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Protocol for Study M21-195

Presbyopia: Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia

VERSION:	2.0	DATE:	21 October 2021
SPONSOR:	AbbVie Inc.*	PLANNED NUMBER OF SITES:	Approximately 20 sites in the United States
ABBVIE INVESTIGATIONAL PRODUCT:	AGN-190584	EudraCT:	Not applicable

FULL TITLE: A Phase 3, Multicenter, Double-masked, Randomized, Vehicle-controlled, Parallel-group Study Evaluating the Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 3, Multicenter, Double-masked, Randomized, Vehicle-controlled, Parallel-group Study Evaluating the Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia	
Background and Rationale:	This study evaluates pilocarpine HCl 1.25% (AGN-190584) as a noninvasive, reversible, pharmacological treatment for presbyopia. The purpose of this study is to evaluate AGN-190584 when administered twice daily.
Objective(s) and Endpoint(s):	The objective of this study is to evaluate the safety and efficacy of AGN-190584 when administered bilaterally, twice daily for 14 days in subjects with presbyopia. The primary efficacy endpoint is the proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose). The key secondary endpoint is the proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose). Additional secondary endpoints are the proportion of subjects gaining 2 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose); and the proportion of subjects achieving 20/40 or better in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose). Plasma concentrations of AGN-190584 will be assessed at selected sites in approximately 10% of all enrolled subjects. Safety will be assessed based on adverse events, vital signs, mesopic and photopic high-contrast binocular CDVA, intraocular pressure, slit-lamp biomicroscopy, manifest refraction, dilated fundoscopic examination, postdose tolerability (for subjects reporting specific ocular symptoms), drop comfort, and pregnancy test.
Investigator(s):	Multicenter
Study Site(s):	Approximately 20 sites in the United States
Study Population and Number of Subjects to be Enrolled:	Approximately 200 male and female subjects with objective and subjective evidence of presbyopia
Investigational Plan:	This is a Phase 3, multicenter, 14-day, double-masked, randomized, vehicle-controlled, parallel-group study evaluating the safety and efficacy of BID bilateral dosing with AGN-190584 in subjects with presbyopia.
Key Eligibility Criteria:	Adult subjects 40 to 55 years of age with objective and subjective evidence of presbyopia

Study Drug and Duration of Treatment:	Eligible subjects will be randomized in a 1:1 ratio to receive either AGN-190584 or vehicle dosed twice daily, in each eye, for 14 days.
Date of Protocol Synopsis:	21 October 2021

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

The decline 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.[1] 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 photorefractive keratectomy (PRK) or laser-assisted in situ keratomilieusis (LASIK), conductive keratoplasty, intraocular lenses, and corneal inlays. However, for each of the existing technologies mentioned above, visual quality is reduced at 1 or more viewing distances (near, intermediate, or distance), and each comes with its own unique safety risks and associated complications. For example, bifocals and progressive lenses (e.g., reading glasses, contacts) produce optical aberrations and can increase the risk of falls.[2,3] Multifocal optics reduce image quality uniformly at all viewing distances. For surgical technologies, surgical risks, the need for repositioning and explantation, and/or regression of effect have limited their widespread adoption.[4-6] 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) contraction of the iris sphincter muscle, resulting in pupil constriction (miosis); 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[7], and 2) contraction of the ciliary muscle, resulting in central lens steepening and lens accommodation (focusing from distance to near).[8]

Pilocarpine ophthalmic solutions are currently used for the reduction of elevated intraocular pressure (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.[9] Currently the use of pilocarpine ophthalmic solution is limited by the commonly experienced adverse event (AE) of temporal and periorbital headache (i.e., brow ache), which is believed to be due to the rapidity of the ciliary muscle contraction.[10] However, AbbVie (formerly Allergan) has established an acceptable safety profile of AGN-190584 in 3 Phase 2 clinical studies (Studies 199201-007, 199201-009, and 199201-010) and 2 Phase 3 studies (1883-301-013 and 1883-302-013). 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 clinical studies were generally low and safety parameters were not clinically significant between subjects who received AGN-190584 compared to subjects who received vehicle or a combination therapy. The majority of AEs reported in any treatment group were mild to moderate in severity. More detailed information regarding clinical safety findings, clinical efficacy findings, chemistry, and pharmacology is provided in the Investigator's Brochure (IB).

2.2 Benefits and Risks to Subjects

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[3], and multifocal 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 subjects have difficulty adjusting to using them.[2,3] As a result, AbbVie is developing a noninvasive, reversible, pharmacological treatment for presbyopia.

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

Considering the Coronavirus Disease - 2019 (COVID-19) pandemic, the benefits and risks to subjects participating in this study have been evaluated. Based on the limited information to date, no additional risk to study subjects is anticipated with the use of AGN-190584; however, the risk of study activity participation should be evaluated by the investigator.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Objectives

The primary objective of this study is to evaluate the safety, efficacy, and pharmacokinetics of AGN-190584 when administered bilaterally, twice daily for 14 days in subjects with presbyopia.

Hypotheses

The clinical hypotheses are that AGN-190584 ophthalmic solution dosed bilaterally, twice daily (Hour 0 and Hour 6) for 14 days will demonstrate a significant improvement in distance-corrected near visual acuity (DCNVA) over vehicle after the second dose, and AGN-190584 ophthalmic solution dosed bilaterally, twice daily for 14 days will demonstrate an acceptable safety and tolerability profile.

Table 1. Hypotheses for the Primary and the Key Secondary Efficacy Endpoints

Hypothesis	Efficacy Endpoints
H1	**Primary:** The proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)
H2	**Key Secondary:** The proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)

DCNVA = distance-corrected near visual acuity; CDVA = corrected distance visual acuity

Estimands

Estimand attributes are described in Table 2.

Table 2. Summary of the Estimand Attributes of the Primary and the Key Secondary Efficacy Endpoints

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Estimand for the primary endpoint	AGN-190584 or vehicle	The proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)	ITT	The composite strategy will be applied to handle the intercurrent events. Missing data will be regarded as a nonresponder for the primary endpoint.	The difference and the corresponding 95% confidence interval in the proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 between AGN-190584 and vehicle.
Estimand for the key secondary endpoint	AGN-190584 or vehicle	The proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)	ITT	The composite strategy will be applied to handle the intercurrent events. Missing data will be regarded as a nonresponder for the key secondary endpoint.	The difference and the corresponding 95% confidence interval in the proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 between AGN-190584 and vehicle.

DCNVA = distance-corrected near visual acuity; CDVA = corrected distance visual acuity; ITT = intent to treat

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose).

3.3 Secondary Endpoints

Key Secondary Endpoint

1. Proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)

Supportive Secondary Endpoints

1. Proportion of subjects gaining 2 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)
2. Proportion of subjects achieving 20/40 or better in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)

3.4 Additional Efficacy Endpoints

1. Change from baseline in mesopic Near Vision Presbyopia Task-based Questionnaire (NVPTQ) Performance score at Day 14, Hour 9 (3 hours after the second dose)
2. Change from baseline in Presbyopia Impact and Coping Questionnaire (PICQ) Coping score at Day 14, Hour 3
3. Change from baseline in Visual Function Assessment application (VFA app) at Day 14, Hour 9 (3 hours after the second dose)
    - Change from baseline in average number of blinks per minute
    - Change from baseline in median working distance (centimeters)
    - Change from baseline in median magnification level (%) from the original size
    - Change from baseline in reading speed (words per minute)
    - Change from baseline in median contrast level (%) based on the original value

3.5 Pharmacokinetic Endpoints

Blood samples for the quantitation of AGN-190584 in subject's plasma will be collected from approximately 10% of enrolled subjects at selected sites.

3.6 Safety Endpoints

The safety measurements will include AE, vital signs (blood pressure and heart rate), mesopic and photopic, high-contrast, binocular CDVA, IOP, slit-lamp biomicroscopy, manifest refraction, dilated fundoscopic examination, postdose tolerability assessment, drop comfort questionnaire, and pregnancy test.

3.7 Patient Reported Outcomes

Patient-reported outcome (PRO) questionnaires are administered in this study. The **VFA app** should be administered as well.

At screening, subjects will answer questions on vision functioning and health-related quality of life using the **NEI VFQ-25**, including the near vision subscale items (Questions A3 to A5) from the Appendix of Optional Additional Questions.

Subjects will also complete the Ocular Surface Disease Index (**OSDI**) at screening, which assesses symptoms of ocular irritation and their impact on vision-related functioning.

Each subject will also perform 4 paper-based near vision reading tasks under mesopic conditions. Subjects will subsequently rate their vision-related reading ability and satisfaction with their vision-related reading ability by completing the **NVPTQ**.

Subjects will also answer questions assessing the impact of presbyopia on their life and need for compensatory coping mechanisms using the **PICQ**.

Subjects will also answer single-item questions on their overall global impression of status (**PGIS**) and their overall global impression of change (**PGIC**).

After study drug administration, subjects will complete the **Drop Comfort Questionnaire** to evaluate comfort of the study drug after administration.

Finally, the **VFA app** will be used to assess the subject's ability to read on electronic devices.

For questionnaires completed on an electronic platform, if technical issues prevent the questionnaire from being completed, responses can be written down on source documents (preferably a paper copy of the questionnaire if available) and entered when the electronic platform is available.

4 INVESTIGATIONAL PLAN

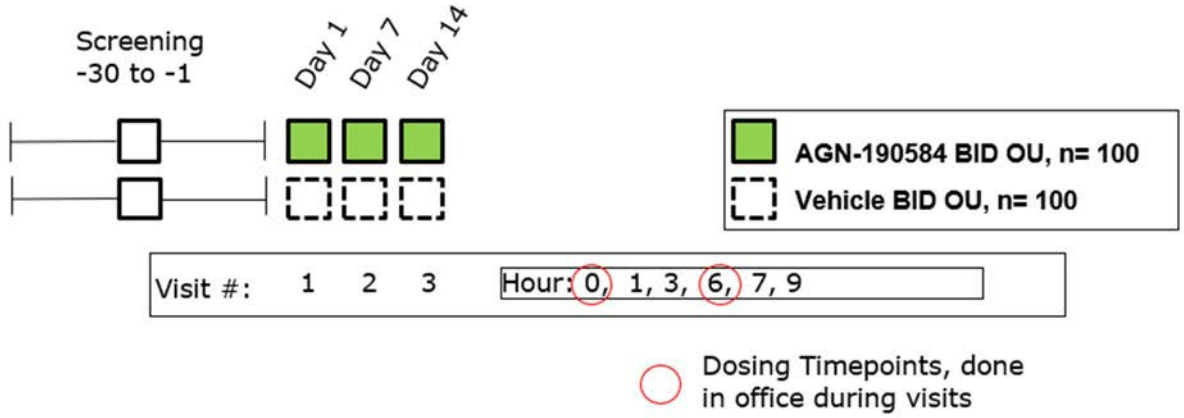
4.1 Overall Study Design and Plan

This is a Phase 3, multicenter, double-masked, parallel-group, vehicle-controlled study in subjects with presbyopia. Subjects will receive AGN-190584 or vehicle dosed twice daily, bilaterally, for 14 days. Approximately 200 subjects with presbyopia will be enrolled at approximately 20 sites in the United States.

The study consists of the following visits: screening (Days -30 to -1), Day 1 (baseline), Day 7 (± 2 days), and Day 14 (± 2 days). A study schema is shown in Figure 1. Subjects will receive either AGN-190584 or vehicle dosed twice daily, bilaterally, for 14 days beginning on Day 1. On nonvisit days, subjects will be instructed to instill one drop of the dispensed study drug in each eye twice daily, with each dose administered 6 hours apart. On visit days, study drug will be instilled bilaterally by designated site personnel at Hour 0 (8 AM ± 1 hour) and Hour 6 (time measured 6 hours from the time of completion of the Hour 0 study drug administration). Study procedures on visit days are provided in the Activity Schedule (Appendix D) and further guidance regarding study procedures are located in the Operations Manual (Appendix F).

Adult subjects 40 to 55 years of age with objective and subjective evidence of presbyopia will be enrolled. See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schema



At selected sites, blood will be collected for pharmacokinetic (PK) on Days 1 and 14 at Hours 0, 0.25, 0.5, 1, 3, 6 [pre-dose], 6.25, 6.5, 7, 9, 12

4.2 Discussion of Study Design

Choice of Control Group

A vehicle control group is a recognized comparative evaluator of safety and efficacy in clinical trials.

Appropriateness of Measurements

Standard statistical, PK, and clinical procedures will be used in this study. All efficacy and safety-related measurements in this study are commonly used for assessing presbyopia. All clinical procedures in this study are standard and generally accepted.

Suitability of Subject Population

The study population will include male and female adults 40 to 55 years of age with objective and subjective evidence of presbyopia. Subjects with any evidence of ocular conditions that could affect the safety of the subject or interpretation of efficacy parameters will not be enrolled.

Selection of Doses in the Study

The dose selection in this study is based on modeling and the analysis of safety and efficacy data from Phase 2 Studies 1991201-007, 199201-009, 199201-010 and Phase 3 Studies 1883-301-013 and 1883-302-013. AGN-190584 (pilocarpine hydrochloride) 1.25% is expected to be efficacious with an acceptable safety profile.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult male or female, 40 to 55 years of age inclusive at the time of the screening visit
- 3. Are willing and able to comply with procedures required in this protocol.

Disease/Condition Activity

- 4. Subject meets the following ocular conditions:
  - Subjective complaints of poor near vision that impact activities of daily living, as defined by at least a moderate impact (score ≥ 3) on at least 1 question on the 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
  - Best cycloplegic distance correction at screening in the range of spherical -4.00 D to +1.00 D inclusively and cylinder ≤ ±2.00 D with photopic, high-contrast binocular CDVA of 20/25 or better at the screening and baseline visits

- Photopic, high-contrast binocular CDVA of 20/32 or better by habitual monofocal correction (either spectacles or contact lenses), or willing to wear new monofocal correction spectacles to achieve photopic, high-contrast CDVA of 20/32 or better during the study
- Mesopic, high-contrast binocular DCNVA of 20/40 (J3) to 20/100 (J10) at the screening and baseline visits
- Photopic, high-contrast, near visual acuity correctable to 20/40 (J3+) or better in each eye at the screening visit
- Mesopic pupil diameter < 8.0 mm in both eyes at the screening visit

5. Subject does not meet any of the following ocular conditions:

- 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
- Corneal abnormalities (including keratoconus, corneal scar, Fuchs' endothelial dystrophy, guttata, or edema) in either eye that are likely to interfere with visual acuity
- Narrow iridocorneal angles (Shaffer grade ≤ 2 or lower on gonioscopy examination), history of angle-closure glaucoma, or previous iridotomy
- 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
- Lens opacity in either eye that is determined to cause significant disturbance of the central visual axis on screening biomicroscopy
- Diagnosis of any type of glaucoma or ocular hypertension
- Bifocal or multifocal spectacles or contact lenses for habitual correction. Subjects willing to wear study-provided monofocal correction (either spectacles or contact lenses) during the study can be enrolled.
- Had cataract surgery, phakic intraocular lens surgery, corneal inlay surgery, radial keratotomy, or any intraocular surgery. However, subjects with history of PRK or LASIK with CDVA meeting inclusion criteria will be allowed to enroll.
- Presence of any ocular condition that, in the opinion of the investigator, could affect the safety of the subject or interpretation of efficacy parameters (e.g., uveitis, retinal detachment)
- Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes

Subject History

6. No history of the following:

- Uncontrolled systemic disease
- Any clinical condition or previous surgery that might affect the absorption, distribution, biotransformation, or excretion of AGN-190584

- A condition or a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study
- Abnormal or clinically significant results according to the investigator or designee, on physical/ophthalmic examination or medical history
- clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months
- clinically significant medical conditions/disease state or any other reason that the investigator determines would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive the study drug
- allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class (cholinergic agonist)

- 7. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., polymerase chain reaction [PCR]) test result. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed, and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criterion:
- 8. At least 14 days since the first PCR test result have elapsed in an asymptomatic subject or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms

Contraception

- 9. For all females of childbearing potential; a negative urine pregnancy test at the screening visit and at baseline prior to the first dose of study drug
- 10. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Study Day 1 through study exit. Female subjects of nonchildbearing potential do not need to use birth control.
- 11. Female who is not pregnant or breastfeeding, and is not considering becoming pregnant or donating eggs during the study or for approximately 30 days after the last dose of study drug.

