodium Fluorescein Corneal Staining

Sodium fluorescein corneal staining assessments will be assessed and graded according to the Oxford Scale per Appendix 8, Section 10.8. Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints. Details are outlined in Appendix 8, Section 10.8.

8.2.9. Dilated Fundoscopic Examination

The fundus (indirect) ophthalmoscope examination assessments should be conducted through a dilated pupil. The examinations will include evaluation of the lens, vitreous, fundus, and optic nerve. The cup to disc ratio will be assessed. The investigator should note if the pupil dilated normally. Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints. Details are outlined in Appendix 10, Section 10.10.

8.2.10. Contrast Sensitivity (Stages 2a and 2b only)

Contrast sensitivity assessments will be conducted with participant's best distance correction, except for participants in Cohort 8, for which contrast sensitivity will be conducted with habitual distance correction. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details will be outlined in the study procedures manual.

8.2.11. Photopic and Mesopic High-contrast CDVA (Stages 2a and 2b only)

Photopic and mesopic high-contrast CDVA will be conducted with the participant's best distance correction, except for participants in Cohort 8, for which photopic and mesopic high-contrast CDVA will be conducted with the participant's habitual distance correction. The assessment is to be measured binocularly. Pupil diameter must be measured in each individual eye. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints.

For all lighting conditions, different charts must be used for the repeated visual acuity measures within the same day.

Details will be outlined in the study procedures manual.

8.2.12. Manifest Refraction (Stages 2a and 2b only)

Manifest refraction (distance and near, mesopic and photopic) will be performed according to standard clinical practice in both mesopic and photopic conditions. If a participant loses ≥ 1 line of CDVA or DCNVA compared with Hour 0 of the same study visit at Hour 1 after dosing, a manifest refraction should be repeated under the same lighting conditions.

Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details will be outlined in the study procedures manual.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3, Section 10.3.

AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and any other study-specific terms as relevant and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs from the signing of the ICF until EOS Visit will be collected at the timepoints specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3), and as observed or reported spontaneously by study participants.

All SAEs from the signing of the ICF until up to 30 days after last dosing will be collected at the timepoints specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3, Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that Legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a Legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate, according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female participants, and if indicated, female partners of male participants, will be collected from signing of the ICF and until the EOS.
- If a pregnancy is reported, the investigator should inform the sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7, Section 10.7.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.4. Treatment of Overdose

Treatment of overdose is not applicable.

8.5. Pharmacokinetics

Blood and tear samples for quantification of AGN-241622 in participant's plasma and tears will be collected from all enrolled participants in Cohorts 1 to 6, PK tear samples will be collected from enrolled participants in Cohort 8, and neither PK blood nor tear samples will be collected from enrolled participants in Cohort 7.

Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints.

8.5.1. Blood PK Sampling Procedure

- For Cohorts 1 to 6, a qualified phlebotomist will collect 5 mL of each participant's blood via an indwelling catheter or venipuncture from either arm into one 6 mL vacutainer tube containing K_2EDTA as an anticoagulant.

- Plasma samples of approximately 2.5 mL will be collected for measurement of plasma concentrations of AGN-241622 at each of the timepoints specified in the SoA from enrolled participants in Cohorts 1 to 6 (Sections 1.3.1 and 1.3.2).
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. PK blood samples to determine AGN-241622 concentrations should be drawn at the nominal times, relative to the dosing time, and the actual time of the blood draw must be recorded in the source documents and eCRFs. Samples must be taken within 5 minutes of the nominal times. Predose samples must be drawn within 15 minutes of the dosing time.
- Study center staff will record the atomic clock times of all blood draws for each participant and will label vacutainer and polypropylene tubes with a coded label that corresponds to the participant number and blood draw time. The central laboratory will supply the coded labels, vacutainers, and polypropylene tubes.
- Samples will be used to evaluate the pharmacokinetics of AGN-241622. Each plasma sample will be divided into 2 aliquots (1 each for primary and backup PK samples). Samples collected for analyses of AGN-241622 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unmask the study will not be reported to study centers or masked personnel until the study has been unmasked.

Bioanalytical representatives will be unmasked for PK sample bioanalysis during the conduct of the study. The unmasking of bioanalytical representatives is to be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

Blood Volume Collection

Within 30 minutes from the time of the blood draw, blood samples must be centrifuged at no less than 2000 g for 15 minutes at approximately 4°C. After centrifugation, the plasma samples will be harvested and aliquoted into 2 cryovials (1 primary and 1 backup). The samples should be placed on wet ice immediately after aliquoting and transferred to a –20°C freezer within 1 hour of processing to plasma.

