Title Page

Protocol Title: A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

Protocol Number: 1883-301-013
Amendment Number: 1

Product: AGN-190584

Brief Protocol Title: Phase 3 efficacy study of AGN-190584 in participants with presbyopia

Development Phase: 3

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

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	05 December 2018
Original Protocol	13 October 2018

Amendment 1 (05 December 2018)

Overall Rationale for the Amendment:

The following is a summary of changes made to the original protocol, some of which are based on communication with the FDA.

Section No. and Name	Description of Change	Brief Rationale
Throughout	Update figures, tables, appendices, and text to a 30-day study intervention timeline	A 30-day study intervention period is an adequate duration to demonstrate safety and efficacy of AGN-190584
1.1. Synopsis; 1.3. Schedule of Activities; 3. Objectives and Endpoints; 8. Study Assessments and Procedures; 10.7. Appendix 7	Add OD and OS measurements for mesopic and photopic CDVA, DCIVA, and DCNVA	In addition to binocular measurements, individual eye measurements were added to mesopic and photopic CDVA, DCIVA, and DCNVA to provide a more complete assessment of these endpoints
1.1. Synopsis; 4.1. Overall Design; 9.2. Sample Size Determination	Modify participant dropout rate to 10% and participants completing the study per study intervention group to approximately 135	The participant dropout rate assumption was modified to 10% (versus 20%) as this is a sufficiently conservative estimate of participants who may not complete the 30-day study. Assumptions for the sample size calculation and their basis were clarified.
1.1. Synopsis; 6.3. Measures to Minimize Bias: Randomization and Blinding; 9.4.1.3. Secondary Analyses; 9.4.4.1. Subgroup Analyses	Modify “baseline DCNVA” to “baseline binocular DCNVA” for randomization and analysis	“Baseline DCNVA” was modified to “baseline binocular DCNVA” to clarify this stratification parameter during randomization and statistical analysis
1.3. Schedule of Activities; 8.8. Biomarkers and Other	Add determination of dominant eye	Collection of participant dominant/nondominant eye data was clarified

Section No. and Name	Description of Change	Brief Rationale
Assessments; 10.7. Appendix 7		
1.3. Schedule of Activities; 10.7.1. Screening Visit (Days -30 to -1)	Modify screening DCNVA assessment that will be repeated 3 times with different charts to OD only	OD was added to clarify that the screening visit DCNVA (to be repeated 3 times with different charts) is for OD only
7.1. Discontinuation of Study Intervention	Added a guideline to encourage participants who discontinue the study intervention early to stay in the study for the safety assessments at Day 30	This was added to promote a continuation of safety assessments if a participant discontinues study intervention before the end of the study
9.1. Statistical Hypotheses	Update of statistical hypotheses	The statistical hypotheses for the primary and key secondary efficacy endpoints were clarified
9.2. Sample Size Determination	Update of sample size justification	The vehicle group intervention effect was updated based on previous phase 2 study results; the intervention effect for the non-emmetropes group was added. The total number of participants to complete the study was changed to 135 for each treatment group
9.4.1. Efficacy Analyses	Remove key secondary efficacy endpoint (change from baseline letters AUC_{0-10} in mesopic, high contrast, binocular DCNVA at Day 30) and its analysis method	This key secondary efficacy endpoint is not required to demonstrate the efficacy of AGN-190584
9.4.1.1. Analysis Endpoints	Remove secondary efficacy endpoint (photopic, high contrast, binocular DCIVA mean change from baseline letters AUC_{0-10} at Day 30) and its analysis method	This secondary efficacy endpoint is not required to demonstrate the efficacy of AGN-190584
9.4.1.1. Analysis Endpoints	Add secondary efficacy endpoint (Change from baseline photopic, high contrast, binocular DCIVA letters at Day 30, Hour 3)	This secondary efficacy endpoint was added to evaluate the efficacy of AGN-190584 for DCIVA
9.4.1.3. Secondary Analyses	Update change from baseline analysis (MMRM)	The change from baseline analysis model (MMRM) was updated to include the following additional fixed effects: visit, visit by study intervention group interaction, and baseline value by visit interaction
9.4.4.1 Subgroup Analyses	Update subgroup analyses	Subgroup analyses by gender and race was added
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

Protocol Number: 1883-301-013

Brief Title: Phase 3 efficacy study of AGN-190584 in participants with presbyopia

Study Rationale:

In previous studies, Allergan established the safety and efficacy of several (0.5% to 1.5%) concentrations of AGN-190584 dosed once daily, bilaterally or in the nondominant eye, over a period of up to 28 days in participants with presbyopia. Study 1883-301-013 is a multicenter, double-masked, randomized, vehicle-controlled, parallel group, Phase 3 study evaluating the efficacy, safety, and pharmacokinetics of AGN-190584 (1.25% pilocarpine) dosed once daily, bilaterally, over a period of 30 days in participants with presbyopia.

Objectives and Measures:

The objectives of this study are to evaluate the efficacy, safety, and pharmacokinetics of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia.

Objectives	Measures
To evaluate the efficacy of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia.	• Mesopic and photopic, high contrast distance-corrected near visual acuity (DCNVA) for each eye and binocularly • Mesopic and photopic, high contrast distance-corrected intermediate visual acuity for each eye and binocularly • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • Patient reported outcomes questionnaires: o Mesopic and Photopic Near Vision Presbyopia Task-based Questionnaire o Presbyopia Impact and Coping Questionnaire o Presbyopia Patient Satisfaction Questionnaire o Single-Item Patient Global Impression of Change o Single-Item Patient Global Impression of Status o Single-Item Patient Expectations for Treatment Efficacy
To evaluate the safety and tolerability of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• Adverse events • Photopic and mesopic high contrast corrected distance visual acuity for each eye and binocularly • Near Contrast sensitivity • Vital signs (blood pressure and heart rate) • Study drug tolerability and drop comfort assessments • Temporal/supraorbital headache visual analog scale • Intraocular pressure • Slit-lamp biomicroscopy • Manifest refraction • Dilated funduscopic examination • Pregnancy test for women of childbearing potential
To evaluate the pharmacokinetics of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• Plasma concentrations of AGN-190584 (sampled at selected sites; approximately 10% of all enrolled participants)

Overall Study Design:

This is a multicenter, double-masked, randomized, parallel-group, vehicle-controlled, Phase 3 study in participants with presbyopia. The study population will consist of adult male and female participants with objective and subjective evidence of presbyopia.

Number of Participants:

Approximately 150 participants per group will be enrolled to achieve at least 135 participants per group completing the study based on an assumed dropout rate of 10%. Participants who prematurely discontinue from the study will not be replaced.

Number of Sites:

There will be approximately 50 sites in the United States.

Intervention Groups and Study Duration:

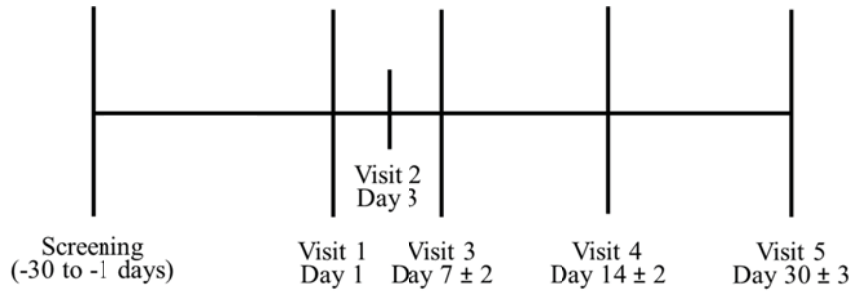
Participants will be randomized in a 1:1 ratio to receive either AGN-190584 or vehicle dosed once daily, in each eye, for 30 days. This randomization will be stratified by age (2 groups: ≤ 50 years and > 50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes. This study consists of the following visits: screening (Days -30 to -1), Day 1 (baseline), and Days 3, 7, 14, and 30.

Data Monitoring Committee: No

1.2. Schema

The study schema is provided in Figure 1-1.

Figure 1-1 Study Schema



1.3. Schedule of Activities

Study procedures are recommended to be done in sequence as listed in the schedules below (Table 1-1 and Table 1–2).

Table 1-1 Schedule of Visits and Procedures: Screening to Visit 3

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Informed consent	X															
Iris color assessment	X															
Demography	X															
Medical and ophthalmic history	X															
Pre-study/ concomitant medication query	X	X								X			X			
NEI VFQ-25 and near vision subscale in the Appendix of Optional Additional Questions	X															Near vision subscale includes questions A3 to A5 in the Appendix of Optional Additional Questions
OSDI	X															
AE query	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X			X					X	X		X	X		Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
Urine pregnancy test	X	X														WOCBP only
Review inclusion and exclusion criteria	X	X														

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Determination of dominant eye	X															
Contact IxRS for kit assignment/ randomization		X														IxRS will be used to dispense medication. Please refer to the IxRS manual for additional information
PICQ		X														Conducted with participant's habitual distance correction
Single-item Patient Expectations for Treatment Efficacy Question		X														Conducted with participant's habitual distance correction
Depth of focus measurement		X			X					X	X		X	X		
Pupillary reaction to light assessment	X															
Perform under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target)																Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Dark adaptation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5 to 10 minutes in mesopic conditions
Mesopic Manifest Refraction (distance and near)	X															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.
Mesopic, high contrast CDVA + pupil diameter	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Mesopic, high contrast DCIVA	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Mesopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye. At screening, repeat the DCNVA assessment OD 3 times with different charts.
Single-item PGIS		X														Conducted with participant's best distance correction
Mesopic NVPTQ		X														Conducted with participant's best distance correction
Perform under photopic conditions (≥ 80 cd/m^2; 251 lux at target):																Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Photopic manifest refraction (distance and near)	X															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.
Photopic, high contrast CDVA + pupil diameter	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Photopic, high contrast DCIVA	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
Photopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Near Contrast sensitivity assessment		X			X					X	X		X	X		Conducted with participant's best distance correction
Photopic NVPTQ		X														Conducted with participant's best distance correction

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Slit-lamp biomicroscopy	X	X			X					X	X		X	X		
Fluorescein Corneal staining	X															
IOP measurement	X	X			X											
Gonioscopy/ angle assessment	X															
Dilating drop administration	X															Minimum 30-minute wait after administration of dilating drops
Cycloplegic refraction	X															Distance, photopic
Dilated funduscopic examination	X															Investigator should note if the pupil dilated normally.
Contact IxRS for participant ID number	X															
Temporal/ supraorbital headache VAS assessment		X		X	X					X	X		X	X		Conducted before dosing at Hour 0 of each visit
PK blood draw		X														Conducted at selected sites only; Hour 0 blood draw must be done before study intervention administration.
Study intervention administration		X								X			X			Hour 0 starts after study intervention administration.
Tolerability assessment/drop comfort questionnaire		X								X			X			
Study intervention dispensing									X							Refer to Section 6.2 regarding study intervention dispensation.

Table 1–2 Schedule of Visits and Procedures: Visit 4 to Visit 5/Early Exit

Procedure	Study Days (Visits)																Notes
	Day 14 (Visit 4)								Day 30/Early Exit (Visit 5)								
Visit Windows	± 2 days								± 3 days								
Hours	0	0.25	0.5	1	3	6	8	10	0	0.25	0.5	1	3	6	8	10	Study intervention administration Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Concomitant medication query	X								X								
AE query	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X			X					X			X					Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
Urine pregnancy test									X								WOCBP only
PICQ													X				Conducted with participant's habitual distance correction
PPSQ													X				Conducted with participant's habitual distance correction
Depth of focus measurement	X			X					X			X					
Perform under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):																	Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Dark adaptation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5 to 10 minutes in mesopic conditions
Mesopic, high contrast CDVA + pupil diameter	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Mesopic, high contrast DCIVA	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.

Procedure	Study Days (Visits)																Notes
	Day 14 (Visit 4)								Day 30/Early Exit (Visit 5)								
Visit Windows	± 2 days								± 3 days								
Hours	0	0.25	0.5	1	3	6	8	10	0	0.25	0.5	1	3	6	8	10	Study intervention administration Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Mesopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Single-item PGIS				X									X				Conducted with participant's best distance correction
Single-item PGIC				X									X				Conducted with participant's best distance correction
Mesopic NVPTQ				X									X				Conducted with participant's best distance correction
Perform under photopic conditions (≥ 80 cd/m^2; 251 lux at target):																	Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Photopic, high contrast CDVA + pupil diameter	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Photopic, high contrast DCIVA	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
Photopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Near contrast sensitivity assessment	X			X					X			X					Conducted with participant's best distance correction
Photopic NVPTQ				X									X				Conducted with participant's best distance correction
Slit-lamp biomicroscopy	X			X					X			X					

Procedure	Study Days (Visits)																Notes
	Day 14 (Visit 4)								Day 30/Early Exit (Visit 5)								
Visit Windows	± 2 days								± 3 days								
Hours	0	0.25	0.5	1	3	6	8	10	0	0.25	0.5	1	3	6	8	10	Study intervention administration Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
IOP measurement	X			X					X			X					
Temporal/ supraorbital headache VAS assessment	X		X	X					X		X	X					Conducted before dosing at Hour 0 of each visit
PK blood draw									X	X	X	X	X	X	X	X	Conducted at selected sites only; Hour 0 blood draw must be done before study intervention administration.
Study intervention administration	X								X								Hour 0 starts after study intervention administration.
Tolerability assessment/ drop comfort questionnaire	X								X								
Dilating drop administration																X	Minimum 30-minute wait after administration of dilating drops
Dilated funduscopic examination																X	Investigator should note if the pupil dilated normally

2. Introduction

Allergan is investigating pilocarpine HCl ophthalmic solution 1.25% (AGN-190584) as a noninvasive, reversible, pharmacological 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

In previous studies, Allergan established the safety and efficacy of various concentrations of AGN-190584 dosed once daily, bilaterally or in the nondominant eye, over a period of up to 28 days in participants with presbyopia. Study 1883-301-013 is a multicenter, double-masked, randomized, vehicle-controlled, parallel group, Phase 3 study evaluating the safety, efficacy, and tolerability of AGN-190584 dosed once daily, bilaterally, over a period of 30 days in participants with 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 (eg, 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, and 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, pharmacological treatment for presbyopia.