Concomitant Medications

- 12. Subject must not use any medications that may have a substantial effect on visual function or the optical properties of the eye (defined in Section 5.3) at least 2 weeks prior to the first dose of study drug, Day 1.
- 13. Subject must not use any ocular medications other than the study drug or medications administered to conduct study procedures at the screening and Day1 (baseline) visit
- 14. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug, be currently enrolled in another clinical study, or have been previously enrolled in this study.

- 15. Subject must not have enrolled in the Phase 3 AGN-190584 Studies 1883-301-013 or 1883-302-013.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Nonchildbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of nonchildbearing potential due to meeting any of the following criteria:

1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
    - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
    - Nonsurgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
2. Postmenopausal female
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause

- Females, of Childbearing Potential
    - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug.
    - Females must commit to one of the following methods of birth control:
        - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to study Baseline Day 1
        - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1
        - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
        - Intrauterine device
        - Intrauterine hormone-releasing system
        - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject)
        - Practice true abstinence, defined as: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence

[e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method)

5.3 Prohibited Medications and Therapy

During the study, the following are prohibited.

- Use of medications that may have a substantial effect on visual function or the optical properties of the eye is prohibited 2 weeks prior to the Day 1 visit and during the study:
  - Systemic medications with potential ocular side effects, including topiramate, hydroxychloroquine, ethambutol, phosphodiesterase 5 inhibitors (sildenafil, vardenafil, tadalafil), or tamoxifen
  - Ophthalmic, systemic, or intranasal anticholinergics and α-adrenergic receptor agonists with potential pupillary or accommodative effects, including oxymetazoline, tetrahydrozoline, phenylephrine, naphazoline, cyclopentolate, atropine
  - Cholinergic agonists such as pilocarpine, carbachol, and aceclidine
  - Alpha adrenergic antagonists including phentolamine mesylate
  - Tricyclic antidepressants
- Use of systemic antihistamines (including those used in over-the-counter (OTC) cold and flu preparations) is prohibited within 3 days prior to a study visit and on visit days.
- Use of selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs) is not prohibited if dosage is consistent for at least 30 days prior to randomization and throughout the study.
- Use of ocular medications other than the study drug or medications administered to conduct study procedures is 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 subject as the primary consideration. When possible, AbbVie should be notified before the prohibited medication/treatment is administered.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded through study exit.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with AGN-190584 can be located in the AGN-190584 IB.

Subjects must be able to safely discontinue any prohibited medications as described in the Eligibility Criteria (Section 5.1) and Prohibited Medications and Therapy (Section 5.3). Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

COVID-19 Pandemic-related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected vaccines (e.g., messenger ribonucleic acid, 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 subject.

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 AGN-190584, when possible, is preferred to be given at least ± 14 days from the final SARS-CoV-2 vaccine administration.

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 subjects 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 electronic case report form. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

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 subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

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

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection will be discontinued. Follow subsequent protocol Section 5.6 for subjects who discontinue study drug.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Subjects who prematurely discontinue study drug treatment will be encouraged to stay in the study for safety assessments, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks.

5.7 Study Drug

AGN-190584 or matching vehicle manufactured by AbbVie will be administered bilaterally twice daily beginning on Day 1 (Baseline) and should be taken at approximately the same time each day (6 hours apart). On the day before office visits, the study drug must be administered no less than 12 hours before the scheduled visit time. The study site personnel will document compliance and any missed doses should be reported to the investigator by the subject.

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit.

AbbVie will provide study drug for AGN-190584 or matching vehicle. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

AGN-190584 and matching vehicle will be packaged in bottles with quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Table 3. Study Drug Identification

	Investigational Product	Investigational Product Vehicle
Investigational product name	AGN-190584	Vehicle
Active ingredient	Pilocarpine HCl 1.25%	Not applicable
Mode/Route of administration (ROA)	Topical eyedrop	Topical eyedrop
Formulation	Pilocarpine HCl 1.25% Ophthalmic Solution (011430X) Lot T1484 Manufactured at Allergan Sales, LLC	Oxymetazoline HCl and Pilocarpine HCl Placebo Ophthalmic Solution (11258X) Lot T1469 Manufactured at Allergan Sales, LLC
Dosage form	Topical eyedrop	Topical eyedrop
Dose and units	1 drop in each eye twice daily	1 drop in each eye twice daily
Drug preparation/packaging	Study drug will be provided in sterile, 5 mL bottles in a carton. Each bottle & carton will be labeled as required per country requirement.	Study drug will be provided in sterile, 5 mL bottles in a carton. Each bottle & carton will be labeled as required per country requirement.
Masking	Masked	Masked
Frequency of administration	Twice daily to each eye, 6 hours apart	Twice daily to each eye, 6 hours apart
Volume of study drug	3.5 mL per bottle	3.5 mL per bottle
Storage conditions	In a refrigerator, refrigerated: 2°C to 8°C	In a refrigerator, refrigerated: 2°C to 8°C

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, a new screening number will be assigned by the IRT. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

Subjects will be randomized in a 1:1 ratio to receive either AGN-190584 or vehicle dosed twice daily, in each eye, for 14 days.

Randomization will be further stratified by the following stratification factors:

- Age group: ≤ 50 years and > 50 years
- Baseline binocular mesopic DCNVA severity: 20/63 or better, and worse than 20/63; with a maximum of 50% enrolled subjects with baseline binocular mesopic DCNVA of 20/63 or better

- Iris color: brown and nonbrown
- Emmetrope status: emmetrope and nonemmetrope; with a maximum of 25% enrolled subjects with nonemmetrope. A subject will be considered as emmetrope if both eyes of the subject satisfy the 2 criteria: 1) -0.5D to +0.75D in sphere, inclusively; and 2) ≤ 0.75D in Cylinder.

All AbbVie personnel with direct oversight of the conduct and management of the study (with the exception of the AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain masked to each subject's treatment throughout the study. To maintain the masking, the AGN-190584 and vehicle containers provided for the study will be identical in appearance. The IRT will provide access to unmasking subject treatment information in the case of a medical emergency.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying the IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: AGN-190584

An AE is defined as any untoward medical occurrence in a subject 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical drug, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a Serious adverse event (SAE) within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject
Life-threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical drug had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Drug to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but, based on medical judgment, may jeopardize the subject and may require medical or surgical drug to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events, whether solicited or spontaneously reported by the subject, will be collected from the time of study drug administration through study exit, unless spontaneously report after study exit. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an investigational medicinal product (IMP) related to any dose administered that result in an SAE as defined above
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable reference safety information), and meets one of the above serious criteria

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following adverse events of special interest will be monitored during the study:

- Headache
- Visual disturbance

Subjects reporting a headache AE (including any AE related to headache or migraine) will be provided the supplemental headache AE assessment form to further assess the headache AE and grade the degree of severity.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the statistical analysis plan (SAP).

7.2 Definition for Analysis Populations

The intent to treat (ITT) population will consist of all randomized subjects. Subjects will be summarized according to the randomized study drug.

The safety population will consist of all subjects who received at least 1 administration of study drug. Subjects will be summarized according to the study drug actually received.

The PK population will consist of all subjects with evaluable plasma concentrations of AGN-190584.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The following methods will be used to address potential intercurrent events for both the primary and key secondary endpoints:

- Subjects who prematurely discontinued study drug before the Day 14 visit will be considered as nonresponders.
- Subjects who die before assessment of the endpoint will be considered as nonresponders for the endpoint.
- Subjects who are lost to follow-up and are missing data for the endpoint will be considered as nonresponders for the endpoint.

Missing data will be regarded as a nonresponder, for both the primary and key secondary endpoints.

7.4 Statistical Analyses for Efficacy

The efficacy analyses will be conducted on the ITT population based on treatment as randomized. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the first dose of study drug or randomization if no study drug is given. All statistical tests will be 2-sided at a significance level of 0.05. All confidence intervals (CIs) will be 2-sided 95%.

Summary and Analysis of the Primary Endpoint

The proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 will be

summarized by treatment group using the ITT population. As presented in the estimand for the primary efficacy endpoint in Section 3.1, the composite strategy will be used to handle the intercurrent events. Subjects with intercurrent events prior to Day 14 Hour 9 will be considered as nonresponders for the primary efficacy endpoint. Subjects who have missing data for the primary efficacy endpoint will be categorized as nonresponders in the primary efficacy analysis.

The comparison of the proportions between AGN-190584 and Vehicle will be made using the Pearson's chi-square test. The treatment difference will be provided with a 2-sided 95% CI using the normal approximation based on the pooled variance without continuity correction.

Summary and Analysis of Secondary Endpoints

Summary and Analysis of Key Secondary Endpoint

Similar as for the primary endpoint, the proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 will be summarized by treatment group using the ITT population. As presented in the estimand for the key secondary efficacy endpoint in Section 3.1, the composite strategy will be used to handle the intercurrent events. Subjects with intercurrent events prior to Day 14 Hour 9 will be considered as nonresponders for the key secondary efficacy endpoint. Subjects who have missing data for the key secondary efficacy endpoint will be categorized as nonresponders in the key secondary efficacy analysis.

The comparison of the proportions between AGN-190584 and vehicle will be made using the Pearson's chi-square test. The treatment difference will be provided with a 2-sided 95% CI using the normal approximation based on pooled variance without continuity correction.

Summary and Analysis of Supportive Secondary Endpoints

The supportive secondary endpoints will be analyzed using the same method as described in the analysis of the efficacy endpoints will be described in the SAP.

Subgroup Analysis for Efficacy

The primary and key secondary endpoints will be summarized by age group, sex, race, ethnicity, baseline binocular DCNVA severity, iris color, and emmetropes status.

7.5 Pharmacokinetic Analysis

Pharmacokinetic Parameters

Plasma PK parameters following the first and second doses on Day 1 and Day 14 will be calculated separately using standard Phoenix WinNonlin equations. PK parameters calculated after the first and second dose on Day 1 will include area under the concentration versus time curve from 0 to the end of the dosing interval ($AUC_{0\text{-}tau}$), maximum observed concentration (C_{max}), and time to maximum observed concentration (T_{max}). Additionally, the observed concentration at the end of the dosing interval (C_{trough}), and peak-to-trough ratio will be calculated after the first dose on Day 1.

Steady-state PK parameters calculated after the first and second dose on Day 14 will include $AUC_{0\text{-}tau,ss}$, $C_{max,ss}$, and $T_{max,ss}$. Additionally, $C_{trough,ss}$ and peak-to-trough ratio will be calculated after the first dose on Day 14. Systemic accumulation will be assessed by calculating the accumulation index (AI) for AUC and C_{max} on Day 14.

Additional PK parameters may be calculated, as necessary.

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

Statistical Analyses of Pharmacokinetic Data

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

7.6 Statistical Analyses for Safety

The safety analysis will be performed using the safety population; and subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of study drug.

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 subjects with TEAEs during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

If more than one AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the greatest severity and strictest causality for the summarizations by severity and by relationship to study drug.

Summary tables will be provided for subjects with SAEs and subjects with AEs leading to discontinuation of study drug. Listings of all AEs, SAEs, and AEs leading to discontinuation of study drug by subject will be presented.

Adverse events of special interest will be summarized by treatment group and the details will be described in the SAP.

Detailed methods for the analysis of other safety variables will be described in the SAP.

7.7 Overall Type I Error Control

A fixed sequence testing procedure will be applied to control the overall familywise Type I error rate at $\alpha = 0.05$ for the primary and secondary hypotheses sequentially. The hypotheses for primary endpoint and the secondary endpoints will be tested in a sequential order:

- **H1 Primary:** The proportion of subjects gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)
- **H2: Key Secondary:** The proportion of subjects gaining 3 lines or more in photopic, high-contrast, binocular DCNVA with no more than 5-letter loss in photopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)
- **H3 Supportive Secondary:** The proportion of subjects gaining 2 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)
- **H4 Supportive Secondary:** The proportion of subjects achieving 20/40 or better in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose)

If at any step a test fails, the test procedure will stop and no further hypotheses will be tested.

7.8 Sample Size Determination

The sample size calculation was considered for the primary efficacy endpoint, the response of gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA with no more than 5-letter loss in mesopic CDVA with the same refractive correction at Day 14, Hour 9 (3 hours after the second dose).

Assuming a responder rate of 25% in the AGN-190584 group and 7% in the vehicle group, and 5% dropout rate, a sample size of 100 subjects per study drug group will provide greater than 90% power using chi-square test at a 2-sided significance level of 5%.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that

have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AI	accumulation index
AUC	area under the plasma concentration-time curve
AUC0-tau	area under the plasma concentration-time curve from time 0 to the end of the dosing interval
AUC0-tau,ss	area under the plasma concentration-time curve from time 0 to the end of the dosing interval, steady state
BID	twice daily
CDVA	corrected distance visual acuity
CI	confidence interval
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration, steady state
COVID-19	Coronavirus Disease - 2019
C_{trough}	observed plasma concentration at the end of the dosing interval
$C_{trough,ss}$	observed plasma concentration at the end of the dosing interval, steady state
DCNVA	distance-corrected near visual acuity
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IOP	intraocular pressure
IRT	interactive response technology
ITT	intent to treat
LASIK	laser-assisted in situ keratomilieusis
NEI VFQ-25	25-item National Eye Institute Visual Function Questionnaire
NVPTQ	Near Vision Presbyopia Task-based Questionnaire
OSDI	Ocular Surface Disease Index
OTC	over-the-counter
PCR	polymerase chain reaction

PGIC	global impression of change
PGIS	global impression of status
PICQ	Presbyopia Impact and Coping Questionnaire
PK	pharmacokinetic(s)
PRK	photorefractive keratectomy
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed concentration
$T_{max,ss}$	time to maximum observed concentration, steady state
VFA app	Visual Function Assessment application

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-195: A Phase 3, Multicenter, Double-masked, Randomized, Vehicle-controlled, Parallel-group Study Evaluating the Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia

Protocol Date: 21 October 2021

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Senior Manager, Clinical Trial	Clinical Program Development
[redacted]	Associate Director, Medical Writing	Medical Writing
[redacted]	Therapeutic Area - Medical Director	Clinical Development
[redacted]	Statistics Therapeutic Area Head	Statistics
[redacted]	Director	Statistics
[redacted]	VP, Non-Clinical and Translational Science	Non-Clinical and Translational Sciences

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the study. The individual activities are described in detail in the **Operations Manual**.

Procedure	Screening	Study Days (Visits)																		
		Day 1 (Visit 1)							Day 7 (Visit 2)						Day 14/Early Exit (Visit 3)						
Visit Windows	Days -30 to -1	N/A							± 2 days						± 2 days						
Hours		0	1	3	6	7	9	12	0	1	3	6	7	9	0	1	3	6	7	9	12
Informed consent	✓																				
Contact IRT for subject ID number	✓																				
Iris color assessment	✓																				
Demography	✓																				
Medical and ophthalmic history	✓																				
Prestudy/ concomitant medication query	✓	✓							✓						✓						
NEI VFQ-25 and near vision subscale in the Appendix of Optional Additional Questions[a]	✓																				
OSDI[b]	✓																				
AE query[c]	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs[d]	✓	✓				✓									✓				✓		
Urine pregnancy test[e]	✓	✓													✓						
Dominant eye determination	✓																				
Contact IRT for kit assignment/ randomization[f]		✓																			
PICQ[g]		✓									✓						✓				
Pupillary reaction to light assessment	✓																				
Perform under mesopic conditions (10 to 11 lux at target) Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.																					

