Title Page

Protocol Title: Evaluating the Impact of AGN-190584 on Night-driving Performance

Protocol Number: 1883-306-013

Compound: AGN-190584

Study Phase: 3b

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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	Please refer to the final page of this protocol for the date of approval for Amendment 1.
Original Protocol	24 September 2020

Amendment 1

In accordance with criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, this amendment is considered to not be substantial and has no significant impact on the safety of study participants.

Overall Rationale for the Amendment 1:

This summary includes changes made to the original Protocol 1883-306-013 (24 September 2020). The primary rationale for this protocol amendment is the update to the serious adverse event (SAE) reporting process per company procedure.

Following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes.

Minor editorial and document formatting revisions have not been summarized.

Section No. and Name	Description of Change	Brief Rationale
Title page	Updated the sponsor/emergency medical contact for the study from [redacted] MD to [redacted] MD	The medical safety physician contact information was changed to Therapeutic Area Medical Director contact information.
Section 1.2, Figure 1-1	Second dosing visit (Visit 4) and second driving visit (Visit 5) day ranges changed to 15 to ~~50~~ 57 and 22 to ~~64~~ 71 respectively.	Corrections of Visits 4 and 5 day ranges; error in the upper bound.
Section 1.3, Schedule of Activities, Table 1-1.	~~Randomization~~ Second Dosing Visit (Visit 4)	This is a crossover design study and randomization is at Visit 2. There is no additional randomization at Visit 4.
	Driving test to be performed ~~approximately~~ 1 hour ± 15 min after study intervention instillation~~.~~	Updated for clarity
Section 2.3, Benefit/Risk Assessment	Considering the COVID-19 pandemic, the benefit and risk to participants in this study have been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of AGN-190584.	Added per sponsor procedure to account for any potential impact of the COVID-19 pandemic on the study's risk/benefit assessment.

Section No. and Name	Description of Change	Brief Rationale
Section 4.3, Justification for Dose	The analyses and CSRs ~~preparation~~ for these studies ~~are in progress~~ have been completed.	At the time of the original protocol completion, the 1883-301-013 and 1883-302-013 CSRs were in progress. These CSRs have been completed.
Section 6.4, Study Intervention Compliance	Detail added to clarify that study drug will be delivered to the subject if they are unable to attend due to COVID-19, and a statement added that for Visit 2 and Visit 4, if a subject is unable to come to site the visit will be rescheduled.	Added per sponsor procedure during the COVID-19 pandemic
Section 6.5.2, Permitted Interventions	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 it is necessary for the participant's welfare and/or if a stable dosing regimen is established.	Updated for clarification
	Detail added on COVID-19 pandemic-related vaccination guidance	Added per sponsor procedure during the COVID-19 pandemic
Section 7, Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Reasons for ~~discontinuation from the study intervention and/or the study~~ EOS or EOT may include the following ~~commonly used or other acceptable terms~~: • Withdrawal ~~from treatment~~ by subject (EOS) • Withdrawal from treatment by subject (EOT)	The reasons for discontinuation from the study intervention and/or the study were updated to include COVID-specific reasons and match the updated case report form.
Section 7.2, Participant Discontinuation/Withdrawal from the Study	Detail added on COVID-19 pandemic-related acceptable protocol modification	Added per sponsor procedure during the COVID-19 pandemic
Section 8.1, Efficacy Assessments – Driving Performance	~~Approximately~~ After 1 hour ± 15 minutes following study intervention instillation and ~~following the~~ visual function assessments, ~~each participant will be driven to the start~~ participants will start the driving test at the beginning of the closed road driving circuit.	Updated for clarity
Section 8.1.1, Sign Recognition	The percentage of signs ~~sign items~~ correctly reported ~~is~~ will be calculated from the reported total number of signs and the number of signs correctly identified.	Updated for clarification

Section No. and Name	Description of Change	Brief Rationale
Section 8.1.2, Hazard Avoidance	The percentage of hazards hit will be ~~recorded~~ calculated from the reported total number of hazards and the number of hazards hit.	Updated section for clarification after discussions with site
Section 8.1.3, Driving Time	Time to complete the road course will be recorded for each run (in minutes and seconds).	Clarified driving time recording after discussions with the site
Section 8.1.4, Lane-Keeping	Lane-keeping will be recorded by 2 video cameras mounted on the vehicle roof and ~~scored post-testing as the percentage of time out of the lane~~ calculated post-testing from the reported total driving time and reported time outside of lane.	Clarified lane-keeping assessment after discussion with the site
Section 8.1.7, Pupil Diameter	Pupil diameter will be measured during distance fixation (~~3 measures~~) using a NeurOptics Pupillometer for mesopic/photopic lights levels specified in the SoA (Section 1.3).	Removed the details of performing 3 measures for the pupil diameter for accuracy, as different visits require different numbers of measurements.
Section 8.2.4, Mesopic and Photopic BDCVA and DCNVA	Binocular BCDVA and DCNVA will be tested using logMAR charts at 4 m and 40 cm under 2 lighting conditions: mesopic luminance (~~3.2 to 3.5 cd/m^2~~; 10 to 11 lux) and photopic luminance (~~≥ 80 cd/m^2~~; ≥ 251 lux) under normal room lighting.	Changed from cd/m^2 to lux units to measure binocular BCDVA and DCNVA testing
Section 8.2.5, Mesopic and Photopic HDVA	Binocular HDVA will be tested using logMAR charts at 4 m ~~and 40 cm~~ under 2 lighting conditions: mesopic luminance (~~3.2 to 3.5 cd/m^2~~; 10 to 11 lux) and photopic luminance (~~≥ 80 cd/m^2~~; ≥ 251 lux) under normal room lighting.	Changed from cd/m^2 to lux units to measure HDVA. Also corrected to remove 40 cm.
Section 10.1.7, Source Documents	Additional bullet point added: • During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.	Added per sponsor procedure during the COVID-19 pandemic
Section 10.1.10, Compliance with Protocol	Protocol deviations (including those that may be due to the COVID-19 pandemic) will be discussed with the investigator upon identification.	Added per sponsor procedure during the COVID-19 pandemic
Section 10.2.4, Reporting of SAEs	Updated reporting process for SAEs with use of electronic data capture	Updated in line with sponsor process for reporting