Study center staff will send plasma samples to the bioanalytical laboratory or the central laboratory for storage after the last collection on Day 1 (for Stage 1) and after the last collection on Days 1 and 14 (for Stage 2). On the day of shipment, the sponsor and the specified laboratory will be notified by email as to the time and method of shipment.

8.5.2. Tear PK Sampling Procedure

Tear collections for ocular pharmacokinetics will be conducted at all sites in all participants (except for Cohort 7). Tear samples will be collected from left eye only. The same eye must be sampled throughout the study. Information regarding tear collection procedures will be provided in the study procedure manual.

8.5.3. PK Sample Bioanalysis

Concentrations of AGN-241622 in plasma and tear will be determined using validated or qualified liquid chromatography-tandem mass spectrometry methods.

8.6. Pharmacodynamics

In Stages 1, 2a, and 2b, pupil diameter will be assessed as a measure of pharmacodynamic activity in participants. Pupil diameter for near (40-cm) and distance (4-meter) targets will be measured with the pupillometer in mesopic conditions during Stage 1 and mesopic and photopic conditions in Stage 2.

Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study. Refer to Sections 1.3.1, 1.3.2, and 1.3.3 for assessment timepoints.

8.8.1. Determination of Iris Color

The investigator will assess iris color on a gross, macroscopic level using the following classification: brown, blue, grey, green, or hazel.

8.8.2. Determination of Dominant Eye (Stages 2a and 2b only)

Participants will be asked to extend their arms out in front of them at eye level, with their palms facing away, fingers together and facing upward. Participants will bring their hands together, forming a small window by overlapping their thumbs and overlapping their fingers. Participants will select a small object at least 10 feet in front of them and look at it with both eyes through the view window in their hands. While remaining focused on the object, participants will close the right eye and take note of whether the image remains visible. If the image remains visible, the left eye is the dominant eye. If the image is no longer visible, the right eye is the dominant eye. This will be confirmed by closing the left eye and taking note of whether the image remains visible. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints.

8.8.3. OSDI

Severe dry eye disease (defined as an OSDI score of > 33) will be assessed. Details will be outlined in the study procedures manual.

8.8.4. Pupillary Reaction to Light

The swinging light test is used to detect pupillary reaction to light. The test will be performed for Stage 1 and in either mesopic conditions (preferred) or photopic conditions for Stages 2a and 2b. In this test, a steady light is used. The light is shone into one eye, and then quickly switched to

the other. This is repeated back and forth, with an assessment of constriction when light is shone on the pupil. Details will be outlined in the study procedures manual.

8.8.5. Cycloplegic Refraction (Stages 2a and 2b only)

Cycloplegic refraction (photopic) will be performed at distance at least 30 minutes after instillation of the dilating eye drops. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details will be outlined in the study procedures manual.

8.8.6. Gonioscopy/Angle Assessment

Gonioscopy will be performed to assess the iridocorneal (anterior chamber) angle. For slit lamp gonioscopy, the assessor's preferred gonioscopy lens may be used. Details are outlined in Appendix 12, Section 10.12.

8.8.7. Dark Adaptation (Stages 2a and 2b only)

Dark adaptation assessments will be assessed at 5 to 10 minutes in mesopic conditions. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10. Health Economics

Six PRO questionnaires are administered in this study; 2 of which consist of a single question.

At the Screening Visit, participants (Stages 2a and 2b) will answer questions on vision functioning and health-related quality of life using the NEI VFQ-25, including the Near Vision Subscale items (Questions A3 to A5) from the Appendix of Optional Additional Questions. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details are outlined in the study procedures manual.

In Stages 2a and 2b only, each participant will perform 4 different near vision paper-based reading tasks under mesopic conditions. Participants will subsequently rate their vision-related reading ability, and satisfaction with their vision-related reading ability on the NVPTQ. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details are outlined in the study procedures manual.

In Stage 2b only, each participant will also perform 1 near vision electronic-based reading task (on iPhone/iPod) under photopic conditions. Participants will subsequently rate their vision-related reading ability, and satisfaction with their vision-related reading ability on the e-NVPTQ. Refer to Section 1.3.3 for assessment timepoints. Details are outlined in the study procedures manual.