Pilocarpine is a muscarinic receptor agonist that mimics the actions of the parasympathetic neurotransmitter, acetylcholine, on smooth muscle. This causes 2 effects that enhance near vision: 1) constriction of the iris sphincter muscle, resulting in pupil 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).

Pilocarpine 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 ophthalmic solution is limited by the commonly experienced AE of temporal and periorbital headache (ie, 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 AGN-190584 in 3 Phase 2 clinical studies (Studies 199201-007, 199201-009, and 199201-010). This is likely because the posology of pilocarpine evaluated for the treatment of presbyopia to date is of lower concentration (0.5% to 1.5%) and less frequently administered (once to twice daily) than for the treatment of glaucoma (1.0% to 4.0% administered up to 4 times daily). As a result, discontinuation rates for all Phase 2 clinical studies were generally low and safety parameters were not clinically significant between participants that received AGN-190584 compared to participants that received vehicle or a combination therapy. The majority of AEs reported in any treatment group were mild to moderate in intensity.

Efficacy measures for Phase 2 clinical studies included mesopic uncorrected near visual acuity line and letter improvement. Of the various concentrations of AGN-190584 evaluated, near vision was most improved compared with vehicle under mesopic and photopic conditions at the 1.0% and 1.5% pilocarpine concentrations, respectively.

More detailed information regarding clinical safety findings, clinical efficacy findings, chemistry, and pharmacology is provided in the IB.

2.3. Benefit/Risk Assessment

Currently available approaches to presbyopia correction include nonsurgical options (spectacles or contact lenses) and surgical options (PRK or LASIK, conductive keratoplasty, intraocular lenses, or corneal inlays). Each approach has its own risk-benefit ratio. Because the risk-benefit ratio with nonsurgical options is generally lower than that of surgical procedures, both historical and contemporary practice has been to attempt nonsurgical or pharmacological treatment before resorting to more invasive alternatives.

Although the use of spectacles and contact lenses to correct presbyopia is widespread, this approach has limitations. Multifocal spectacles impair depth perception and edge-contrast sensitivity at critical distances for detecting obstacles in the environment (Lord 2002), and varifocal lenses have a corridor of nondistorted vision. For these reasons, older people are more than twice as likely to fall when wearing multifocal spectacles, and many participants have difficulty adjusting to using them (Johnson 2007, Lord 2002). As a result, Allergan is developing a noninvasive, reversible, pharmacological treatment for presbyopia.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AGN-190584 may be found in the IB.

3. Objectives and Endpoints

Objectives	Measures
To evaluate the efficacy of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia.	• Mesopic and photopic, high contrast DCNVA for each eye and binocularly • Mesopic and photopic, high contrast DCIVA for each eye and binocularly • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO questionnaires: o Mesopic and Photopic NVPTQ o PICQ o PPSQ o Single-Item PGIC o Single-Item PGIS o Single-Item Patient Expectations for Treatment Efficacy
To evaluate the safety and tolerability of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• AEs • Photopic and mesopic high contrast CDVA for each eye and binocularly • Near Contrast sensitivity • Vital signs (blood pressure and heart rate) • Study drug tolerability and drop comfort assessments • Temporal/supraorbital headache VAS • IOP • Slit-lamp biomicroscopy • Manifest refraction • Dilated funduscopic examination • Pregnancy test for WOCBP
To evaluate the pharmacokinetics of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• Plasma concentrations of AGN-190584 (sampled at selected sites; approximately 10% of all enrolled participants)

4. Study Design

4.1. Overall Design

This is a multicenter, double-masked, randomized, parallel-group, vehicle-controlled, Phase 3 study in participants with presbyopia. Participants will receive AGN-190584 or vehicle dosed once daily, bilaterally, for 30 days. Approximately 300 participants with presbyopia will be enrolled at approximately 50 sites in the United States.

This study consists of the following visits: screening, Day 1 (baseline), and Days 3, 7, 14, and 30. A study schema is located in Section 1.2 and the SoA is located in Section 1.3.

Approximately 150 participants per group will be enrolled to achieve at least 135 participants per group completing the study. Participants who prematurely discontinue from the study will not be replaced.

4.1.1. Clinical Hypotheses

- AGN-190584 ophthalmic solution dosed bilaterally, once daily for 30 days will demonstrate a significant improvement in DCNVA over vehicle.
- AGN-190584 ophthalmic solution dosed bilaterally, once daily for 30 days will demonstrate an acceptable safety and tolerability profile.

4.2. Scientific Rationale for Study Design

The current Phase 3 clinical study is designed to evaluate the efficacy, safety, and tolerability of AGN-190584 versus vehicle over a 30-day study intervention period when administered once daily bilaterally in participants with presbyopia.

Allergan Phase 2 Studies 199201-007 and 199201-009 support the administration of AGN-190584 monotherapy as an effective and safe treatment for presbyopia in doses up to 1.5%. The current Phase 3 study will evaluate AGN-190584 in an expanded participant population to establish efficacy and safety.

4.3. Justification for Dose

Through modeling and evaluation of the Phase 2 results (Studies 199201-007, 199201-009, and 199201-010), Allergan has determined the optimal dose of AGN-190584 to be 1.25% for the treatment of presbyopia.

4.4. End of Study Definition

The EOS 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 phases of the study including the last visit.

5. Study Population

The study population will consist of adult male and female participants with objective and subjective evidence of presbyopia.

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:

1.	**Age**
1.01	Participant must be 40 to 55 years of age inclusive, at the time of the screening visit
2.	**Type of Participant and Presbyopia Characteristics**
2.01	In good general health at the screening visit, as determined by the investigator
2.02	Subjective complaints of poor near vision that impact activities of daily living, as defined by at least a moderate impact (score ≥ 3) on at least 1 question on NEI VFQ-25 Questions 5 to 7 in the main questionnaire and Near Vision Subscale, Questions A3 to A5 in the Appendix of Optional Additional Questions at the screening visit.
2.03	Emmetropes or non-emmetropes with best distance correction in the range of spherical -4.00 D to +1.00 D inclusively and cylinder ≤ ±2.00 D with photopic, high contrast CDVA of 20/25 or better in each eye at the screening and baseline visits
2.04	Photopic, high contrast CDVA of 20/32 or better in each eye by habitual mono-focal correction (either spectacles or contact lenses), or willing to wear new mono-focal correction spectacles to achieve photopic, high contrast CDVA of 20/32 or better during the study
2.05	Mesopic, high contrast DCNVA of 20/40 (J3) to 20/100 (J10) in each eye at the screening and baseline visits
2.06	Photopic, high contrast, near visual acuity correctable to 20/40 (J3+) or better in each eye at the screening and baseline visits
2.07	Mesopic pupil diameter < 8.0 mm in both eyes at the screening visit
3.	**Sex**

3.01	Male and 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 or a legally authorized representative 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 (eg, Written Authorization for Use and Release of Health and Research Study Information for the United States)
5.	**Other**
5.01	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:

1.	**Medical Conditions**
1.01	Uncontrolled systemic disease
1.02	Clinically significant disease state, in the opinion of the examining investigator or designee, in any body system
1.03	Any clinical condition or previous surgery that might affect the absorption, distribution, biotransformation, or excretion of AGN-190584. History of cataract surgery, phakic intraocular lens surgery, corneal inlay surgery, radial keratotomy, or any intraocular surgery. However, participants with history of PRK or LASIK with CDVA meeting inclusion criteria will be allowed to enroll.
1.04	Known allergy or sensitivity to the study intervention or its components or other cholinergic agonist medications
2.	**Prior/Concomitant Therapy**

2.01	Concurrent use of any topical ophthalmic medications, including artificial tears, other than the study intervention during the course of the study
2.02	Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes
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
3.02	Participation in a blood or plasma donation program within 30 days prior to study intervention administration
4.	**Diagnostic Assessments**
4.01	Presence of any ocular condition that, in the opinion of the investigator, could affect the safety of the participant or interpretation of efficacy parameters (eg, uveitis, retinal detachment)
4.02	Severe dry eye disease (defined as total corneal staining ≥ grade 3 on the 5-point Oxford scale and an OSDI score of > 33) at the screening visit
4.03	Corneal abnormalities (including keratoconus, corneal scar, Fuchs' endothelial dystrophy, guttata, or edema) in either eye that are likely to interfere with visual acuity
4.04	Narrow iridocorneal angles (Shaffer grade ≤ 2 or lower on gonioscopy examination), history of angle-closure glaucoma, or previous iridotomy
4.05	History of iris trauma, Adie's tonic pupil, abnormal pupil shape in either eye, or anisocoria > 1 mm between pupils under mesopic conditions at the screening visit
4.06	Lens opacity in either eye that is determined to cause significant disturbance of the central visual axis on screening biomicroscopy
4.07	Diagnosis of any type of glaucoma or ocular hypertension
4.08	Bifocal or multifocal spectacles or contact lenses for habitual correction. Participants willing to wear study-provided monofocal correction (either spectacles or contact lenses) during the study can be enrolled
4.09	Abnormal and clinically significant results according to the investigator or designee, on physical/ophthalmic examination or medical history

5.	**Other**
5.01	Females who are pregnant, nursing, or planning a pregnancy during the study. WOCBP or males with partners of childbearing potential and do not agree to use reliable contraception during the study.
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.

5.3. Lifestyle Considerations

Participants who wear bifocal or multifocal spectacles or contact lenses will be provided with a pair of monofocal spectacles 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 with improved distance correction (20/32 or better). Participants are required to wear the newly provided spectacles 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. Either monofocal spectacles or contact lenses can be worn between study visits, but only spectacles can be worn on the study visit days. Reading glasses are allowed between visits when needed.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes 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 intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study Intervention Name	AGN-190584	Vehicle
Dosage Formulation	Topical eye drop	Topical eye drop
Identity of Formulation	Pilocarpine HCl 1.25% Ophthalmic Solution Lot 98279 Manufactured at Allergan Waco	Pilocarpine HCl Placebo Ophthalmic Solution Lot 98273 Manufactured at Allergan Waco
Drug Substance	Pilocarpine 1.25%	Not applicable
Route of Administration	Topical eye drop	Topical eye drop
Dosing Instructions	1 drop in each eye once daily	1 drop in each eye once daily
Packaging and Labeling	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 per protocol Keep Out of Reach of Children Caution: New Drug--Limited by Federal (or United States) law to investigational use	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 per protocol Keep Out of Reach of Children Caution: New Drug--Limited by Federal (or United States) law to investigational use
Manufacturer	Allergan Sales, LLC.	Allergan Sales, LLC.
Number and Timing of Interventions	1 drop bilaterally, once daily	1 drop bilaterally, once daily
Volume Per Intervention	3.5 mL per bottle	3.5 mL per bottle

As this is a double-masked study, AGN-190584 and Vehicle will be supplied in identically appearing bottles and cartons.

6.1.1. Study Supplies

The following study supplies will be provided by Allergan:

- Unilateral pupillometer
- Distance, near, and intermediate visual acuity charts

- Pelli-Robson near contrast sensitivity charts
- Light meters
- Oxford scale
- Yellow barrier filter for corneal fluorescein staining (if needed)
- Sodium fluorescein DET strips (if needed)
- Lectern
- Continuous temperature monitoring device (if needed)

The following study supplies will be provided by the investigator:

- Dilating eye drops (1.0% tropicamide ophthalmic solution and 2.5% phenylephrine ophthalmic solution)
- Artificial tears/lubricating solution for gonioscopy
- Topical anesthetic (0.5% proparacaine ophthalmic solution)
- Occluder
- Urine pregnancy test kits
- Stopwatch
- Ruler/tape measure to measure 4-meter lane
- Internet connection (high-speed connection for eCRF completion) equipment for all other examinations and measures

6.1.2. Instructions for Use and Administration

Participants will be instructed not to instill study intervention on the visit days. Study intervention will be instilled bilaterally by designated site personnel at Hour 0 (8 AM ± 1 hour) of Visits 1 to 5. In-between office visits, participants will be instructed to instill one drop of the dispensed study intervention in the morning once daily into both eyes.

6.2. Preparation/Handling/Storage/Accountability

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.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. 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. All study intervention must be stored upright, in a refrigerator, and protected from freezing.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Include participant ID number, bottle/carton serial or lot number, date of implantation, and date of explantation, if applicable.

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

All unused study intervention and empty bottles/cartons must be returned to the sponsor at the conclusion of the study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for. Unused drug supplies and empty drug bottles/cartons will be returned to the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using the IxRS. Randomization and kit assignment will be conducted on Day 1 (baseline). At Day 1, participants will be randomized in a 1:1 ratio into 1 of the 2 study groups. This randomization will be stratified by age (2 groups: ≤ 50 years and > 50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes. A maximum of 50% (75 per arm) of the participants enrolled will have brown iris color, and a maximum of 25% (38 per arm) of the participants will be non-emmetropes (a sphere outside of -0.50 D to +0.75 D and/or a cylinder greater than 0.75 D).

Before the study is initiated, login information and directions for the IxRS will be provided to each site. Study intervention and vehicle will be dispensed at the study visits summarized in the SoA (Section 1.3).

The identity of study intervention will be masked to the participants and study centers. The IxRS 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 Allergan 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, Allergan 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.

6.4. Study Intervention Compliance

Study intervention will be administered by designated site personnel on visit days and at home by the participant in-between office visits, ideally prior to starting their day. On the day before office visits, the study intervention must be administrated no less than 16 hours before the scheduled visit time.

On visit days, study intervention compliance will be assumed to be 100% when dosing has been recorded in the eCRF.

In-between office visits, study intervention compliance will be closely monitored by counting the number of bottles dispensed and returned.

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.

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 visit along with the reason the medication is taken.