Procedure	Screening	Study Days (Visits)																		
		Day 1 (Visit 1)							Day 7 (Visit 2)						Day 14/Early Exit (Visit 3)						
Visit Windows	Days -30 to -1	N/A							± 2 days						± 2 days						
Hours		0	1	3	6	7	9	12	0	1	3	6	7	9	0	1	3	6	7	9	12
Dark adaptation[h]	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Mesopic manifest refraction (distance and near)[i]	OD, OS																				
Mesopic, high-contrast CDVA + pupil diameter[j]	OU	OU	OU	OU	OU	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	
Mesopic, high-contrast DCNVA + pupil diameter[k]	OU	OU	OU	OU	OU	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	
Mesopic NVPTQ[l]		✓												✓						✓	
Perform under photopic conditions (≥251 lux at target): Carry out in the order specified. Different charts must be used for the repeated visual acuity measures within the same day.																					
Photopic manifest refraction (distance and near)[i]	OD, OS																				
Photopic high-contrast CDVA + pupil diameter[j]	OU	OU	OU	OU	OU	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	
Photopic, high-contrast DCNVA + pupil diameter[k]	OU	OU	OU	OU	OU	OU	OU		✓	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	
Single-item PGIS[l]		✓												✓							
Single-item PGIC[l]														✓							
Visual Function Assessment application (VFA app)[m]		✓												✓							
Slit-lamp biomicroscopy	✓	✓	✓			✓			✓	✓			✓		✓	✓			✓		
Fluorescein corneal staining	✓																				
IOP measurement	✓	✓	✓			✓			✓	✓			✓		✓	✓			✓		

Procedure	Screening	Study Days (Visits)																		
		Day 1 (Visit 1)							Day 7 (Visit 2)						Day 14/Early Exit (Visit 3)						
Visit Windows	Days -30 to -1	N/A							± 2 days						± 2 days						
Hours		0	1	3	6	7	9	12	0	1	3	6	7	9	0	1	3	6	7	9	12
Gonioscopy/angle assessment	✓																				
Dilating drop administration	✓																			✓	
Cycloplegic refraction[n]	✓																				
Dilated fundoscopic examination[o]	✓																			✓	
Review inclusion and exclusion criteria	✓	✓																			
PK[p]		✓	✓	✓	✓	✓	✓	✓							✓	✓	✓	✓	✓	✓	✓
Study drug administration[q]		✓			✓				✓			✓			✓			✓			
Drop comfort questionnaire		✓			✓				✓			✓			✓			✓			
Post-Dose Tolerability Assessment[r]		✓			✓				✓			✓			✓			✓			
Study drug dispensing to subject							✓														

Study drug administration:

Hour 0 must be at 8 AM ± 1 hour; Hours 1, 3, and 6 (± 15 minutes) will be measured from the time of the completion of Hour 0 study drug administration. Hours 7 and 9 (± 15 minutes) will be measured from the time of the completion of the Hour 6 dose administration (within 15 minutes). Ocular examinations within each lighting condition (mesopic or photopic) may be grouped together by distance (e.g., all near assessments performed in sequence, and all distance assessments performed in sequence) at the investigator's discretion.

a. Near vision subscale includes questions A3 to A5 in the Appendix of Optional Additional Questions. This questionnaire will be completed on paper.

b. OSDI will be completed on paper.

c. Subjects reporting a headache AE will be provided the supplemental headache AE assessment form.

d. Blood pressure and heart rate measured after subject has been at rest (seated) for at least 5 minutes

e. WOCBP only

f. IRT will be used to dispense medication. Please refer to the IRT manual for additional information.

g. Conducted with subject's habitual distance correction.

h. 5 to 10 minutes in mesopic conditions.

i. If a subject loses ≥ 1 line (≥ 5 letters) of CDVA or DCNVA compared with Hour 0 of the same study visit at Hour 1 after dosing, a manifest refraction should be repeated under the same lighting conditions.

j. Conducted with subject's best distance correction. CDVA to be measured binocularly. Pupil diameter must be measured in each individual eye.

k. Conducted with subject's best distance correction. DCNVA to be measured binocularly. Pupil diameter must be measured in each individual eye.

l. Conducted with subject's best distance correction

m. Conducted with subject's best distance correction. Half-eye style trial frames with full field trial lenses only.

n. Distance, photopic. Minimum 30-minute wait after administration of dilating drops.

o. Investigator should note if the pupil dilated normally. Minimum 30-minute wait after administration of dilating drops.

p. Blood collection for PK at selected sites (on Days 1 and 14 at Hours 0, 0.25, 0.5, 1, 3, 6 [pre-dose], 6.25, 6.5, 7, 9, and 12). Collection windows of ± 5 minutes should be used for Hours 0.25, 0.5, 6.25, and 6.5; and collection windows of ± 15 minutes should be used for all other blood collection timepoints. Predose samples must be drawn within 15 minutes of the dosing time.

q. Hour 0 starts after study drug administration. Second dose should be applied within 15 minutes after Hour 6. Site staff will administer study drug during study visits. Subjects will administer the study drug at home in between visits.

r. Conducted 5 to 10 minutes post-dosing. Only those who reported ocular discomfort symptom(s) will be further queried on the severity and duration of each symptom.

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	17 June 2021

The purpose of this version is to make minor clarifications throughout the protocol and incorporate the following protocol updates and modifications:

- Title Page – Study emergency contact and protocol version number were updated.
- Synopsis – Postdose tolerability was added as a safety assessment (an inadvertent omission in the original protocol) and updated synopsis date.
- Section 3.1 – Estimands (Table 2) updated for completeness.
- Section 3.4 – Detail was added to the additional efficacy endpoints for clarity.
- Section 3.6 – Postdose tolerability was added as a safety measure (an inadvertent omission in the original protocol).
- Section 3.7 – Instructions were added for cases of technical issues interfering with digital questionnaires completion.
- Section 5.1 (Disease/Condition Activity) – Minor changes were made to the inclusion criteria as follows: timing of when cycloplegic distance correction criterion must be met (at screening) was added, and requirements for photopic, high-contrast, near visual acuity were clarified (this criterion applies to each eye separately, not both eyes).
- Section 5.2 – Minor corrections were made related to contraception requirements for postmenopausal females.
- Section 7.2 – PK population was added (an inadvertent omission in the original protocol).
- Section 7.5 – PK analysis language clarified and updated to align with the current wording in the PK analysis plan
- Section 7.6 – Planned summaries for AEs leading to discontinuation were corrected (AEs leading to discontinuation of study drug will be summarized and listed, not AEs leading to study discontinuation).
- Appendix C – Protocol signatories were updated.
- Appendix D – Collection windows for hourly assessments were clarified, the order of assessments was updated (the order that assessments are listed in the table now indicates the suggested order). A footnote was added for OSDI and detail was added to the NEI VFQ-25 footnote to indicate that these measures should be completed on paper. Footnote "p" (previously "e") was put in correct order and applied to all PK timepoints for clarification; other footnotes were renumbered appropriately.
- Appendix E – A summary of changes made to the original protocol was added.

- Appendix F – The Operations Manual was updated as follows: study emergency contact and SAE reporting email were updated, clarifications about paper vs. electronic assessments and potential technical glitches were added, inclusion criteria were updated per changes made in Section 5.1, clarifying details related to the DCNVA assessment, NVPTQ administration, and Supplemental Headache-AE Assessment were added, SAE reporting information was updated, an OSDI scoring appendix was added, timing of Hours 7 and 9 in relation to the second dose was clarified (i.e., 1 and 3 hours after the second dose, respectively), and other minor corrections and clarifications were made.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M21-195

Presbyopia: Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	AGN-190584

FULL TITLE: A Phase 3, Multicenter, Double-masked, Randomized, Vehicle-controlled, Parallel-group Study Evaluating the Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] MD AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Mobile: [redacted] Email: [redacted]
Safety Concerns	Ophthalmology Safety Team 1 North Waukegan Road North Chicago, IL 60064	Toll Free: +1 (833) 942-2226 Email: SafetyManagement_Ophthalmology@abbvie.com
SAE Reporting outside of EDC	Email: IR-Clinical-SAE@abbvie.com	Fax: +1 (714) 796-9504 Back-up: +1 (714) 246-5295

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the Coronavirus Disease - 2019 (COVID-19) pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Study visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, reschedule the visit within the visit window if possible.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING:

INTERVIEW	• Review inclusion and exclusion criteria • Informed consent • Contact IRT for subject ID number	• Prestudy/concomitant medication query • Adverse event query • Demography • Medical and ophthalmic history
PRO	• NEI VFQ-25 and near vision subscale in the appendix of optional questions	• OSDI
EXAM	• Dominant eye determination • Gonioscopy/angle assessment • Cycloplegic refraction • Dilated fundoscopic examination • Slit lamp biomicroscopy • Fluorescein corneal staining • IOP measurement • Pupillary reaction to light assessment • Iris color assessment • Vital signs	• Photopic manifest refraction (distance and near, both eyes) • Photopic, high-contrast CDVA and pupil diameter (both eyes) • Photopic, high-contrast DCNVA and pupil diameter (both eyes) • Mesopic manifest refraction (distance and near, both eyes) • Mesopic, high-contrast CDVA and pupil diameter (both eyes) • Mesopic, high-contrast DCNVA and pupil diameter (both eyes)
LAB	• Urine pregnancy test (women of childbearing potential)	

DAY 1:

INTERVIEW	• Drop comfort questionnaire (Hours 0, 6, post dosing) • Review inclusion and exclusion criteria (Hour 0) • Post-dose tolerability assessment (Hours 0, 6)	• Prestudy/concomitant medication query (Hour 0) • Adverse event query (Hours 0, 1, 3, 6, 7, 9)
PRO	• Single-item PGIS (Hour 0) • Visual Function Assessment Application (Hour 0)	• Mesopic NVPTQ (Hour 0) • PICQ (Hour 0)
EXAM	• Photopic, high-contrast CDVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Photopic, high-contrast DCNVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Slit-lamp biomicroscopy (Hours 0, 1, 7) • IOP measurement (Hours 0, 1, 7)	• Dark adaptation (Hours 0, 1, 3, 6, 7, 9) • Mesopic, high-contrast CDVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Mesopic, high-contrast DCNVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Vital signs (Hours 0, 7)
LAB	• Urine pregnancy test (women of childbearing potential) (Hour 0)	• Blood collection for PK at selected sites (Hour 0, 0.25, 0.5, 1, 3, 6 (predose), 6.25, 6.5, 7, 9, 12)
TREATMENT	• Contact IRT for kit assignment/randomization (Hour 0)	• Study intervention administration (Hours 0, 6) • Study intervention dispensing

Study intervention administration: Hour 0 must be at 8AM ± 1 hour; Hours 1, 3, and 6 (± 15 minutes) will be measured from the time of the completion of Hour 0 study intervention administration. Hours 7 and 9 (± 15 minutes) will be measured from the time of the completion of the Hour 6 dose administration (within 15 minutes). Hour 7 is 1 hour after the second dose, and Hour 9 is 3 hours after the second dose.

Day 7:

INTERVIEW	• Drop comfort questionnaire (Hours 0, 6) • Post-dose tolerability assessment (Hours 0, 6)	• Prestudy/concomitant medication query (Hour 0) • Adverse event query (Hours 0, 1, 3, 6, 7, 9)
PRO	• Single-item PGIS (Hour 9) • Visual Function Assessment Application (Hour 9)	• Single-item PGIC (Hour 9) • Mesopic NVPTQ (Hour 9) • PICQ (Hour 3)
EXAM	• Photopic, high-contrast CDVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Photopic, high-contrast DCNVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Slit-lamp biomicroscopy (Hours 0, 1, 7) • IOP measurement (Hours 0, 1, 7)	• Dark adaptation (Hours 0, 1, 3, 6, 7, 9) • Mesopic, high-contrast CDVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Mesopic, high-contrast DCNVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9)
TREATMENT	• Study intervention administration (Hours 0, 6)	

Study intervention administration: Hour 0 must be at 8AM ± 1 hour; Hours 1, 3, and 6 (± 15 minutes) will be measured from the time of the completion of Hour 0 study intervention administration. Hours 7 and 9 (± 15 minutes) will be measured from the time of the completion of the Hour 6 dose administration (within 15 minutes). Hour 7 is 1 hour after the second dose, and Hour 9 is 3 hours after the second dose.

Day 14/Early Exit:

INTERVIEW	• Drop comfort questionnaire (Hours 0, 6) • Post-dose tolerability assessment (Hours 0, 6)	• Prestudy/concomitant medication query (Hour 0) • Adverse event query (Hours 0, 1, 3, 6, 7, 9)
PRO	• Single-item PGIS (Hour 9) • Visual Function Assessment Application (Hour 9)	• Single-item PGIC (Hour 9) • Mesopic NVPTQ (Hour 9) • PICQ (Hour 3)
EXAM	• Dilating drop administration (Hour 9) • Dilated fundoscopic examination (Hour 9) • Photopic, high-contrast CDVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Photopic, high-contrast DCNVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Slit-lamp biomicroscopy (Hours 0, 1, 7)	• Dark adaptation (Hours 0, 1, 3, 6, 7, 9) • Mesopic, high-contrast CDVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Mesopic, high-contrast DCNVA and pupil diameter (Hours 0, 1, 3, 6, 7, 9) • Vital signs (Hours 0, 7) • IOP measurement (Hours 0, 1, 7)
LAB	• Urine pregnancy test (women of childbearing potential) (Hour 0)	• Blood collection for PK at selected sites (Hour 0, 0.25, 0.5, 1, 3, 6 (predose), 6.25, 6.5, 7, 9, 12)
TREATMENT	• Study intervention administration (Hours 0, 6)	

Study intervention administration: Hour 0 must be at 8AM ± 1 hour; Hours 1, 3, and 6 (± 15 minutes) will be measured from the time of the completion of Hour 0 study intervention administration. Hours 7 and 9 (± 15 minutes) will be measured from the time of the completion of the Hour 6 dose administration (within 15 minutes). Hour 7 is 1 hour after the second dose, and Hour 9 is 3 hours after the second dose.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study, the benefits and risks anticipated from participation in the study, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the

subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the study can be found in the informed consent form.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Medical and Ophthalmic History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment. Any abnormal findings from screening assessments should be captured as medical history.

3.3 Adverse Event Assessment

Please refer to Section 4.1.

3.4 Drop Comfort Questionnaire

The questionnaire should be administered to the subjects immediately after drop instillation. The Subject Evaluation of Drop Comfort single-item question should be assessed immediately.

For questionnaires completed on an electronic platform, if technical issues prevent the questionnaire from being completed, responses can be written down on source documents (preferably a paper copy of the questionnaire if available) and entered when the electronic platform is available.

3.5 Post-Dose Tolerability Assessment

Five to ten minutes after administration of the study drug during the study visit, you should ask the subject how they are feeling about the eyedrops as indicated in the post-dose tolerability assessment guidance document.

3.6 Patient-Reported Outcomes

Subjects will be asked to complete patient-reported outcomes (PRO) questionnaires. Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the

instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

Patient-reported outcome categories and testing conditions are summarized in Table 1.

Table 1. PRO Categories and Testing Conditions

PRO	Category*	Lighting Condition	Correction Used	Screening	Visit 1 (Day 1)	Visit 2 (Day 7)	Visit 3 (Day 14)
OSDI	Subject self-administered			X			
Drop Comfort Questionnaire					Hour 0, 6	Hour 0, 6	**Hour 0, 6**
NEI VFQ-25**	Interviewer-administered (clinician form)	Photopic	Habitual distance	X	-	-	-
NVPTQ	Subject self-administered (subject form)	Mesopic	Best distance		Hour 0	Hour 9 (3 hours after 2nd dose)	**Hour 9 (3 hours after 2nd dose)**
PICQ**	Subject self-administered (subject form)	Photopic	Habitual distance		Hour 0	Hour 3	**Hour 3**
VFA app***	N/A	Photopic	Best distance, Only half-eye style trial frames with full field trial lenses are allowed		Hour 0	Hour 9 (3 hours after 2nd dose)	**Hour 9 (3 hours after 2nd dose)**
Single-item PGIS**	Subject self-administered (subject form)	Photopic	Best distance		Hour 0	Hour 9 (3 hours after 2nd dose)	**Hour 9 (3 hours after 2nd dose)**
Single-item PGIC**	Subject self-administered (subject form)	Photopic	Best distance		-	Hour 9 (3 hours after 2nd dose)	**Hour 9 (3 hours after 2nd dose)**

N/A = not applicable; NEI VFQ-25 = 25-item National Eye Institute Visual Function Questionnaire; NVPTQ = Near Vision Presbyopia Task-Based Questionnaire; OSDI = Ocular Surface Disease Index; PGIC = patient global impression of change; PGIS = patient global impression of status; PICQ = Presbyopia Impact and Coping Questionnaire; PRO = patient-reported outcome; VFA app = Visual Function Assessment application

* For subject self-administered PROs, choose 'Subject form' in Medidata for 'Interviewer administered' PROs, choose 'Clinician form' in Medidata.