In Stages 2a and 2b only, participants will also answer questions assessing the impact of presbyopia on their life – and need for compensatory coping mechanisms – using the PICQ. Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details are outlined in the study procedures manual.

In Stages 2a and 2b only, participants will also answer single questions on their overall patient global impression of status (PGIS), and their overall patient global impression of change (PGIC). Refer to Sections 1.3.2 and 1.3.3 for assessment timepoints. Details are outlined in the study procedures manual.

Health care resource utilization outcomes are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

No statistical hypotheses will be tested in this study.

9.2. Sample Size Determination

The sample sizes for each study stage were not determined based on statistical consideration.

The sample sizes for each cohort are expected to provide sufficient data to assess safety, PK parameters (as applicable), and efficacy (as applicable) of each dose of AGN-241622.

9.3. Populations for Analyses

For each stage, analysis populations will consist of participants as defined below:

Population	Description
ITT	The ITT population includes all randomized participants. Participants will be summarized according to the randomized study intervention.
Safety	The safety population includes all dosed participants who receive/take ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they actually received.
PK	The PK population includes all participants who have evaluable PK parameters.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the analysis populations to be included in the analyses, and procedures to account for missing, unused, and spurious data. Detailed analysis plans of Stages 1, 2a, and 2b will be provided separately in the SAP. Baseline is defined as last nonmissing assessment before the first dose of study intervention. Section 9.4.1 is a summary of the main statistical analyses of the efficacy endpoints in Stages 2a and 2b.

9.4.1. Efficacy Analyses

In Stage 2, the efficacy analyses will be conducted based on the ITT population. When needed, exploratory statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and 95% CIs will also be estimated.

Further details are provided in the SAP.

9.4.1.1. Analysis Endpoints

The efficacy endpoints are as follows:

Primary Efficacy Endpoint

- Proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 14, Hour 3

Other Efficacy Endpoints

- Proportion of participants gaining 2 lines or more in mesopic, high contrast, binocular, DCNVA
- Change from baseline in mesopic, high-contrast, binocular DCNVA letters
- Change from baseline in mesopic pupil diameter (mm)
- Change from baseline in photopic pupil diameter (mm)
- Change from baseline in photopic, high-contrast, binocular DCIVA letters
- Change from baseline in NVPTQ (paper based) Performance score
- Change from baseline in NVPTQ (paper based) Satisfaction score
- Change from baseline in PICQ Coping score
- Change from baseline in PICQ Impact score

9.4.1.2. Primary Analyses

The proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 14, Hour 3 will be summarized for each AGN-241622 dose by treatment intervention using frequency tables. Missing data will be regarded as 3-line gain failure (nonresponder).

9.4.1.3. Other Analyses

All endpoints related to proportion of participants gaining 2 or 3 lines or more will be analyzed by timepoint using frequency tables. All endpoints related to change from baseline will be analyzed using summary tables. No data imputation will be used for the other efficacy endpoint analyses.

The analyses for additional efficacy endpoints will be described in the SAP.

9.4.2. Safety Analyses

The safety analyses will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, vital signs, 12-lead ECG, and clinical laboratory assessments. Other safety parameters will be defined in the SAP.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

For each study cohort, the number and percentage of participants reporting TEAEs during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity. AE assessments will be presented by cohort and study intervention.

If more than one AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with SAEs and participants with AEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 3, Section 10.3.

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline and changes from baseline at each assessment will be presented by study stage, cohort, and study intervention, and by pooled vehicle in each stage, for each clinical laboratory assessment.

The criteria and analysis for PCS laboratory values will be detailed in the SAP.

9.4.2.3. Vital Signs

For each stage, descriptive statistics for vital signs (systolic and diastolic blood pressure, heart rate, weight, respiration rate, and temperature) at baseline and changes from baseline at each postdose timepoint will be presented by study stage, cohort, and study intervention and by pooled vehicle in each stage.

Vital sign values will be considered to be PCS if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. Analysis will be detailed in the SAP.

9.4.2.4. Electrocardiograms

For each stage, descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTc) at baseline, each postdose timepoint, and EOS; and changes from baseline at each postdose timepoint and at EOS will be presented by stage, cohort, and study intervention, and by pooled vehicle in each stage.

The criteria for PCS ECG values and analysis will be detailed in the SAP.

9.4.2.5. Other Safety Analyses

All other safety endpoints will be analyzed with descriptive statistics. Detailed methods for the other safety endpoints will be described in the SAP.

