CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214028Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	214-028
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Division/Office	Division of Ophthalmology/Office of Specialty Medicine (DO/OSM)
Reviewer Name(s)	Sonal D. Wadhwa, MD
Review Completion Date	9/27/21
Established/Proper Name	Pilocarpine hydrochloride ophthalmic solution 1.25%
(Proposed) Trade Name	Vuity
Applicant	AbbVie Inc.
Dosage Form(s)	Topical solution
Applicant Proposed Dosing Regimen(s)	One drop OU QD
Applicant Proposed Indication(s)/Population(s)	Treatment of presbyopia in adults
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of presbyopia in adults

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Glossary

AC	advisory committee
AE	adverse event
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Pilocarpine hydrochloride is a cholinergic muscarinic agonist that activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. Pilocarpine HCl 1.25% contracts the iris sphincter muscle therefore constricting the pupil to enhance the depth of focus and improve near and intermediate visual acuity while maintaining some pupillary response to light. Pilocarpine hydrochloride ophthalmic solution 1.25% also contracts the ciliary muscle potentially shifting the eye to a more myopic state.

The application for Pilocarpine is submitted as a 505(b)(2) application listing Salagen NDA 20-237 and Isopto Carpine NDA 200-890 as reference drug products.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 214-028 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Pilocarpine for the treatment of presbyopia in adults.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes that administration of Pilocarpine OU QD improves presbyopia in adults. Studies Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013) demonstrate ability of Pilocarpine 1.25% to temporarily improve presbyopia. The most common ocular adverse events for pilocarpine at > 5% are headache and conjunctival hyperemia. The benefit of pilocarpine hydrochloride ophthalmic solution 1.25% OU QD in treating patients with presbyopia outweighs the risks to patients with presbyopia.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age. • Both non-surgical (reading glasses) and surgical methods (i.e., IOL exchange) for the correction of presbyopia are available. • Currently there is no pharmacologic treatment for presbyopia.	Without the use of pilocarpine or reading glasses older patients will have difficulty reading small text or doing activities (e.g., sewing) at close proximity.
Current Treatment Options	• The current standard of care is use of refractive correction, i.e., reading glasses. • There are no approved drug products for the treatment of presbyopia	Will give patients an option of non-invasive, reversible, pharmacologic treatment for presbyopia.
Benefit	Will provide another treatment option for presbyopia.	Will give patients an option of non-invasive, reversible, pharmacologic treatment for presbyopia.
Risk and Risk Management	Labeling will identify the expected adverse reactions. Pilocarpine risks are well known.	Pilocarpine in concentrations from 0.5% though 8% have been marketed for decades. Routine monitoring and reporting of all adverse events are expected to be adequate.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section where discussed, if applicable
X	The patient experience data that was submitted as part of the application include:			
	X	Clinical outcome assessment (COA) data, such as		See Sec 6.1 Study endpoints
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age. In 2005, 1.044 billion people globally were estimated to have presbyopia, and prevalence is expected to increase to 1.782 billion by 2050 (Holden 2008).

The exact cause of presbyopia is not known. The most likely cause of progressive presbyopia is a loss of elasticity of the crystalline lens, although changes in the lens's curvature from continual growth and loss of power of the ciliary muscles have also been postulated to contribute to its pathogenesis. The ability to focus on near objects declines throughout life, from an accommodation of about 20 D (ability to focus at 50 mm away) in a child, to 10 D at age 25 years (100 mm), and plateaus at 0.5 to 1 D at age 60 years (ability to focus down to 1 to 2 meters only). The first signs of presbyopia are eye strain, difficulty seeing in dim light, and problems focusing on small objects and/or fine print and are usually first noticed between the ages of 40 and 50 years. Uncorrected near-vision impairment caused by presbyopia may have a negative impact on activities of daily living, career options, and self-esteem.

2.2. Analysis of Current Treatment Options

There are currently no approved therapeutic products in the US for presbyopia. Both non-surgical and surgical methods for the correction of presbyopia are available. Traditional non-surgical methods of refractive correction for presbyopia include the use of dedicated reading spectacles, bifocal or multifocal spectacles, and monovision or multifocal contact lenses. A number of surgical techniques are also used for the treatment of presbyopia, which include monovision PRK or LASIK, conductive keratoplasty, intraocular lenses, and corneal inlays. However, for each of the existing technologies mentioned above, visual quality is reduced at one or more viewing distances (near, 40 cm; intermediate, 66 cm; distance, 4 m or more) and each comes with its own unique safety risks and complications. Commonly used reading glasses help with near vision but reduce vision at all other distances. Bifocals and progressive lenses (i.e., glasses, contacts) produce optical aberrations especially at intermediate distances, may compromise intermediate vision, and can increase the risk of falls. Multifocal optics reduce image quality uniformly at all viewing distances. The widespread number of surgical technologies is limited due to surgical risks, the need for repositioning, explantation, or regression of effect. Thus, there remains a need for improved methods for correcting presbyopia.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Other pilocarpine products (i.e., Salagen NDA 20-237 and Isopto Carpine NDA 200-890) are currently approved by the FDA. Salagen (pilocarpine hydrochloride) Tablets is indicated for xerostomia (dry mouth). Isopto Carpine ((pilocarpine hydrochloride ophthalmic solution) is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, the management of acute-angle closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and induction of miosis. The concentration of Isopto Carpine approved for reduction of IOP is 1% to 4% (1 drop administered to both eyes up to 4 times daily). The pharmacological mechanism is believed to be related to ciliary muscle constriction that opens the trabecular meshwork and facilitates the aqueous humor outflow to decrease the intraocular pressure.