** These questionnaires should be answered under normal room lighting, which would likely meet the photopic cutoff of > 251 lux specified in the study protocol. For simplicity, photopic is used to define lighting conditions for these questionnaires.

*** Detailed instructions for the VFA app are provided in Section 7.2.

Note: The OSDI and NEI VFQ-25 questionnaires will be on paper. All other questionnaires will be administered on an electronic platform (i.e., cellphone or tablet). The VFA app is administered on an iPhone provided by the site. For questionnaires completed on an electronic platform, if technical issues prevent the questionnaire from being completed, responses can be written down on source documents (preferably a paper copy of the questionnaire if available) and entered when the electronic platform is available. Please contact your clinical research associate to obtain a paper copy of the questionnaire if needed.

The PRO instruments should be completed prior to drug administration on Day 1, and prior to any discussion of Adverse event (AE) or any review of laboratory findings.

General Considerations

1. The questionnaires should be completed in an area that is quiet and has adequate privacy.
2. Make the subject as comfortable as possible and reassure the subject that his or her answers are confidential and will not impact the type of medical care he or she receives.
3. Attempt to administer the questionnaire to the subject privately.
4. The study site personnel should choose the correct visit number for the questionnaires to correspond to the visit day/schedule before administering the questionnaire (e.g., Visit 1, Day 1).
5. When the questionnaires are finished, thank the subject for participating.
6. Questionnaires for a visit should not be completed after the subject has left the investigator's office on that visit day (e.g., questionnaires for Visit 1 should not be completed at any other time than at Visit 1).

Visual Function Assessment application (VFA app)

The VFA app should be administered per the schedule specified in Table 1. Detailed instructions on the VFA app are provided in Section 7.2. Of note, this measure should be administered under photopic conditions, with best distance correction. Only half eye style trial frames with full field trial lenses are permitted for best distance correction while administering the VFA app.

OSDI

The OSDI (Ocular Surface Disease Index) consists of 12 questions, graded on a 5-point scale from All of the Time (4) to None of the Time (0). The subject will complete the OSDI.

The OSDI is scored using the formula: (sum of scores x 25)/number of questions answered.

1. Add the subtotals from questions 1-5, 6-9, and 10-12 to get the total score.
2. Multiply this total by 25.

3. Divide this number by the number of questions answered (i.e., those questions that were scored on the 4-to-0 scale, not counting those marked 'N/A') to get the subject's OSDI score.
4. You can also use the worksheet that AbbVie provided to calculate the OSDI score.

Sites will transcribe the subject's responses on the paper OSDI questionnaire into the electronic data capture (EDC).

Administration of the NEI VFQ-25

1. Subjects should answer this questionnaire using their habitual distance correction.
2. Explain that they will be asked a series of questions, and this is a necessary and important part of the clinical study in which they are participating.
3. The questionnaire process may take up to 25 minutes, including time to review study instructions. However, this time may vary from subject to subject and from visit to visit. Please allow sufficient time to complete the questionnaires.
4. The instructions for the VFQ-25 advise the subject to answer the questions as if he or she is wearing his or her glasses or contacts without near correction. The purpose of this study is to assess subjects' difficulty with near vision when the subject is not wearing glasses or contacts with near correction. As a result, before administration of the VFQ-25 begins (i.e., before the initial instructions are read to the subject), please advise subjects that for this study 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.
5. The VFQ-25, including all questions from the Appendix of Optional Additional Questions, will be administered by site personnel who have received documented training. However, particular items of interest for confirming inclusion criteria only include the near vision subscale (items 5-7) and the near vision questions from the Appendix of Optional Additional Questions (items A3-A5). Responses to all VFQ-25 items will be used in psychometric validation analyses of the VFA app.

During the NEI VFQ-25 Questionnaire Administration

1. Read the instructions on the questionnaires to the subject.
2. After reading the instructions to the subject, make sure that the subject understands the instructions (including the fact that any references to glasses or contacts should be interpreted as referring to distance correction only – if required); and is ready to begin the questionnaire.
3. Read each question slowly, exactly as worded, followed by the appropriate answer choices (if applicable), and mark the answer choice for the subject.
4. Repeat questions and answer choices as needed; do not rephrase the question.
5. Do not "lead" the subject to a particular answer. Allow the subject to respond how he or she feels. If the subject is unsure how to answer, explain that there are no right or wrong answers and ask him or her to answer to the best of his or her ability.

6. If the subject wants to change his or her answer to a question after the site has marked an answer choice, study site personnel can **mark** a different response **and add a note to indicate the final answer.**
7. Continue to move the interview forward. Do not get "stuck" on a particular question.
8. Reassure the subjects throughout the interview that they are doing well, as appropriate.

Checking the Questionnaire

Study site personnel should check the following before the subject leaves the site:

1. In order to be eligible for the study, the subject must: have a score ≥ 3 on at least one item from either the VFQ-25 Near Vision Subscale (items 5-7) or from the Appendix of Optional Additional Questions (A3-A5) (i.e., a score of ≥ 3 on at least one out of these six questions). If the subject does not have a score of 3 or above for at least one of these six items (items 5-7 or A3-5), the subject is not eligible to participate in the study.
2. If a subject communicates information regarding AEs during the course of the interview, assure that these are documented appropriately.

Sites will transcribe the responses on the paper NEI VFQ-25 questionnaire into the EDC.

Subject Self-Administration of the Single-Item Subject Global Impression of Change, Single-Item Subject Global Impression of Status, and Presbyopia Impact and Coping Questionnaire

Instruct the subject to read the instructions at the top of the page carefully before answering the question.

Single Item PGIC Questionnaire

Subjects will be asked to complete a single-item questionnaire asking about their impression of the study medication's effect on their near vision. Subjects should answer this questionnaire under photopic conditions using their best distance correction.

Single Item PGIS Questionnaire

Subjects will be asked to complete a single-item questionnaire asking about their impression of their problems seeing up close over the past 7 days. Subjects should answer this questionnaire under photopic conditions using their best distance correction.

Presbyopia Impact and Coping Questionnaire

This questionnaire includes 14 questions about the degree to which subjects were impacted by their difficulty seeing up close; or engaged in coping behaviors during the previous 7 days. Subjects should answer this questionnaire using their habitual distance correction.

Near Vision Presbyopia Task-Based Questionnaire

The Near Vision Presbyopia Task-Based Questionnaire (NVPTQ) includes 12 questions on 4 paper-based reading tasks (book, newspaper, menu, nutrition label). Subjects will be asked to read a text passage,

and answer 3 questions about their ability to read, whether they squinted while reading, and satisfaction with their ability to read. After a subject has completed the task, the study staff should proceed with the next task (i.e., ask the subject to read the next text passage and answer the 3 questions). Subjects should read text passages and answer questions under mesopic conditions, using their best distance correction.

Lighting Conditions

Subjects should read text passages and answer questions under mesopic conditions, using their best distance correction. Please see definition of mesopic lighting (Section 3.9) for other efficacy measures.

Task Preparation

1. Each of the four reading task examples (book, newspaper, menu, nutrition label) should be stacked upon a lectern facing the subject, in the following order:
    a. Paragraph from a book
    b. Newspaper article
    c. Menu
    d. Nutrition Label
2. The lectern should be set so that the task examples are perpendicular to the table and so that the examples are at the subject's eye level. Do not adjust the lectern once the subjects have begun reading the tasks.
3. Subjects should be given a different task example each time they are asked to complete the NVPTQ (i.e., at each visit). For instance, subjects should be given tasks labelled "Example A1, A2, etc." during their first assessment. At their next assessment, subjects should be given tasks labeled "Example B1, B2, etc.", and so on. Review the NVPTQ in Mesopic Conditions Worksheet history to ensure that subjects are not receiving the same task example during the course of the trial. Record the task example numbers for this assessment.

Subject Preparation

1. Seat the subject so that the distance between the subject's eyes and the lectern is 40 cm. Ensure that the subject does not move his/her head significantly during the time he/she is reading the tasks.
2. Use the NVPTQ in Mesopic Conditions Worksheet provided to confirm proper setup of tasks (i.e., ensure tasks are on the lectern, and are in the correct order)
3. Provide the NVPTQ to the subject. It may be helpful to provide the questionnaire on a fixed surface to minimize time spent re-adjusting the subject position between tasks.
4. Instruct the subject to read the NVPTQ instructions.
5. Before administering the reading tasks, remind the subject of the following:
    a. Remember to read the text for each of the reading samples. You can read the tasks out loud or to yourself.

b. Do not move the reading material closer to or farther away from yourself.

c. Do not adjust the location of where you are sitting or lean forward.

6. Provide the subject with Task #1 (Book).
7. After the subject has finished reading Task #1, instruct the subject to read and complete the questionnaire items pertaining to Task #1 (items 1-3 in the task-oriented questionnaire). (IMPORTANT: Before giving the questions to the patient, adjust the brightness on the device to the lowest possible setting.)
8. After completion of the Task #1 questions, provide the subject with Task #2 questions. Repeat steps 6 and 7 for Tasks #2-4.

Subject Vision Correction for Tasks

Subjects should read text passages and answer questions under mesopic conditions, using their best distance correction. Subjects are required to read the tasks on their own. Study staff are not permitted to provide assistance for the reading tasks. Subjects are not allowed to use their reading glasses, or any other form of near-vision correction, while reading the text passages or answering the questions. If the subject is unable to read the questionnaire after performing the tasks, site personnel may read the questionnaire to the subject and record their answers. Please note - site personnel are NOT allowed to assist subjects with reading the actual task examples, they may ONLY assist with the questionnaire about the task examples.

Once a subject requires interviewer assistance with the task-related questionnaire, the questionnaire must be interviewer administered (preferably by the same interviewer) at all subsequent assessments for the remainder of the study.

3.7 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure and pulse rate will be obtained at visits as specified in Section 2.1. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 5 minutes.

3.8 Clinical Laboratory Tests

Pregnancy Tests (Urine)

Pregnancy testing should not be performed for postmenopausal women.

A urine pregnancy test will be performed at screening, Day 1, and Day 14 (or upon confinement in each period) for all female subjects of childbearing potential. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

If the baseline urine pregnancy test is negative, then dosing with study drug may begin.

If the baseline or post-baseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required.

Unless a woman is suspected to have become pregnant, additional pregnancy testing during the clinical trial is not necessary.

3.9 Lighting Conditions and Distance Specifications for Examinations

Testing room illumination must be adjusted to the following levels at the target using the provided light meter, and maintained consistently throughout the study:

- Photopic conditions: ≥ 251 lux at target
- Mesopic conditions: 10 to 11 lux at target*
  - * Procedures under mesopic conditions should be performed after 5-10 minutes of dark adaptation. No waiting time is needed for procedures under photopic conditions.

Visual acuity measures will be tested using the appropriate charts at the following distances:

- Near: 40 centimeters
- Distance: 4 meters

Table 2. Quick Reference for Procedures and Performance Specifications

Procedure	Performed at	Lighting condition(s)
Manifest refraction	Distance / Near	Mesopic / Photopic
Cycloplegic refraction	Distance	Photopic
DCNVA + near pupil diam.	Near	Mesopic / Photopic
CDVA + distance pupil diam.	Distance	Mesopic / Photopic

Testing Areas

Sites must have a dedicated exam room/area for mesopic procedures and/or 4-meter testing area (lane). The dedicated exam room must be capable of consistent lighting to perform mesopic procedures.

The area to test visual acuity or VA lane must be a full 4-meter testing distance from the chart to the subject's eye, without mirror accommodations. The testing area should be dedicated for procedures, have consistent lighting preferably from the ceiling, and be free of distractions. The VA lane must be capable of photopic and mesopic lighting conditions. Conditions will be confirmed by the AbbVie-provided light meter.

Light Meter

The light meter provided by AbbVie should be used to measure room illumination at the target. Before taking any measurement, make sure the power switch is turned to the "on" position, and the range switch is turned to the "2000 position," as shown in Figure 1.

Figure 1. Light Meter

When measuring room illumination/lighting conditions:

1. Remove the light sensor cover.
2. Position the light sensor in the middle of the (mounted) distance VA chart with the sensor facing outward to the room.
    a. Chart should either be mounted on the wall or on a stable stand.
3. Adjust room lighting until light meter reading achieves the mesopic or photopic range required.
4. Lighting conditions on the distance VA chart confirms lighting for VA assessments associated regardless of distance;
    a. i.e., if mesopic lighting has been confirmed and mesopic VA measurements are being performed, lighting does not need to be checked from distance → intermediate → near and vice versa.
5. Upon changing lighting conditions, lighting should be re-checked (as per steps 1 to 4) prior to performing the associated procedures (e.g., change from mesopic to photopic).

a. For mesopic procedures, subjects should be dark adapted at least 5-10 minutes prior to the start of procedures, once lighting conditions are confirmed.

3.10 Pupillary Reaction to Light

The 'swinging light test' is used to measure pupillary reaction to light. It is a means of detecting differences between the two eyes and how they respond to a light shone in one eye at a time. This test can be conducted under either photopic or mesopic conditions (it is easier to see under mesopic conditions).

In a normal swinging light test, the pupils of both eyes will constrict equally regardless of which eye is stimulated by the light. In an abnormal test, there is less pupil constriction in the eye with retinal or optic nerve disease.

Procedure:

Using a bright torch which can be focused to give a narrow, even beam of light. Perform the following:

- Ask the subject to focus on a distant object, such as a Snellen chart or a picture. This is to prevent the near-pupil response (pupil constriction when moving focus from distance to near). While performing the test, take care not to get in the way of the fixation target.
- Move the whole torch deliberately from side to side so that the beam of light is directed directly into each eye. Do not swing the beam from side to side around a central axis (e.g., by holding it in front of the person's nose), as this can also stimulate the near response.
- Keep the light source at the same distance from each eye to ensure that the light stimulus is equally bright in both.
- Keep the beam of light steadily on the first eye for at least 3 seconds. This allows the pupil size to stabilize. Note whether the pupil of the eye being illuminated reacts briskly and constricts fully to the light. Also note what happens to the pupil of the other eye: does it also constrict briskly?
- Move the light quickly to shine in the other eye. Again, hold the light steady for 3 seconds. Note whether the pupil being illuminated stays the same size, or whether it gets bigger. Note also what happens to the other eye.
- Repeat the test, observing what happens to the pupils of OU when one eye and then the other eye is illuminated.
- Judge whether the subject's pupillary reaction to light is normal or abnormal. Enter into the source document and eCRF.

3.11 Determination of Dominant Eye

1. Participants will be asked to extend their arms out in front of them at eye level, with their palms facing away, fingers together and facing upward.

2. With hands together, a small window will be formed by overlapping their thumbs and overlapping their fingers.
3. Participants will select a small object at least 10 feet in front of them and look at it with both eyes through the view window in their hands.

While remaining focused on the object, participants will close the OD and open the OS, taking care not to move the position of the hands, and take note of whether the image remains visible. If the image remains visible, the OS is the dominant eye. If the image is no longer visible, the OD is the dominant eye. This will be confirmed by closing the OS and opening the OD, taking care not to move the position of the hands, and taking note of whether the image remains visible.

3.12 Manifest Refraction

Manifest refraction should be conducted at the Screening visit under mesopic and photopic light conditions, for both distance and near (this is considered the "baseline manifest refraction"). Manifest refraction can be conducted per the site's standard clinical practice or following the procedures instructed below. The investigator may choose any appropriate method to conduct manifest refraction, including a phoropter, trial frames with loose lenses inserted. The prescriptions obtained from the manifest refraction conducted at the Screening visit (for mesopic and photopic distance, if not the same) will be used as the best distance correction during the study visits for:

- Corrected Distance Visual Acuity (CDVA) and Distance-Corrected Near Visual Acuity (DCNVA)
- Some PRO measures under each lighting condition

Note: If the subject's habitual monofocal distance correction is the same as the manifest refractions under both mesopic and photopic conditions, then their habitual correction can be used for the procedures above.