9.4.3. PK Analyses

Detailed PK analyses will be described in the PK analysis plan.

The principal parameters describing the PK of AGN-241622 will be derived from plasma and tear concentrations using noncompartmental analysis with the software program Phoenix WinNonlin (Version 8.0 or newer). Plasma and tear concentrations BLQ will be treated as zero for all PK calculations. The actual sampling times will be used in the calculation of PK parameters.

9.4.3.1. PK Parameters

Stage 1

The following PK parameters in plasma will be calculated based on standard Phoenix WinNonlin equations: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, λ_z, $t_{1/2}$, CL/F, and V_z/F. In tears, the PK parameters to be calculated include $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, λ_z, and $t_{1/2}$.

Stage 2

The following PK parameters in plasma following dosing on Day 1 and Day 14 will be calculated based on standard Phoenix WinNonlin equations: $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, C_{max}, C_{min}, T_{max}, λ_z, $t_{1/2}$, CL/F, V_z/F, and accumulation ratio. In tears, the PK parameters to be calculated includes $AUC_{0\text{-}t,}$ $AUC_{0\text{-}tau}$, C_{max}, T_{max}, λ_z, and $t_{1/2}$.

The AUC parameters will be calculated by using the linear-log trapezoidal rule.

Estimates of $t_{1/2}$ will be calculated based on λ_z. The λ_z will be determined by performing a regression analysis on the terminal linear phase of semilogarithmic plots of individual AGN-241622 concentration-time data using a minimum of 3 concentration-timepoints in the elimination phase excluding C_{max}. λ_z will be considered to be valid if $r^2 > 0.8$.

9.4.3.2. Statistical Analyses of PK Data

No formal statistical analyses will be performed on the PK data. Descriptive statistics will be provided for the plasma and tear concentrations of AGN-241622 at each nominal timepoint by study cohort for participants in the PK population. Descriptive statistics will be provided for all PK parameters of AGN-241622 by study cohort for all participants in the PK population. Details of the analyses of PK concentrations and parameters will be described in the PK analysis plan finalized before database lock.

9.4.4. Other Analyses

Additional details on exploratory analyses will be described in the SAP finalized before database lock.

9.5. Interim Analyses

No formal interim analysis is planned for this study.

9.6. Data Monitoring Committee (DMC)

An internal independent review team (comprised of but not limited to, a medical safety physician, statistician, clinical pharmacologist, and a clinical representative) will make up the DMC for the study. The composition of the independent team will be documented in the DMC Charter, TMF, and clinical study report. The members of the independent team will be different from the study team members who manage and maintain the study conduct activities, including data collection, data clarification, analysis development, safety monitoring, study center monitoring and management. The DMC will convene after the conclusion of each cohort in Stages 1 and 2a and conduct a comprehensive review of unmasked study data to recommend to either proceed to the next cohort(s), stop the next cohort(s), or modify the dose level or sample size of the next cohort(s). In addition, the FDA will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort. Following the completion of Cohort 6 (Stage 2a), the DMC will review unmasked safety, exposure, and exploratory efficacy data to recommend dose selection for Stage 2b or additional dose strength to investigate.

All details of the committee membership, procedures for safety review, frequency of review and communication between the safety review committee and other information will be detailed in the DMC charter.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the CIOMS International Ethical Guidelines
  - Applicable ICH/ISO GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; any identifiable participant information will only be transferred in accordance with the signed Informed Consent provisions.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local privacy and data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their personal data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Management of privacy incidents relating to clinical trial participant personal data, as well as handling of data participant rights requests (if applicable), should be handled in accordance with the agreed upon CTA provisions.

10.1.5. Dissemination of Clinical Study Data

Study information and tabular study results will be posted to the US National Institutes of Health website www.clinicaltrials.gov.

Study data and information may be published in non-promotional, peer-reviewed publications either by or on behalf of the sponsor.

Clinical study reports, safety updates, and annual reports will be provided to the regulatory authorities as required.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plans.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study procedures manual.

10.1.8. Study and Site Start and Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest as the sponsor 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.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC’s reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Refer to the Central Laboratory Manual for further details regarding central laboratory collection and shipment procedures.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. The investigator or qualified site personnel must review all laboratory results for any AEs. Laboratory test results that represent AEs should be reflected on an AE eCRF page. Investigators must document their review of each laboratory safety report.
- Evaluation and management of abnormal laboratory results should be conducted according to local site practice.