3.2. Summary of Pre-submission/Submission Regulatory Activity

(b) (4)

(b) (4) The applicant conducted 3 Phase 2 studies evaluating the safety and efficacy of pilocarpine, oxymetazoline, and/or pilocarpine and oxymetazoline combination therapies (Studies 199201-007, 199201-009, and 199201-010). Results from these studies led to the conclusion that the early indications of an efficacy contribution from oxymetazoline in Study 199201-007 were not substantial or reproducible, and that oxymetazoline did not offer additional clinically meaningful improvements in safety or efficacy when combined with pilocarpine to improve uncorrected near visual acuity (UNVA) in Studies 199201-009 and 199201-010. Therefore, the applicant proceeded with the development of pilocarpine monotherapy for the treatment of presbyopia. Through modeling and evaluation of the Phase 2 study results, the sponsor believes the optimal dose of pilocarpine hydrochloride ophthalmic solution monotherapy to be 1.25% for the treatment of presbyopia.

The Phase 3 clinical development program in support of the proposed indication consists of 2 Phase 3 studies [Gemini 1 (Study 1883-301-013) and Gemini 2 (1883-302-013)], which used the intended commercial formulation. The objectives of these studies were to evaluate the efficacy and safety of pilocarpine hydrochloride ophthalmic solution 1.25% versus vehicle when administered bilaterally, once daily for 30 days in participants with presbyopia. The 2 studies are broadly identical in design, except in Study 1883-301-013 (Gemini 1) the systemic pharmacokinetics of pilocarpine hydrochloride ophthalmic solution 1.25% were characterized in a subset of approximately 10% of all enrolled participants.

The following meetings were conducted under IND 122483 for this application:

- End of Phase 2 Meeting Minutes 11/30/18
- End of Phase 2 Response to PRO Information Request 11/21/18
- Pre-NDA Meeting 12/11/19
- Type C Meeting 7/21/20

3.3. Foreign Regulatory Actions and Marketing History

Pilocarpine is not approved in any country for presbyopia.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI was consulted and inspected 2 sites (Drs. David Wirta and Jennifer Kim). Based on the results of these inspections, OSI found the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

4.2. Product Quality

The CMC review has been completed. See CDTL review for complete findings.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

The Pharm/Tox review was finalized on 10/22/21. All nonclinical elements of the NDA were referenced from NDA 020237 (Salagen), literature references or through the conduct of the applicant's GLP studies.

For nonclinical systemic safety, pharmacology and drug metabolism, the Applicant references NDA 20-237 (Salagen). The Applicant also references Isopto carpine NDA 200-890. However, no nonclinical information was derived from NDA 200890. The Applicant provided all nonclinical ocular toxicity studies. The ocular toxicity studies performed by the Applicant used a combination (fixed or unfixed) of pilocarpine and oxymetazoline. (b) (4) No adverse toxicity was associated with the combination of pilocarpine/oxymetazoline and oxymetazoline

did not appear to influence the absorption or ocular distribution of pilocarpine when administered in combination. Formulations used in the nonclinical studies were identical or very similar to the to-be-marketed formulation in excipient content. Therefore, these studies should be adequate to assess risk of pilocarpine as monotherapy in the to-be-marketed formulation.

In conclusion, the Pharm/Tox review concluded that from the nonclinical pharmacology/toxicology discipline standpoint, NDA 214028 is approvable at the proposed dose indicated.

4.5. Clinical Pharmacology

The Clinical Pharmacology review team deemed that the systemic PK exposure of Pilocarpine HCl 1.25% ophthalmic solution had been well characterized in this NDA. The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 214028 and finds the application acceptable.

4.6. Devices and Companion Diagnostic Issues

Based on the Genus decision, the Agency determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. The Agency will now be regulating these products as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (dispenser). As the drug constituent part provides the PMOA, CDER has primary jurisdiction over these products.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name	Study Design	Test Product	Number of Subjects	Duration of Treatment
199201-007	Phase 2, multi-center, double-masked, randomized, 4-arm comparison, Vehicle controlled	Group 1 Oxy 0.125% followed by vehicle in the non-dominant eye, and vehicle alone in the dominant eye (15 patients) Group 2 Pilo 1.0% followed by vehicle in the non-dominant eye, and vehicle alone in the dominant eye (17 patients) Group 3 Concurrent use of oxy 0.125% followed by Pilo 1.0% in the non-dominant eye, and vehicle alone in the dominant eye (16 patients) Group 4 Concurrent use of oxy 0.125% followed by Pilo 1.0%, in OU (17 patients)	65	In-office, once-daily administration in each eye for 3 consecutive days, and then, following a 5 ± 2-day washout period, in-office administration BID in each eye for 3 consecutive days
199201-009	Phase 2, multi-center, double-masked, randomized, 4-arm comparison, vehicle controlled	Group 1 Oxymetazoline (0%, 0.0125%, 0.05%, or 0.125%) and pilocarpine 0% Group 2 Oxymetazoline (0%, 0.0125%, 0.05%, or 0.125%) and pilocarpine 0.5% Group 3 Oxymetazoline (0%, 0.0125%, 0.05%, or 0.125%) and pilocarpine 1% Group 4 Oxymetazoline (0%, 0.0125%, 0.05%, or 0.125%) and pilocarpine 1.5%	163 [2 participants discontinued prior to receiving any study treatment (1 each due to withdrawal of consent and loss to follow-up)]	Each dosing period was once daily for 2 consecutive days, followed by a 7-21 day washout before the next 2-day dosing period, until exit after the fifth 2-day dosing period