Section No. and Name	Description of Change	Brief Rationale
Section 10.5, Appendix 5: Study Tabular Summary	Value column: 22 to ~~64~~ 71 days, with a 30-day screening period	Corrected the number of days in trial length row
	Parameter column: Planned Number of Enrolled Participants Value column: Approximately ~~40~~ 54	Corrected the number of enrolled participants
Section 10.6, Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information	Updated reporting process for pregnancy with use of electronic data capture	Updated in line with sponsor process for reporting

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

Evaluating the Impact of AGN-190584 on Night-driving Performance

Study Number:

1883-306-013

Study Rationale:

In previous studies, the sponsor 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 30 days in participants with presbyopia. As with all miotics, participants were advised to exercise caution in night driving and other hazardous occupations under poor illumination.
Study 1883-306-013 is evaluating the effect of AGN-190584 compared with vehicle when dosed in both eyes on driving performance under real-world, night-lighting conditions in participants with presbyopia.

Objectives and Measures:

Objectives	Measures
To evaluate night-driving performance in real-world driving conditions in participants with presbyopia treated with AGN-190584 versus vehicle	• Overall driving performance • Hazard avoidance • Road sign recognition • Road sign recognition distance • Pedestrian recognition distance • Lane-keeping • Driving time • Pupil diameter • Halometer • Night-driving experience questionnaire
To evaluate safety in participants with presbyopia treated with AGN-190584 versus vehicle	• Mesopic/photopic HDVA • AEs • Pregnancy tests for WOCBP • Slit-lamp biomicroscopy

Overall Design:

This is a single center, randomized, double-masked, crossover, Phase 3b study evaluating the effect of AGN-190584 compared with vehicle when dosed in both eyes on driving performance under real-world, night-lighting conditions in participants with objective and subjective evidence of presbyopia. Approximately 54 participants will be enrolled at one study site (Queensland University of Technology, Australia). At the randomization/first dosing visit (Visit 2), participants will be randomized in a 1:1 ratio to one of the 2 study intervention sequences, either AGN-190584 followed by vehicle after a minimum 1-week washout period (study intervention sequence 1), or vehicle followed by AGN-190584 after a minimum 1-week washout period (study intervention sequence 2). All participants will receive the first dose at Visit 2 and continue daily dosing through the end of the first driving visit (Visit 3). After the first driving visit (Visit 3) and a minimum 1-week washout period, participants will complete a second dosing visit (Visit 4) and continue daily dosing following the assigned study intervention sequence through the end of the study (Visit 5, second driving visit). There will be a 7- to 14-day study intervention adaptation period before each driving visit (Visits 3 and 5) and a 7- to 42-day washout period between Visits 3 and 4.

Disclosure Statement:

This is a crossover treatment study with 2 arms that is participant and investigator masked.

Number of Participants:

The sample size calculation is based on the primary efficacy endpoint (overall composite driving Z score of AGN-190584 versus vehicle [Visit 3 versus Visit 5] approximately 1 hour after study intervention instillation). Assuming no difference between treatment groups and variance of 0.11, approximately 40 participants will be required to obtain 90% power for a 1-sided noninferiority test with type 1 error of 0.025 and noninferiority margin of -0.25 units in mean overall composite driving Z score. Therefore, approximately 54 participants will be enrolled to achieve 40 participants completing the study assuming an anticipated dropout rate of 25% or less.

Intervention Groups and Duration:

- Each participant will receive 2 ophthalmic solutions (AGN-190584 [pilocarpine HCl 1.25% ophthalmic solution] and its vehicle) in a crossover design as described above.
- Study intervention will be administered by the investigator or designated site personnel at Visits 2, 3, 4, and 5, consisting of 1 drop in each eye.
- Participants will be supplied with randomized study intervention at Visit 2 (randomization/first dosing visit) and instructed to dose at home 1 drop in each eye, once daily in the morning between 08:00 and 10:00 for 7 to 14 days (adaptation period). On the scheduled day of Visit 3 (first driving visit), the participant will not instill study intervention at home (study intervention will be instilled by site personnel during the visit). Study intervention supplied at Visit 2 will be collected from the participant at Visit 3.

- At least a 7-day and up to a 42-day washout period will be observed between Visits 3 and 4.
- Participants will be supplied with new study intervention (following the study intervention sequence assigned at Visit 2) at Visit 4 and instructed to dose at home one drop in each eye, once daily in the morning between 08:00 and 10:00 for 7 to 14 days (adaptation period). On the scheduled day of Visit 5 (second driving visit), the participant will not instill study intervention at home (study intervention will be instilled by site personnel during the visit). Study intervention supplied at Visit 4 will be collected from the participant at Visit 5 (study exit).

	Visit 2 through Visit 3	Washout Period	Visit 4 through Visit 5
Study intervention sequence 1	AGN-190584		Vehicle
Study intervention sequence 2	Vehicle		AGN-190584

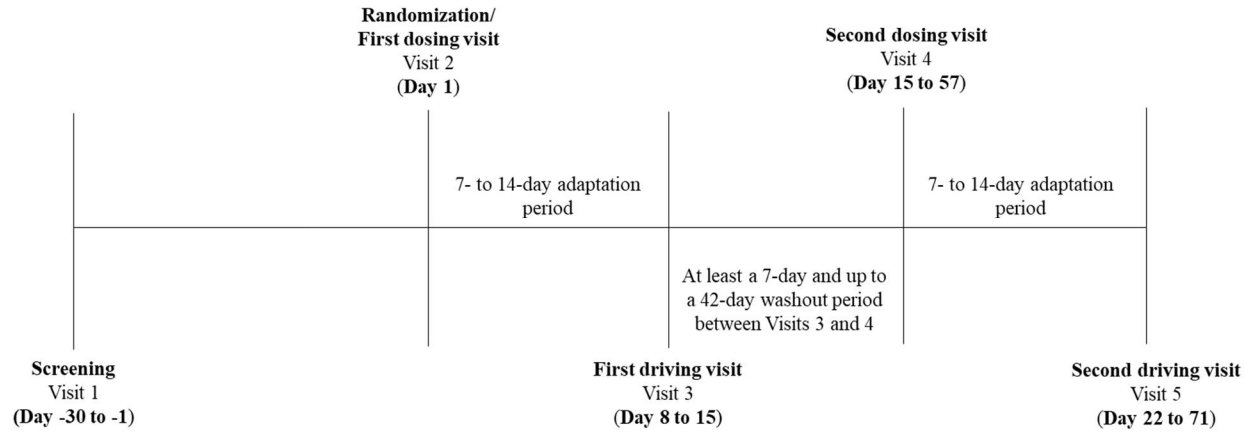
Data Monitoring Committee:

No

1.2. Schema

The study schema is provided in Figure 1-1.