Table 10-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Glycated hemoglobin Hematocrit	RBC indices: MCV MCH MCHC %Reticulocytes Morphology	WBC count with differential (absolute): Neutrophils Bands Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN, uric acid	Potassium	AST	Total, direct, and indirect bilirubin
	Creatinine	Sodium	ALT	Total Protein
	Creatine kinase	Magnesium	Phosphorus	Bicarbonate
	Glucose [fasting]	Calcium	Alkaline phosphatase	Cholesterol, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Clarity, color, and presence of blood • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine drug screen and alcohol test (to include at minimum: benzoylecgonine [cocaine], methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, phencyclidine, and cotinine) at timepoints listed in Sections 1.3.1, 1.3.2, and 1.3.3. • Serum human chorionic gonadotropin pregnancy test at screening and urine test at timepoints listed in Sections 1.3.1, 1.3.2, and 1.3.3 (for women of childbearing potential). • Serology (HIV type 1 and type 2 antibody, hepatitis B surface antigen, and hepatitis C virus antibody) • All study-required laboratory assessments will be performed by a central laboratory, with the exception of the following: o Urine dipstick kits may be used to conduct drugs-of-abuse screens and pregnancy tests at the study center post-screening. Alternatively, a breathalyzer may be used for an alcohol screen.			

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease); for example:
    - The test result is associated with accompanying symptoms, and/or
    - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
    - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
    - The test result is considered to be an AE by the investigator or sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, *lack of efficacy* or *failure of expected pharmacological action* also constitutes an AE or SAE.

- *Lack of efficacy* or *failure of expected pharmacological action* per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether *hospitalization* occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via a medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities or daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

  An event is defined as *serious* when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the investigator's brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours
• Contacts for SAE reporting can be found on the protocol title page. • Email is the preferred method to transmit SAE information. • Facsimile transmission of the SAE information is also acceptable. • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

10.4. Appendix 4: Abbreviations

Abbreviation/Term	Definition
λz	terminal elimination rate constant
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from time 0 to time t
$AUC_{0\text{-}tau}$	area under the plasma/tear concentration versus time curve from time 0 to the end of the dosing period
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CDVA	corrected distance visual acuity
CFR	Code of Federal Regulations
CIOMS	Declaration of Helsinki and Council for International Organizations of Medical Sciences
CL/F	apparent clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTA	Clinical Trial Agreement
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
DMC	data monitoring committee
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
e-NVPTQ	electronic Near Vision Presbyopia Task-based Questionnaire
EOS	end-of-study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug

Abbreviation/Term	Definition
IOP	intraocular pressure
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IWRS	interactive web response system
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LASIK	laser-assisted in situ keratomileusis
LDPE	low-density polyethylene
MAOI	monoamine oxidase inhibitor
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
N/A	not applicable
NCI	National Cancer Institute
ND	nondominant
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
NOAEL	no observed adverse effect level
NVPTQ	Near Vision Presbyopia Task-based Questionnaire
OSDI	Ocular Surface Disease Index
Oxy	oxymetazoline
PCS	potentially clinically significant
PDE5	phosphodiesterase type 5
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Status
PICQ	Presbyopia Impact and Coping Questionnaire
Pilo	pilocarpine
PK	pharmacokinetic
PRK	photorefractive keratectomy
PRO	patient-reported outcome
QD	once daily
QT	electrocardiographic time from the beginning of the QRS complex to the end of the T wave on ECG (a measure of ventricular depolarization and repolarization)
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
r^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation/Term	Definition
SNRI	serotonin norepinephrine reuptake inhibitor
SoA	schedule of activities
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TBD	to be determined
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{max}	time to maximum concentration
TMF	trial master file
V_z/F	apparent volume of distribution during terminal elimination
WBC	white blood cell
WOCBP	women of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Death	The absence of life or state of being dead (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (e.g., ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A First-in-Human, Phase 1/2, Dose-ascending, Multicenter, Masked, Randomized, Vehicle-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AGN-241622 in Healthy Participants and Participants with Presbyopia (Stage 1 and Stage 2) and Efficacy in Participants with Presbyopia (Stage 2)
	Clinical Study Sponsor	Allergan Sales, LLC
	Trial Phase Classification	Phase 1/2
	Trial Indication	Presbyopia
	Trial Indication Type	Treatment
	Trial Type	**Stage 1:** Safety, Tolerability, Pharmacokinetics **Stages 2a and 2b:** Safety, Tolerability, Pharmacokinetics, Efficacy
	Trial Length	**Stage 1:** Approximately 20 days **Stages 2a and 2b:** Approximately 60 days each
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	**Stage 1:** 36 participants **Stage 2a:** 36 participants **Stage 2b:** approximately 60 participants (Cohort 7) and 12 participants (Cohort 8)
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Healthy Subject Indicator	**Stage 1:** Yes **Stage 2:** No
	Planned Minimum Age of Subjects	40 years
	Planned Maximum Age of Subjects	65 years
	Sex of Participants	Male or female
	Stable Disease Minimum Duration	Not applicable
Treatments	Investigational Therapy or Treatment	AGN-241622 ophthalmic solutions
	Intervention Type	Drug