Study Name	Study Design	Test Product	Number of Subjects	Duration of Treatment
199201-010	Phase 2, multi-center, double-masked, randomized, parallel group, 5-arm comparison, vehicle controlled	Group 1 Vehicle control OU (28 patients) Group 2 Fixed combination oxy 0.0125% and pilo 0.5%, OU (30 patients) Group 3 Fixed combination oxy 0.05% and pilo 1.0%, OU (30 patients) Group 4 Fixed combination oxy 0.125% and pilo 1.5%, OU (32 patients) Group 5 Fixed combination oxy 0.125% and pilo 1.5%, non-dominant eye and vehicle to the dominant eye (31 patients)	151	Each of the 5 groups had 28 ± 3 days of dosing followed by a 14 ± 2-day follow-up period
1883-301-013	Phase 3, multi-center, double-masked, randomized, parallel group, vehicle controlled	Vehicle control (159 patients) Pilo HCl 1.25% (163 patients)	322	Each of the 2 groups (Pilo HCl 1.25% and vehicle) had 30 ± 3 days of once daily dosing in each eye
1883-302-013	Phase 3, multi-center, double-masked, randomized, parallel group, vehicle controlled	Vehicle control (215 patients) Pilo HCl 1.25% (212 patients)	427	Each of the 2 groups (Pilo HCl 1.25% and vehicle) had 30 ± 3 days of once daily dosing in each eye

5.2. Review Strategy

The sources of clinical data utilized in this review include the studies listed in Section 5.1. The two studies which provide the main support for safety and efficacy were:
Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013)

6.1.1. Study Design

Gemini 1 (1883-301-013): A Phase 3, Multicenter, Double-masked, Randomized, Vehicle-controlled, Parallel-group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

Primary Objective
The objectives of this study were to evaluate the efficacy, safety, tolerability, and pharmacokinetics of AGN-190584 (pilocarpine ophthalmic solution) 1.25% when administered bilaterally, once daily for 30 days in participants with presbyopia.

Trial Design
This was a multicenter, double-masked, randomized, parallel-group, vehicle-controlled, Phase 3 study in participants with presbyopia. Participants received AGN-190584 1.25% or vehicle dosed once daily, bilaterally, for 30 days. Approximately 300 participants with presbyopia were to be enrolled at approximately 50 sites in the US. Approximately 150 participants per group were to be enrolled to achieve at least 135 participants per group completing the study.

Participants were randomized in a 1:1 ratio into 1 of the 2 study groups (AGN-190584 or vehicle). This randomization was stratified by age (2 groups: ≤ 50 years and > 50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusive, and worse than 20/60), iris color (brown and non-brown), and emmetrope status (emmetropes and non-emmetropes). A maximum of 50% (75 per arm) of the participants enrolled were to have brown iris color, and a maximum of 25% (38 per arm) of the participants were to be non-emmetropes (a sphere outside of -0.50 D to +0.75D and/or a cylinder greater than 0.75 D). This study consisted of the following visits: screening, Day 1 (baseline), and Days 3, 7, 14, and 30/early exit.

Figure 1-1 Study Schema

Source: CSR Protocol Number: 1883-301-013, Appendix 16.1.1

Inclusion Criteria

- Participant must be 40 to 55 years of age inclusive, at the time of the screening visit
- In good general health at the screening visit, as determined by the investigator
- Subjective complaints of poor near vision that impact activities of daily living, as defined by at least a moderate impact (score ≥ 3) on at least 1 question on NEI VFQ-25 Questions 5 to 7 in the main questionnaire and Near Vision Subscale, Questions A3 to A5 in the Appendix of Optional Additional Questions at the screening visit
- Emmetropes or non-emmetropes with best distance correction in the range of spherical -4.00 D to +1.00 D inclusively and cylinder ≤ ±2.00 D with photopic, high contrast CDVA of 20/25 or better in each eye at the screening and baseline visits
- Photopic, high contrast CDVA of 20/32 or better in each eye by habitual mono-focal correction (either spectacles or contact lenses), or willing to wear new mono-focal correction spectacles to achieve photopic, high contrast CDVA of 20/32 or better during the study
- Mesopic, high contrast DCNVA of 20/40 (J3) to 20/100 (J10) in each eye 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 and baseline visits
- Mesopic pupil diameter < 8.0 mm in both eyes at the screening visit
- Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
- Written informed consent from the participant or a legally authorized representative has been obtained prior to any study-related procedures
- Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (i.e., Written Authorization for Use and Release of Health and Research Study Information for the US)
- Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