Figure 1-1 Study Schema



1.3. Schedule of Activities (SoA)

Study procedures are recommended to be completed in sequence as listed in the schedule below (Table 1-1).

Table 1-1 Schedule of Visits and Procedures

Procedures	Study Days (Visits)							Notes
	Screening (Visit 1)	Randomization/ First Dosing Visit (Visit 2)	First Driving Visit (Visit 3)		Washout Period	Second Dosing Visit (Visit 4)	Second Driving Visit/ Early Exit (Visit 5)	
Visit Windows	Days -30 to -1	Day 1 (to be scheduled between 08:00 and 10:00)	Days 8 to 15		7 to 42 days	Days 15 to 57 (to be scheduled between 08:00 and 10:00)	Days 22 to 71	7- to 14-day study intervention adaptation period between Visits 2/3 and 4/5
			Before Dosing	After Dosing			Before Dosing / After Dosing	Before dosing (before study intervention instillation) and after dosing (approximately 1 hour after study intervention instillation)
Informed consent	X							
Iris color assessment	X							
Demography	X							
Medical and ophthalmic history	X							
Confirm participant did not dose at home			X				X	On the day of both driving visits, confirm that the participant did not instill study intervention at home.
Practice driving test			X				X	Participant will complete at least 1 practice session on the driving course at Visits 3 and 5.
Prestudy/ concomitant medication query	X	X	X	X		X	X / X	
AE query	X	X	X	X		X	X / X	Please see Section 8.3 and Section 10.2.

Procedures	Study Days (Visits)							Notes
	Screening (Visit 1)	**Randomization/ First Dosing Visit (Visit 2)**	**First Driving Visit (Visit 3)**		**Washout Period**	**Second Dosing Visit (Visit 4)**	**Second Driving Visit/ Early Exit (Visit 5)**	
	Days -30 to -1	Day 1 (to be scheduled between 08:00 and 10:00)	Days 8 to 15		7 to 42 days	Days 15 to 57 (to be scheduled between 08:00 and 10:00)	Days 22 to 71	7- to 14-day study intervention adaptation period between Visits 2/3 and 4/5
Visit Windows			**Before Dosing**	**After Dosing**			**Before Dosing** / **After Dosing**	Before dosing (before study intervention instillation) and after dosing (approximately 1 hour after study intervention instillation)
Vital signs	X							Blood pressure and heart rate measured after participant has been at rest (seated) for at least 5 minutes. Please see Section 8.2.2.
Urine pregnancy test	X	X	X			X	X	WOCBP only. Please see Section 8.2.3.
OSDI	X							Please see Section 0, Item 4.02 (exclusion criteria).
NEI VFQ 25	X							Please see Section 5.1, Item 2.02 (inclusion criteria).
Slit-lamp biomicroscopy	X	X	X	X		X	X	Please see Section 8.2.1.1.
Mesopic conditions: allow for dark adaptation (5 to 10 minutes in mesopic conditions). Perform under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target).	X							Carry out in the order specified.
Mesopic, high-contrast BCDVA	X							Measurement is conducted at screening visit for OD, OS, and OU with best distance correction.

Procedures	Study Days (Visits)							Notes
	Screening (Visit 1)	**Randomization/ First Dosing Visit (Visit 2)**	**First Driving Visit (Visit 3)**		**Washout Period**	**Second Dosing Visit (Visit 4)**	**Second Driving Visit/ Early Exit (Visit 5)**	
	Days -30 to -1	Day 1 (to be scheduled between 08:00 and 10:00)	Days 8 to 15		7 to 42 days	Days 15 to 57 (to be scheduled between 08:00 and 10:00)	Days 22 to 71	7- to 14-day study intervention adaptation period between Visits 2/3 and 4/5
Visit Windows			**Before Dosing**	**After Dosing**			**Before Dosing** / **After Dosing**	Before dosing (before study intervention instillation) and after dosing (approximately 1 hour after study intervention instillation)
Mesopic, high-contrast DCNVA	X							Measurement is conducted at screening visit for OD, OS, and OU with best distance correction.
Mesopic pupil diameter	X							Please see Section 5.1, Item 2.07 (inclusion criteria) for screening visit and also Section 8.1.7 for additional details.
Halometer	X							Please see Section 8.1.8.
Photopic conditions: perform under photopic conditions ($\geq$ 80 cd/m^2; 251 lux at target).	X							Carry out in the order specified.
Photopic, high-contrast BCDVA	X							Measurement is conducted at screening visit for OD, OS, and OU with best distance correction.
Photopic, high-contrast DCNVA	X							Measurement is conducted at screening visit for OD, OS, and OU with best distance correction.
Photopic, high-contrast, binocular HDVA	X							Measurement is conducted OU only with habitual correction

Procedures	Study Days (Visits)							Notes
	Screening (Visit 1)	**Randomization/ First Dosing Visit (Visit 2)**	**First Driving Visit (Visit 3)**	**Washout Period**	**Second Dosing Visit (Visit 4)**	**Second Driving Visit/ Early Exit (Visit 5)**		
	Days -30 to -1	Day 1 (to be scheduled between 08:00 and 10:00)	Days 8 to 15	7 to 42 days	Days 15 to 57 (to be scheduled between 08:00 and 10:00)	Days 22 to 71		7- to 14-day study intervention adaptation period between Visits 2/3 and 4/5
Visit Windows			**Before Dosing**	**After Dosing**		**Before Dosing**	**After Dosing**	Before dosing (before study intervention instillation) and after dosing (approximately 1 hour after study intervention instillation)
Photopic manifest refraction (distance and near)	X							Please see Section 8.2.1.2.
Mesopic conditions: allow for dark adaptation (5 to 10 minutes in mesopic conditions). Perform under mesopic conditions (3.2 to 3.5 cd/m^2; 10 to 11 lux at target).			X	X		X	X	Carry out in the order specified.
Mesopic, high-contrast, binocular HDVA			X	X		X	X	At the driving visits, measurement is conducted with habitual correction for OU only.
Mesopic pupil diameter			X	X		X	X	Please see Section 8.1.7.
Halometer			X			X		Please see Section 8.1.8.