	Dose per Administration	**Stage 1:** AGN-241622 [redacted] single dose left eye (Cohort 1), AGN-241622 [redacted] single dose left eye (Cohort 2), and AGN-241622 [redacted] single dose left eye (Cohort 3) **Stage 2a:** AGN-241622 [redacted] once daily x 14 days in both eyes (Cohort 4), AGN-241622 [redacted] once daily x 14 days in both eyes (Cohort 5), and AGN-241622 [redacted] once daily x 14 days in both eyes (Cohort 6) **Stage 2b:** AGN-241622 (dose TBD) once daily x 14 days in both eyes
	Dose Units	**Stage 1:** 1 drop in left eye once **Stages 2a and 2b:** 1 drop in each eye once daily x 14 days
	Dosing Frequency	**Stage 1:** 1 drop in left eye once **Stages 2a and 2b:** 1 drop in each eye once daily x 14 days
	Route of Administration	Topical eye drop
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2 arms per cohort
	Trial Is Randomized	Yes
	Trial Blinding Schema	Double-masked (except Cohort 7, which is single-masked)
	Adaptive Design	Yes

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined timeframe in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom with spermicide plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, nonvasectomized male participants must refrain from donating sperm throughout the study, up through 30 days after the last dose of study intervention.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined timeframe.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • IUD • IUS • Etonogestrel implant (i.e., Nexplanon®) • Bilateral tubal occlusion (e.g., Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (i.e., ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be used during the study intervention period.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at the Screening Visit and also a negative urine test on Day -1 (Stage 1) and Day 1 (Stages 2a and 2b).

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.8. Appendix 8: Biomicroscopic Examination

Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil.

Eyelid/Eyelid Margins/Lashes

Edema

0	(None)	=	No edema
+0.5	(Trace)	=	Localized, minimal (trace) swelling
+1	(Mild)	=	Localized, mild swelling
+2	(Moderate)	=	Diffuse, moderate swelling
+3	(Severe)	=	Diffuse, severe swelling

Erythema

0	(None)	=	No erythema
+0.5	(Trace)	=	Localized, minimal (trace) flush reddish color
+1	(Mild)	=	Localized, mild, flush reddish color
+2	(Moderate)	=	Diffuse reddish color encompassing the entire lid margin
+3	(Severe)	=	Deep diffuse reddish color of lid margins and superior and/or inferior eyelid

Conjunctiva (Bulbar)

Hyperemia

0	(None)	=	No hyperemia
+0.5	(Trace)	=	Minimal (trace) flush, reddish color
+1	(Mild)	=	Mild flush, reddish color
+2	(Moderate)	=	Bright red color
+3	(Severe)	=	Deep, bright diffuse redness

Edema

0	(None)	=	No edema
+0.5	(Trace)	=	Localized, minimal (trace) swelling
+1	(Mild)	=	Localized, mild swelling
+2	(Moderate)	=	Diffuse, moderate swelling
+3	(Severe)	=	Diffuse, severe swelling

Conjunctiva (Palpebral)

Hyperemia

0	(None)	=	No hyperemia
+0.5	(Trace)	=	Minimal (trace) flush, reddish color
+1	(Mild)	=	Mild flush, reddish color
+2	(Moderate)	=	Bright red color
+3	(Severe)	=	Deep, bright diffuse redness

Edema

0	(None)	=	No edema
+0.5	(Trace)	=	Localized, minimal (trace) swelling
+1	(Mild)	=	Localized, mild swelling
+2	(Moderate)	=	Diffuse, moderate swelling
+3	(Severe)	=	Diffuse, severe swelling

Cornea

Edema

0	(None)	=	No edema
+0.5	(Trace)	=	Localized, minimal (trace) epithelial haze
+1	(Mild)	=	Dull glass appearance of epithelium that may include fine localized microcystic changes
+2	(Moderate)	=	Dull glass appearance of the epithelium with large number of cystic changes with or without stromal edema
+3	(Severe)	=	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Superficial Punctate Keratopathy

0	=	No superficial punctate keratopathy
+0.5	=	Trace
+1	=	Mild
+2	=	Moderate
+3	=	Severe

Anterior Chamber

The anterior chamber will be evaluated for pathology. If pathology is present, it will be described.