Exclusion Criteria

- Uncontrolled systemic disease
- Clinically significant disease state, in the opinion of the examining investigator or designee, in any body system
- Any clinical condition or previous surgery that might affect the absorption, distribution, biotransformation, or excretion of AGN-190584. History of cataract surgery, phakic intraocular lens surgery, corneal inlay surgery, radial keratotomy, or any intraocular surgery. However, participants with history of PRK or LASIK with CDVA meeting inclusion criteria will be allowed to enroll.
- Known allergy or sensitivity to the study intervention or its components or other cholinergic agonist medications
- Concurrent use of any topical ophthalmic medications, including artificial tears, other than the study intervention during the course of the study
- Concurrent use of temporary or permanent punctal plugs or history of punctal cautery in one or both eyes
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
- Participation in a blood or plasma donation program within 30 days prior to study intervention administration
- Presence of any ocular condition that, in the opinion of the investigator, could affect the safety of the participant or interpretation of efficacy parameters (i.e., uveitis, retinal detachment)
- 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. Participants willing to wear study-provided monofocal correction (either spectacles or contact lenses) during the study can be enrolled
- Abnormal and clinically significant results according to the investigator or designee, on physical/ophthalmic examination or medical history

- Females who are pregnant, nursing, or planning a pregnancy during the study. WOCBP or males with partners of childbearing potential and do not agree to use reliable contraception during the study.
- The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.

Treatments Administered

The study interventions used in this study were AGN-190584 or its vehicle, dosed at 1 drop in each eye once daily. Participants were instructed not to instill study intervention on the visit days. Study intervention was to be instilled bilaterally by designated site personnel at Hour 0 (8 AM ± 1 hour) of Visits 1 to 5. Between office visits, participants were instructed to instill 1 drop of the dispensed study intervention in the morning once daily into both eyes.

Investigational Product

Study Intervention Name	AGN-190584	Vehicle
Dosage Formulation	Topical eye drop	Topical eye drop
Identity of Formulation	Pilocarpine HCl 1.25% Ophthalmic Solution Lot 98279 Manufactured at Allergan Waco	Pilocarpine HCl Placebo Ophthalmic Solution Lot 98273 Manufactured at Allergan Waco
Drug Substance	Pilocarpine 1.25%	Not applicable
Route of Administration	Topical eye drop	Topical eye drop
Dosing Instructions	1 drop in each eye once daily	1 drop in each eye once daily
Packaging and Labeling	Study intervention will be provided in sterile, 5 mL bottles. Each bottle will be labeled as required per country requirement. An investigational caution label will appear on the individual bottle and the outer carton: Use as directed per protocol Keep Out of Reach of Children Caution: New Drug--Limited by Federal (or United States) law to investigational use	Study intervention will be provided in sterile, 5 mL bottles. Each bottle will be labeled as required per country requirement. An investigational caution label will appear on the individual bottle and the outer carton: Use as directed per protocol Keep Out of Reach of Children Caution: New Drug--Limited by Federal (or United States) law to investigational use
Manufacturer	Allergan Sales, LLC.	Allergan Sales, LLC.
Number and Timing of Interventions	1 drop bilaterally, once daily	1 drop bilaterally, once daily
Volume Per Intervention	(b)(4) mL per bottle	(b)(4) mL per bottle

Source: CSR Protocol Number: 1883-301-013, Appendix 16.1.1

Study Flow Chart

Schedule of Visits and Procedures: Screening to Visit 3

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

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

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

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

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

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

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

Source: CSR Protocol Number: 1883-301-013, Appendix 16.1.1

List of Investigators

Gemini 1 (1883-301-013)

Site Number	Principal Investigator Name and Address	Number of Subjects Randomized
005	Gary W. Jerkins, MD 4306 Harding Pike, Suite 206B Nashville, TN 37205	16
008	Francis W. Price, Jr., MD 9002 North Meridian Street, Suite 100 Indianapolis, IN 46260	14
009	Edward Raymond Rashid, MD 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	12
014	David L. Wirta, MD 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	45
018	Majid Moshirfar, MD 11820 South State Street, Suite 100 Draper, UT 84020	12
019	Vincent Restivo. Jr. MD 11901 West Parmer Lane, Suite 400 Cedar Park, TX 78613	16
021	Jeffrey Whitman, MD 11442 North Central Expressway Dallas, TX 75243	5
022	Michael J. Depenbusch, MD 1500 West Ray Road Chandler, AZ 85224	11