Procedures	Study Days (Visits)							Notes
	Screening (Visit 1)	**Randomization/ First Dosing Visit (Visit 2)**	**First Driving Visit (Visit 3)**		**Washout Period**	**Second Dosing Visit (Visit 4)**	**Second Driving Visit/ Early Exit (Visit 5)**	
	Days -30 to -1	Day 1 (to be scheduled between 08:00 and 10:00)	Days 8 to 15		7 to 42 days	Days 15 to 57 (to be scheduled between 08:00 and 10:00)	Days 22 to 71	7- to 14-day study intervention adaptation period between Visits 2/3 and 4/5
Visit Windows			**Before Dosing**	**After Dosing**			**Before Dosing** / **After Dosing**	Before dosing (before study intervention instillation) and after dosing (approximately 1 hour after study intervention instillation)
Photopic conditions: perform under photopic conditions (≥ 80 cd/m^2; 251 lux at target).			X	X			X / X	
Photopic, high contrast, binocular HDVA			X	X			X / X	Measurement is conducted OU only with habitual correction.
Photopic pupil diameter			X	X			X / X	Please see Section 8.1.7.
Fluorescein corneal stain	X							Please see Section 0, Item 4.02 (exclusion criteria).
IOP measurement	X	X				X		Please see Section 0, Item 4.07 (exclusion criteria).
Gonioscopy/angle assessment	X							Please see Section 0, Item 4.04 (exclusion criteria).
Dilated fundoscopic examination	X							Please see Section 8.2.1.3.
Review inclusion and exclusion criteria	X	X						Please see Section 5.1 and Section 0 (inclusion and exclusion criteria).

Procedures	Study Days (Visits)							Notes
	Screening (Visit 1)	**Randomization/ First Dosing Visit (Visit 2)**	**First Driving Visit (Visit 3)**		**Washout Period**	**Second Dosing Visit (Visit 4)**	**Second Driving Visit/ Early Exit (Visit 5)**	
	Days -30 to -1	Day 1 (to be scheduled between 08:00 and 10:00)	Days 8 to 15		7 to 42 days	Days 15 to 57 (to be scheduled between 08:00 and 10:00)	Days 22 to 71	7- to 14-day study intervention adaptation period between Visits 2/3 and 4/5
Visit Windows			**Before Dosing**	**After Dosing**			**Before Dosing** / **After Dosing**	Before dosing (before study intervention instillation) and after dosing (approximately 1 hour after study intervention instillation)
Contact IxRS for participant ID	X							Please refer to the IxRS manual for additional information.
Contact IxRS for kit assignment/random-ization		X				X		Please refer to the IxRS manual for additional information.
Study intervention instillation		X	X			X	X	1 drop in each eye performed by designated study center personnel (Visits 2 through 5). Dosing at home is described in Section 6.1.
Dispense study intervention		X				X		Dispense study intervention and instruct how to dose during adaptation period. Participant to dose one drop in each eye, once daily between 0800 and 1000. Participant will not dose at home on the day of a driving visit.
Driving test				X				Please refer to Section 8.1 for additional details. **Driving test to be performed 1 hour ± 15 min after study intervention instillation.**
Halometer				X				Please see Section 8.1.8.
Night-driving Experience Questionnaire				X				Please see Section 8.1.9.
Collect study intervention				X				Collect unused study intervention used during adaptation period.
Study exit								

2. Introduction

The sponsor is investigating pilocarpine HCl 1.25% ophthalmic solution (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, the sponsor 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 30 days in participants with presbyopia. As with all miotics, participants were advised to exercise caution in night driving and other hazardous occupations under poor illumination.
Study 1883-306-013 is a single-center, randomized, double-masked, crossover, Phase 3b study evaluating the effect of AGN-190584 compared with vehicle when dosed in both eyes on driving performance under real-world, night-lighting conditions 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 one 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, 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, the sponsor 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 who received AGN-190584 compared to participants who received vehicle or a combination therapy. The majority of AEs reported in any treatment group were mild to moderate in intensity.

Efficacy measures for 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. Efficacy and safety of AGN-190584 (1.25%) were also evaluated in 2 Phase 3 studies (1883-301-013 and 1883-302-013), for which the analyses and CSRs are, at the time this protocol was finalized, still in progress.

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, the sponsor is developing a noninvasive, reversible, pharmacological treatment for presbyopia.

Considering the COVID-19 pandemic, the benefit and risk to participants in this study have been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of AGN-190584 and no potential interactions are anticipated between the COVID-19 vaccine and the study drug.

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 Measures

Objectives	Measures
To evaluate night-driving performance in real-world driving conditions in participants with presbyopia treated with AGN-190584 versus vehicle	• Overall driving performance • Hazard avoidance • Road sign recognition • Road sign recognition distance • Pedestrian recognition distance • Lane-keeping • Driving time • Pupil diameter • Halometer • Night driving experience questionnaire
To evaluate safety in participants with presbyopia treated with AGN-190584 versus vehicle	• Mesopic/photopic HDVA • AEs • Pregnancy tests for WOCBP • Slit-lamp biomicroscopy

4. Study Design

4.1. Overall Design

This is a single-center, randomized, double-masked, crossover, Phase 3b study evaluating the effect of AGN-190584 compared with vehicle when dosed in both eyes on driving performance under real-world, night-lighting conditions in participants with objective and subjective evidence of presbyopia.

The study consists of 5 visits (screening [Visit 1], randomization/first dosing [Visit 2], first driving [Visit 3], second dosing [Visit 4], and second driving [Visit 5] visits) with a crossover of AGN-190584 and vehicle. There will be a 7- to 14-day study intervention adaptation period before each driving visit (Visits 3 and 5) and a 7- to 42-day washout period between Visits 3 and 4. Participants will require transport to and from both of the driving visits.