Iris/Pupil

The iris/pupil will be evaluated for pathology. If pathology is present, it will be described.

Sodium Fluorescein Corneal Staining

The examination will be performed with the slit lamp at 10x magnification. The dry eye test sodium fluorescein strip will be moistened with 0.9% saline and gently touched on the superior bulbar conjunctiva. A stopwatch will be started immediately after application. The corneal staining will be graded approximately 2 minutes after instillation of the sodium fluorescein. The entire cornea will be evaluated for staining using the supplied yellow barrier filter placed directly in front of the objective lens of the slit lamp. The slit lamp's cobalt blue filter must be used to illuminate the cornea. Corneal sodium fluorescein staining should be evaluated as close to the 2-minute timepoint as possible. Refer to the table outlined in the laminated chart provided to grade the staining (Figure 10-1).

Only the cornea will be graded. Once grading of the right eye is complete, the entire procedure will be repeated for the left eye.

For grades 0 to 2, the dot count will be collected and recorded. Dot counts need not be collected or recorded for grades 3 and higher.

Figure 10-1 Oxford Scale for Grading Corneal and Conjunctival Staining

Note: For this study, only the cornea will be graded.

10.9. Appendix 9: Study Intervention Tolerability/Drop Comfort Assessment

The presence and severity of ocular symptoms will be elicited from the participant for their treated eye(s), as applicable. Symptoms including blurred vision, foreign body sensation, pain, burning/stinging, tearing, and itching will be classified using a 5-point grading scale with 0 = none, +0.5 = trace, +1 = mild, +2 = moderate, and +3 = severe. The duration of symptoms (< 1 minute, 1 to 5 minutes, > 5 minutes) will be captured once immediately after the drop of each dose of study intervention. If any other ocular symptoms are present, these will also be captured.

Participants will be asked to rate the overall comfort of the eye drops using a 6-point scale (i.e., soothing, very comfortable, comfortable, uncomfortable, very uncomfortable, or intolerable) immediately after the drop instillation for the right and left eyes separately, as applicable.

10.10. Appendix 10: Fundus (Indirect) Ophthalmoscope Examination

The fundus assessments should be conducted through a dilated pupil. The examinations will include evaluation of the lens, vitreous, fundus, and optic nerve. The cup to disc ratio will be assessed.

Lens

Lens Assessment: Use biomicroscopic examination, indirect lenses, direct/indirect ophthalmoscopy, etc., as appropriate, to visualize.

Lens Status: The lens will be evaluated for pathology. If pathology is present, it will be described.

Cataract Assessment: Under dilated opthalmoscope examination, the presence and severity of nuclear, cortical and posterior subcapsular cataract lens opacities will be evaluated. At the first dilated opthalmoscope examination, each type of cataract, if present, will be graded using the scale below. At the last follow-up dilated opthalmoscope examination, each type of cataract will be assessed for change from baseline and if changed, the current severity will be graded using the scale below:

0	=	None
+1	=	Mild
+2	=	Moderate
+3	=	Severe

Vitreous

The vitreous will be evaluated for pathology. If pathology is present, it will be described. It will be noted if the condition is not evaluable.

Fundus

The fundus (posterior pole; periphery, when dilated) will be evaluated for pathology. If pathology is present, it will be described. It will be noted if the condition is not evaluable.

Optic Nerve

The optic nerve will be evaluated for pathology. If pathology is present, it will be described. It will be noted if the condition is not evaluable.

Cup/disc ratio will be reported using a 0.0 to 1.0 scale. It will be noted if the condition is not evaluable.