From screening to the EOS, site staff will question each participant specifically on the use of concomitant medications. Site staff must notify the sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who used prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

6.5.1. Prohibited Interventions and Washout Before the Study

Use of medications that may have a substantial effect on visual function or the optical properties of the eye is prohibited 2 weeks prior to Day 1 visit and during the study:

- systemic medications with potential ocular side effects, including topiramate, hydroxychloroquine, ethambutol, phosphodiesterase 5 inhibitors (sildenafil, vardenafil, tadalafil), or tamoxifen
- ophthalmic, systemic, or intranasal anticholinergics and α-adrenergic receptor agonists with potential pupillary or accommodative effects, including oxymetazoline, pilocarpine, tetrahydrozoline, phenylephrine, naphazoline, cyclopentolate, atropine, beta-blockers, or antihistamines
- systemic maprotiline, tricyclic antidepressants, or monoamine oxidase inhibitors

6.5.2. Permitted Interventions

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 enrollment 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.

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

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.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

6.5.4. Prohibited Interventions During the Study

Use of ocular medications other than study intervention or medications administered to conduct study procedures are prohibited from the screening visit until study exit.

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

6.6. Dose Modification

Dose modification is not applicable.

6.7. Intervention after the End of the Study

No interventions after the end of the study are planned.

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.

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

- AE
- Lack of efficacy
- 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 (Section 1.3) for data to be collected at the time of early exit.

Participants who discontinue the study intervention early will be encouraged to stay in the study for the safety assessments at Day 30.

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.

- 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.
- See the SoA (Section 1.3) for data to be collected at the time of early exit.

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 will 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.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor promptly 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- The maximum amount of blood collected for PK from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 45 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Efficacy assessments are: mesopic and photopic, high contrast DCNVA for each eye and binocularly, mesopic and photopic, high contrast DCIVA for each eye and binocularly, mesopic and photopic pupil diameter (distance and near), PRO questionnaires (NVPTQ, PICQ, PPSQ, and Single-Item PGIS, PGIC, and Patient Expectations for Treatment Efficacy), and depth of focus.

Timing and measurement details are provided in Table 8-1. For additional detail on efficacy assessments, please see the Procedure Manual.

Table 8-1 Efficacy Assessments

Assessment	Timing	Measurement
Visual Acuity		
Mesopic, high contrast DCNVA for each eye and binocularly	• Screening • Days 1, 14, and 30: Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	• 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.
Photopic, high contrast DCNVA for each eye and binocularly	• Screening • Days 1, 14, and 30: Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	
Mesopic and photopic, high contrast DCIVA for each eye and binocularly	• Screening • Days 1, 14, and 30: Hours 0, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	
Pupil Diameter		
Mesopic pupil diameter (distance)	• Screening • Days 1, 14, and 30: Hours 0, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	• Pupil diameter for near (40-cm) and distance (4-meter) targets will be measured with the pupillometer in mesopic and photopic conditions.
Mesopic pupil diameter (near)	• Screening • Days 1, 14, and 30: Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	
Photopic pupil diameter (distance)	• Screening • Days 1, 14, and 30: Hours 0, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	

Assessment	Timing	Measurement
Photopic pupil diameter (near)	• Screening • Days 1, 14, and 30: Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10 • Days 3 and 7: Hours 0, 1, and 3	
Depth of focus	• Screening • Hours 0 and 1 at all visits thereafter	• Depth of focus will be measured on each eye with a phoropter.
PRO Questionnaires		
Mesopic and Photopic NVPTQ	• Day 1, Hour 0 • Day 14, Hour 1 • Day 30, Hour 3	• Comprised of 12 questions on 4 reading tasks (ie, 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) • Participants will complete specific reading tasks under mesopic and photopic conditions without any near-vision correction • Participants will then answer 3 questions for each task, rating their vision-related reading ability and satisfaction with their vision-related reading ability • There is no explicit recall period used for the NVPTQ; the intention is for patients to complete the NVPTQ immediately after completing each task. • For more details on instructions and questions in NVPTQ, please see Appendix 8
PICQ	• Day 1, Hour 0 • Day 30, Hour 3	• Participants will answer 20 questions about the degree to which they were impacted by their difficulty seeing up close (eg, found daily near-vision tasks difficult, or experienced self-consciousness); or engaged in coping behaviors (eg, changed the font size on electronic screens) during the previous 7 days • For more details on instructions and questions in PICQ, please see Appendix 8
PPSQ	• Day 30, Hour 3	• Participants will answer 7 questions related to the following: o how the study intervention worked to help with their difficulty seeing up close o how satisfied they were with the study intervention's effects on their ability to perform tasks in their daily life o the extent to which the study intervention met their expectations and was easy to use o the likelihood that they would use the study intervention over their previous method of vision correction • There is no explicit recall period for PPSQ. • For more details on instructions and questions in PPSQ, please see Appendix 8

Assessment	Timing	Measurement
Single-Item PGIS Question	• Day 1, Hour 0 • Day 14, Hour 1 • Day 30, Hour 3	• Participants will answer a single-item question about their global impression of the status of their near-vision acuity in the past 7 days, under mesopic conditions • See Appendix 8 for a copy of PGIS
Single-Item PGIC Question	• Day 14, Hour 1 • Day 30, Hour 3	• Participants will answer a single-item question about their global impression of change in their near-vision acuity under mesopic conditions • See Appendix 8 for a copy of PGIC
Single-Item Patient Expectations for Treatment Efficacy	• Day 1, Hour 0	• Participants will answer a single-item question about their expectations for treatment efficacy • See Appendix 8 for a copy of "Expectations for Treatment Efficacy"

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Vital Signs

Vital signs will be assessed as follows:

- Blood pressure and pulse rate will be assessed.
- Systolic and diastolic blood pressure will be measured using an appropriate sphygmomanometer after participants have been at rest (seated) for at least 5 minutes. Blood pressure will be recorded in mm Hg.
- Heart rate will be measured in bpm after the participant has been in a resting state (seated) for at least 5 minutes. Pulse will be counted for 30 seconds, multiplied by 2, and recorded in bpm.
- 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. Manual techniques will be used only by adequately trained personnel; whenever possible, the same person should perform all manual assessments as much as possible.
- Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.

8.2.2. Pregnancy Testing

Pregnancy test kits will be provided by the investigator and will be administered according to the instructions provided with the tests. WOCBP must have a negative test result before receiving

study intervention. This test will also be performed at the Day 30 (Early Exit) visit, and may be performed at any other visit, at the investigator's discretion. At each visit, the investigator should discuss contraceptive use compliance with WOCBP. Additional details are provided in Appendix 6.

8.2.3. Photopic and Mesopic, High Contrast Corrected Distance Visual Acuity for Each Eye and Binocularly

Photopic and mesopic, high contrast CDVA, for each eye and binocularly, will be assessed using the provided visual acuity charts for distance vision in a room with mesopic lighting conditions (defined by lighting 3.2 to 3.5 candelas [cd]/m^2 [10 to 11 lux] measured at the target) and photopic lighting conditions (defined by lighting $\geq$ 80 cd/m^2 [251 lux] measured at the target). Forced choice letter by-letter scoring will be used for each test and the total number of correct letters or the highest value (number) of the grid identified (as applicable) will be recorded. Further details are outlined in the Procedure Manual.

8.2.4. Near Contrast Sensitivity

Near contrast sensitivity assessment will be conducted under photopic conditions. A Pelli-Robson contrast sensitivity chart will be used. The logarithmic contrast sensitivity value of the last triplet of which at least 2 letters are correctly read is marked as the contrast sensitivity. Further details are outlined in the Procedure Manual.

8.2.5. Study Intervention Tolerability and Drop Comfort Assessments

The presence and severity of ocular symptoms will be elicited from the participant for both eyes after dosing. 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 second eye is instilled with a drop 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 (ie, soothing, very comfortable, comfortable, uncomfortable, very uncomfortable, and intolerable) immediately after the second eye is instilled with a drop of study intervention, for both eyes.

8.2.6. Temporal/Supraorbital Headache Visual Analog Scale

Participants will be asked to rate the degree of temporal and supraorbital headache experienced after the second eye is instilled with a drop of study intervention, for the right and left eyes separately. Headache will be reported on an unmarked 100-mm wide VAS, ranging from no pain on the left to worst possible pain on the right.

8.2.7. Intraocular Pressure

IOP must be measured after the biomicroscopic exam is completed and 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 measurer will look through the binocular viewer of the slit lamp at low power. The tension knob will be preset at a low-pressure value (4 to 6 mm Hg). The measurer will follow the image of the fluorescein stained semicircles while slowly rotating the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the measurer will take his/her fingers off the tension knob and record the IOP reading along with the date and time of day.

8.2.8. 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, and 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.

8.2.9. Manifest Refraction

Manifest refraction (distance and near) 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.

Additional details are outlined in the Procedure Manual.

8.2.10. Dilated Funduscopic 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 C/D ratio will be assessed. The investigator should note if the pupil dilated normally.

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 examination, the presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities will be evaluated. At the first dilated examination, each type of cataract, if present, will be graded using the scale below. At the last follow-up dilated 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.

C/D Ratio:

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

8.2.11. Suicidal Risk Monitoring

Suicidal risk monitoring is not applicable to this ophthalmology study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE 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 (ie, repeat treatment) or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

All AEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.3), 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.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 2. 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.

The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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 Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/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).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Allergan 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, the investigator will provide Allergan with a copy of any postmortem findings including histopathology.

If a participant is hospitalized and discharged, follow-up attempts must be made to obtain the discharge summary from the hospital and, if obtained, it should be sent to the sponsor.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to Allergan within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an 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, IRBs/IECs, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- If a pregnancy is confirmed after the participant has received the study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the EOS visit.
- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform Allergan within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.6. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

8.4. Treatment of Overdose

Treatment of overdose is not applicable to this ophthalmology study.

8.5. Pharmacokinetics

Blood samples for quantitation of pilocarpine in participant's plasma will be collected from approximately 10% of enrolled participants at selected sites.

8.5.1. Blood Pharmacokinetic Sampling Procedure

- 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 separated from each blood sample collected for measurement of plasma concentrations of pilocarpine as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided by Allergan. The actual date and time (24-hour clock time) of each sample will be recorded. PK blood samples to determine pilocarpine 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 taken outside the allowable time window will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs. 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 lab will supply the coded labels, vacutainers, and polypropylene tubes. The study center will be responsible for all other supplies.
- Samples will be used to evaluate the pharmacokinetics of pilocarpine. Each plasma sample will be divided into 2 aliquots (1 each for primary and backup PK samples). Samples collected for analyses of pilocarpine 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 investigative sites or blinded 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 Allergan'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 Collected per Participant

- Approximately 10% of participants at selected sites
- PK blood samples: 45 mL (9 blood samples, 5 mL each)

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 two approximately 1.25 mL samples in cryovials (one primary and one backup). The samples should be placed on wet ice immediately after aliquoting and transferred to a –20°C freezer within one hour of processing to plasma.

Study center staff will send plasma samples to the central lab for storage at the end of each period. Before shipment and on the day of shipment, the sponsor and the central lab will be notified by email as to the time and method of shipment. Primary and backup samples will be shipped to the central lab in separate shipments on separate days.

8.5.2. Pharmacokinetic Sample Bioanalysis

Plasma concentrations of pilocarpine in plasma will be determined using validated liquid chromatography-tandem mass spectrometry methods.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

8.8.1. Biomarkers

Biomarkers are not evaluated in this study.

8.8.2. Determination of Dominant Eye

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. Details will be outlined in the Procedure Manual.

8.9. Health Economics

Seven PRO instruments (questionnaires) are administered in this study (Appendix 8); three of which consist of a single-item.

At screening, participants 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.

Each participant will also perform four different near vision reading tasks under mesopic and photopic conditions. Participants will subsequently rate their vision-related reading ability, and satisfaction with their vision-related reading ability on the NVPTQ.

Participants will also answer questions measuring overall satisfaction with the treatment using the PPSQ, and questions assessing the impact of presbyopia on their life – and need for compensatory coping mechanisms – using the PICQ.

Participants will also answer single-item questions on their overall global impression of status (PGIS), and their overall global impression of change (PGIC). At baseline, participants will answer a single-item on their expectations of treatment efficacy.

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

For additional detail on PRO assessments, please see the PRO Assessments Manual.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null and alternative hypotheses for the primary efficacy endpoint are:

- H_0: AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days have the same effect in the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3;
- H_A: AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days do not have the same effect in the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3.

The null and alternative hypotheses for the key secondary efficacy endpoint are:

- H_0: AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days have the same effect in the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6;

- H_A: AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days do not have the same effect in the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6.

9.2. Sample Size Determination

The primary efficacy endpoint is the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3. The key secondary efficacy endpoint is the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The sample size calculation is based on the key secondary efficacy endpoint. The vehicle group intervention effect is assumed to be 3.6%, as observed in the Phase 2 study. AGN-190584 effect is assumed to be 16% in emmetropes and 12% in non-emmetropes. This gives an overall AGN-190584 effect of 15% assuming emmetropes will be 75% of the study population. 135 participants will be required in each study intervention group to detect the above difference with a power of 90% or greater at the 2-sided 5% significance level. Assuming a 10% dropout rate, approximately 150 participants per study intervention group will be randomized.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The ITT population includes all randomized participants. Participants will be summarized according to the randomized study intervention.
- The safety population includes all treated participants who receive ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and unmasking and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

The efficacy analyses will be based on the ITT population. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the first dose of study intervention. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

9.4.1.1. Analysis Endpoints

The primary and secondary efficacy endpoints are listed below and analyses will be described in the following sections. The analyses for other efficacy endpoints listed below will be described in the SAP.

Primary Efficacy Endpoint:

- Proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3.

Key Secondary Efficacy Endpoint:

- Proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6.

Secondary Efficacy Endpoints:

1. Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 8.
2. Change from baseline mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.5.
3. Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 1.
4. Mesopic NVPTQ Performance score mean change from baseline at Day 30, Hour 3.
5. Change from baseline photopic, high contrast, binocular DCIVA letters at Day 30, Hour 3.
6. Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 10.
7. Change from baseline mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.25.
8. Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 3.
9. Mesopic NVPTQ Satisfaction score mean change from baseline at Day 30, Hour 3.
10. PICQ Coping score mean change from baseline at Day 30, Hour 3.
11. PICQ Impact score mean change from baseline at Day 30, Hour 3.

9.4.1.2. Primary Analyses

The proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3 will be analyzed using chi-square test. Missing data will be regarded as 3-line gain failure.

9.4.1.3. Secondary Analyses

The key secondary efficacy endpoint is the proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6.