Approximately 54 participants will be enrolled at one study site (Queensland University of Technology, Australia) and approximately 40 participants are expected to complete the study based on an anticipated dropout rate of 25% or less. Participants who prematurely discontinue from the study will not be replaced.

4.2. Scientific Rationale for Study Design

The current Phase 3b clinical study is designed to evaluate the effect of AGN-190584 compared with vehicle when dosed in both eyes on driving performance under real-world, night-lighting conditions in participants with presbyopia.

Phase 2 Studies 199201-009 and 199201-010 supported the administration of AGN-190584 monotherapy as an effective and safe treatment for presbyopia at doses up to 1.5%. The nearly completed Phase 3 Studies 1883-301-013 and 1883-302-013 evaluated AGN-190584 1.25% in an expanded participant population to establish efficacy and safety (data analysis and CSRs in progress).

As with all miotics, participants should be advised to exercise caution in night driving and other hazardous occupations in poor illumination. Participants should be advised not to drive or use machinery until vision is cleared. This study is being conducted to better understand and quantify the effect of AGN-190584 on night driving under real-world conditions.

4.3. Justification for Dose

Through modeling and evaluation of the Phase 2 results (Studies 199201-007, 199201-009, and 199201-010), the sponsor has determined the optimal dose of AGN-190584 to be 1.25% for the treatment of presbyopia. AGN-190584 1.25% was evaluated in 2 nearly completed Phase 3 studies (1883-301-013 and 1883-302-013). The analyses and CSRs for these studies have been completed.

4.4. End of Study Definition

The EOS is defined as the date of the last driving 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 driving 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 from medical history
2.02	Subjective complaints of poor near vision that impacts 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 or near vision subscale, Questions A3 to A5 in the Appendix of Optional Additional Questions, at the screening visit Note: Please advise the participant that for this questionnaire they are to interpret the instructions as referring to glasses or contacts they need for seeing objects at a distance (if required), not their reading glasses or bifocals.
2.03	Photopic, high-contrast, best distance correction in the range of spherical -4.00 D to +1.00 D inclusively and cylinder ≤ ±2.00 D with photopic at the screening visit and photopic, high-contrast BCDVA of 20/25 or better OD and OS at the screening visit
2.04	Photopic, high-contrast HDVA of 20/32 or better OU at screening as well as before and 1 hour after dosing at both driving tests. Only monofocal correction (either spectacles or contact lenses) is allowed for the driving tests. If the participant does not have monofocal correction of 20/32 or better OU, the study site will provide monofocal spectacles.
2.05	Mesopic, high-contrast DCNVA of 20/40 to 20/100 OD and OS at screening
2.06	Photopic, high-contrast near visual acuity correctable to 20/40 or better in each eye at the screening visit
2.07	Mesopic pupil diameter < 8.0 mm in both eyes at the screening visit

3.	**Sex**
3.01	Male or female
4.	**Informed Consent**
4.01	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
4.02	Written informed consent from the participant 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.
5.	**Other**
5.01	Participant must hold a valid driver's license as governed by local regulations.
5.02	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 a 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
2.03	Prior/concomitant use of any interventions outlined in Section 6.5.1 (prohibited interventions and washout before the study).
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
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 are permissible, although they cannot be used at the driving visits.
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 who 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 a pair of monofocal spectacles with the same or improved distance correction (20/32 or better) as their new habitual correction for use at the driving visits. Bifocal or multifocal spectacles or contact lenses for habitual correction are permissible throughout the study, although they cannot be used at the driving visits.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study and sign the ICF 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 (ie, reason for failure), eligibility criteria, and any SAEs.

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 interventions intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Study Intervention Name	AGN-190584	Vehicle
Dosage Formulation	Topical ophthalmic solution	Topical ophthalmic solution
Identity of Formulation	Pilocarpine HCl 1.25% Ophthalmic Solution Manufactured at Allergan Waco	Oxymetazoline HCl and Pilocarpine HCl Placebo Ophthalmic Solution Manufactured at Allergan Waco
Drug Substance	Pilocarpine HCl 1.25%	Not applicable
Route of Administration	Topical eyedrop	Topical eyedrop
Dosing Instructions	1 drop in each eye at Visits 2 through 5 and at home as instructed	1 drop in each eye at Visits 2 through 5 and at home as instructed
Packaging and Labeling	Study intervention will be provided in sterile, 5 mL bottles. Each bottle will be labeled in compliance with local labeling regulations.	Study intervention will be provided in sterile, 5 mL bottles. Each bottle will be labeled in compliance with local labeling regulations.
Manufacturer	Allergan Sales, LLC.	Allergan Sales, LLC.
Number and Timing of Interventions	1 drop bilaterally, once at Visits 2 through 5 and at home as instructed	1 drop bilaterally, once at Visits 2 through 5 and at home as instructed
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 to the study center in identically appearing bottles and cartons.

Please refer to the SoA (Table 1-1) for the timing of study visits referenced below. As described in the SoA (Table 1-1) and Section 6.3, the study site will contact the IxRS for study intervention kit assignment.

Study intervention will be administered by the investigator or designated site personnel at Visits 2, 3, 4, and 5.

Participants will be supplied with study intervention at Visit 2 (randomization/first dosing visit) and instructed to dose at home 1 drop in each eye, once daily in the morning between 08:00 and 10:00 for 7 to 14 days (adaptation period). On the scheduled day of Visit 3 (first driving visit), the participant will not instill study intervention at home. Participants will be reminded by the study site before driving visits to not instill study intervention on the day of the visit. If the participant arrives for a driving visit having instilled study intervention at home that same day, the driving visit must be rescheduled for another day. Study intervention dispensed to the participant at Visit 2 will be collected by the study site at Visit 3.

After the washout period (crossover), participants will be supplied with study intervention at Visit 4 (second dosing visit) and again instructed to dose at home 1 drop in each eye, once daily

in the morning between 08:00 and 10:00 for 7 to 14 days (adaptation period). On the scheduled day of Visit 5 (second driving visit), the participant will not instill study intervention at home. Participants will be reminded by the study site before driving visits to not instill study intervention on the day of the visit. If the participant arrives for a driving visit having instilled study intervention at home that same day, the driving visit must be rescheduled for another day. Study intervention dispensed to the participant at Visit 4 will be collected by the study site at Visit 5.