A repeat manifest refraction should be done under the same lighting condition in subjects who lose ≥ 1 line (defined as 5 or more letters) at Hour 1 in either eye in CDVA or DCNVA compared with Hour 0 of the same visit. The repeated manifest refraction should be conducted with the same method as at the screening visit. The results of the repeated manifest refraction need to be recorded in the source document and entered into EDC.

Determine Subject's Approximate Refraction

Prior to manifest refraction, measure the subject's current distance spectacles (habitual correction) with a lensometer, or perform autorefraction if the subject does not wear distance spectacles. This measurement will be the starting point for refracting the subject on the phoropter.

New monofocal correction:

If subject's habitual distance correction (1) is insufficient to achieve distance visual acuity of 20/32 or better, or (2) are not monofocal lenses (i.e., if they are bifocal or progressive), then the study site should provide new, monofocal distance correction spectacles to achieve a corrected distance vision of 20/32 or better.

This new monofocal distance correction or subject's own habitual correction may be used for distance-corrected visual acuity measures (i.e., in place of trial frames or phoropter) if they have the same prescription as their best correction under the corresponding lighting condition (e.g., some subjects may not tolerate best correction as habitual correction, but a new Rx may still get them to qualify at 20/32 or better – these subjects may not use their new Rx for visual acuity testing). However, if the subject's best distance correction is different between mesopic and photopic conditions, a trial frame is still needed for the condition that the new monofocal distance correction or subject's own habitual correction is different from the best distance correction.

Manifest Refraction

Manifest refraction is performed for distance (4 m) and near (40 cm), under both mesopic and photopic conditions.

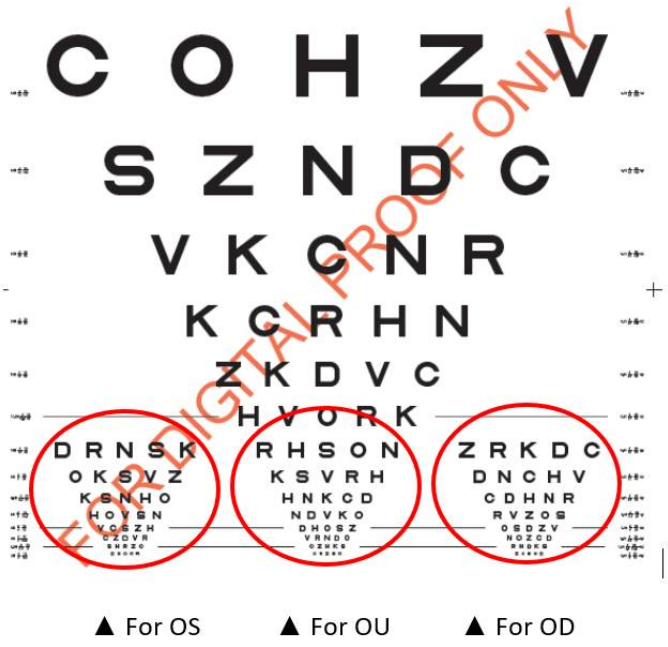
To start, the subject's current distance spectacles are measured with a lensometer; if no spectacles are worn, auto refraction is done. One of these measurements is used as the beginning approximate refraction.

The investigator may use any appropriate method to conduct the manifest refraction, including phoropter, trial frames with loose lenses inserted, or loose lenses. The AbbVie-provided distance and near visual acuity charts should be used for each measure.

The distance and near visual acuity charts provided by AbbVie have three blocks of letters – one each for right eye (OD), left eye (OS), and OU (Figure 2). Please use the appropriate letters for distance and near measures. Note that only OD and OS blocks will be used for manifest refraction.

Note: In the rare case if a subject's best corrected vision is 20/63 or worse, subjects should read the central OU section because there are no corresponding letters for OD or OS on the charts. If both OD and OS are 20/63 or worse, use a different chart to avoid memorizing. For vision better than 20/63, the subject should read the OD or OS sections of the chart as usual.

Figure 2. Visual Acuity Chart Use



Manifest refraction should be done in the following order, beginning with the OD (OS occluded):

1. Enter approximate refraction (from Determine Subject's Approximate Refraction) into the phoropter.
2. Determine SPHERE power:
   a. With subject looking at the smallest legible line on the appropriate VA chart (near/distance), add +0.25 spherical lens.
      i. Ask the subject, is it "Better, worse, or is there no change?"

         <u>If BETTER or NO CHANGE:</u>

         Replace the +0.25 spherical lens with one with an additional +0.25 D. Check VA again, and repeat the process until adding +0.25 D makes the subject's VA worse.

         <u>If WORSE:</u>

         Add a lens that is 0.25 D more minus or less plus than the previous lens. If this improves VA, even by one letter, continue to repeat the process until there is no more improvement in VA.

      ii. Re-challenge with +0.25 sphere until the subject responds that the +0.25 sphere makes their VA worse. **The final sphere is the most plus or least minus lens that achieves the best VA.**
3. Determine CYLINDER power and axis:

NOTE: The following description is for minus cylinder. Adjust accordingly for plus cylinder refraction by replacing the negative axis (red) with the positive axis (white) in the instructions for cylinder axis below.

Ask the subject to look at a line on the visual acuity chart, which is one line larger than the smallest line the subject can read. Ask the subject to focus on a round letter such as "C," "G," or "O" if one is present.

a. IF CYLINDER **WAS NOT** PRESENT in the initial approximate refraction:

   i. Place the cross-cylinder with the negative axis (red) first at 90°, then at 180°, then 45° and 135°. If the subject states that the vision is improved at any one of these four axis positions, place cylindrical lens power in the refractor at the preferred axis and proceed to refine the axis. If the subject prefers none of the four positions, skip the refining cylinder power step.

   IF CYLINDER **WAS** PRESENT in the initial approximate refraction:

   ii. Position the cross-cylinder first with the negative axis 45° to the right of the cylinder axis (position one), and secondly with the negative axis at 45° to the left of the cylinder axis (position two). Flip the crossed cylinder and ask, which position improves the vision (position one or position two?).

b. If subject responds that NEITHER POSITION IS BETTER and if this was the first test of the axis position, move the axis of the cylinder 15° to the right or left and repeat.

If the subject PREFERS ONE POSITION TO THE OTHER, rotate the cylinder axis toward the preferred axis of the cross-cylinder. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

4. Refine CYLINDER power:

   a. Ask the subject to look at the lowest line on the visual acuity chart that can be read.

   b. Align the cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better.

   c. If the subject prefers the positive (white) axis coincident with the cylinder axis, decrease the minus power of the cylinder by 0.25 diopter.

   d. If a subject indicates a change that would introduce positive cylinder power, remove all cylinder power and continue testing for negative cylinder power at an axis 90° away from the previous axis.

   e. If the subject prefers the negative (red) axis coincident with the cylinder axis, increase the cylinder power by -0.25 diopters and retest.

   f. For each 0.50 diopter change in cylinder power, adjust the sphere by 0.25 diopters of the opposite power.

5. End the refraction:

   a. End the refraction by challenging with +0.25 spherical power and adjust the sphere until the subject responds that the additional positive sphere makes the vision worse.

b. Record the lens correction obtained in this refraction for the OD on the appropriate form.

c. Record the visual acuity in Snellen Equivalents as the lowest line read with two, one, or no misses.

d. REPEAT the entire refraction process for the OS.

Note: When determining whether refraction meets entry criteria, either plus OR minus cylinder notation may be used.

6. Near Refraction:

a. Best near add should be used when conducting near manifest refraction, including the near VA measurement. The recorded near prescription should also include the near add. Both best near refraction and near add need to be captured and entered into EDC.

b. Inclusion criterion 7 "Photopic, high-contrast, near visual acuity correctable to 20/40 (J3+) or better in each eye at the screening visit" references the near VA measured by the near refraction.

Note:

- When determining whether refraction meets entry criteria, either plus OR minus cylinder notation may be used. Sites do not need to convert the sign when entering the data into the source worksheet of EDC.

3.13 Repeated Manifest Refraction

A *repeat* manifest refraction should be done under the same lighting condition in subjects who lose ≥ 1 line (defined as 5 or more letters) in either eye in CDVA or DCNVA at Hour 1 compared with Hour 0 of the same visit. The investigator should choose the same method to conduct the repeat manifest refraction as at the screening visit. The results of the repeat manifest refraction must be recorded in the source document and entered into EDC; **however, this new refraction is NOT used for the rest of the study. The original correction from the screening manifest refraction should continue to be used.**

3.14 Cycloplegic Refraction

Cycloplegic refraction is used to confirm the manifest refraction and to determine emmetrope status. It is performed using distance VA charts, under photopic conditions, after subjects are dilated using 1% tropicamide and 2.5% phenylephrine. Refraction is to be performed a minimum of 30 minutes after administration of dilating drops.

When determining whether refraction meets entry criteria, **either plus OR minus cylinder notation may be used**, and considered for each eye individually.

Example: An *emmetrope* may meet criteria in plus cylinder notation for one eye and minus cylinder notation in the other; however, if one eye in either notation does not meet emmetrope criteria, the subject would be a *nonemmetrope*.

If a subject's cycloplegic refraction vision is 20/63 or worse, the subject should read the central OU section because there are no corresponding letters for OD or OS on the charts. For vision better than 20/63, the subject should read the OD or OS sections of the chart as usual.

3.15 Visual Acuity Measures

General Considerations for all VA Measures

Sites should use a consistent evaluator to conduct all visual acuity measures. If a consistent evaluator is not possible, an overlap between two evaluators is required. This is a long and fatiguing study that involves multiple VA measurements at multiple timepoints. It is important for all evaluators to consistently allow subjects to take time to blink and consistently encourage them to try their best to read at each measurement across all timepoints at all study visits.

For all VA measures, start with the lowest line the subject can read and move to the next line below if 3 or more letters are read correctly. The Snellen equivalent is calculated as the last line when 3 or more letters are read correctly—that is, if only 0, 1, or 2 letters on a line can be read, do not proceed to the next line. The number of letters calculation should include all letters read correctly, including the letters on the line when 1 or 2 letters were read. The VA score should be the last line on which 3 or more were read correctly.

Use of Screening Manifest Refraction

Visual acuity measurements for CDVA and DCNVA are performed OU using the subject's best **distance** correction based on the screening manifest refraction results per lighting condition:

- If screening (photopic/mesopic) manifest refraction requires correction, trial frames/lenses or phoropter (or new monofocal correction or habitual correction IF appropriate - see Section 3.12) should be used to provide correction.
- Results from screening should be used to provide the correction throughout the trial; the screening best-corrected vision performed under (mesopic/photopic) conditions will be used post screening for
  - mesopic results for mesopic VA measurements
  - photopic results for photopic VA measurements

If no correction is needed, the VA measurements should be completed without the trial lenses/frames.

Chart Usage

AbbVie will provide multiple charts for each type of visual acuity measurement. Charts for each VA measurement are labeled with specific identifiers and use different letters. Each chart contains a unique identifying number that corresponds to a worksheet provided. The worksheet is to be used to capture the results of each VA evaluation.

To ensure proper VA measurement, different charts should be used at each timepoint and no charts should be used in successive VA measures. This should prevent the memory effect. Please note that VA

worksheets labeled 'mesopic' and 'photopic' can refer to the same chart. When rotating different worksheets ensure rotation extends into both mesopic and photopic worksheets.

The worksheets provided by AbbVie are labeled the same way as the corresponding charts. Section 7.3 contains tables of which VA charts should be used for each VA measure, according to timepoint and lighting conditions. Please refer to these tables for the preferred chart rotations to minimize learning effects. It may help to print this appendix for reference.

Corrected Distance Visual Acuity (CDVA)

1. CDVA is performed with the best distance correction determined by the screening manifest refraction under the corresponding lighting conditions.
2. Trial frames and trial lenses or phoropter (or new monofocal correction or habitual correction IF appropriate – see Section 3.12) should be used if correction is needed per the manifest refraction results. If no correction is needed, complete the CDVA without the trial frames or phoropter.
3. AbbVie will provide 3 double-sided distance charts labeled 23214-1 (Front and Back), 23214-2 (Front and Back), and 23214-3 (Front and Back), found at the bottom right-hand corner of the front side. Charts are similar, only differing in letters.
    a. Site should refer to Section 7.3 on which chart should be used at each timepoint.
    b. Use the corresponding CDVA worksheet based on the chart selected.
4. The chart should be mounted on the wall or stable stand (eg, lectern) that is 4 meters away from the subject's eyes and at approximately eye level to the average height of the seated subject.
5. Conduct the CDVA measurement OU:
6. Ask the subject to:
    a. Read the lowest line visible starting with the middle of the chart.
    b. If read correctly, count the number of letters and proceed to the next line noting letters correct per line, until 2 or fewer letters can be read correctly on that line, then stop.
    c. VA score (Snellen equivalent) is the lowest line on which 3 or more letters are read correctly. (Note: it is possible that there is more than one line of 3 or 4 correctly read letters; always record the lowest line as the VA score).
    d. Use the provided worksheet to calculate the number of letters read in the preceding lines and record the associated VA score (Snellen equivalent).
7. CDVA measured under mesopic and photopic conditions as per protocol timepoints
8. The number of letters, VA score, and chart number will be entered into the eCRF for OU. Identify the letters on the worksheet read correctly to enable you to score and verify the result (e.g., by crossing out incorrect letters).

3.16 Distance-Corrected Near Visual Acuity (DCNVA)

1. DCNVA is performed with the best distance correction determined by the screening manifest refraction under the corresponding lighting conditions.
2. Trial frames and trial lenses or phoropter (or new monofocal correction or habitual correction IF appropriate –see Section 3.12) should be used if correction is needed per the manifest refraction results. If no correction is needed, complete the DCNVA without the trial frames or phoropter.
3. AbbVie will provide 8 near charts that are labeled as 23213-1 (Front and Back), 23213-2 (Front and Back), 23213-3 (Front and Back), and 23213-4 (Front and Back), found at the bottom right-hand corner of the front side. All charts have the same settings and only differ in letters.
   a. Site should refer to Section 7.3 on which chart should be used at each timepoint.
   b. Use the corresponding DCNVA worksheet based on the chart selected.
4. The chart should be mounted on a lectern or held by the subject or site staff. Use the attached string to keep 40 cm from the chart by aligning the end of the string to the lateral canthus of the subject's OS.
5. For the measurement OU ask the subject to:
   a. Read the lowest line visible starting with the middle of the chart.
   b. If read correctly, count the number of letters and proceed to the next line, noting letters correct per line, until 2 or fewer letters can be read correctly on that line, then stop.
   c. VA score (Snellen equivalent) is the lowest line on which 3 or more letters are read correctly. (Note: It is possible that there is more than one line of 3 or 4 correctly read letters; always record the lowest line as the VA score).
   d. Use the provided worksheet to calculate the number of letters read in the preceding lines and record the associated VA score (Snellen equivalent).
6. DCNVA needs to be measured under both mesopic and photopic conditions in the order specified and at the timepoints listed in the protocol.
7. The number of letters, VA score, and chart number will be entered into the eCRF for OU.

   Note:

   - Mesopic DCNVA is repeated 3 times at the screening visit for practice. Please reference Section 7.3 for the charts that should be used. Evaluators should consistently allow subjects to take time to blink and consistently encourage them to try their best to read at each measurement. The results of the three measurements are expected to be the same or very similar, and at least one of the three should meet the inclusion criteria on mesopic DCNVA. Please enter the last qualifying score into EDC.
   - Per inclusion criterion 3 (bullet 4), Mesopic, high-contrast DCNVA has to be 20/40 (J3) to 20/100 (J10) at the screening and baseline visits.

3.17 Pupil Diameter

The pupil diameter will be measured at the timepoints listed in the study protocol.

Pupil Diameter

AbbVie will provide a NeurOptics VIP-300 unilateral pupillometer to perform all pupil diameter measurements per protocol timepoints. The provided pupillometer is housed in a protective hard-shell case that includes the following:

- Pupillometer
- Lithium-ion battery
- Two opaque rubber eyecups
- Medical grade power supply for the charging station
- The charging station

Measuring Pupil Diameter

Pupil diameters should be measured with the provided pupillometer for distance/near VA and under mesopic/photopic conditions, per eye. The following VA charts should be utilized:

- Near pupil diameter: 40 cm (near) visual acuity chart
- Distance pupil diameter: 4 meter (distance) visual acuity chart.