10.11. Appendix 11: IOP

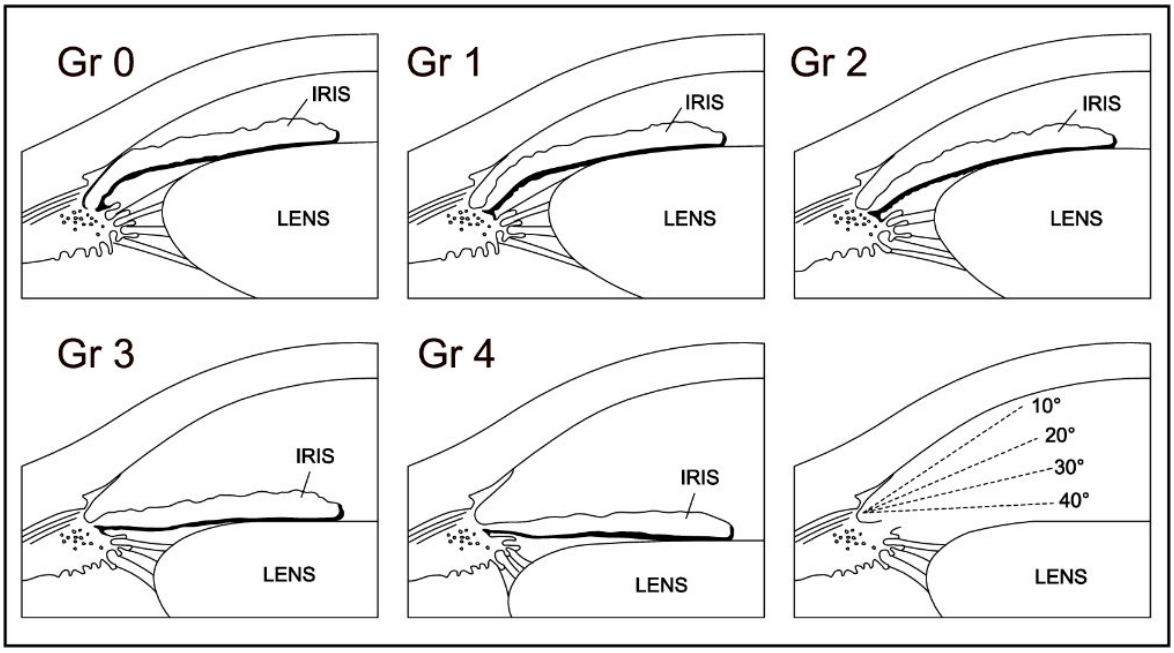
IOP should be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. Measurements will be taken using a Goldmann applanation tonometer affixed to a slit lamp with the participant seated. The participant and slit lamp should be adjusted so that the participant's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight fitting neckwear should be loosened. Both eyes will be tested, with the right eye preceding the left eye. The examiner looks through the binocular viewer of the slit lamp at low power. The tension knob is preset at a low pressure value (4 to 6 mm Hg). The examiner follows the image of the sodium fluorescein-stained semicircles while slowly rotating the tension knob until the inner borders of the sodium fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the examiner will take his/her fingers off the tension knob and record the IOP reading along with the date and time of day.

10.12. Appendix 12: Gonioscopy/Angle Assessment

Gonioscopy will be performed to assess the iridocorneal (anterior chamber) angle. For slit lamp gonioscopy, the assessor's preferred gonioscopy lens may be used. The room lights should be turned off during the examination and all participants should be examined in the same room with the same slit lamp and with consistent lighting conditions.

The assessor will begin by applying adequate topical anesthesia (topical proparacaine 0.5%) to the participant's eye. With the participant sitting comfortably at the slit lamp, the corneal surface of the lens will be wetted with an artificial tear or lubricating solution and the gonioscopy lens will be placed on the participant's eye. A bright, narrow light beam will be directed away from the pupil to avoid inducing miosis and the angle assessment will be performed under high magnification. With the participant maintaining their gaze in the primary position, the assessor will examine/grade the 6 o'clock (inferior angle) position using the Shaffer anterior chamber angle grading system depicted in Figure 10-2. Lens tilting should be minimized; only minor movement of the lens is permissible, otherwise, the angle findings may be distorted and a closed, or a narrow angle may appear open. Excess pressure should not be used as this may cause indentation; the presence of corneal striations is an indication that the cornea is being indented.

Figure 10-2 Anterior Chamber Angle Grading



Source: Becker and Shaffer. Clinical interpretation of gonioscopic findings. 8th ed. In: Stamper RL, Lieberman MF, Drake MV, editors. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. Amsterdam: Mosby Elsevier, 2009:78-90.

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