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 is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Include participant ID number and bottle/carton serial or lot number, as 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. 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 Masking

All participants will be centrally assigned to randomized study intervention using the IxRS. Participant IDs will be assigned at the screening visit. Randomization and kit assignment will be conducted at the randomization/first dosing visit (Visit 2). At the randomization/first dosing visit (Visit 2), participants will be randomized in a 1:1 ratio to one of the 2 study intervention sequences, either AGN-190584 followed by vehicle after a minimum 1-week washout period (study intervention sequence 1), or vehicle followed by AGN-190584 after a minimum 1-week washout period (study intervention sequence 2). All participants will receive the first dose at Visit 2 and continue daily dosing through the end of the first driving visit (Visit 3). After the first driving visit (Visit 3) and a minimum 1-week washout period, participants will complete a second dosing visit (Visit 4) and continue daily dosing following the assigned study intervention sequence through the end of the study (Visit 5, second driving visit). The IxRS will be contacted again at the second dosing visit (Visit 4) for kit dispensing before study intervention instillation.

Before the study is initiated, login information and directions for the IxRS will be provided to the 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 the study center. 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 the sponsor prior to unmasking a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unmasked, the sponsor must be notified within 24 hours after breaking the mask. The date and reason that the mask was broken must be recorded in the source documentation.

As described in Section 6.1, study intervention will be administered by the investigator or designated site personnel at Visits 2, 3, 4, and 5, and at home by the participant between Visits 2/3 and 4/5 to allow for study intervention adaptation before each driving test (Visits 3 and 5).

6.4. Study Intervention Compliance

Study intervention will be administered by designated site personnel on visit days and at home by the participant during the adaptation periods (in the morning between 08:00 and 10:00). On the days of the driving tests (Visits 3 and 5), the participant will not instill study intervention at home (as it will be instilled by site staff during the visit). Participants will be instructed to return study intervention dispensed at Visits 2 and 4 at Visits 3 and 5, respectively.

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

Participants will be encouraged to consistently instill study intervention during the adaptation periods as instructed at home in between Visits 2/3 and 4/5.

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient study drug shipment can be made from the study site to the subject if allowed by local regulations. The sponsor will submit any required notifications to the regulatory authority as applicable. For Visit 2 and Visit 4, if a subject is unable to come to site the visit will be rescheduled.

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 second driving visit, 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, or may have interaction with the study intervention is prohibited during the study:

- Ophthalmic, systemic, or intranasal cholinergic receptor agonist/antagonist and α-adrenergic receptor agonist/antagonist with potential pupillary or accommodative effects, including oxymetazoline, commercially available pilocarpine, tetrahydrozoline, phenylephrine, naphazoline, cyclopentolate, atropine, or antihistamines
    - Note: Over-the-counter antihistamines used PRN between study visits are allowed but must not be used within 24 hours of any study visit.
- Systemic medications with potential for acute ocular side effects (eg, tricyclic antidepressants with anticholinergic effects), or with chronic ocular side effects that have been reported (eg, hydroxychloroquine related retinopathy)

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 it is necessary for the participant's welfare and/or 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 second driving visit will be recorded in the eCRF as a concomitant

medication; any medication started after the second driving visit will not be considered a concomitant medication and should not be captured in the eCRF.

COVID-19 Pandemic-related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected vaccines (eg, mRNA, nonreplicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the participant.

The potential impact of AGN-190584 on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug(s) AGN-190584 is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration, when possible.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with presbyopia and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

6.5.4. Prohibited Interventions During the Study

All interventions listed in Section 6.5.1 are also prohibited during the study.

Use of ocular medications other than the 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, the sponsor 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 receives study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

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

Reasons for EOS or EOT may include the following:

- Completed study (EOS)
- Completed treatment (EOT)
- Adverse event (EOT)
- Death (EOS)
- Lost to follow-up
- Withdrawal by subject (EOS)
- Withdrawal from treatment by subject (EOT)
- Non-compliance with study drug (EOT)
- Study terminated by sponsor
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Progressive disease (EOS)
- COVID-19 infection
- COVID-19 logistical restrictions
- Other (specify)

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 the second driving visit.

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.

COVID-19 Pandemic-related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure participant safety and continuity of care.

The investigator should contact the sponsor medical contact before discontinuing a participant from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

During the study drug dosing period, a participant with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 14 days since first PCR test result have passed in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for participants must be discussed with the sponsor medical contact, along with the possibility of premature discontinuation from the study drug dosing period.

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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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 immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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 the screening or either driving visit purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

8.1. Efficacy Assessments – Driving Performance

Efficacy assessments for night-driving performance metrics include: sign recognition (Section 8.1.1), hazard avoidance (Section 8.1.2), driving time (Section 8.1.3), lane-keeping (Section 8.1.4), pedestrian recognition distance (Section 8.1.5), overall composite driving Z-score (Section 8.1.6), pupil diameter (Section 8.1.7), halometer (Section 8.1.8), and a night-driving experience questionnaire (Section 8.1.9).

The night-driving evaluation will be performed at both driving visits. Please see the SoA in Section 1.3 for the timing of events at each visit.

Pupil diameter and halometer measurements will be performed separately from the driving test. Please see the SoA in Section 1.3 for the timing of events at each visit.

After 1 hour ± 15 minutes following study intervention instillation and visual function assessments, participants will start the driving test at the beginning of the closed road driving circuit. The circuit is representative of a rural road, and includes hills, bends, curves, intersections, lengthy straight sections, and standard road signs and lane markings. The circuit does not include artificial ambient lighting. All experimental sessions will be conducted during times when the road surface is dry and there is no rain. Driving performance will be assessed after nautical twilight (evening nautical twilight is defined to begin at sunset and end when the center of the sun is 12 degrees below the horizon).

Participants will undergo a 5-minute familiarization period with the instrumented vehicle and provided with standard instructions regarding the driving circuit and the tasks.

8.1.1. Sign Recognition

Participants will be instructed to verbally report the content of the standard road signs as they drive around the circuit (Figure 8-1). The percentage of signs correctly reported will be calculated from the reported total number of signs and the number of signs correctly identified. The recognition distance to one specific sign will also be recorded as sign recognition distance in meters.