The key secondary efficacy endpoint will be analyzed using a chi-square test. Missing data will be regarded as 3-line gain failure.

All analyses for other secondary efficacy endpoints will be based on observed data only. Secondary endpoints 1, 3, 6, and 8 will be analyzed using a chi-square test. Secondary endpoints 2, 4, 5, and 7 will be analyzed using MMRM with study intervention group, visit, visit by study intervention group interaction, age group, baseline binocular DCNVA severity, iris color, emmetropes/non-emmetropes, baseline value, and baseline value by visit interaction as fixed effects. The within-participant correlation error structure is unstructured. Secondary endpoints 9, 10, and 11 will be analyzed using analysis of covariance with study intervention group, age group, baseline binocular DCNVA severity, iris color, emmetropes/non-emmetropes, and baseline domain score as fixed effects.

To control the overall Type 1 error rate in the efficacy analysis, a sequential testing procedure will be used. The test for the key secondary endpoint will be implemented only if the primary efficacy endpoint yields statistically significant results. All other secondary efficacy endpoints will be tested only if the key secondary efficacy endpoint is statistically significant. A proper multiple comparison procedure will be pre-specified in the SAP.

9.4.1.4. Other Efficacy Analyses

Detailed methods for the analyses of other efficacy variables will be described in the SAP.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, vital signs (blood pressure and heart rate), mesopic and photopic, high contrast, binocular CDVA, near contrast sensitivity, study intervention tolerability and drop comfort assessments, temporal/supraorbital headache assessment using VAS, IOP, slit-lamp biomicroscopy, manifest refraction, dilated funduscopic examination, and pregnancy test. For each safety parameter, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline.

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 treatment-emergent SAE if it is a TEAE that additionally meets any SAE criteria.

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.

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.

9.4.2.2. Other Safety Analyses

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

9.4.3. Pharmacokinetic Analyses

9.4.3.1. Pharmacokinetic Parameters

The following PK parameters will be calculated based on standard Phoenix WinNonlin equations: $AUC_{0\text{-last.ss}}$, maximum plasma drug concentration at steady state, time of maximum plasma drug concentration at steady state, $C_{min,ss}$, and peak-to-trough ratio.

$C_{min,ss}$ will be determined observationally as the drug concentration during the dosing interval at steady state.

$AUC_{0\text{-last,ss}}$ will be calculated by using the linear-log trapezoidal rule.

9.4.3.2. Statistical Analyses of Pharmacokinetic Data

Details of the statistical analyses of PK data will be described in the pharmacokinetic analysis plan finalized before database lock.

9.4.4. Other Analyses

Additional exploratory analyses on visual acuities will be described in the SAP to be finalized prior to database lock.

Additional PRO exploratory analyses will be described in a separate SAP to be finalized prior to database lock.

9.4.4.1. Subgroup Analyses

The primary and key secondary endpoints will be analyzed by age group, gender, race group, baseline binocular DCNVA severity, iris color, and emmetropes/non-emmetropes.

9.5. Interim Analyses

No interim analysis is planned.

9.5.1. Data Monitoring Committee

Not applicable.

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 Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/International Organization for Standardization GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, 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 overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators 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 or his/her legally authorized representative 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, Health Insurance Portability and Accountability Act requirements, where applicable, 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 or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- 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.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the United States National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, 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.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- 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.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, GCP: Consolidated Guidance and records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor 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

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- 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.
- 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. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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. • 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. **AESI** An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. There are no AESIs identified for the study intervention AGN-190584.

Events <u>Meeting</u> the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition 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 • 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 the lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease or disease progression, 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. Any abnormal test result that is determined to be an error does not require recording as an AE. • Medical or surgical procedure (eg, 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

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

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 intervention 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 intervention 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 (eg, 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. 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 intervention 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.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Allergan in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Allergan. 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 Allergan.
- 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	
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 of 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 one 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 or 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 IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 Allergan. 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 Allergan.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE/SADE Reporting
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone 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. • Contacts for SAE reporting can be found on the protocol title page.

10.3. Appendix 3: Abbreviations

Abbreviation/Term	Definition
AE	adverse event
AESI	adverse event of special interest
$AUC_{0\text{-last,ss}}$	area under the plasma concentration versus time curve from time 0 to the last measurable concentration, at steady state
bpm	beats per minute
C/D	cup to disc
CDISC	Clinical Data Interchange Standards Consortium
CDVA	corrected distance visual acuity
CFR	Code of Federal Regulations
$C_{min,ss}$	minimum plasma drug concentration at steady state
CRF	case report form
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
DET	dry eye test
eCRF	electronic case report form
EOS	end of the study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
ID	identification
IEC	independent ethics committee
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat
IxRS	interactive electronic response system
LASIK	laser-assisted in situ keratomileusis
MMRM	mixed model repeated measure
NCI	National Cancer Institute
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
NVPTQ	Near Vision Presbyopia Task-based Questionnaire
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index

Abbreviation/Term	Definition
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Status
PICQ	Presbyopia Impact and Coping Questionnaire
PK	pharmacokinetic
PPSQ	Presbyopia Patient Satisfaction Questionnaire
PRK	photorefractive keratectomy
PRO	patient reported outcomes
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
TEAE	treatment-emergent adverse event
VAS	visual analog scale
WOCBP	women of childbearing potential

10.4. Appendix 4: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
AE	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 SAE, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Lack of efficacy	The lack of expected or desired effect related to a therapy (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)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial

CDISC Submission Value	CDISC Definition
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)

10.5. Appendix 5: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia
	Clinical Study Sponsor	Allergan, Inc.
	Trial Phase Classification	Phase 3 Trial
	Trial Indication	Presbyopia
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety Pharmacokinetics
	Trial Length	30 days plus up to 30-day screening period
	Planned Country of Investigational Sites	United States
	Planned Number of Participants	300
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Diagnosis Group	Presbyopia
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	40
	Planned Maximum Age of Participants	55
	Sex of Participants	Male or female
	Stable Disease Minimum Duration	Not specified

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	AGN-190584 (Pilocarpine HCl 1.25% Ophthalmic Solution)
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Cholinergic agonist
	Dose per Administration	1 bilaterally
	Dose Units	Drop
	Dosing Frequency	Once daily
	Route of Administration	Topical eye drop
	Current Therapy or Treatment	No
	Added on to Existing Treatments	No
	Control Type	Vehicle
	Comparative Treatment Name	AGN-190584 Vehicle
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	1:1
	Trial Blinding Schema	Double-masked
	Stratification Factors	Age (2 groups: ≤ 50 years and > 50 years); baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60); iris color (brown and non-brown), and emmetropes/non-emmetropes
	Adaptive Design	No
	Study Stop Rules	None

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

WOCBP

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

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   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. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

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 10–1.

Table 10–1 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 • 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 • Intrauterine device • Intrauterine hormone-releasing system • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion Intrauterine copper contraceptive (ie, 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.

Female participants of childbearing potential are eligible to participate if they agree to use an acceptable method of contraception consistently and correctly.

Acceptable birth control methods that result in a failure of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Nonhormonal intrauterine device

Combinations of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at screening and also a negative test on Day 1.
- Additional pregnancy testing should be performed at study exit, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Urine pregnancy testing will be used unless the study site requires the use of serum testing, in which case serum testing will be used.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Allergan 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 Allergan. 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. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to Allergan 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.
- If a pregnancy is confirmed after the participant has received study intervention, the partcipant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit.

10.7. Appendix 7: Study Schedule Supplement

10.7.1. Screening Visit (Days -30 to -1)

The screening visit can occur any time from 30 days to 1 day prior to Day 1 (Visit 1, baseline). The following are to be performed at screening:

- Informed consent
- Iris color assessment
- Demography
- Medical and ophthalmic history
- Pre-study and concomitant medication query
- NEI VFQ-25 and near vision subscale in the Appendix of Optional Additional Questions. The near vision subscale includes questions A3 to A5 in the Appendix of Optional Additional Questions.
- OSDI
- AE query
- Vital signs (blood pressure and heart rate measured after participant has been at rest [seated] for at least 5 minutes)
- Urine pregnancy test for WOCBP only
- Review inclusion and exclusion criteria
- Determination of dominant eye
- Pupillary reaction to light assessment
- Perform the following under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - Dark adaptation (5 to 10 minutes in mesopic conditions)
    - Mesopic Manifest refraction (distance and near)

  - Mesopic, high contrast CDVA + pupil diameter (conducted with participant's best distance correction; CDVA to be measured OD, OS, and binocularly; pupil diameter must be measured in each individual eye)
  - Mesopic, high contrast DCIVA (conducted with participant's best distance correction; DCIVA to be measured OD, OS, and binocularly)
  - Mesopic, high contrast DCNVA + pupil diameter (conducted with participant's best distance correction; DCNVA to be measured OD, OS, and binocularly; pupil diameter must be measured in each individual eye; at screening, repeat the DCNVA assessment OD 3 times with different charts)

- Perform the following under photopic conditions ($\geq$ 80 cd/m^2; 251 lux at target):
  - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
  - Photopic manifest refraction (distance and near)
  - Photopic, high contrast CDVA + pupil diameter (conducted with participant's best distance correction; CDVA to be measured OD, OS, and binocularly; pupil diameter must be measured in each individual eye)
  - Photopic, high contrast DCIVA (conducted with participant's best distance correction; DCIVA to be measured OD, OS, and binocularly)
  - Photopic, high contrast DCNVA + pupil diameter (conducted with participant's best distance correction; DCNVA to be measured OD, OS, and binocularly; pupil diameter must be measured in each individual eye)
- Slit-lamp biomicroscopy
- Fluorescein corneal staining
- IOP measurement
- Gonioscopy/angle assessment
- Dilating drop administration (minimum 30-minute wait after administration of dilating drops)

- Cycloplegic refraction (distance, photopic)
- Dilated funduscopic examination (investigator should note if the pupil dilated normally)
- Contact IxRS for participant ID number

10.7.2. Day 1 (Visit 1, Baseline)

Study intervention administration at Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.

The following are to be performed on Day 1:

- Concomitant medication query (Hour 0)
- AE query (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
- Vital signs (Hours 0 and 1)
    - Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
- Urine pregnancy test for WOCBP only (Hour 0)
- Review inclusion and exclusion criteria (Hour 0)
- Contact IxRS for kit assignment/ randomization (Hour 0)
    - IxRS will be used to dispense medication. Please refer to the IxRS manual for additional information.
- PICQ (Hour 0)
    - Conducted with participant's habitual distance correction
- Single-item Patient Expectations for Treatment Efficacy Question (Hour 0)
    - Conducted with participant's habitual distance correction
- Depth of focus measurement (Hours 0 and 1)
- Perform the following under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Dark Adaptation (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
        - 5 to 10 minutes in mesopic conditions

- Mesopic, high contrast CDVA + pupil diameter (Hours 0, 1, 3, 6, 8, and 10)
    - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
- Mesopic, high contrast DCIVA (Hours 0, 1, 3, 6, 8, and 10)
    - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
- Mesopic, high contrast DCNVA + pupil diameter (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
    - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
- Single-item PGIS (Hour 0)
    - Conducted with participant's best distance correction
- Mesopic NVPTQ (Hour 0)
    - Conducted with participant's best distance correction

- Perform the following under photopic conditions (≥ 80 cd/m^2; 251 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Photopic, high contrast CDVA + pupil diameter (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Photopic, high contrast DCIVA (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.

  - Photopic, high contrast DCNVA + pupil diameter (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
    - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
  - Near contrast sensitivity assessment (Hours 0 and 1)
    - Conducted with participant's best distance correction
  - Photopic NVPTQ (Hour 0)
    - Conducted with participant's best distance correction

- Slit-lamp biomicroscopy (Hours 0 and 1)
- IOP measurement (Hours 0 and 1)
- Temporal/supraorbital headache VAS assessment (Hours 0, 0.5, and 1)
  - Conducted before dosing at Hour 0 of each visit
- PK blood draw (Hour 0)
  - Conducted at selected sites only; Hour 0 blood draw must be done before study intervention administration.
- Study intervention administration (Hour 0)
  - Hour 0 starts after study intervention administration.
- Tolerability assessment/drop comfort questionnaire (Hour 0)
- Study intervention dispensing (Hour 10)
  - Refer to Section 6.2 regarding study intervention dispensation.

10.7.3. Day 3 (Visit 2)

Study intervention administration at Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.

The following are to be performed on Day 3:

- Concomitant medication query (Hour 0)
- AE query (Hours 0, 1, and 3)
- Vital signs (Hours 0 and 1)
    - Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
- Depth of focus measurement (Hours 0 and 1)
- Perform the following under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Dark adaptation (Hours 0, 1, and 3)
        - 5 to 10 minutes in mesopic conditions
    - Mesopic, high contrast CDVA + pupil diameter (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Mesopic, high contrast DCIVA (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Mesopic, high contrast DCNVA + pupil diameter (Hours 0, 1, 3)

        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.

- Perform the following under photopic conditions (≥ 80 cd/m^2; 251 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Photopic, high contrast CDVA + pupil diameter (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Photopic, high contrast DCIVA (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Photopic, high contrast DCNVA + pupil diameter (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Near contrast sensitivity assessment (Hours 0 and 1)
        - Conducted with participant's best distance correction
- Slit-lamp biomicroscopy (Hours 0 and 1)
- Temporal/ supraorbital headache VAS assessment (Hours 0 and 1)
    - Conducted before dosing at Hour 0 of each visit
- Study intervention administration (Hour 0)
    - Hour 0 starts after study intervention administration.
- Tolerability assessment/drop comfort questionnaire (Hour 0)

10.7.4. Day 7 ± 2 Days (Visit 3)

Study intervention administration at Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.

The following are to be performed on Day 7 ± 2 days:

- Concomitant medication query (Hour 0)
- AE query (Hours 0, 1, and 3)
- Vital signs (Hours 0 and 1)
    - Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
- Depth of focus measurement (Hours 0 and 1)
- Perform the following under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Dark adaptation (Hours 0, 1, and 3)
        - 5 to 10 minutes in mesopic conditions
    - Mesopic, high contrast CDVA + pupil diameter (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Mesopic, high contrast DCIVA (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Mesopic, high contrast DCNVA + pupil diameter (Hours 0, 1, 3)

        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.