025	Joseph Tauber, MD 4400 Broadway Street, Suite 202 Kansas City, MO 64111	3
026	Matthew D. Paul MD 69 Sand Pit Road, Suite 101 Danbury, CT 06810	6
031	Paul J. Hartman, MD 2100 South Clinton Avenue Rochester, NY 14618	13
035	John C. Meyer, MD 1536 Story Avenue Louisville, KY 40206	10
038	William C. Christie, MD 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066	21
040	Christopher Lievens, OD 1245 Madison Avenue Memphis, TN 38104	9
046	Vrinda Hershberger, MD, PhD 502 East New Haven Avenue Melbourne, FL 32901	4
049	Gregory Douglas Parkhurst, MD 9725 Datapoint Drive, Suite 200 San Antonio, TX 78229	7
053	David Alan Davis, MD 6385 Corporate Drive, Suite 307 Colorado Springs, CO 80919	9
061	Satish Modi, MD, CPI 23 Davis Avenue Poughkeepsie, NY 12603	3
062	Terrence S. Spencer, MD 2800 Third Street Rapid City, SD 57701	4
066	Cathleen McCabe, MD 6002 Pointe West Boulevard Bradenton, FL 34209	5
071	Jay L. Schwartz, DO 8416 East Shea Boulevard, Suite C-101 Scottsdale, AZ 85260	2
083	Komal Bharat Desai, MD 11261 Nall Avenue Leawood, KS 66211	6
088	Joseph Martel, MD 11216 Trinity River Drive Rancho Cordova, CA 95670	8
091	Inna Ozerov, MD 7261 Sheridan Street, Suite 100B, Suite 210 Hollywood, FL 33024	7

093	Ramesh Ayyala, MD 12901 Bruce B Downs Boulevard, MDC21 Tampa, FL 33612	2
098	Jason R. Miller, OD 9711 Sawmill Parkway, Unit C Powell, OH 43065	10
105	Kerry K. Assil, MD 450 North Roxbury Drive Floor 3 Beverly Hills, CA 90210	2
113	Eugene E. Protzko, MD 2023 Pulaski Highway Havre de Grace, MD 21078	13
119	Patricia B. Sierra, MD 1515 River Park Drive, Suite 100 Sacramento, CA 95815	3
123	Vance Thompson, MD 3101 West 57th Street Sioux Falls, SD 57108	3
124	Andrew Jennings Hendershot, MD 915 Olentangy River Road, Suite 5000 Columbus, OH 43212	2
125	Rodrigo Belalcazar- Ardila, MD 425 West 51 Place Hialeah, FL 33012	14
130	Bruce Segal, MD 5258 Linton Boulevard, Suite 302-Suite 301A Delray Beach, FL 33484	14
133	Thomas K. Mundorf, MD 1718 East Fourth Street, Suite 908 Charlotte, NC 28204	1
135	Steven Mansberger, MD 1040 Northwest 22nd Avenue, Suite 200 Portland, OR 97210	10
139	Jeffrey Sage DO 1127 Wilshire Boulevard, Suites 300, 1206, 1600 Los Angeles, CA 90017	1

Study Endpoints

Primary Efficacy Endpoint

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

Key Secondary Efficacy Endpoint

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

Secondary Efficacy Endpoints

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

Statistical Analysis Plan

Analysis Populations
The following 2 populations were utilized for statistical analyses:

- The ITT population consisted of all randomized participants. Analyses using the ITT population was based on the study intervention assigned.
- The safety population consisted of all participants who received at least 1 administration of study intervention. The analyses using the safety population were based on the actual study intervention received.

Efficacy endpoints were analyzed using the ITT population and safety endpoints were analyzed using the safety population.

Primary Efficacy Analysis
The primary efficacy endpoint was the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 3. The primary efficacy endpoint was analyzed using a chi-square test with a 2-sided 95% confidence interval (CI); missing data was imputed as 3-line gain failure.

Gemini 2 (1883-301-302): A Phase 3, Multicenter, Double-masked, Randomized, Vehicle-controlled, Parallel-group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

Primary Objective
The objectives of this study were to evaluate the efficacy, safety, and tolerability of AGN-190584 1.25% when administered bilaterally, once daily for 30 days in participants with presbyopia.

Trial Design
This was a multicenter, double-masked, randomized, parallel-group, vehicle-controlled, Phase 3 study in participants with presbyopia. Participants received AGN-190584 1.25% or vehicle dosed once daily, bilaterally, for 30 days. Approximately 400 participants with presbyopia were to be enrolled at approximately 50 sites in the United States. Approximately 200 participants per group were to be enrolled.

Participants were randomized in a 1:1 ratio into 1 of the 2 study groups (AGN-190584 or vehicle). This randomization was stratified by age (2 groups: ≤ 50 years and > 50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusive, and worse than 20/60), iris color (brown and non-brown), and emmetrope status (emmetropes and non-emmetropes). A maximum of 50% (100 per arm) of the participants enrolled were to have brown iris color, and a maximum of 25% (50 per arm) of the participants were to be non-emmetropes (a sphere outside of -0.50 D to +0.75 D and/or a cylinder greater than 0.75 D).

Inclusion/Exclusion Criteria
Essentially identical to Gemini 1.

Treatments Administered
Identical to Gemini 1.

Investigational Product
Identical to Gemini 1.