Figure 8-1 Night-time View of Road Hazards and Signs

8.1.2. Hazard Avoidance

Participants will be instructed to report and avoid hitting any of the large, low-contrast, grey foam hazards (220 cm × 80 cm × 15 cm) positioned orthogonally in the driving lane along the roadway (Figure 8-1), the locations of which are altered between runs. The percentage of hazards hit will be calculated from the reported total number of hazards and the number of hazards hit.

8.1.3. Driving Time

Time to complete the road course will be recorded for each run (in minutes and seconds).

8.1.4. Lane-Keeping

Lane-keeping will be recorded by 2 video cameras mounted on the vehicle roof and calculated post-testing from the reported total driving time and reported time outside of lane. Lane crossings where the participant is responding to a hazard on the road are not included.

8.1.5. Pedestrian Recognition Distance

Two experimenters will act as pedestrians and walk in place at the end of a 400 m straight section of roadway. These pedestrians, known as pedestrians 1 and 2, will not be surrounded by any visual clutter or lighting. For each driving lap, the pedestrians walk in place as the vehicle approaches, facing directly towards the oncoming vehicle (this allows for the inclusion of naturalistic motion and ensures the safety of the pedestrian). The pedestrians will wear retro-reflective strips on either the torso or on the moveable joints in the biomotion configuration (Figure 8-2), which has been shown to allow good discrimination between different levels of spherical blur (Wood 2015). Pedestrian recognition distances will be assessed using the in-vehicle GPS logging system and the known positions of pedestrians enable calculation of the distance at which drivers first recognize the pedestrians. Several retroreflective bollards (ie, cones) will be positioned around the circuit to generate clutter to minimize expectation effects.

Figure 8-2 Experimental Pedestrian in Reflective Gear

8.1.6. Composite Driving Z Score

A composite driving Z score will also be derived to capture the overall driving performance of each participant compared with the whole group, as has been used in previous studies (Wood 2002, Wood 2009, Wood 2010, Wood 2014). The composite score is calculated using the average of Z scores for the following component driving measures: percent hazards hit, percent sign recognition and recognition distance, pedestrian recognition distances (pedestrians 1 and 2), and percent of time outside of lane (lane-keeping). The composite score is an important measure to account for differences in how participants prioritize the various driving tasks, where some components may have been performed better to the detriment of other components, and has been used in the previous studies listed above.

8.1.7. Pupil Diameter

Pupil diameter will be measured during distance fixation using a NeurOptics Pupillometer for mesopic/photopic lights levels specified in the SoA (Section 1.3).

8.1.8. Halometer

The halo produced by glare from a bright white LED attached to the center of an iPad screen (iPad 4, Apple Inc., Cupertino, California, USA) will be determined as the position closest to the LED where 2 out of 3 presentations of a randomly presented, high-contrast 20/50 letter (0.4 logMAR) are correctly identified (Buckhurst 2015, Kimlin 2017). A seen-to-not-seen approach will be used with a 0.1˚ step size along 8 meridians. The halo area (cm^2) will be determined by calculating the area of the halo surrounding the LED glare source.

8.1.9. Night-driving Experience Questionnaire

A night-driving experience questionnaire consisting of 12 questions will be administered to participants to evaluate their night driving experience after the driving tests and is provided in Appendix 7 (Section 10.7).

8.2. Safety Assessments

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

8.2.1. Ophthalmic Examinations

8.2.1.1. 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.

8.2.1.2. Manifest Refraction

Manifest refraction (distance and near) will be performed according to standard clinical practice in photopic conditions.

8.2.1.3. Dilated Fundoscopic Examination

The fundus assessments should be conducted through a dilated pupil (using 1% tropicamide). 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.

8.2.2. 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 recorded in bpm.
- Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.

8.2.3. 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. Pregnancy tests will be performed at all study visits, and may be performed at any other visit (as applicable), at the investigator's discretion. At each visit, the investigator should discuss contraceptive use compliance with WOCBP (see Appendix 6, Section 10.6).

8.2.4. Mesopic and Photopic BCDVA and DCNVA

Binocular BCDVA and DCNVA will be tested using logMAR charts at 4 m and 40 cm under 2 lighting conditions: mesopic luminance (10 to 11 lux) and photopic luminance (≥ 251 lux) under normal room lighting. Testing will be conducted with the optimal distance refractive correction. 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, in logMAR. Different logMAR charts will be used for each lighting condition and distance measured.

8.2.5. Mesopic and Photopic HDVA

Binocular HDVA will be tested using logMAR charts at 4 m under 2 lighting conditions: mesopic luminance (10 to 11 lux) and photopic luminance (≥ 251 lux) under normal room lighting. Testing will be conducted with the participant's habitual monovision distance refractive correction. 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, in logMAR. Different logMAR charts will be used for each lighting condition and distance measured.

8.2.6. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments are not applicable to this study.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

Suicidal risk monitoring and behavior risk monitoring are 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 (Section 10.2).

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 AE and SAE Information

All AEs and 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.

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 (Section 10.2). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The investigator is 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 (Section 10.2).

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All 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 the sponsor 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 the sponsor 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 the sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for SAEs

- 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 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 the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6 (Section 10.6).
- 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.

8.4. Treatment of Overdose

Treatment of overdose is not applicable to this ophthalmology study.

8.5. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

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

- H_0: The difference in mean overall composite driving Z score between AGN-190584 and vehicle (AGN-190584 minus vehicle) is < -0.25.
- H_A: The difference in mean overall composite Z score between AGN-190584 and vehicle (AGN-190584 minus vehicle) is ≥ -0.25.

9.2. Sample Size Determination

The sample size calculation is based on the primary efficacy endpoint. Assuming no difference between treatment groups and variance of 0.11, approximately 40 participants will be required to obtain 90% power for a 1-sided noninferiority test with type 1 error of 0.025 and noninferiority margin of -0.25 units in mean overall composite driving Z score. Therefore, approximately 54 participants will be enrolled to achieve 40 participants completing the study assuming an anticipated dropout rate of 25% or less.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
ITT	The ITT population includes all randomized participants.
Safety	The safety population includes all treated participants who receive ≥ 1 administration of study intervention.