- Perform the following under photopic conditions (≥ 80 cd/m^2; 251 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Photopic, high contrast CDVA + pupil diameter (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Photopic, high contrast DCIVA (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Photopic, high contrast DCNVA + pupil diameter (Hours 0, 1, and 3)
        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Near contrast sensitivity assessment (Hours 0 and 1)
        - Conducted with participant's best distance correction
- Slit-lamp biomicroscopy (Hours 0 and 1)
- Temporal/ supraorbital headache VAS assessment (Hours 0 and 1)
    - Conducted before dosing at Hour 0 of each visit
- Study intervention administration (Hour 0)
    - Hour 0 starts after study intervention administration.
- Tolerability assessment/drop comfort questionnaire (Hour 0)

10.7.5. Day 14 ± 2 Days (Visit 4)

Study intervention administration at Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.

The following are to be performed on Day 14 ± 2 days:

- Concomitant medication query (Hour 0)
- AE query (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
- Vital signs (Hours 0 and 1)
    - Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
- Depth of focus measurement (Hours 0 and 1)
- Perform the following under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Dark Adaptation (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
        - 5 to 10 minutes in mesopic conditions
    - Mesopic, high contrast CDVA + pupil diameter (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Mesopic, high contrast DCIVA (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Mesopic, high contrast DCNVA + pupil diameter (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)

        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Single-item PGIS (Hour 1)
        - Conducted with participant's best distance correction
    - Single-item PGIC (Hour 1)
        - Conducted with participant's best distance correction
    - Mesopic NVPTQ (Hour 1)
        - Conducted with participant's best distance correction
- Perform the following under photopic conditions (≥ 80 cd/m^2; 251 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Photopic, high contrast CDVA + pupil diameter (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Photopic, high contrast DCIVA (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Photopic, high contrast DCNVA + pupil diameter (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Near contrast sensitivity assessment (Hours 0 and 1)
        - Conducted with participant's best distance correction

    - Photopic NVPTQ (Hour 1)
        - Conducted with participant's best distance correction
- Slit-lamp biomicroscopy (Hours 0 and 1)
- IOP measurement (Hours 0 and 1)
- Temporal/supraorbital headache VAS assessment (Hours 0, 0.5, and 1)
    - Conducted before dosing at Hour 0 of each visit
- Study intervention administration (Hour 0)
    - Hour 0 starts after study intervention administration.
- Tolerability assessment/drop comfort questionnaire (Hour 0)

10.7.6. Day 30 ± 3 Days/Early Exit (Visit 5)

Study intervention administration at Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.

The following are to be performed on Day 30 ± 3 days:

- Concomitant medication query (Hour 0)
- AE query (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
- Vital signs (Hours 0 and 1)
    - Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
- Urine pregnancy test (Hour 0)
    - WOCBP only
- PICQ (Hour 3)
    - Conducted with participant's habitual distance correction
- PPSQ (Hour 3)
    - Conducted with participant's habitual distance correction
- Depth of focus measurement (Hours 0 and 1)
- Perform the following under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Dark Adaptation (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
        - 5 to 10 minutes in mesopic conditions
    - Mesopic, high contrast CDVA + pupil diameter (Hours 0, 1, 3, 6, 8, and 10)

        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Mesopic, high contrast DCIVA (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Mesopic, high contrast DCNVA + pupil diameter (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Single-item PGIS (Hour 3)
        - Conducted with participant's best distance correction
    - Single-item PGIC (Hour 3)
        - Conducted with participant's best distance correction
    - Mesopic NVPTQ (Hour 3)
        - Conducted with participant's best distance correction
- Perform the following under photopic conditions (≥ 80 cd/m^2; 251 lux at target):
    - Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
    - 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.
    - Photopic, high contrast CDVA + pupil diameter (Hours 0, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Photopic, high contrast DCIVA (Hours 0, 1, 3, 6, 8, and 10)

        - Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
    - Photopic, high contrast DCNVA + pupil diameter (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
        - Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
    - Near contrast sensitivity assessment (Hours 0 and 1)
        - Conducted with participant's best distance correction
    - Photopic NVPTQ (Hour 3)
        - Conducted with participant's best distance correction
- Slit-lamp biomicroscopy (Hours 0 and 1)
- IOP measurement (Hours 0 and 1)
- Temporal/supraorbital headache VAS assessment (Hours 0, 0.5, and 1)
    - Conducted before dosing at Hour 0 of each visit
- PK blood draw (Hours 0, 0.25, 0.5, 1, 3, 6, 8, and 10)
    - Conducted at selected sites only; Hour 0 blood draw must be done before study intervention administration.
- Study intervention administration (Hour 0)
    - Hour 0 starts after study intervention administration.
- Tolerability assessment/drop comfort questionnaire (Hour 0)
- Dilating drop administration (Hour 10)
    - Minimum 30-minute wait after administration of dilating drops
- Dilated funduscopic examination (Hour 10)
    - Investigator should note if the pupil dilated normally

10.8. Appendix 8: Patient Reported Outcomes Questionnaires, Descriptions, and Instructions

10.8.1. National Eye Institute Visual Function Questionnaire 25

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your overall health is*:**

(Circle One)

READ CATEGORIES:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. **At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

(Circle One)

READ CATEGORIES:

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?
(Circle One)

READ CATEGORIES:		
	None of the time	1
	A little of the time	2
	Some of the time	3
	Most of the time	4
	All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:
(Circle One)

READ CATEGORIES:		
	None	1
	Mild	2
	Moderate	3
	Severe, or	4
	Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

16. **How much difficulty do you have driving at night? Would you say you have:** (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. **How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DRIVING

A10. [This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.....	1	2	3	4	5

10.8.2. Near Vision Presbyopia Task-based Questionnaire

Near Vision Presbyopia Task-based Questionnaire (NVPTQ)

Instructions: This questionnaire includes 12 questions on four reading tasks that you are about to complete.

You will be asked to read text from the following examples:

- Paragraph from a book
- Newspaper article
- Menu
- Nutrition label

We will then ask you some follow-up questions about your ability to read each example, as well as your satisfaction with reading.

Please perform each reading task as you normally would, without squinting. You may read each example either out loud or to yourself. We only want to know how well you can see the text for each example, therefore you will not be asked any questions about your ability to understand what you are reading. There are no right or wrong answers.

#	Question
Task #1: Reading a book – Please check ONE box for each question.	

1. Rate your ability to read the text in the book:

□0 I could not read any of the text due to problems seeing up close
□1 Poor
□2 Fair
□3 Good
□4 Very good
□5 Excellent

2. Did you squint while reading the text in the book?

□0 No, I did not squint
□1 Yes, and squinting helped me read some or all of the text
□2 Yes, but I still could not read any of the text

3. How satisfied are you with your ability to read the text in the book?

□0 Very dissatisfied
□1 Dissatisfied
□2 Neither satisfied nor dissatisfied
□3 Satisfied
□4 Very satisfied

#	Question
Task #2: Reading a newspaper – Please check ONE box for each question.	

4. Rate your ability to read the text in the newspaper:

□0 I could not read any of the text due to problems seeing up close
□1 Poor
□2 Fair
□3 Good
□4 Very good
□5 Excellent

5. Did you squint while reading the text in the newspaper?

□0 No, I did not squint
□1 Yes, and squinting helped me read some or all of the text
□2 Yes, but I still could not read any of the text

6. How satisfied are you with your ability to read the text in the newspaper?

□0 Very dissatisfied
□1 Dissatisfied
□2 Neither satisfied nor dissatisfied
□3 Satisfied
□4 Very satisfied

#	Question
Task #3: Reading a menu – Please check ONE box for each question.	

7. Rate your ability to read the text in the menu:

□0 I could not read any of the text due to problems seeing up close
□1 Poor
□2 Fair
□3 Good
□4 Very good
□5 Excellent

8. Did you squint while reading the text in the menu?

□0 No, I did not squint
□1 Yes, and squinting helped me read some or all of the text
□2 Yes, but I still could not read any of the text

9. How satisfied are you with your ability to read the text in the menu?

□0 Very dissatisfied
□1 Dissatisfied
□2 Neither satisfied nor dissatisfied
□3 Satisfied
□4 Very satisfied

#	Question
Task 4: Reading a nutrition label – Please check ONE box for each question.	

10. Rate your ability to read the text in the nutrition label:

□0 I could not read any of the text due to problems seeing up close
□1 Poor
□2 Fair
□3 Good
□4 Very good
□5 Excellent

11. Did you squint while reading the text in the nutrition label?

□0 No, I did not squint
□1 Yes, and squinting helped me read some or all of the text
□2 Yes, but I still could not read any of the text

12. How satisfied are you with your ability to read the text in the nutrition label?

□0 Very dissatisfied
□1 Dissatisfied
□2 Neither satisfied nor dissatisfied
□3 Satisfied
□4 Very satisfied

10.8.3. Presbyopia Impact and Coping Questionnaire

Presbyopia Impact and Coping Questionnaire (PICQ)

Instructions: This questionnaire includes 20 questions about the impacts you may experience as a result of your problems seeing up close **over the past 7 days**. Please check ONE box for each question. There are no right or wrong answers.

Item #	Question
1.	Over the past 7 days, how **often** did you need to use or do something (for example, wear glasses, squint, etc.) to help you read **normal** sized text at a close distance on paper (for example, a menu or book)? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time
2.	Over the past 7 days, how **often** did you need to use or do something (for example, wear glasses, squint, etc) to help you read **small** sized text at a close distance on paper (for example, a nutrition label or prescription bottle)? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time

Item #	Question

Instructions: For questions 3-11, please choose only ONE answer from either column A or column B. Do not check more than one box per question.

3. Over the past 7 days, how **often** did you need to use or do something (for example, wear glasses, squint, etc.) to help you read information on a **computer**?

Column A	Column B
□0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 I did not use a computer over the past 7 days

4. Over the past 7 days, how **often** did you need to use or do something (for example, wear glasses, squint, etc.) to help you read information on a **cell phone**?

Column A	Column B
□0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 I did not use a cell phone over the past 7 days

Item #	Question

5. Over the past 7 days, how **often** did you need to increase the font size (or use the zoom feature) on a computer, tablet, or cell phone in order to read the information displayed?

Column A	Column B
□0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 I did not use a computer, tablet, or cell phone over the past 7 days □10 I permanently increased the font size on my computer, tablet, or cell phone prior to the past 7 days

6. Over the past 7 days, how **often** did you need to use glasses in order to help you read text at a close distance?

Column A	Column B
□0 Never. I did not need to use my glasses because the text at a close distance was clear □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 Never, because I do not use glasses to read text at a close distance

Item #	Question

7. Over the past 7 days, how **often** did you have to adjust the brightness setting on a computer, tablet or cell phone in order to read the information on the screen?

Column A	Column B
□0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 I did not use a computer, tablet or cell phone over the past 7 days

8. Over the past 7 days, how **often** did you have to switch between wearing and not wearing distance glasses when looking at something up close and then looking at something far away?

Column A	Column B
□0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 I did not wear distance glasses over the past 7 days

Item #	Question

9. Over the past 7 days, how **often** did you rely on others to read materials because of your problems seeing up close?

Column A	Column B
□0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 Never because I used or did something to help (glasses, contacts, squinting, etc.)

10. Over the past 7 days, how **difficult** was it to work with small objects (for example, sewing, crafting, electrical wiring, woodworking, fishing) due to your problems seeing up close?

Column A	Column B
□0 Not at all difficult □1 A little difficult □2 Somewhat difficult □3 Quite a bit difficult □4 Very difficult	□9 I did not work with small objects over the past 7 days

Item #	Question

11. Over the past 7 days, how **often** did you feel annoyed when trying to read materials at a close distance?

Column A	Column B
□0 Never, and did not use anything to help (no glasses, no contacts, etc.) □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time	□9 Never, because I used something to help (glasses, contacts, etc.)

12. Over the past 7 days, how **often** did you find yourself holding reading materials farther out or closer to you, in order to read the text?

□0 Never
□1 Rarely
□2 Some of the time
□3 Most of the time
□4 All of the time

13. Over the past 7 days, how **often** did you have to squint to read something at a close distance?

□0 Never
□1 Rarely
□2 Some of the time
□3 Most of the time
□4 All of the time

Item #	Question
14.	Over the past 7 days, how **often** did you have to adjust the lighting in a room, or move closer to a light source, so that you were able to read something at a close distance? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time
15.	Over the past 7 days, how **often** did you have to rest your eyes because of reading something at a close distance? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time
16.	Over the past 7 days, how **often** did your problems seeing up close make you feel older? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time

Item #	Question
17.	Over the past 7 days, how **often** did you feel self-conscious because of your problems seeing up close? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time
18.	Over the past 7 days, how **often** did you feel less confident because of your problems seeing up close? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time
19.	Over the past 7 days, how **often** did it take you longer to complete a task (for example, a task that involved reading at work, cooking, etc) due to your problems seeing up close? □0 Never □1 Rarely □2 Some of the time □3 Most of the time □4 All of the time

Item #	Question
20.	Over the past 7 days, how **inconvenient** was it to switch from looking at something up close to looking at something far away (for example, looking at a book and then looking up at the TV)? □0 Not at all inconvenient □1 A little inconvenient □2 Somewhat inconvenient □3 Very inconvenient □4 Extremely inconvenient

10.8.4. Presbyopia Patient Satisfaction Questionnaire

Presbyopia Patient Satisfaction Questionnaire (PPSQ)

Instructions: This questionnaire includes 7 questions about how your study medication works to help with your problems seeing up close, and how satisfied you are with how it works. Please check ONE box for each question. There are no right or wrong answers.