  Note: Pupillometer Use
- *From the home screen, select 'settings' (the gear icon), and select **LIGHTS OFF mode.***
- *MUST BE in **LIGHTS OFF mode** NOT in "variable" mode (the current mode will be displayed)*

While measuring pupil size in 1 eye, the fellow eye should remain open and focused on the appropriate distance or near vision chart. Pupil measurements will be measured over 2 seconds and the readings recorded. Ensure that the pupillometer eyecup does not cover the subject's eye, as sufficient ambient light is necessary for an accurate measurement. Holding the pupillometer so that approximately 1-2 inches separates the subject's eye from the eyecup should allow sufficient ambient light entry.

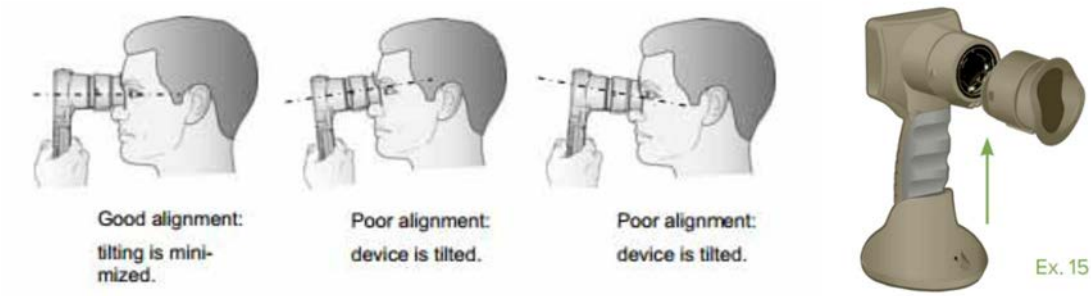
Subject Preparation

1. With any spectacles removed, instruct the subject to focus at the target distance with the eye that is not being tested.
2. Ask the subject to keep his/her head straight and both eyes wide open during both targeting and measurement. In some cases, if targeting becomes a problem, it may be necessary to gently hold the subject's eye open with your finger.
3. The operator should position the instrument at a right angle to the subject's axis of vision and any tilting of the instrument should be minimized (See Figure 3 below). When taking the

measurement, remember not to cover the subject's eye with the eyecup, so as to allow for sufficient ambient light to enter.

4. It may be helpful for the operator to be at the same level as the subject when performing the scan to minimize tilting. If necessary, both subject and operator can sit down facing each other during targeting and measurement. (See Figure 3 below).
5. The pupillometer should not be used without the eyecup positioned correctly (see Figure 3 below). The eyecup has a tab in the rim that fits into the indentation in the lens shield of the pupillometer. Position the tab in the eyecup rim into the indent in the lens shield and press into place. The tabs on either side of the lens shield should also snap into holes on either side of the eyecup.

Figure 3. Pupillometer Alignment and Eyecup Positioning



Pupil Measurement

1. From the main screen, select **settings** icon (nut and bolt) and then the top left "eye" icon to toggle between "**Light off**" and "Variable" mode. Measurements must be performed using the LIGHT OFF MODE.
2. Position the pupillometer in front of the intended eye (do not cover the eye, hold to allow ambient light to enter), and ensure the subject is focused at the appropriate target (near or distance) with his/her other eye.
3. Press and hold either the **OD** or **OS** button until the eye is centered on the touchscreen and the display shows a circle around the pupil. Once the circle appears (green for OD and yellow for OS), release the button, holding the pupillometer in place for approximately 2 seconds, making sure the subject maintains an open eye position.
4. When the pupil measurement is complete, pupil data are analyzed, and results are displayed. If the measurement was affected by a tracking problem (e.g., excessive blinks), results are reported as NA.
5. Repeat this process for the other eye.
6. From the results page, you may select the **Video** icon to view playback of the scan. Records can also be deleted using the **Delete** icon.

7. All measurements will be recorded in the source worksheet and the eCRF, rounded to the nearest tenth. Printouts of pupil values do not need to be saved as long as values are recorded in the source. Please refer to the NeurOptics VIP-300 Pupillometer Instruction Manual for more detailed operating instructions.

3.18 Slit-lamp Biomicroscopy

Biomicroscopic examinations should 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:

<u>Edema</u>			
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
<u>Erythema</u>			
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

Crusting:

0	(None)
+0.5	(Trace)
+1	(Mild)
+2	(Moderate)
+3	(Severe)

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

Note: Subconjunctival hemorrhage, discharge, blanching, follicles, pterygium encroaching on visual axis, pterygium not encroaching on visual axis are graded as 0, + 0.5, +1, +2, +3.

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

Note: Subconjunctival hemorrhage, discharge, blanching, follicles, pterygium encroaching on visual axis, pterygium not encroaching on visual axis are graded as 0, + 0.5, +1, +2, +3.

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

Note: Punctate epithelial staining, Filaments, Infiltrates, Edema, Cornea Gutatta, Endothelial Pigment, Keratic Precipitates, Neovascularization, Opacity(ies), Stromal Haze are graded 0, + 0.5, +1, +2, +3.

Anterior Chamber:

Cells, Flare, Anterior Synechiae, Hypopyon, Hyphema will be graded as 0,+ 0.5, +1, +2, +3, +4.

Iris/Pupil:

Rubeosis Iridis, anterior chamber angle involved, Rubeosis Iridis, anterior chamber not involved, Afferent Pupillary Defect, Posterior Synechiae, Transillumination Defects, Pseudoexfoliative Material, Peripheral Iridectomy, Laser Peripheral Iridotomy will be evaluated with no grading.

3.19 Fluorescein Corneal Staining

The corneal staining should be graded 2 minutes after instillation of the sodium fluorescein. Examination will be performed with the slit lamp at approximately 10X magnification. Evaluate the entire cornea for staining using the supplied yellow barrier filter placed directly in front of the objective lens of slit lamp. The slit lamp's cobalt blue filter must be used to illuminate the cornea. Corneal fluorescein staining must be evaluated at the 2-minute timepoint. Refer to the Oxford Scheme outlined in the laminated chart provided to grade the staining.

3.20 IOP

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

3.21 Gonioscopy

Gonioscopy will be performed to assess the iridocorneal (anterior chamber) angle. You may use your preferred indirect gonioscopy lens (e.g., Posner, Zeiss 4-mirror lens, etc.). When gonioscopic photography is being performed you should use the appropriate gonioscopic lens for the photography.

General steps to performing gonioscopy:

- Room lights should be turned off during the examination. All participants should be examined in the same room with the same slit lamp if possible to do so, and with consistent lighting conditions.
- Perform the angle assessment under high magnification.
- With the participant comfortable at the slit lamp, wet the corneal surface of your lens with an artificial tear or lubricating solution and place your gonioscopy lens on the participant's eye.
- Direct a bright, narrow light beam away from the pupil to avoid inducing miosis.
- Have the participant maintain their gaze in the primary position while you examine the iridocorneal angle.
- Minimize tilting the lens; only minor movement of the lens is permissible. Otherwise, the angle findings may be distorted and a closed or narrow angle may appear open. Do not apply pressure that may cause indentation. The presence of corneal striations is an indication that the cornea is being indented.
- Examine the iridocorneal angle for peripheral anterior synechiae and other angle pathology.

3.22 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 should 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 should be evaluated. Capsular bag should also 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 should be evaluated for pathology. If pathology is present, it will be described. It will be noted if the condition is not evaluable. Cells, Vitreous Haze, Vitreous Hemorrhage and Posterior Vitreous Detachment should be graded the severity grades: +0.5, +1, +2, +3, +4, not evaluable, not applicable).

Fundus:

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

Macula:

The macula will be evaluated for any of the following pathology: intraretinal fluid, subretinal fluid, intraretinal hemorrhage, subretinal hemorrhage, rhegmatogenous detachment, tractional detachment, pigment epithelial detachment.

Retina Periphery:

The retina periphery will be evaluated for any of the following pathology and the approximate clock location:

Retinal hemorrhage, retinal tear, rhegmatogenous retinal detachment macula center attached, rhegmatogenous retinal detachment macula center detached, tractional retinal detachment macula center attached, tractional retinal detachment macula center detached, and exudative retinal detachment macula center attached, exudative retinal detachment macula center detached, other retinal detachment, round (atrophic) retinal hole, lattice degeneration.

Optic Nerve:

The optic nerve should be evaluated for pathology. If pathology is present, it will be described along with approximate clock location. It will be noted if the condition is not evaluable.

C/D Ratio:

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

3.23 Pharmacokinetics Sampling (Selected Sites Only)

Pharmacokinetic (PK) samples for quantification of AGN-190584 in plasma will be collected at selected sites in approximately 10% of all enrolled subjects. Please refer to the Central Laboratory Manual for full collection, processing, and shipping information for pharmacokinetic blood samples.

Blood Pharmacokinetic Sampling Procedure

A qualified phlebotomist will collect 5 mL of each subject's blood via an indwelling catheter or venipuncture from either arm into one 6 mL vacutainer tube containing dipotassium ethylenediaminetetraacetic acid as an anticoagulant.

- Plasma samples of approximately 2.5 mL will be separated from each blood sample collected for measurement of plasma concentrations of AGN-190584 as specified in the Protocol Activity Schedule (Appendix D).
- Instructions for the collection and handling of biological samples will be provided by AbbVie. The actual date and time (24-hour clock time) of each sample will be recorded. Pharmacokinetic blood samples to determine pilocarpine concentrations should be drawn at the nominal times, relative to the dosing time, and the actual time of the blood draw must be recorded in the source documents and Electronic case report form (eCRF). Samples taken outside the allowable time window will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs. Predose samples must be drawn within 15 minutes of the dosing time.
- Study center staff will record the atomic clock times of all blood draws for each participant and will label vacutainer and polypropylene tubes with a coded label that corresponds to the participant number and blood draw time. The central lab will supply the coded labels,

vacutainers, and polypropylene tubes. The study center will be responsible for all other supplies.

- Samples will be used to evaluate the pharmacokinetics of pilocarpine. Each plasma sample will be divided into 2 aliquots (1 each for primary and backup PK samples). Samples collected for analyses of pilocarpine plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

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

Blood Volume Collected per Participant

Approximately 10% of participants at selected sites

Pharmacokinetic blood samples: 110 mL (22 blood samples, 5 mL each)

Within 30 minutes from the time of the blood draw, blood samples must be centrifuged at no less than 2000 g for 15 minutes at approximately 4°C. After centrifugation, the plasma samples will be harvested and aliquoted into two approximately 1.25 mL samples in cryovials (one primary and one backup). The samples should be placed on wet ice immediately after aliquoting and transferred to a –20°C freezer within one hour of processing to plasma.

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

Pharmacokinetic Sample Bioanalysis

Plasma concentrations of AGN-190584 in plasma will be determined using validated liquid chromatography-tandem mass spectrometry methods.

3.24 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Day 1 and as specified in Section 2.1. The first dose of study drug will be administered after all other Day 1 procedures are completed. At the visits specified in Section 2.1, the site personnel will review returned study drug kits, and empty study drug packaging to verify drug accountability.

Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and lot numbers for all noninvestigational product (IP) dispensed by the site.

3.25 Subject Withdrawal from the Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

3.26 Unscheduled Visits

An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, ocular examinations may be performed at the investigator's discretion.

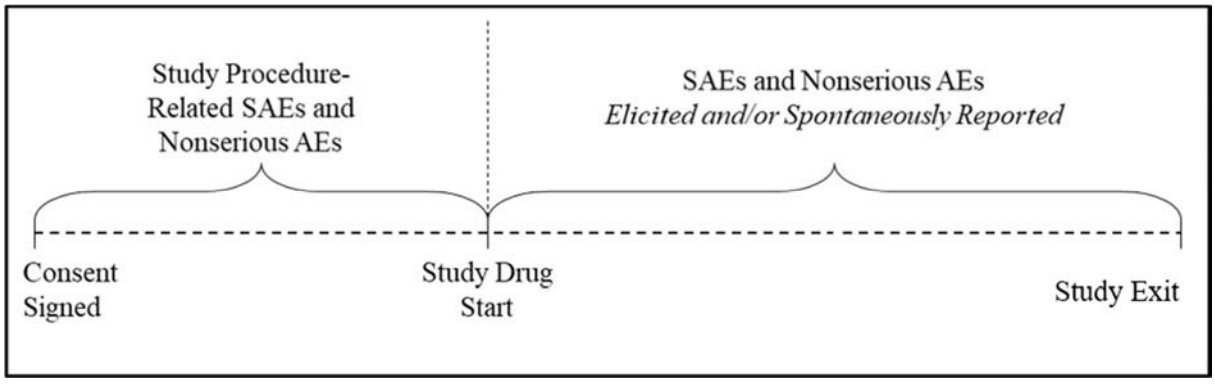
Visits for dispensing new study drug in case of temperature excursion, loss, or damage are not considered Unscheduled Visits.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All adverse events, whether solicited or spontaneously reported by the subject, will be collected from the time of study drug administration through study exit, unless spontaneously report after study exit. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

Figure 4. Adverse Event and Serious Adverse Event Collection Schema



AE = adverse event; SAE = serious adverse event

Note: Spontaneous report only after study exit.

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with 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 forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: IR-Clinical-SAE@abbvie.com
FAX to: +1-714-796-9504 Backup: +1-714-246-5295

For safety concerns, contact the Ophthalmology Safety Team at:

Ophthalmology Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_Ophthalmology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MD**
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Mobile: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

Supplemental Headache AE Assessment

Whenever a headache AE is reported after the initial dosing at Day 1, the subject should be immediately followed up with a supplemental headache AE assessment form to further assess the headache. The supplemental headache AE assessment form contains three visual analog scales (VAS) that the subject will complete to grade the overall severity, the temporal severity (if applicable), and the supraorbital severity (if applicable). The subjects will be asked to make a vertical mark along each horizontal 100 mm long VAS, ranging from No Pain on the left to Worst Possible Pain on the right.

Figure 5. Visual Analog Scale

The evaluator should also ask the subject the additional questions on the headache AE-assessment form. If a headache started after administration of both the first and second doses of study drug, then these additional questions should be answered about whichever headache had worse outcomes. For example, "How long after taking the study drug did the headache/migraine start?" should reflect whichever headache had the quickest onset, and "How long did the headache/migraine last? (if intermittent, approximately how long did each event last)" should reflect whichever headache had the longest duration.

The evaluator should measure the distance from the end of the line to the mark that the subject made with a ruler and record the length on the supplemental headache assessment worksheet.

If a headache is classified as intermittent or recurrent with the same causality and severity, then one supplemental headache AE assessment form should be used. If the subject experiences multiple headaches with different causality or severity, then each headache should have its own supplemental headache AE assessment form.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study CRFs should be completed in the event of COVID-19-related missed/virtual visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections should be captured as AEs. If the event meets the criteria for a SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected SARS-CoV-2 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All AEs associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference safety information.

6 STUDY DRUG AND SUPPLIES

6.1 Study Supplies

AbbVie will supply the following:

- Unilateral pupillometer
- Pupillary distance ruler
- Distance and near visual acuity charts
- Light meters
- Oxford scale
- Yellow barrier filter for corneal fluorescein staining (if needed)
- Sodium fluorescein DET strips (if needed)
- Lectern
- Paper OSDI and NEI VFQ-25 questionnaires
- Tablet for electronic questionnaires
- An iPhone with a screen size of 4.7 to 5.8 inches diagonally for the VFA app. The following iPhone models meet this specification: iPhone 6s, iPhone 6s Plus, iPhone 7, iPhone 7 Plus, iPhone 8, iPhone 8 Plus, iPhone X, iPhone Xs, iPhone 11 Pro, iPhone 12 Mini, and second-generation iPhone SE (introduced in 2020). AbbVie must choose only one model and use across all sites. Subjects will not take the iPhone home, as the VFA app is only administered at site visits, using the site-provided iPhone.
- Laboratory supplies for pharmacokinetic samples for selected sites.

The investigator will supply the following:

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

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

6.2 Treatments Administered

The study drug (AGN-190584) will be dispensed and administered in the form of eyedrops at designated study visits by site personnel. On nonvisit days, subjects will be instructed to take the study drug as described in Section 5.7 of the protocol.