9.4. Statistical Analyses

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 other efficacy endpoints and associated analyses are summarized in the following sections.

Primary Efficacy Endpoint:

- Overall composite driving Z score approximately 1 hour after study intervention instillation

Other Efficacy Analyses:

Other efficacy analyses will include road sign recognition score, lane-keeping score, pedestrian recognition distance, driving time, pupil diameter, halometer, and a night-driving experience questionnaire.

9.4.1.2. Primary Analyses

Overall composite driving Z score will be analyzed using MMRM. The model will include study intervention group, study intervention sequence, and study period as fixed effects and participant nested within sequence of testing as a random effect. The within-participant correlation error structure is unstructured. Noninferiority of AGN-190584 will be concluded if the lower bound of the 95% confidence interval of the least square mean difference between AGN-190584 and vehicle is greater than -0.25.

9.4.1.3. Other Efficacy Analyses

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

9.4.2. Safety Analyses

The safety analyses will be performed using the safety population. 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 with TEAEs during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with ocular TEAEs during the study will be tabulated by preferred term.

If more than 1 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 had 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.

9.5. Interim Analyses

No interim analysis is planned.

9.6. 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 CIOMS International Ethical Guidelines
  - Applicable ICH/ISO 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 conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.5. Dissemination of Clinical Study Data

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, GCP: Consolidated Guidance and records must be attributable, legible, contemporaneous, original, and accurate.
- During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.1.8. Study and Site Start and Closure

For the purpose of clinical trial registries, the study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is first participant first visit, which is considered the first act of recruitment and will be the study start date.

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

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

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

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

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

obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

- The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript.
- The sponsor will comply with the requirements for publication of study results.
- 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 (including those that may be due to the COVID-19 pandemic) will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

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

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 Meeting 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, is not considered an AE. 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

10.2.2. 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 that 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) that 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.

10.2.3. Recording and Follow-up of AE and/or SAE

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 the sponsor 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 the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- 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 the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- 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.

10.2.4. Reporting of SAEs

SAE Reporting

- In the event of an SAE, whether associated with the study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system (RAVE®).
- SAEs that occur prior to the site having access to the RAVE system, or if RAVE is not operable, should be documented on the SAE non-CRF paper forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.
  - The email address is IR-Clinical-SAE@abbvie.com.
  - 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 non-CRF paper form, sent by overnight mail or courier service.
  - Initial notification via telephone does not replace the need for the investigator to complete SAE data capture within the designated reporting timeframes.
- 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
BCDVA	best-corrected distance visual acuity
C/D	cup-to-disc
CDISC	Clinical Data Interchange Standards Consortium
CDVA	corrected distance visual acuity
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTA	clinical trial agreement
DCNVA	distance-corrected near visual acuity
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GPS	global positioning system
HDVA	habitual distance visual acuity
HRT	hormone 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
ISO	International Organization for Standardization
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IxRS	interactive electronic response system
LASIK	laser-assisted in situ keratomileusis

Abbreviation/Term	Definition
LED	light-emitting diode
logMAR	logarithm of the minimum angle of resolution
MMRM	mixed model for repeated measures
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
OTC	over-the-counter
OU	both eyes
PCR	polymerase chain reaction
PK	pharmacokinetic
PRK	photorefractive keratectomy
PRN	as needed
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
TEAE	treatment-emergent adverse event
USA	United States of America
WOCBP	women of childbearing potential

10.4. Appendix 4: Standard Discontinuation Criteria

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

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A). Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
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)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
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)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
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)

CDISC Submission Value	CDISC Definition
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
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	Evaluating the Impact of AGN-190584 on Night-driving Performance
	Clinical Study Sponsor	Allergan Sales, LLC
	Trial Phase Classification	Phase 3b
	Trial Indication	Presbyopia
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	22 to 71 days, with a 30-day screening period
	Planned Country of Investigational Site	Australia
	Planned Number of Enrolled Participants	Approximately 54
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	40
	Planned Maximum Age of Participants	55
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not specified
Treatments	Investigational Therapy or Treatment	AGN-190584 (pilocarpine HCl 1.25% ophthalmic solution)
	Intervention Type	Drug
	Dose per Administration	1 bilaterally
	Dose Units	Drop
	Dosing Frequency	Once daily
	Route of Administration	Topical eyedrop
Trial design	Study Type	Interventional
	Intervention Model	Crossover
	Planned Number of Arms	2
	Trial Is Randomized	Yes
	Trial Blinding Schema	Double-masked
	Adaptive Design	No

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

Definitions:

Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP

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

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

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - 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, confirmation with more than 1 FSH measurement is required.
   - 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 or acceptable method of contraception consistently and correctly as described in Table 10–1.

Table 10–1 Highly Effective and Acceptable 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[b] • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • 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.*
Acceptable Methods *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 A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[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.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period, a negative highly sensitive urine pregnancy test at screening, and a negative test at Visit 2.
- 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. In the event of pregnancy, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware by entering the initial information into the EDC system (RAVE®).
- Pregnancies that occur prior to the site having access to the RAVE system, or if RAVE is not operable, should be documented on pregnancy paper forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.7. Appendix 7: Night-driving Experience Questionnaire

This survey asks questions about your vision during the drive that you just completed. *For questions 1-4, please circle the choice that best describes your answer to each question.*					
1- I was satisfied with the quality of my vision for driving.	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2- My vision did not impact my confidence in driving.	Not at all	A little	Somewhat	Very	Extremely
3- I noticed a double image around distant objects.	Never	Rarely	Some of the time	Most of the time	All of the time
4- I experienced visual disturbance (glare, halo, starburst) in dim lighting.	Never	Rarely	Some of the time	Most of the time	All of the time
For questions 5-12, please mark an (X) in the box that best describes your answer to each question. How difficult were the following driving tasks during the drive that you just completed?	Not difficult at all	A little difficult	Moderately difficult	Very difficult	Extremely difficult
5- Seeing hazards on the road in time to avoid them					
6- Keeping in my lane					
7- Seeing pedestrians at the roadside					
8- Reading the road signs					
9- Judging distances					
10- Reading car gauges (eg, speedometer) without straining my eyes					
11- Adjusting my vision when looking from the road to the speedometer and back					
12- Overall, how difficult was it to see during the driving task?					

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