Item #	Question
1.	Overall, how did your study medication for your problems seeing up close affect your vision? Did your medication make your vision: □0 Far worse □1 Moderately worse □2 Slightly worse □3 No change □4 Slightly better □5 Moderately better □6 Far better □7 Complete improvement (no problems seeing up close)
2.	Overall, how satisfied were you with the effect the study medication had on your ability to perform daily activities (for example, getting ready in the morning, performing tasks at work)? □0 Very dissatisfied □1 Dissatisfied □2 Neither satisfied nor dissatisfied □3 Satisfied □4 Very satisfied

Item #	Question
3.	Overall, how satisfied are you with the effect the study medication had on your ability to see things up close without using anything to help (for example, glasses, contacts, squinting, etc.)? □0 Very dissatisfied □1 Dissatisfied □2 Neither satisfied nor dissatisfied □3 Satisfied □4 Very satisfied
4.	Overall, how satisfied are you with the effect the study medication had on your ability to read in dim light without using anything to help (for example, glasses, contacts, squinting, etc.)? □0 Very dissatisfied □1 Dissatisfied □2 Neither satisfied nor dissatisfied □3 Satisfied □4 Very satisfied
5.	Overall, how satisfied are you with how easy it is to use your study medication for your problems seeing up close? □0 Very dissatisfied □1 Dissatisfied □2 Neither satisfied nor dissatisfied □3 Satisfied □4 Very satisfied

Item #	Question
6.	Overall, to what extent do you feel that your study medication for your problems seeing up close met your expectations? □0 Far worse than expected □1 Worse than expected □2 Met expectations □3 Better than expected □4 Far better than expected
7.	Overall, how likely would you be to use the study medication over your previous form of vision correction (for example, anything you use to help with your problems seeing up close)? □0 Extremely unlikely □1 Unlikely □2 Neutral □3 Likely □4 Extremely likely

10.8.5. Patient Global Impression of Status

Patient Global Impression of Status (PGIS)

Instructions: Please check ONE box when answering the question. There is no right or wrong answer.

Item #	Question
1.	Overall, how would you rate your problems seeing up close in the past 7 days? □0 None □1 Mild □2 Moderate □3 Severe □4 Very severe

10.8.6. Patient Global Impression of Change

Patient Global Impression of Change (PGIC)

Instructions: Please check ONE box when answering the question. There is no right or wrong answer.

Item #	Question
1.	Overall, how did your study medication for your problems seeing up close affect your vision? Did your medication make your vision: □0 Far worse □1 Moderately worse □2 Slightly worse □3 No change □4 Slightly better □5 Moderately better □6 Far better

10.8.7. Patient Expectations for Treatment Efficacy

Expectations for Treatment Efficacy Question

Instructions: This questionnaire includes 1 question about how satisfied you expect to be with how your study medication will work for your problems seeing up close. Please check ONE box when answering the question. There is no right or wrong answer.

Item #	Question
1.	Overall, what is your expectation of how the study medication will affect your vision? Do you expect the medication will make your vision: □0 Far worse □1 Moderately worse □2 Slightly worse □3 No change □4 Slightly better □5 Moderately better □6 Far better □7 Complete improvement (no problems seeing up close)

11. References

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1883-301-013 Protocol Amendment 1

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
05-Dec-2018 10:58 GMT-080	Robinson_Michael	Clinical Development Approval

Title Page

Protocol Title: A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

Protocol Number: 1883-301-013

Compound Number: AGN-190584

Short Title: Phase 3 efficacy study of AGN-190584 in participants with presbyopia

Sponsor Name: Allergan, Inc.

Legal Registered Address: 2525 Dupont Drive, Irvine, CA 92612, USA

Regulatory Agency Identifier Number(s)

Registry	**NDA 214028**
Enter Registry Name	**Phase 3 efficacy study of AGN-190584 in participants with presbyopia**

Approval Date: January 30, 2020

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SAP Version History

This SAP for study 1883-301-013 is based on the protocol amendment 1, dated December 02018.

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1	07/16/2019	Not Applicable	Original version
2	10/23/2019	Multiplicity Adjustment	Amendment 1 to update the secondary endpoints multiplicity adjustment
3	1/21/2020	Used TransCelerate template	Updated to new format using TransCelerate template
4	1/30/2020	Added 2 line gainer analysis	Added 2 line gainer analysis with mesopic DCNVA

1. Introduction

This SAP provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the protocol amendment 1 of study 1883-301-013 (dated 05 December 2018). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for health economics data will be prepared separately.

Objectives and Endpoints

The objectives of this study are to evaluate the efficacy, safety, and pharmacokinetics of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia. Details of the study objectives and corresponding endpoints are described in the table below:

Objectives	Endpoints
To evaluate the efficacy of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia.	• Mesopic and photopic, high contrast DCNVA for each eye and binocularly • Mesopic and photopic, high contrast DCIVA for each eye and binocularly • Mesopic and photopic pupil diameter (distance and near) • Depth of focus • PRO questionnaires: o Mesopic and Photopic NVPTQ o PICQ o PPSQ o Single-Item PGIC o Single-Item PGIS o Single-Item Patient Expectations for Treatment Efficacy
To evaluate the safety and tolerability of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• AEs • Photopic and mesopic high contrast CDVA for each eye and binocularly • Near Contrast sensitivity • Vital signs (blood pressure and heart rate) • Study drug tolerability and drop comfort assessments • Temporal/supraorbital headache VAS • IOP • Slit-lamp biomicroscopy • Manifest refraction • Dilated funduscopic examination
To evaluate the pharmacokinetics of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• Plasma concentrations of AGN-190584 (sampled at selected sites; approximately 10% of all enrolled participants)

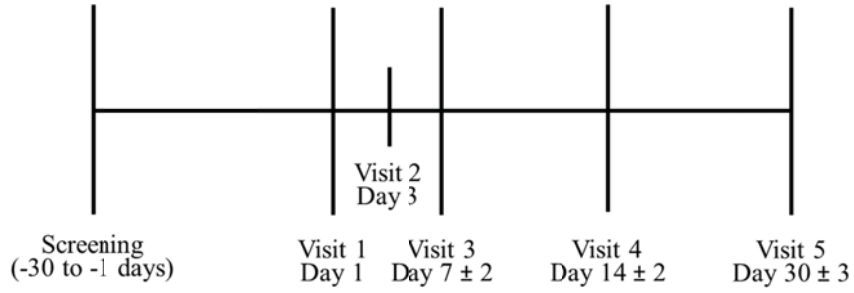
1.1. Study Design

Study 1883-302-013 is a multicenter, double-masked, randomized, vehicle-controlled, parallel group, Phase 3 study evaluating the efficacy and safety of AGN-190584 (1.25% pilocarpine) dosed once daily, bilaterally, over a period of 30 days in participants with presbyopia. The study population will consist of adult male and female participants with objective and subjective evidence of presbyopia. Approximately 150 participants per group will be randomized to achieve at least 135 participants per group completing the study based on an assumed dropout rate of 10%.

Participants will be randomized in a 1:1 ratio to receive either AGN-190584 or vehicle dosed once daily, in each eye, for 30 days. This randomization will be stratified by age (2 groups: ≤ 50 years and > 50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes. This study consists of the following visits: screening (Days -30 to -1), Day 1 (baseline), and Days 3, 7, 14, and 30.

Study interventions, either AGN-190584 or vehicle will be administered as topical eye drops once daily. Following the study schema (Figure 1-1), study intervention will be administered by designated site personnel on visit days and at home by the participant in-between office visits, ideally prior to starting their day. On the day before office visits, the study intervention must be administrated no less than 16 hours before the scheduled visit time.

Figure 1-1 Study Schema



The schedule of activities for Study 1883-301-013 is presented in Table 1-1**Error! Reference source not found.** and Table 1-2**Error! Reference source not found.**.

Table 1-1 Schedule of Visits and Procedures: Screening to Visit 3

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Informed consent	X															
Iris color assessment	X															
Demography	X															
Medical and ophthalmic history	X															
Pre-study/ concomitant medication query	X	X								X			X			
NEI VFQ-25 and near vision subscale in the Appendix of Optional Additional Questions	X															Near vision subscale includes questions A3 to A5 in the Appendix of Optional Additional Questions in the study protocol
OSDI	X															
AE query	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X			X					X	X		X	X		Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
Urine pregnancy test	X	X														WOCBP only
Review inclusion and exclusion criteria	X	X														

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Determination of dominant eye	X															
Contact IxRS for kit assignment/ randomization		X														IxRS will be used to dispense medication. Please refer to the IxRS manual for additional information
PICQ		X														Conducted with participant's habitual distance correction
Single-item Patient Expectations for Treatment Efficacy Question		X														Conducted with participant's habitual distance correction
Depth of focus measurement		X			X					X	X		X	X		
Pupillary reaction to light assessment	X															
Perform under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target)																Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Dark adaptation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5 to 10 minutes in mesopic conditions
Mesopic Manifest Refraction (distance and near)	X															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.
Mesopic, high contrast CDVA + pupil diameter	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Mesopic, high contrast DCIVA	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
Mesopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye. At screening, repeat the DCNVA assessment OD 3 times with different charts.
Single-item PGIS		X														Conducted with participant's best distance correction
Mesopic NVPTQ		X														Conducted with participant's best distance correction
Perform under photopic conditions (≥ 80 cd/m^2; 251 lux at target):																Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Photopic manifest refraction (distance and near)	X															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.
Photopic, high contrast CDVA + pupil diameter	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Photopic, high contrast DCIVA	X	X			X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Photopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Near Contrast sensitivity assessment		X			X					X	X		X	X		Conducted with participant's best distance correction
Photopic NVPTQ		X														Conducted with participant's best distance correction
Slit-lamp biomicroscopy	X	X			X					X	X		X	X		
Fluorescein Corneal staining	X															
IOP measurement	X	X			X											
Gonioscopy/ angle assessment	X															
Dilating drop administration	X															Minimum 30-minute wait after administration of dilating drops
Cycloplegic refraction	X															Distance, photopic
Dilated funduscopic examination	X															Investigator should note if the pupil dilated normally.
Contact IxRS for participant ID number	X															
Temporal/ supraorbital headache VAS assessment		X		X	X					X	X		X	X		Conducted before dosing at Hour 0 of each visit

Procedure	Screening	Study Days (Visits)														Notes
		Day 1 (Visit 1)								Day 3 (Visit 2)			Day 7 (Visit 3)			
Visit Windows	Days -30 to -1	N/A								N/A			± 2 days			
Hours		0	0.25	0.5	1	3	6	8	10	0	1	3	0	1	3	Study intervention administration: Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
PK blood draw		X														Conducted at selected sites only; Hour 0 blood draw must be done before study intervention administration.
Study intervention administration		X								X			X			Hour 0 starts after study intervention administration.
Tolerability assessment/drop comfort questionnaire		X								X			X			
Study intervention dispensing									X							Refer to Section 6.2 of the study protocol regarding study intervention dispensation.

Table 1-2 Schedule of Visits and Procedures: Visit 4 to Visit 5/Early Exit

Procedure	Study Days (Visits)																Notes
	Day 14 (Visit 4)								Day 30/Early Exit (Visit 5)								
Visit Windows	± 2 days								± 3 days								
Hours	0	0.25	0.5	1	3	6	8	10	0	0.25	0.5	1	3	6	8	10	Study intervention administration Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Concomitant medication query	X								X								
AE query	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X			X					X			X					Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes
Urine pregnancy test									X								WOCBP only
PICQ													X				Conducted with participant's habitual distance correction
PPSQ													X				Conducted with participant's habitual distance correction
Depth of focus measurement	X			X					X			X					
Perform under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target):																	Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Dark adaptation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5 to 10 minutes in mesopic conditions
Mesopic, high contrast CDVA + pupil diameter	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.

Procedure	Study Days (Visits)																Notes
	Day 14 (Visit 4)								Day 30/Early Exit (Visit 5)								
Visit Windows	± 2 days								± 3 days								
Hours	0	0.25	0.5	1	3	6	8	10	0	0.25	0.5	1	3	6	8	10	Study intervention administration Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Mesopic, high contrast DCIVA	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.
Mesopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Single-item PGIS				X									X				Conducted with participant's best distance correction
Single-item PGIC				X									X				Conducted with participant's best distance correction
Mesopic NVPTQ				X									X				Conducted with participant's best distance correction
Perform under photopic conditions (≥ 80 cd/m^2; 251 lux at target):																	Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.
Photopic, high contrast CDVA + pupil diameter	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. CDVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Photopic, high contrast DCIVA	X			X	X	X	X	X	X			X	X	X	X	X	Conducted with participant's best distance correction. DCIVA to be measured OD, OS, and binocularly.

Procedure	Study Days (Visits)																Notes
	Day 14 (Visit 4)								Day 30/Early Exit (Visit 5)								
Visit Windows	± 2 days								± 3 days								
Hours	0	0.25	0.5	1	3	6	8	10	0	0.25	0.5	1	3	6	8	10	Study intervention administration Hour 0 must be at 8 AM ± 1 hour; Hours 0.25 and 0.5 (± 5 minutes) and Hours 1, 3, 6, 8, and 10 (± 15 minutes) will be measured from the time of the completion of study intervention administration.
Photopic, high contrast DCNVA + pupil diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Conducted with participant's best distance correction. DCNVA to be measured OD, OS, and binocularly. Pupil diameter must be measured in each individual eye.
Near contrast sensitivity assessment	X			X					X			X					Conducted with participant's best distance correction
Photopic NVPTQ				X									X				Conducted with participant's best distance correction
Slit-lamp biomicroscopy	X			X					X			X					
IOP measurement	X			X					X			X					
Temporal/ supraorbital headache VAS assessment	X		X	X					X		X	X					Conducted before dosing at Hour 0 of each visit
PK blood draw									X	X	X	X	X	X	X	X	Conducted at selected sites only; Hour 0 blood draw must be done before study intervention administration.
Study intervention administration	X								X								Hour 0 starts after study intervention administration.
Tolerability assessment/ drop comfort questionnaire	X								X								
Dilating drop administration																X	Minimum 30-minute wait after administration of dilating drops
Dilated funduscopic examination																X	Investigator should note if the pupil dilated normally

2. Statistical Hypotheses

For the primary efficacy analysis, the null hypothesis is that there is no difference between AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days in the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3. The alternative hypothesis is that there is a difference between AGN-190584 ophthalmic solution and vehicle.

For the key secondary efficacy analysis, the null hypothesis is that there is no difference between AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days in the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The alternative hypothesis is that there is a difference between AGN-190584 ophthalmic solution and vehicle.