Study Flow Chart

Schedule of Visits and Procedures: Screening to Visit 3

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

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

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

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

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

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

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

Source: CSR Protocol Number: 1883-302-013, Appendix 16.1.1

List of Investigators

Gemini 2 (Study 1883-302-013)

Site Number	Principal Investigator Name and Address	Number of Subjects Randomized
001	Keith C. Charles, MD 17560 US Highway 441 Mount Dora, FL 32757	5
002	Jennifer L. Kim, MD 1000 Corporate Center Drive, Suite 100 Morrow, GA 30260	15
003	Sherif El-Harazi, MD, MPH 1510 South Central Avenue, Suite 300 Glendale, CA 91204	29
004	Milton M. Hom, OD 822 East Alosta Avenue #A Azusa, CA 91702	14
007	Eugene B. McLaurin, MD, FACS 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	75
011	Steven M. Silverstein, MD 4240 Blue Ridge Boulevard, Suite 1000 Kansas City, MO 64133	6
012	Robert John Smyth-Medina, MD 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	20
013	Navin Tekwani, MD 9911 Kennerly Road St. Louis, MO 63128	6

014	David L. Wirta, MD 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	45
015	Gustavo Corrales, MD 410 South Washington Street Falls Church, VA 22046	4
017	Kenneth Olander, MD, PhD 622 Smithview Drive Maryville, TN 37803	8
029	Steven Mortenson, MD 3192 Willow Creek Road Prescott, AZ 86301	7
030	Frank Anthony Bucci, MD 158 Wilkes-Barre Township Boulevard Wilkes-Barre, PA 18702	3
032	Mitchell A. Jackson, MD 300 North Milwaukee Avenue, Suite L Lake Villa, IL 60046	10
033	Bradley R. Kwapiszeski, MD 8800 West 75th Street, Suite 140/141 Shawnee Mission, KS 66204	4
036	Sebastian Heersink, MD 2800 Ross Clark Circle Dothan, AL 36301	3
039	Benjamin Travis Dastrup, MD 875 Country Hills Drive Ogden, UT 84403	10
051	Thomas R. Walters, MD 5717 Balcones Drive Austin, TX 78731	28
055	Peter DeBry, MD 7190 Smoke Ranch Road, Suite 110 Las Vegas, NV 89128	7
060	Gerald Walman, MD 10615 West Thunderbird Boulevard, Suite D180 Sun City, AZ 85351	13
069	Thomas Hunter Newsom, MD 4211 US Highway 27 North Sebring, FL 33870	3
073	S. Lance Forstot, MD 838l SouthPark Lane Littleton, CO 80120	13
079	Edward Holland, MD 10794 Saunders Lane Union, KY 41091	8
082	Anthony J. Verachtert, OD 5151 North West 88th Street Kansas City, MO 64154	7

092	Nicole R. Fram, MD 2080 Century Park East, Suite 911 Los Angeles, CA 90067	3
094	Amel Youssef, OD 1012 East Sahara Avenue Las Vegas, NV 89104	10
097	Shane R. Kannarr, OD 2521 North Broadway Pittsburg, KS 66762	14
099	Jerry G. Hu, MD 1872 Norwood Drive, Number 200 Hurst, TX 76054	9
109	Benjamin Knox Lambright, MD 6122 West Corporate Oaks Drive Crystal River, FL 34429	13
102	George O. Waring IV, MD 735 Johnnie Dodds Boulevard, Suite 101 Mount Pleasant, SC 29464	1
131	Louis M. Alpern, MD 4171 North Mesa Street, Building D100 El Paso, TX 79902	15
143	Y. Ralph Chu, MD 9117 Lyndale Avenue South Bloomington, MN 55420	7
147	James A. Katz, MD 8901 West Golf Road, Suite 300 Des Plaines, IL 60016	2
158	Frank W. Bowden, III, MD, FACS 7205 Bonneval Road Jacksonville, FL 32256	2
159	Scott Howard Schecter, OD 2900 West Cypress Creek Road, Suite 1 Fort Lauderdale, FL 33309	8

Study Endpoints

Primary Efficacy Endpoint

- Proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA, without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction, at Day 30, Hour 3

Key Secondary Efficacy Endpoint

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

Secondary Efficacy Endpoints

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

Statistical Analysis Plan

The primary efficacy endpoint was the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA, without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction, at Day 30, Hour 3. The primary efficacy endpoint was analyzed using a chi-square test with a 2-sided 95% CI; missing data were imputed as 3-line gain failure. The key secondary efficacy endpoint was analyzed in the same fashion as the primary efficacy endpoint.

The following 2 populations were utilized for statistical analyses:

- The ITT population consisted of all randomized participants. Analyses using the ITT population were based on the study intervention assigned.

- The safety population consisted of all participants who received at least 1 administration of study intervention. The analyses using the safety population were based on the actual study intervention received.

Efficacy endpoints were analyzed using the ITT population; at 1 study site (Site 051), DCNVA measurements were not conducted correctly at the screening and baseline visits, and all participants from this site were excluded from efficacy analyses. Safety endpoints were analyzed using the safety population.

6.1.2. Study Results

Compliance with Good Clinical Practices

Gemini 1(1883-301-013)
This study was conducted in compliance with GCP and is registered at clinicaltrials.gov, registration # NCT03804268.

Gemini 2 (1883-302-013)
This study was conducted in compliance with GCP and is registered at clinicaltrials.gov, registration #NCT03857542.