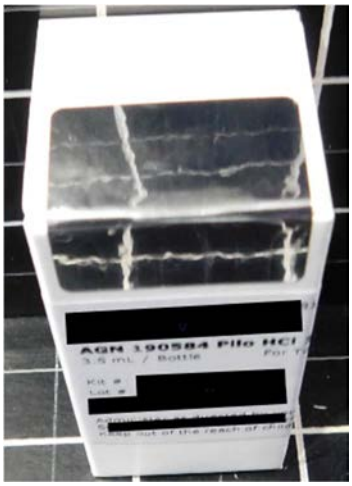
AGN-190584 will be administered in both eyes twice daily in the morning and the afternoon. On the day before office visits, the study drug should not be administered less than 12 hours before the scheduled visit time.

Study drug can only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.3 Packaging and Labeling

As this is a double-masked study, AGN-190584 and vehicle will be supplied in identically appearing bottles and cartons (Figure 6).

Figure 6. AGN-190584 Bottle and Carton



Kit #: XXXXXXX
Lot #: LL-LLLLLL
Subject #: _____
Date Dispensed: _____

AbbVie, North Chicago, IL 60064 USA
M21-195
AGN 190584 Pilo HCl 1.25% Ophthalmic Solution or Vehicle
3.5 mL / Bottle For Topical Ophthalmic Use Only Sterile
Administer as directed by your Investigator.
Store between 2°C to 8°C (36°F to 46°F).
Keep out of the reach of children. Keep bottle in outer carton.
Caution: New Drug - Limited by United States law to investigational use.

- 1 carton = 1 kit
  - Each kit/carton
    - Labeled Carton: Site to complete blank spaces on the carton label
    - Contains one (1) sterile 5 mL bottle with a 3.5 mL fill
    - Affixed label that corresponds to the outer carton/kit label
- IRT will assign one (1) kit/carton per dispensing.

Subjects will be dispensed a carton (1 kit) of IP upon completion of all Day 1 procedures. Subjects should keep the bottle in the outer carton and must bring all used and unused kit(s) for on-site visits as these will be used to perform on-site administration.

All used and unused IP MUST BE returned by the subject to the site at study completion; IP should be destroyed onsite per site SOPs or return to depot.

6.4 Shipment of Study Drug

Shipments will be shipped in preconditioned shippers (no temperature monitors will be included), including packing list and study intervention. Upon receipt of the shipment the site should confirm/verify the shipment contents against the packing list:

- Site # / PI name
- Kit numbers
- Quantity of kits
- Condition of kits
- Expiry (if applicable)
- Lot No.

The original packing list should be filed in the site ISF. Any discrepancies should be reported to the assigned site monitor.

IP Shipment – Temperature Monitoring

No temperature monitors will be included with shipments because the shippers that the study drugs are sent in will be prequalified shippers that will maintain the temperature between 2 °C and 8 °C.

Registering Shipments (Consignments) into IRT

Each shipment of IP has a corresponding consignment assignment as noted on the packing list. These consignments must be registered into the EndPoint IRT system immediately upon receipt.

Storage and Disposition of Study Drug

The IPs are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

Excursion Reporting

Physically set aside affected study intervention under labeled storage conditions, then enter the temperature excursion into ATEMS; ATEMS will automatically provide an assessment and show the new study intervention status.

6.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio into the following treatment groups:

Treatment	Dosing Schedule
AGN-190584 1.25%	1 drop OU, twice daily, 6 hours apart for 14 days
Vehicle	

Stratification is based on the following factors at either screening or Baseline/Day 1:

Age at Screening	• ≤ 50 years • > 50 years	Screening
Binocular Mesopic DCNVA Severity	• 20/63 or Better (≤ 50%) • Worse than 20/63	Baseline/Day 1
Iris color	• Brown • Nonbrown	Screening
Emmetrope status*	• Emmetrope • Nonemmetrope (≤ 25%)	Screening

* Emmetrope status is confirmed via screening cycloplegic refraction. See Section 3.14 for details.

If correction for each eye is within sphere range of -0.50 D to +0.75 D inclusive and ≤ 0.75 D in Cylinder, the subject is considered an emmetrope. If one or both eyes are out of the range, the subject should be considered a nonemmetrope.

> Note: Refractions may be transcribed in *plus or minus cylinder* notation to determine whether inclusion criteria and/or emmetrope definitions are met.

At the screening visit, all subjects will be assigned a unique subject number using the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Sites are to enter required information into IRT either in real time or shortly after a reportable event to ensure timely reporting of the overall study status. Interactive response technology will provide the subject identification number per consented subject; this number will identify the subject throughout the course of the trial. Contact information and user guidelines for IRT use will be provided to each site.

Interactive response technology will control the stratification for the trial. Once a stratum cap has been reached, no additional subjects can be enrolled; therefore, screening entries of age, iris color, and emmetrope status will determine the general stratification, which is confirmed on Baseline/Day 1 with the entry of the 1-hour DCNVA, OU. Once a stratum has been filled no additional subjects meeting those stratum factors can be randomized/enrolled. Therefore, sites must review the screening entries prior to Baseline/Day 1 to ensure proper stratification (with corresponding documentation), updating

IRT entries if needed. Upon randomization these factors cannot be updated and will affect the stratum population.

* NOTE- ERRORS IN ENTERING THE STRATUM GROUP IN IRT MAY IMPACT THE RANDOMIZATION OF THE SUBJECT AND DATA ANALYSIS. PLEASE ENSURE THAT THE ASSIGNED STRATUM GROUP YOU SELECTED IN IRT IS ACCURATE BEFORE PROCEEDING IN THE SYSTEM. AFTER YOU PROCEED, YOU CANNOT CHANGE THE STRATUM GROUP.

6.6 Selection and Timing of Dose for Each Subject

Baseline/Day 1

Upon randomization in IRT, site staff should perform the following prior to administration/dispensing to ensure per kit/carton:

- Verify against carton/kits pulled against assigned carton/kits via IRT printout
- Verify carton/kit label against affixed bottle label

Any discrepancies should be reported to the site monitor upon identification.

Baseline/Day 1 IP administration: Upon completion of all Hour 0 procedures (immediately after VAS if applicable) and prior to the tolerability assessment/drop comfort questionnaire, site staff will administer one (1) drop in each eye with one of the two (2) drop bottles at 8AM ± 1 hour and no sooner than 6 hours + 15 minutes after the first administration.

Site staff will demonstrate the IP administration to educate the subject about the at-home dosing procedures. The site will review the subject instructions for at-home and in-office study visit administration, IP storage/transport, and any warnings. Printed subject dosing instructions should be provided with the IP when dispensed prior to the end of the visit, with any subject education noted within source.

Study Visits: IP Administration/Compliance

On visit days site staff will administer IP at Hour 0 in a similar fashion to Baseline/Day 1 at 8AM ± 1 hour and again 6 hours after the first administration within + 15 minutes.

Subjects are to bring all used and unused IP for study visits, returning all by the end of their participation. On-site administration will occur with the IP dispensed during the Baseline/Day 1 visit that is returned. Therefore, subjects should be instructed to bring all used and unused IP for study visits. At the conclusion of participation all IP dispensed (used and unused) must be returned to the site for destruction.

Subjects should not self-administer IP prior to the visit on the visit day, and should provide staff the approximate time of their last self-administration (last self-administration should occur no sooner on the day before a study visit than 12 hours prior to their scheduled visit time). During study visits, site staff should discuss compliance with daily IP administration and assess reasons for not administering for safety and/or re-education needs, documenting discussion accordingly.

7 Appendices

7.1 STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
BID	twice daily
CDVA	corrected distance visual acuity
COVID-19	Coronavirus Disease - 2019
CRF	case report form
DCNVA	distance-corrected near visual acuity
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
IL	interleukin
IMP	Investigational Medicinal Product
IOP	intraocular pressure
IP	investigational product
IRT	interactive response technology
N/A	not applicable
NEI VFQ-25	25-item National Eye Institute Visual Function Questionnaire
NVPTQ	Near Vision Presbyopia Task-Based Questionnaire
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
OU	both eyes
PD	premature discontinuation
PGIC	patient global impression of change
PGIS	global impression of status
PICQ	Presbyopia Impact and Coping Questionnaire
PK	pharmacokinetic
PRO	patient-reported outcome
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SE	study eye
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
VAS	visual analog scales
VFA app	Visual Function Assessment application

7.2 VFA App Instructions

Background

The VFA app is a custom-developed iOS application that will be used in clinic, in the presence of a clinician, to assess a clinical trial subject's ability to read on electronic devices.

Subjects are asked to read a prespecified text passage on an iPhone. The app will capture coping behaviors adopted by users to help them read better (e.g., blinking, squinting, screen tilt), as well as metrics on their reading performance (e.g., reading speed).

No videos or images are stored permanently within the app, on the device, or transmitted to any external storage.

Conditions for Use

iPhone Specification

Sites should be provided one or more iPhones, depending on the expected maximum number of subjects per a site visit.

A single device needs to be chosen from the candidates provided below and used across all sites:

An iPhone with a screen size of 4.7 to 5.8 inches diagonally. The following iPhone models meet this specification: iPhone 6s, iPhone 6s Plus, iPhone 7, iPhone 7 Plus, iPhone 8, iPhone 8 Plus, iPhone X, iPhone Xs, iPhone 11 Pro, iPhone 12 Mini, and second-generation iPhone SE (introduced in 2020)

Subjects will not take the iPhone home, as the VFA app is only administered at site visits, using the site-provided iPhone.

Light Setting and Correction

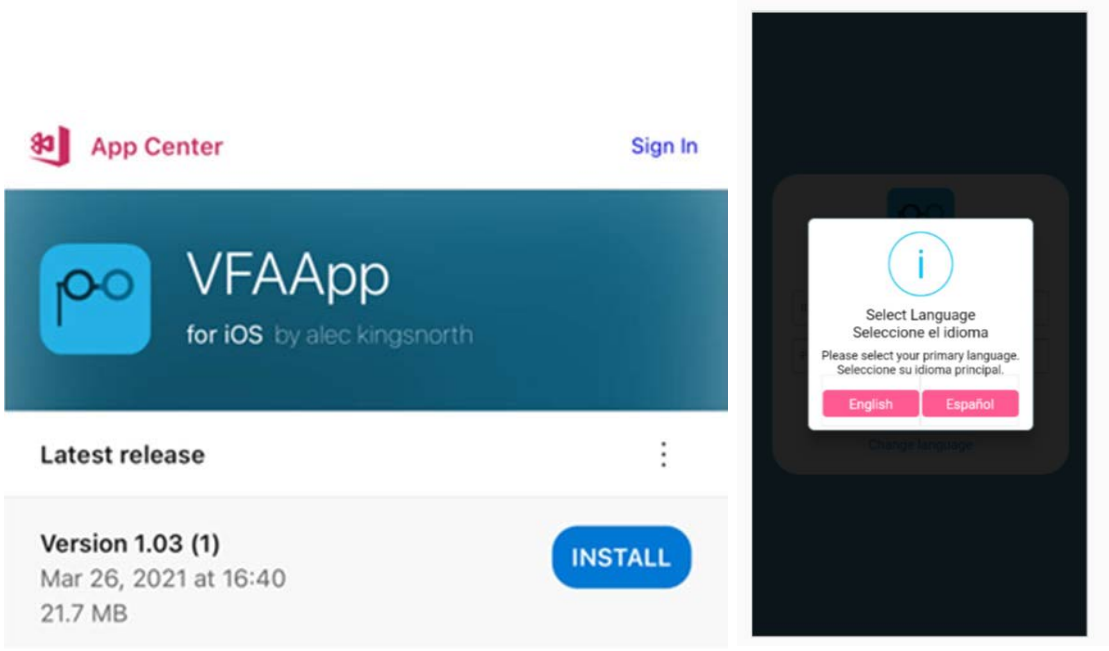
VFA should be administered under photopic conditions, with the subject's best distance correction. No near-vision correction is allowed.

Only half-eye style trial frames or full-field trial lenses can be used for best distance correction while subjects are performing the VFA task. Other forms of correction would interfere with the camera's ability to detect subjects' faces.

Instructions for Downloading the VFA App on iPhone

Before providing sites with iPhones, AbbVie should download the VFA app on each device.

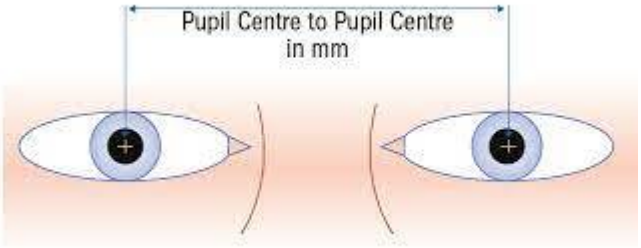
The unique device IDs of the phones need to be e-mailed to [redacted] – this further adds to the app security. A Microsoft's App Center link for the app will be provided for it to be downloaded. You will be asked to select your preferred language the first time you open the app.

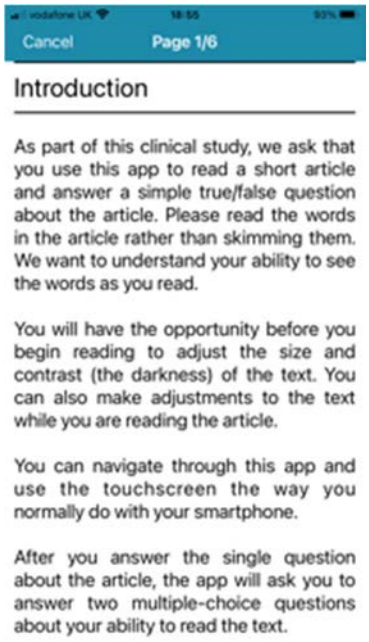


Detailed Instructions

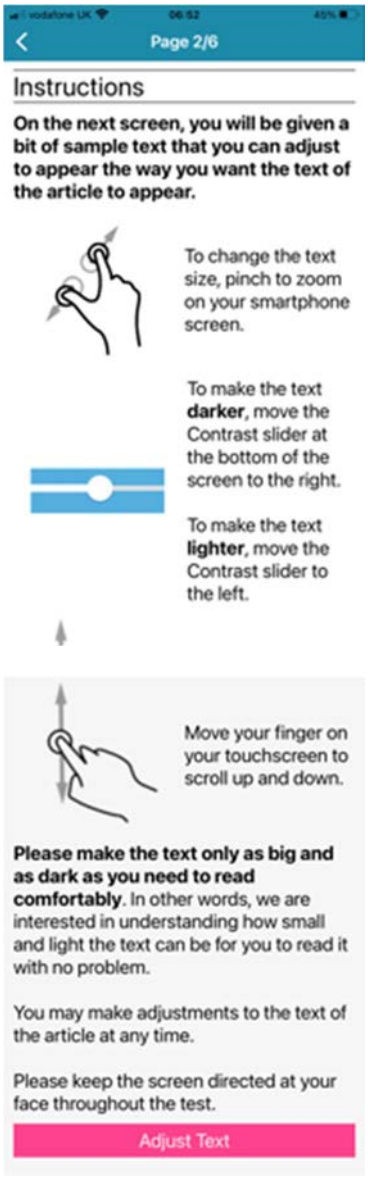
Study Site Personnel: Screens 1 to 3

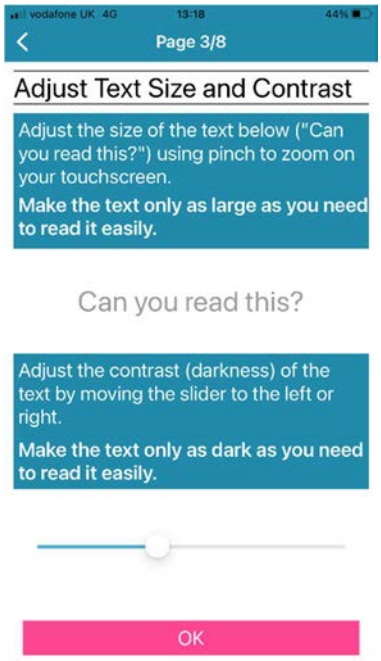
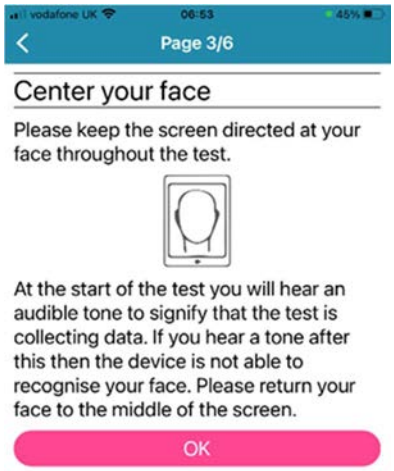
Screen 1: Site login	
	• Login using provided unique site username and password. If lost please email [redacted] • Choose between English or Spanish language, depending on subject preference

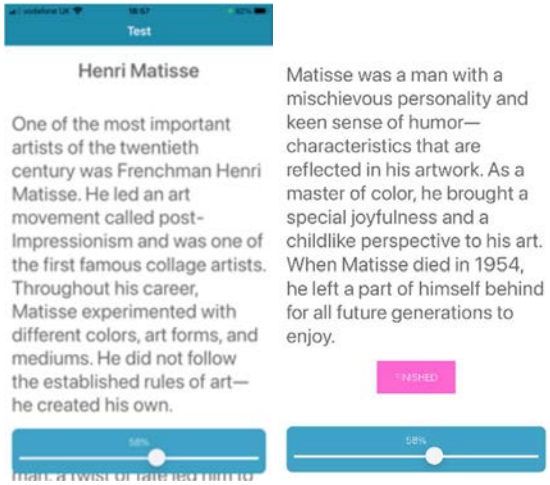
Screen 2: Subject identification and pupillary distance setting 	• Enter the subject ID • Select a text passage based on subject ID and visit number, per the table provided in the Text Choice Selection Guides below. This is to make sure that each subject is assigned a different text passage at each visit (to avoid the learning bias), and text passages are distributed evenly across subjects and visits. E.g., for Subject 6, for Visit 1 select text 4.  • Measure the subject's pupillary distance and adjust the PD dial accordingly. 