The hypotheses will be tested using chi-square tests at a significance level of 5%.

3. Sample Size Determination

The primary efficacy parameter is the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3. The key secondary efficacy parameter is the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The sample size calculation is based on the key secondary efficacy parameter.

The vehicle group intervention effect is assumed to be 3.6%, as observed in the Phase 2 study. AGN-190584 effect is assumed to be 16% in emmetropes and 12% in non-emmetropes. This gives an overall AGN-190584 effect of 15% assuming emmetropes will be 75% of the study population. One hundred thirty-five (135) participants will be required in each study intervention group to detect the above difference with a power of 90% or greater at the 2-sided 5% significance level. Assuming a 10% dropout rate, approximately 150 participants per study intervention group will be randomized.

4. Populations for Analysis

Two analysis populations were defined for this study as follows:

- ITT population will consist of all randomized participants. The analysis using the ITT population will be based on the study intervention assigned.
- The safety population will consist of all participants who received at least 1 administration of study intervention. The analysis using the safety population will be based on the actual study intervention received.

5. Statistical Analyses

5.1. General Considerations

- Efficacy endpoints will be analyzed using the ITT population, and the safety endpoints will be analyzed using the safety population.
- The baseline for efficacy and safety will be the last non-missing assessment prior to the first administration of study intervention. For participants who were randomized but not treated, the baseline value will be the assessment collected on or prior to the randomization date, whichever is later.
- The change from baseline values will be computed as the post-baseline value minus the baseline value.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max).
- Categorical variables will be summarized by number of participants with observed values or events (n), frequency count (n1), and percentage of participants with observed values or events.
- All statistical hypothesis tests will be performed at the 2-sided 5% significance level, unless stated otherwise. All confidence intervals will be at least 2-sided 95% confidence intervals.
- In general, statistical analyses will be performed using SAS version 9.4 or higher. MedDRA version 22.1 will be used to code adverse events, biomicroscopy, and medical history. WHODRUG Enhanced B2 will be used to code medications.

To control the overall Type 1 error rate in the efficacy analysis, a sequential testing strategy will be used for the primary efficacy endpoint and key secondary efficacy endpoint. The test for the key secondary endpoint will be implemented only if the primary efficacy endpoint, yields statistically significant results. There are 11 other secondary efficacy endpoints which will be tested only if the key secondary efficacy endpoint is statistically significant using the graphical procedure described in Section 5.5.

For primary and key secondary analyses, participants with missing data will be regarded as non-responders. Analyses for other secondary efficacy endpoints will be based on observed data only.

5.2. Participant Disposition

Number of participants screened for the study will be provided.

Summary of study disposition post randomization will be provided by study intervention group as randomized for the following:

- Number of participants randomized; this frequency count will be used as the denominator to calculate the percentages described below
- Number and percentage of participants treated
- Number and percentage of participants who completed the study
- Number and percentage of participants who discontinued the study
- Reasons for discontinuation from the study

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The primary efficacy parameter will be the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 3.

5.3.2. Main Analytical Approach

The primary efficacy parameter will be analyzed using a chi-square test with 2-sided 95% confidence interval based on the normal approximation based on pooled variance without continuity correction.

5.3.3. Sensitivity Analysis

As a sensitivity analysis a 2-sided 95% confidence interval using Wilson-Newcombe method will be presented

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Secondary Analysis

The key secondary efficacy endpoint will be the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The key secondary efficacy parameter will be analyzed with the same way as the primary efficacy parameter.

5.4.2. Other Secondary Analyses

Other secondary efficacy endpoints include:

1. Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 8.
2. Change from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.5.
3. Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 1.
4. Change from baseline in Mesopic NVPTQ Performance score at Day 30, Hour 3.
5. Change from baseline in photopic, high contrast, binocular DCIVA letters at Day 30, Hour 3.
6. Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 10.
7. Change from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.25.
8. Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 3.
9. Change from baseline in Mesopic NVPTQ Satisfaction score at Day 30, Hour 3.
10. Change from baseline in PICQ Coping score at Day 30, Hour 3.
11. Change from baseline in PICQ Impact score at Day 30, Hour 3.

All secondary endpoints related to proportion of participants gaining 3 lines or more or achieving 20/40 better (endpoints 1, 3, 6 and 8) will be analyzed with the same way as the primary efficacy parameter.

Timepoints are defined as scheduled measurement times made for each visit. Change from baseline in mesopic, high contrast, binocular DCNVA letters (endpoints 2 and 7) will be analyzed using MMRM by timepoint that includes treatment, visit, treatment by visit interaction, age group, baseline DCNVA severity, iris color, and emmetropes/non-emmetropes as factors as well as baseline DCNVA value, and baseline DCNVA value by visit interaction as covariates under the assumption of MAR. An unstructured covariance matrix will be used as the covariance structure for repeated measurements. A sensitivity analysis will be implemented with the

missing data imputed with the average outcome of the vehicle arm under the assumption of MANR. Change from baseline in photopic, high contrast, binocular DCIVA letters (endpoints 4) will be analyzed with the similar way as change from baseline in mesopic, high contrast, binocular DCNVA letters. Baseline DCIVA will be included as the covariate instead of baseline DCNVA.

NVPTQ and PICO scoring algorithm are provided in Appendix 4. Change from baseline in the mesopic NVPTQ Performance score, Mesopic NVPTQ Satisfaction score, PICQ Coping score, and PICQ Impact score (endpoints 4, 9, 10 and 11) will be analyzed using an ANCOVA model that include treatment, age group, baseline DCNVA severity, iris color, and emmetropes/non-emmetropes as factors as well as baseline PRO score as covariate. Also, the CDF curves will be presented for each of the change from baseline PRO domain scores. The CDF curves (one per domain score for a total of four) represent the cumulative proportion of patients with any particular level of CFB in PRO domain scores at Day 30 Hour 3, by treatment arm. Curves will be produced with a vertical line drawn at the responder threshold.

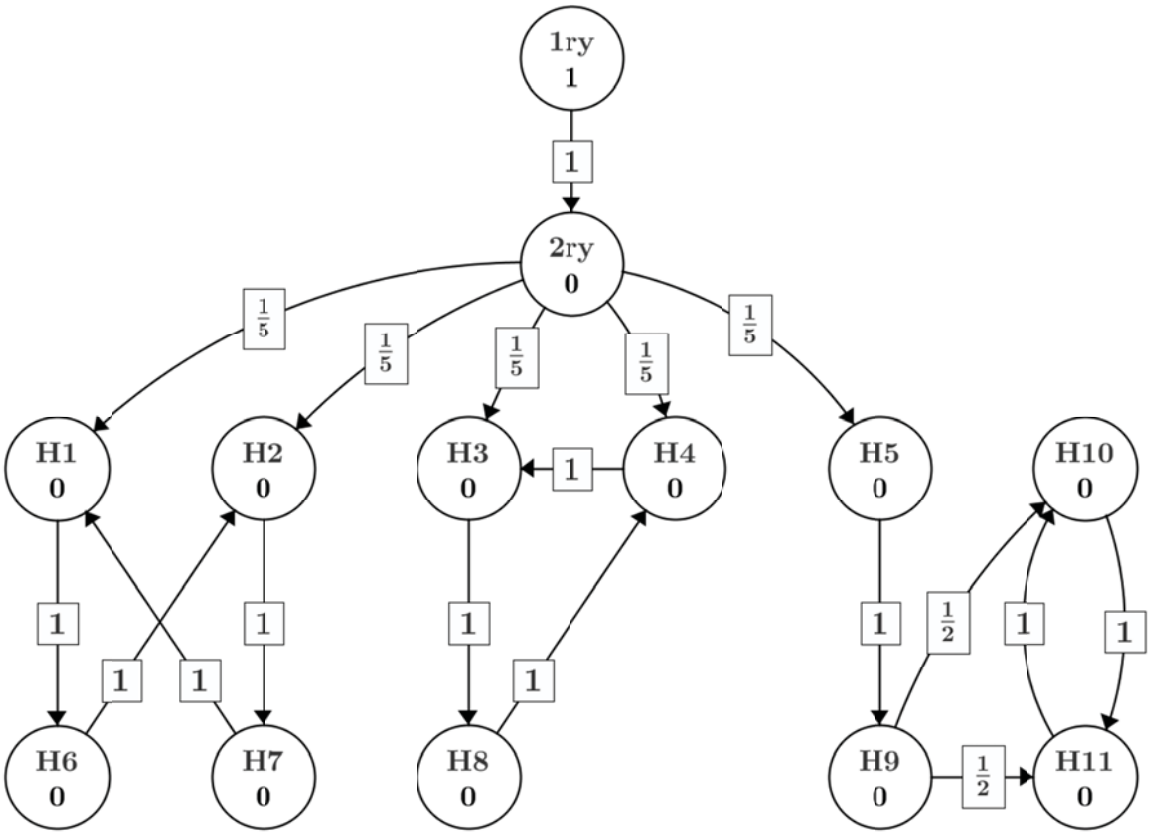
5.4.3. Multiplicity Adjustment

The graphical procedure displayed in Figure 5-1 will be employed to control the overall familywise error rate at α=0.05 for the following hypotheses testing. Let H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, and H11 represent the treatment effect comparisons of AGN-190584 with vehicle. Details of the hypotheses and corresponding efficacy parameters are described in Table 5-1.

Table 5-1 Hypotheses and Corresponding Efficacy Parameters

Hypothesis	Efficacy Parameter
1ry	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 3
2ry	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 6
H1	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 8
H2	Change from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.5
H3	Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 1
H4	Change from baseline in photopic, high contrast, binocular DCIVA letters at Day 30, Hour 3
H5	Change from baseline in Mesopic NVPTQ Performance score at Day 30, Hour 3
H6	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 10
H7	Change from baseline mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.25
H8	Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 3
H9	Change from baseline in Mesopic NVPTQ Satisfaction score at Day 30, Hour 3
H10	Change from baseline in PICQ Coping score at Day 30, Hour 3
H11	Change from baseline in PICQ Impact score at Day 30, Hour 3

Figure 5-1 Graphical Testing Procedure



Specifically, H1, H2, H3, H4 and H5 will be tested at a=0.01 separately. If H1, H2, H3, H4 or H5 is rejected, H6, H7, H8 or H9 will then be tested. If H9 is rejected, H10 and H11 will then be tested.

5.5. Other Efficacy Parameters

Efficacy endpoints below will be summarized descriptively for each time point for each eye separately by treatment group:

- Change from baseline in mesopic near pupil diameter
- Change from baseline in mesopic distance pupil diameter
- Change from baseline in photopic near pupil diameter
- Change from baseline in photopic distance pupil diameter
- Change from baseline in depth of focus

The proportion of participants gaining 2 lines or more from baseline in mesopic, high contrast, binocular DCNVA will be analyzed.

5.6. Safety Analyses

The safety analyses will be performed using the safety population. The safety parameters will include AEs, vital signs (blood pressure and heart rate), mesopic and photopic, high contrast, CDVA, for each eye and binocularly, near contrast sensitivity, study intervention tolerability and drop comfort assessments, temporal/supraorbital headache assessment using VAS, IOP, slit-lamp biomicroscopy, manifest refraction, dilated funduscopic examination, and pregnancy test. For each safety parameter, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

5.6.1. Extent of Exposure

The exposure to study intervention, calculated as (last study intervention date - first study intervention date + 1), will be summarized using descriptive statistics by treatment for the safety population.

5.6.2. Adverse Events

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

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by descending percentage in any group, by SOC and PT, and further categorized by severity and causal relationship to the study intervention. If more than 1 AE is coded to the same PT for the same participant, the participant will be counted only once for that PT using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The incidence of common (≥ 5% of participants in any treatment group) TEAEs will be summarized by SOC, PT, and treatment group.

The total number of TEAEs by severity will be summarized by treatment group. The total number of TEAEs by causal relationship to the study intervention will be summarized by

treatment group. The number and percentage of participants reporting study intervention related TEAE will be tabulated by SOC and PT.

A TESAE is defined as an SAE that is also a TEAE. The number and percentage of participants who have TESAEs will be summarized by PT and treatment group. In addition, the incidence of on-therapy SAEs that lead to death will be summarized separately by PT for each treatment group.

Summary tables will be provided for TEAEs leading to discontinuation and TESAEs. Listings of all TEAEs, SAEs, and AEs leading to discontinuation by participant will be presented.

5.6.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, and pulse rate) and changes from baseline values at each assessment timepoint will be presented by treatment group.

5.6.4. Mesopic, High Contrast, Binocular CDVA

Change from baseline in number of letters in binocular mesopic, high contrast, CDVA will be summarized descriptively for each assessment timepoint by treatment group.

5.6.5. Photopic, High Contrast, Binocular CDVA

Change from baseline in number of letters in binocular photopic, high contrast, CDVA will be summarized descriptively for each assessment timepoint by treatment group.

5.6.6. Study Intervention Tolerability and Drop Comfort Assessments

Ocular tolerability assessment will be performed at each visit. Symptoms of blurred vision, foreign body sensation, pain, burning/stinging, tearing, and itching will be assessed using a 5-point scale (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe) for the severity and a 3-point scale (<1 min, 1 to 5 min, and >5 min) for the duration. Drop comfort will be assessed using a 6-point scale (soothing, very comfortable, comfortable, uncomfortable, very uncomfortable, and intolerable). For the severity, duration, and drop comfort, the number and percentage of participants in each category will be tabulated for each time point by treatment group.

5.6.7. Temporal/Supraorbital Headache Visual Analog Scale

Temporal and supraorbital headache will be separately assessed for each eye using a VAS at each visit. The reported values and the changes from baseline will be summarized using descriptive statistics for each time point for each eye by treatment group.

5.6.8. Intraocular Pressure

IOP is measured for each eye using the Goldmann applanation tonometer at each visit. Tabulations will be based on the worst change (greater increase from baseline) between 2 eyes assessed at each visit. Descriptive statistics for IOP and changes from baseline at each assessment timepoint will be presented by treatment group.