Analysis Populations

Gemini 1 (1883-301-013): Analysis Populations

	Vehicle	AGN-190584
ITT	160	163
Safety	159	163

Gemini 2 (1883-302-013): Analysis Populations

	Vehicle	AGN-190584
ITT	215	212
Safety	215	212

Patient Disposition

Gemini 1(1883-301-013): Patient Disposition

	Vehicle N=160	AGN-190584 N=163
Number of Patients Randomized	160	163
Number of Patients Treated	159	163
Number of Patients Completed Study	153	161
Number of Patients Discontinued From Study	7	2
Reasons for Discontinuation		
AE	2	2
Lack of Efficacy	0	0
Withdrawal by Subject	2	0
Lost to F/U	1	0
Physician Decision	2	0

Gemini 2 (1883-302-013): Patient Disposition

	Vehicle N=215	AGN-190584 N=212
Number of Patients Randomized	215	212
Number of Patients Treated	215	212
Number of Patients Completed Study	209	207
Number of Patients Discontinued From Study	6	5
Reasons for Discontinuation		
AE	1	3
Lack of Efficacy	0	0
Withdrawal by Subject	2	1
Lost to F/U	2	1
Physician Decision	0	0
Other	1	0

Protocol Violations/Deviations

Gemini 1(1883-301-013): Protocol Deviations

	Vehicle N=160	AGN-190584 N=163
Overall	2	1
Inclusion Criteria	1	0
Prohibited Concomitant Medication	1	0
Study Procedure	0	1

Reviewer's Comment:
A total of 3 participants (0.9%) had protocol deviations during the study (1/163 [0.6%] in the AGN-190584 group and 2/160 [1.3%] in the vehicle group). In the AGN-190584 group, the significant deviation was due to study procedure. In the vehicle group, the significant deviations were due to inclusion criteria and prohibited concomitant medication.

Gemini 2 (1883-302-013): Protocol Deviations

	Vehicle N=215	AGN-190584 N=212
Overall	3	0
Inclusion Criteria	2	0
Prohibited Concomitant Medication	1	0

Reviewer's Comment:
A total of 3 participants (0.7%) in the vehicle group had significant protocol deviations during the study, which were: inclusion criteria (2 participants: both did not meet criterion 2.05 requiring that participants have mesopic, high-contrast DCNVA of 20/40 to 20/100 in each eye at the screening and baseline visits) and prohibited concomitant medication (1 participant: dicyclomine and dicycloverine).

Table of Demographic Characteristics
Gemini 1 (1883-301-013): Demographics

	Vehicle N=160	AGN-190584 N=163
Age		
Mean (sd)	49.7 (3.2)	49.5 (3.8)
Min, Max	41, 55	40, 55
Age<=50	93	92
Age>50	67	71
Sex		
Male	38	50
Female	122	113
Race		
White	144	148
African American	12	13
Asian	1	2
American Indian	2	0
Other	1	0
Ethnicity		
Hispanic or Latino	26	31
Not Hispanic or Latino	134	132

Gemini 2 (1883-302-013): Demographics

	Vehicle N=215	AGN-190584 N=212
Age		
Mean (sd)	49.9 (3.5)	49.6 (3.7)
Min, Max	40, 55	40, 55
Age<=50	116	115
Age>50	99	97
Sex		
Male	53	74

Female	162	138
Race		
White	176	171
African American	29	35
Asian	8	5
American Indian	2	1
Other	0	0
Ethnicity		
Hispanic or Latino	41	37
Not Hispanic or Latino	174	175

Other Baseline Characteristics (i.e.. disease characteristics, important concomitant drugs)

Gemini 1(1883-301-013): Baseline Characteristics

	Vehicle N=160	AGN-190584 N=163
Mesopic, High-contrast, Binocular DCNVA		
20/40 to 20/60	62	66
Worse than 20/60	98	97
Iris Color		
Brown	77	78
Non-Brown	83	85
Emmetrope Status		
Emmetrope	123	125
Non-Emmetrope	37	38

Gemini 2 (1883-302-013): Baseline Characteristics

	Vehicle N=215	AGN-190584 N=212
Mesopic, High-contrast, Binocular DCNVA		
20/40 to 20/60	105	103

Worse than 20/60	110	109
Iris Color		
Brown	104	107
Non-Brown	111	105
Emmetrope Status		
Emmetrope	161	161
Non-Emmetrope	54	51

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
On visit days, study intervention was administered by designated site personnel. On these days, compliance was considered 100%. Between office visits, the participants in the study self-dosed and compliance was monitored via consistent reminders and questioning participants at study visits regarding at-home dosing.