Screen 3: Subject instructions  	• Read the instructions on screen 3 to the subject clearly, and press continue. • Then hand the smartphone to the subject.

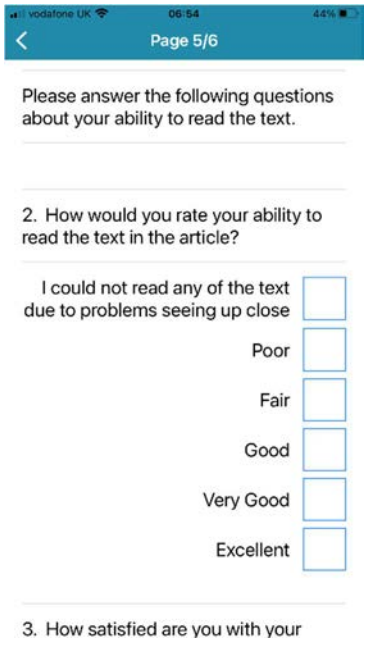
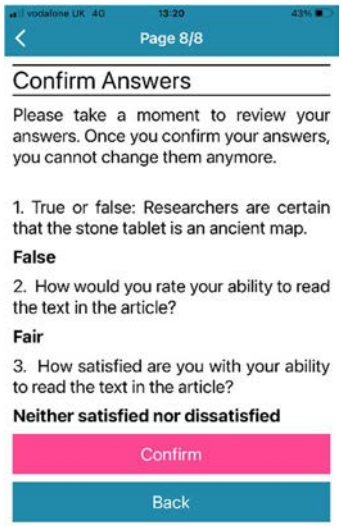
Subject: Screens 4 to 13

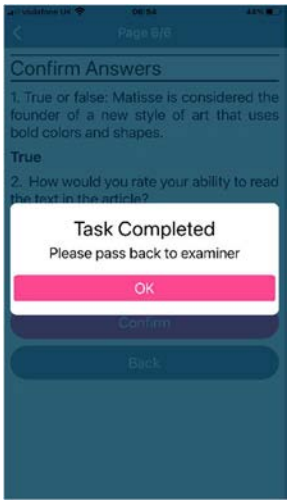
Screen 4: Screen manipulation details 	• Ask the subject to read the instructions and press continue to progress.

Screen 5: Initial size/contrast setting 	• Explain to the subject that he/she can pinch to change size and move the slider to change contrast. • Ask him/her to take a moment to apply these adjustments if needed. Remind him/her to make text only as dark and large as he/she needs to read it easily.
Screen 6: Phone orientation: 	• The subject must hold the smartphone so the screen is directed towards his/her face – if not, a tone will bleep. A tone during the task will warn him/her that the phone position needs to be adjusted. • If the face is not detected once he/she is holding the phone in the right position, the operator should check the lighting level and that the lens angle in the trial frame is not causing reflections.

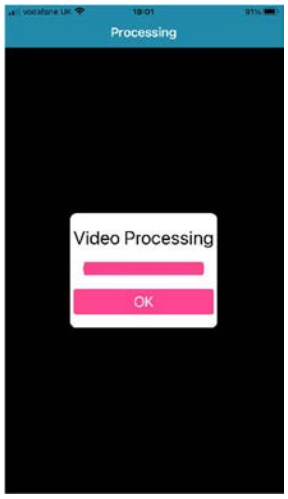
Screen 7: Confirmation of being ready to start reading 	• The subject clicks "OK" when ready to start reading the text passage.
Screen 8: Reading task 	• The subject reads silently, scrolling to the bottom of the screen and pressing "Finished" once he/she has read all the text. • He/she can adjust the text size and contrast at any time as practiced.

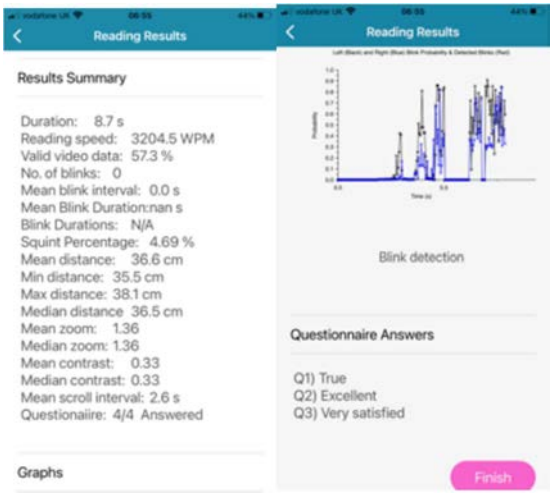
Screen 9: Reading completion confirmation 	• Confirmation that reading has been completed
Screen 10: Question on text comprehension 	• The subject answers a simple true/false question about the text he/she has read – click the box to tick.

Screen 11: Question on ability to read the text 	• The subject answers two questions about the subject's ability to read the article – click the box to tick.
Screen 12: Answer review and confirmation 	• This screen gives subjects the opportunity to confirm/change responses before submitting them. • Explain to subjects that once they click the 'Confirm' button, <u>they cannot go back and change responses.</u>

Screen 13: Task completion confirmation 	• At this point, the subject should hand the phone back to the study site personnel.

Study Site Personnel: Screens 14, 15

Screen 14: Video processing 	• This screen represents a short delay while face video is processed and features extracted – the video is not saved. • Press 'OK' to continue.

Screen 15: Summary report 	• Results are displayed and automatically saved and transmitted to the Cloud. • If the Wi-Fi fails, the data will automatically be transmitted when the phone is next in contact with a Wi-Fi connection.

Handling Wi-Fi Connectivity Issues During the VFA App Administration

Wi-Fi issue while data is being transferred to the cloud-based storage

Every app on iOS has local storage called an app sandbox. No other app or even the user can get into this app sandbox, only the app itself. This is a fundamental feature of the iOS operating system, and why it is so secure. The data get temporarily stored in the app's sandbox if the app does not have an internet connection, and will try again periodically; we call this secure 'Caching.' If the internet connection resumes and a response from the server is received the data get sent and cleared from the cache or successfully submitted. The app can only access the specific user's cache if the user is logged in. So once the connection is resolved, the site study personnel need to log in to the app again for data to be transferred to the cloud storage.

Wi-Fi issue at some point before subjects complete the task

The app will continue as normal once connection is restored. Any data that can't be sent will be stored in the cache, waiting for two things, one for internet connection, and two for the right authenticated user to be logged in before sending again. So once the connection is resolved, the site study personnel should log in to the app again, and the subject can complete the task.

Text Choice Selection Guides

Table 3. Text Choice Selection Guide for English Language

SUBJECT ID*	Visit 1 Text No.	Visit 2 Text No.	Visit 3 Text No.
1	EN 1	EN 2	EN 5
2	EN 5	EN 4	EN 1
3	EN 3	EN 4	EN 2
4	EN 2	EN 1	EN 3
5	EN 5	EN 1	EN 4
6	EN 4	EN 3	EN 5
7	EN 2	EN 3	EN 1
8	EN 1	EN 5	EN 2
9	EN 4	EN 5	EN 3
10	EN 3	EN 2	EN 4
11	EN 1	EN 3	EN 4
12	EN 2	EN 4	EN 5
13	EN 3	EN 5	EN 1
14	EN 4	EN 1	EN 2
15	EN 5	EN 2	EN 3

* This column should be filled with unique study subject IDs at each site.

Table 4. Text Choice Selection Guide for Spanish Language

SUBJECT ID*	Visit 1 Text No.	Visit 2 Text No.	Visit 3 Text No.
1	SP 1	SP 2	SP 5
2	SP 5	SP 4	SP 1
3	SP 3	SP 4	SP 2
4	SP 2	SP 1	SP 3
5	SP 5	SP 1	SP 4
6	SP 4	SP 3	SP 5
7	SP 2	SP 3	SP 1
8	SP 1	SP 5	SP 2
9	SP 4	SP 5	SP 3
10	SP 3	SP 2	SP 4
11	SP 1	SP 3	SP 4
12	SP 2	SP 4	SP 5
13	SP 3	SP 5	SP 1
14	SP 4	SP 1	SP 2
15	SP 5	SP 2	SP 3

* This column should be filled with unique study subject IDs at each site.

7.3 Ocular Surface Disease Index Scoring

OSDI Scoring Sheet **Completed Worksheet: (Initials):** _____ **Date**: _____

Please Note*: *The OSDI Scoring Sheet below is NOT for participant use - it is to be used only to score the OSDI and should not be given to participants.

Instructions: Use the gray scoring guide below to convert patient answers to numerical values. Enter the numerical value for each question in the box next to that question. Use the OSDI Calculation Table on the next page to get the patient's OSDI Score.

#	Question	Score
1	Eyes that are sensitive to light	
2	Eyes that feel gritty	
3	Painful or sore eyes	
4	Blurred vision	
5	Poor vision	
6	Reading	
7	Driving at night	
8	Working with a computer or bank machine (ATM)	
9	Watching TV	
10	Windy conditions	
11	Places or areas with low humidity (very dry)	
12	Areas that are air conditioned	
OSDI Scoring		
Number of N/A's entered (for numbers 6 -12 only):		
Number of questions answered (exclude N/As):		
Total Score (sum of numbers 1 – 12):		
OSDI Score (from OSDI Calculation Table on the next page):		

OSDI Scoring Guide	
Number	**Patient Response**
4	All of the time
3	Most of the time
2	Half of the time
1	Some of the time
0	None of the time
N/A	Not Applicable

OSDI Calculation Table (Screening)

Find the participant's total score across, then the OSDI score from the number of questions answered (down). Note: number of questions answered excludes N/A answers.
Example: If the total score is 7, and the patient answered 10 questions then their OSDI is 17.5

Total Score / # of questions answered	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
12	0.0	2.1	4.2	6.3	8.3	10.4	12.5	14.6	16.7	18.8	20.8	22.9	25.0	27.1	29.2	31.3	33.3	35.4	37.5	39.6	41.7
11	0.0	2.3	4.5	6.8	9.1	11.4	13.6	15.9	18.2	20.5	22.7	25.0	27.3	29.5	31.8	34.1	36.4	38.6	40.9	43.2	45.5
10	0.0	2.5	5.0	7.5	10.0	12.5	15.0	17.5	20.0	22.5	25.0	27.5	30.0	32.5	35.0	37.5	40.0	42.5	45.0	47.5	50.0
9	0.0	2.8	5.6	8.3	11.1	13.9	16.7	19.4	22.2	25.0	27.8	30.6	33.3	36.1	38.9	41.7	44.4	47.2	50.0	52.8	55.6
8	0.0	3.1	6.3	9.4	12.5	15.6	18.8	21.9	25.0	28.1	31.3	34.4	37.5	40.6	43.8	46.9	50.0	53.1	56.3	59.4	62.5
7	0.0	3.6	7.1	10.7	14.3	17.9	21.4	25.0	28.6	32.1	35.7	39.3	42.9	46.4	50.0	53.6	57.1	60.7	64.3	67.9	71.4
6	0.0	4.2	8.3	12.5	16.7	20.8	25.0	29.2	33.3	37.5	41.7	45.8	50.0	54.2	58.3	62.5	66.7	70.8	75.0	79.2	83.3
5	0.0	5.0	10.0	15.0	20.0	25.0	30.0	35.0	40.0	45.0	50.0	55.0	60.0	65.0	70.0	75.0	80.0	85.0	90.0	95.0	100.0

Note: Screening scores in the red shaded region (> 33) are not included for enrollment

KEY: Excluded in the Study / Included in the Study

Total Score / # of questions answered	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
12	43.8	45.8	47.9	50.0	52.1	54.2	56.3	58.3	60.4	62.5	64.6	66.7	68.8	70.8	72.9	75.0	77.1	79.2	81.3	83.3
11	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9
10	52.5	55.0	57.5	60.0	62.5	65.0	67.5	70.0	72.5	75.0	77.5	80.0	82.5	85.0	87.5	90.0	92.5	95.0	97.5	100.0
9	58.3	61.1	63.9	66.7	69.4	72.2	75.0	77.8	80.6	83.3	86.1	88.9	91.7	94.4	97.2	100.0				
8	65.6	68.8	71.9	75.0	78.1	81.3	84.4	87.5	90.6	93.8	96.9	100.0								
7	75.0	78.6	82.1	85.7	89.3	92.9	96.4	100.0												
6	87.5	91.7	95.8	100.0																

Total Score / # of questions answered	41	42	43	44	45	46	47	48
12	85.4	87.5	89.6	91.7	93.8	95.8	97.9	100.0
11	93.2	95.5	97.7	100.0				

7.4 Visual Acuity Charts Used for Each Visual Acuity Measure

Table 5. Screening Visit Visual Acuity Charts

Screening Visit	Charts Used:	
VA Measure	**Mesopic**	**Photopic**
Manifest Refraction *Near*	23213-1 Front	23213-1 Back
Manifest Refraction *Distance*	23214-1 Front	23214-1 Back
CDVA	23214-2 Front	23214-2 Back
DCNVA *(Repeated 3x for OU)*	23213-2 Front 23213-2 Back 23213-3 Front	23213-3 Back
Cycloplegic Refraction *Distance*	--	23214-1 Front

Table 6. Day 1 (Baseline), Day 7 (Visit 2), and Day 14 (Exit/Visit 3) Visual Acuity Charts

Day 1 (Baseline) Day 7 (Visit 2) Day 14 (Exit/Visit 3)	**Charts Used**	
VA Measure	**Mesopic**	**Photopic**
Hour 0		
CDVA	23214-1 Front	23214-1 Back
DCNVA	23213-1 Front	23213-1 Back
Hour 1		
CDVA	23214-2 Front	23214-2 Back
DCNVA	23213-2 Front	23213-2 Back
Hour 3		
CDVA	23214-3 Front	23214-3 Back
DCNVA	23213-3 Front	23213-3 Back
Hour 6		
CDVA	23214-1 Front	23214-1 Back
DCNVA	23213-4 Front	23213-4 Back
Hour 7 (1 hour after the second dose)		
CDVA	23214-2 Front	23214-2 Back
DCNVA	23213-1 Front	23213-1 Back
Hour 9 (3 hours after the second dose)		
CDVA	23214-3 Front	23214-3 Back
DCNVA	23213-2 Front	23213-2 Back