5.6.9. Slit Lamp Biomicroscopy

Biomicroscopy will be performed in each eye at each visit, by slit lamp examination, without pupil dilation, including but not limited to lids/lashes, conjunctiva, cornea, and anterior chamber. Observations for the examination will be graded on a 5-point scale (0=none, 0.5=trace, 1=mild, 2=moderate, 3=severe) except for the anterior chamber (in cells: 0=0 cells, +0.5=1-5 cells, +1=6-15 cells, +2=16-25 cells, +3=26-50 cells, and +4=>50 cells; in flare: 0=none, +1=faint, +2=moderate, +3= marked and +4=intense).

The number and percentage of participants with clinically significant biomicroscopy findings will be tabulated by finding category, assessment timepoint and treatment group. A clinically significant finding is defined as more than one severity grade increase (worsening) from baseline in one or both eyes. If a pathology is recorded at a follow-up visit but not at baseline, the baseline will be imputed with the same pathology, with a grade of zero (none).

5.6.10. Pregnancy Tests

Positive test results for WOCBP will be listed.

5.7. Other Analyses

5.7.1. Health Outcomes Analyses

Additional PRO exploratory analyses will be described in a separate SAP.

5.7.2. Subgroup Analyses for Efficacy Parameters

The primary and key secondary endpoints will be summarized by age group (≤50 years and >50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes.

5.8. Interim Analyses

No interim analysis is planned for this study.

5.8.1. Data Monitoring Committee

Data monitoring committee is not required for this study.

6. Supporting Documentation

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
bpm	beats per minute
CDF	cumulative distribution function
CDVA	corrected distance visual acuity
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
eCRF	electronic case report form
ID	identification
IOP	intraocular pressure
ITT	intent-to-treat
IxRS	interactive electronic response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
MMRM	mixed model repeated measure
MNAR	missing not at random
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
NVPTQ	Near Vision Presbyopia Task-based Questionnaire
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Status
PICQ	Presbyopia Impact and Coping Questionnaire
PPSQ	Presbyopia Patient Satisfaction Questionnaire
PRO	patient reported outcomes

PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
VAS	visual analog scale
WHO DDE	World Health Organization Drug Dictionary Enhanced
WOCBP	women of childbearing potential

6.2. Appendix 2: Changes to Protocol-Planned Analyses

The subgroup analyses for the primary and key secondary endpoints by gender and race groups will not be conducted.

The proportion of participants gaining 2 lines or more from baseline in mesopic, high contrast, binocular DCNVA will be analyzed.

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographics

Demographic parameters (age; age groups of ≤ 50 years and > 50 years; sex; race; ethnicity) will be summarized descriptively by treatment group for the ITT populations.

6.3.2. Baseline Characteristics

Baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes will be summarized descriptively with frequency and percentage by treatment group for the ITT population.

6.3.3. Protocol Deviations

Unique participants reporting significant protocol deviations will be summarized in total and by treatment group for all randomized participants.

6.3.4. Medical History

Medical and surgical history will be summarized by treatment group for the Safety Population. Medical history includes prior medical history (prior to Day 1, first dose date) and still ongoing.

6.3.5. Prior/Concomitant medications

Prior medication is defined as any medications taken prior to the start of study intervention. *Concomitant medication* is defined as any medication taken on or after the start of study intervention regardless of the start date of the medication.

The number and percentage of participants with prior and concomitant medication use will be summarized by treatment group and Anatomical Therapeutic Chemical code for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within the same therapeutic class, the participant will be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc.) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be reviewed during the course of the study and may be pooled under a single coded drug name for analyses. No statistical comparisons will be performed.

6.4. Appendix 4: Pro Scoring Algorithm

6.4.1. NVPTQ Performance Domain Score

To account for the impact of squinting on performance, the responses to the pair of performance and squinting items on each task is combined into a new testlet variable informed by a series of item response theory models. For performance and squinting, this new testlet variable is created by combining all possible response categories according to Table 1.

Table 1.Testlet variable values based on combining performance item responses and squinting item responses

Squinting / Performance	Yes, but I still could not read any of the text (2)	Yes, and squinting helped me read some or all of the text (1)	No, I did not squint (0)
I could not read any of the text due to problems seeing up close (0)	0	0	0
Poor (1)		0	1
Fair (2)		1	2
Good (3)		2	3
Very Good (4)		3	4
Excellent (5)		4	5

Note. The values in parentheses are the raw values corresponding to the item response. These are the variable values in the ADaM datasets.

If the response to either the performance or squinting item within a task is missing, then the corresponding testlet is assigned a missing value. Because the four tasks are highly related, there is no limit on the number of missing testlet scores to be able to calculate the performance domain score. The performance domain score is calculated as the average of the non-missing testlet values as follows:

NVPTQ Performance Score = (Book testlet + Newspaper testlet + Menu testlet + Nutrition Label testlet) / (# testlets with non-missing responses)

The NVPTQ Performance Score ranges from 0 to 5, with 0 corresponding to poorest performance and 5 corresponding to best performance. Thus, higher scores correspond to better outcomes This algorithm puts the performance score on the original performance item response metric, which also ranges from 0 to 5, so the performance item responses can be referenced when interpreting the score. Individual-level score changes of 0.75 points or greater can be considered clinically meaningful; i.e., an individual whose NVPTQ Performance Score increases by at least 0.75 points from baseline can be considered a responder.

6.4.2. NVPTQ Satisfaction Domain Score

To account for the impact of squinting on satisfaction, the responses to the pair of satisfaction and squinting items on each task is combined into a new testlet variable informed by a series of item response theory models. For satisfaction and squinting, this new testlet variable is created by combining all possible response categories according to Table 2.

Table 2.Testlet variable values based on combining satisfaction item responses and squinting item responses

Squinting / Satisfaction	Yes, but I still could not read any of the text (2)	Yes, and squinting helped me read some or all of the text (1)	No, I did not squint (0)
Very dissatisfied (0)	0	0	0
Dissatisfied (1)		0	1
Neither satisfied nor dissatisfied (2)		1	2
Satisfied (3)		2	3
Very satisfied (4)		3	4

Note. The values in parentheses are the raw values corresponding to the item response. These are the variable values in the ADaM datasets.

If the response to either the satisfaction or squinting item within a task is missing, then the corresponding testlet is assigned a missing value. Because the four tasks are highly related, there is no limit on the number of missing testlet scores to be able to calculate the satisfaction domain score. The satisfaction domain score is calculated as the average of the non-missing testlet values as follows:

NVPTQ Satisfaction Score = (Book testlet + Newspaper testlet + Menu testlet + Nutrition Label testlet) / (# testlets with non-missing responses)

The NVPTQ Satisfaction Score ranges from 0 to 4, with 0 corresponding to greatest dissatisfaction and 4 corresponding to greatest satisfaction . Thus, higher scores correspond to better outcomes. This algorithm puts the satisfaction score on the original satisfaction item response metric, which also ranges from 0 to 4, so the satisfaction item responses can be referenced when interpreting the score. Individual-level score changes of 1.00 points or greater can be considered clinically meaningful; i.e., an individual whose NVPTQ Satisfaction Score increases by at least 1.00 points from baseline can be considered a responder.

6.4.3. PICQ Coping Score

The coping domain consists of the following 8 items:

- Item 1: Normal-sized text
- Item 2: Small-sized text
- Item 3: Information on a computer
- Item 4: Information on a cell phone
- Item 5: Increase font size
- Item 6: Use glasses to read close
- Item 12: Hold reading materials farther out or closer
- Item 13: Squint to read

Each of these items includes response categories ranging from 0, corresponding to “Never”, to 4, corresponding to “All of the time.” Items 3, 4, 5, and 6 include additional response categories, labeled with values of 9 or 10, to indicate that the question is not applicable because the subject did not use the object being evaluated (e.g., “I did not use a computer over the past 7 days”) or because the subject did not have the opportunity to change his behavior (e.g., “I permanently increased the font size on my computer, tablet, or cell phone prior to the past 7 days”). Responses in these “not applicable” categories labeled 9 or 10 are assigned missing values.

Because of the similarity of the content of certain item pairs, two new testlet variables are created prior to scoring. The testlet variable for Item 1 and Item 2 is calculated by computing the mean of the non-missing responses to the two items. The testlet variable for Item 3 and Item 4 is calculated by computing the mean of the non-missing responses to the two items. If either item in the testlet pair has a missing value, the testlet value is assigned the value of the non-missing item. If both items in the testlet pair have missing values, then the testlet is assigned a missing value.

Items 1&2 Testlet = (Item 1 + Item 2)/ # non-missing responses to Item 1 and Item 2

Items 3&4 Testlet = (Item 3 + Item 4) /# non-missing responses to Item 3 and Item 4

After the testlet variables have been created, the coping domain score is calculated as the mean of the non-missing values to the coping testlets and single coping items. Because the coping items are well-related and internally consistent, and because missing data are expected for some items due to the "not applicable" response categories, there is no limit on the number of missing item responses to be able to calculate the coping domain score.

PICQ Coping Score = (Item 1&2 Testlet + Item 3&4 Testlet + Item 5 + Item 6 + Item 12 + Item 13) /# non-missing responses to the 6 components of the coping score

The PICQ Coping Score ranges from 0 to 4, with 0 corresponding to least amount of coping and 4 corresponding to the greatest amount of coping. Thus, higher scores correspond to poorer outcomes. This algorithm puts the coping score on the original item response metric, which also ranges from 0 to 4, so the coping item responses can be referenced when interpreting the score. Individual-level score changes of 1.00 points or greater can be considered clinically meaningful; i.e., an individual whose PICQ Coping Score decreases by at least 1.00 points from baseline can be considered a responder.

6.4.4. PICQ Impact Score

The impacts domain consists of the following 6 items:

- Item 9: Rely on others
- Item 15: Rest eyes
- Item 16: Feel older
- Item 17: Feel self-conscious
- Item 19: Take longer to complete a task
- Item 20: Inconvenient

The first five impacts items include response categories ranging from 0, corresponding to "Never", to 4, corresponding to "All of the time." Item 20 uses response categories ranging from 0, corresponding to "Not at all", to 4, corresponding to "Extremely." Item 9 includes an additional response category, labeled with a value of 9, to indicate that the question is not applicable because the subject did not have the opportunity to experience the impact (i.e., "Never because I used or did something to help"). Responses in this "not applicable" category labeled 9 are assigned missing values.

Because of the similarity of the content of Item 16 and Item 17, a new testlet variable is created prior to scoring by computing the mean of the non-missing responses to the two items. If either item in the testlet pair has a missing value, the testlet is assigned the value of the non-missing item. If both items in the testlet pair have missing values, then the testlet is assigned a missing value.

Items 16&17 Testlet = (Item 16 + Item 17) /# non-missing responses to Item 16 and Item 17

After the testlet variable has been created, the impacts domain score is calculated as the mean of the non-missing values to the impacts testlet and single impacts items. Because the impacts items are well-related and internally consistent, and because missing data are expected for some items due to the "not applicable" response categories, there is no limit on the number of missing item responses to be able to calculate the impacts domain score.

PICQ Impacts Score = (Item 9 + Item 15 + Items 16&17 Testlet + Item 19 + Item 20) /# non-missing responses to the 5 components of the impacts score

The PICQ Impacts Score ranges from 0 to 4, with 0 corresponding to least amount of impacts and 4 corresponding to the greatest amount of impacts. Thus, higher scores correspond to poorer outcomes. This algorithm puts the impacts score on the original item response metric, which also ranges from 0 to 4, so the impacts item responses can be referenced when interpreting the score. Individual-level score changes of 1.00 points or greater can be considered clinically meaningful; i.e., an individual whose PICQ Impacts Score decreases by at least 1.00 points from baseline can be considered a responder.

6.5. Data handling convention

6.5.1. Visit Time Windows

For ITT and safety by-visit analyses, all follow-up visits or the exit visit, participants will be reassigned with the visit number based on the number of days from the first dose date according to the following windows corresponding to relevant analysis.

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Statistical Analyses Window
Pretreatment	Baseline	Day 1 (Visit 1)	Treatment Day ≤ 1, pre-dose/randomization
Treatment	Day 1	Day 1 (Visit 1)	Treatment Day 1, post dose/randomization
	Day 3	Day 3 (Visit 2)	Treatment Day [2, 4]

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Statistical Analyses Window
	Day 7	Day 7 (Visit 3)	Treatment Day [5, 10]
	Day 14	Day 14 (Visit 4)	Treatment Day [11, 21]
	Day 30	Day 30 (Visit 5)	Treatment Day [22, 45]

If multiple assessments were taken within an analysis window, the assessment obtained on the day closest to the target day will be used; in the case of a tie, the assessment obtained on the later day will be used in the analysis.

6.5.2. Missing Date of the Last Dose of Study Intervention

When the date of the last dose of study intervention is missing for a participant in the safety population, all efforts should be made to obtain the date from the investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

6.5.3. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If the severity of a TEAE is missing, the maximum severity will be assigned to the event for the summarization by severity. The value will be displayed as missing in the data listing.

6.5.4. Missing Causal Relationship to Study Drug for Adverse Events

If the relationship to the study intervention is missing for a TEAE, the event will be considered related to the study intervention for the summarization. The value will be displayed as missing in the data listing.

6.5.5. Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing):

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study intervention, the date of the first dose of study intervention will be assigned to the missing start date.
- If the stop date is before the date of the first dose of study intervention, the stop date will be assigned to the missing start date.

6.5.6. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

6.5.6.1. Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day.

6.5.6.2. Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study intervention is missing, impute it as descripted in Section 6.5.3. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study intervention, the month and day of the last dose of study intervention will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the last dose of study intervention, *December 31* will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last dose of study intervention, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study intervention, the day of the last dose of study intervention will be assigned to the missing day.
- If either the year of the incomplete stop date is before the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete stop date is after the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study intervention, the first day of the month will be assigned to the missing day.

7. References

Not Applicable.

ALLERGAN

1883-301-013 Statistical Analysis Plan

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
30-Jan-2020 16:21 GMT-080	Lee_Sungwook	Biostatistics Approval
31-Jan-2020 08:59 GMT-080	Liu_Haixia	Clinical Development Approval
31-Jan-2020 10:08 GMT-080	Chhun_Chip	Biostatistics Approval
03-Feb-2020 07:42 GMT-080	Liu_Jeen	Management Approval