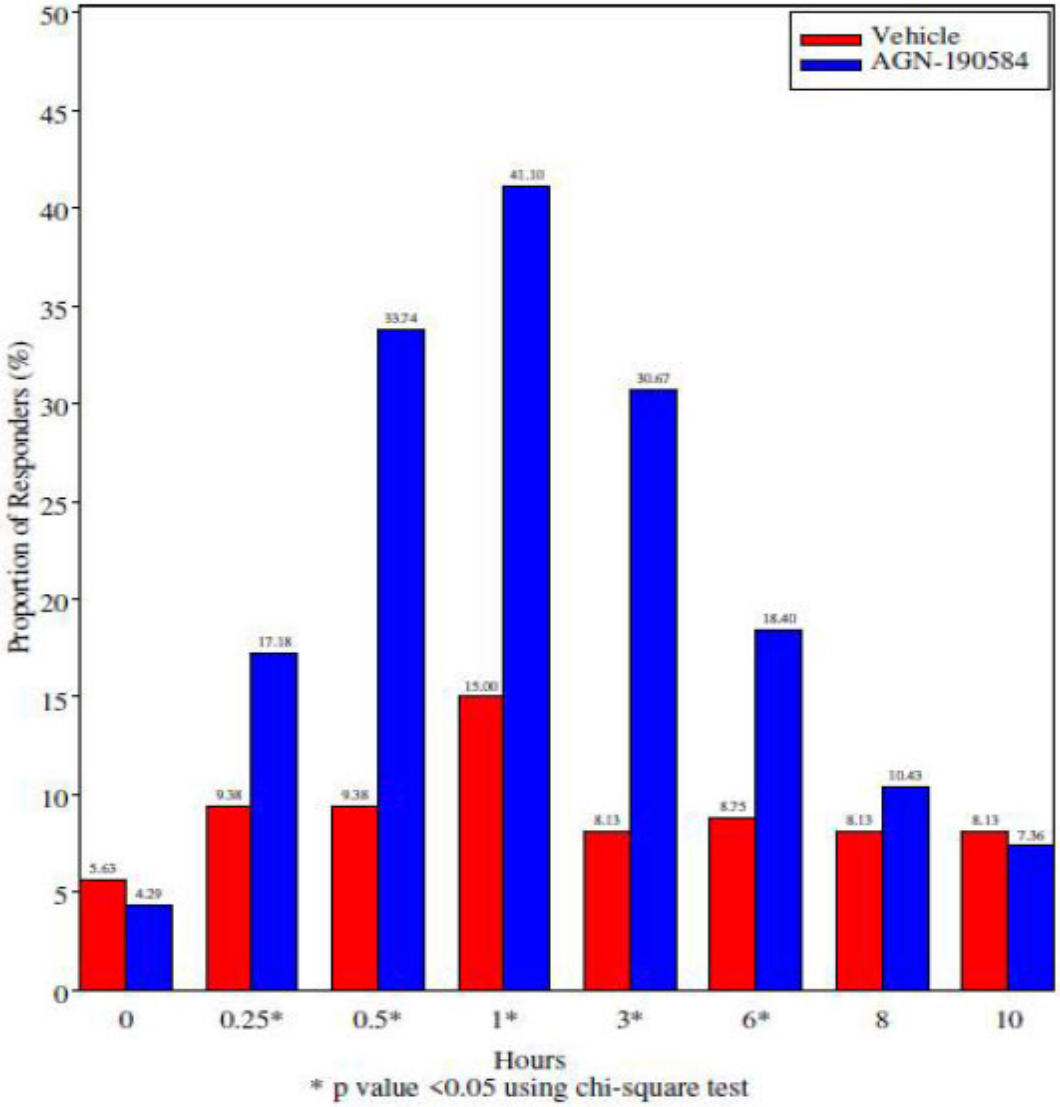
Efficacy Results – Primary Endpoint

Gemini 1 (1883-301-013)
The primary efficacy endpoint was the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 3. The primary efficacy endpoint was analyzed using a chi-square test with a 2-sided 95% confidence interval (CI); missing data was imputed as 3-line gain failure.

Gemini 1(1883-301-013): Mesopic, High Contrast, Binocular DCNVA: Analysis of Participants With 3-Line Improvement (ITT Population)

	Vehicle N=160	AGN-190584 N=163
Day 1, 0.25 Hour		
Responder Rate	5/159 (3.1%)	11/161 (6.8%)
Difference %		3.7%
95% CI		(-1.1, 8.4)
P-value		0.1302
Day 30, 3 Hour		
Responder Rate	13/153 (8.5%)	50/163 (30.7%)
Difference %		22.5%
95% CI		(14.3, 30.8)
P-value		<0.0001

Figure 11-1 **Proportion of Participants with at Least Three Line Improvement from Baseline at Day 30: Mesopic, High-contrast, Binocular DCNVA (ITT Population)**



Source: Figure 14.2-5.3

Reviewer's Comment:

At Day 30, Hour 3, the proportion of participants with a 3-line, mesopic DCNVA improvement was 30.7% (50/163) in the AGN-190584 group compared with 8.1% (13/160) in the vehicle group. The percent rate difference between groups (95% CI) of 22.5% (14.3, 30.8) was statistically significant (p < 0.0001) in favor of the AGN-190584 group.

Post-hoc analysis

An additional analysis of the primary efficacy endpoint was performed with the added criterion that participants did not lose more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3.

At Day 30, Hour 3, the proportion of participants that achieved a 3-line, mesopic DCNVA improvement without losing more than 5 letters of CDVA with the same refractive correction was 30.7% (50/163) in the AGN-190594 group compared with 8.1% (13/160) in the vehicle group. The percent rate difference between groups (95% CI) of 22.5% (14.3, 30.8) was statistically significant ($p < 0.0001$) in favor of the AGN-190584 group.

Reviewer's Comment:

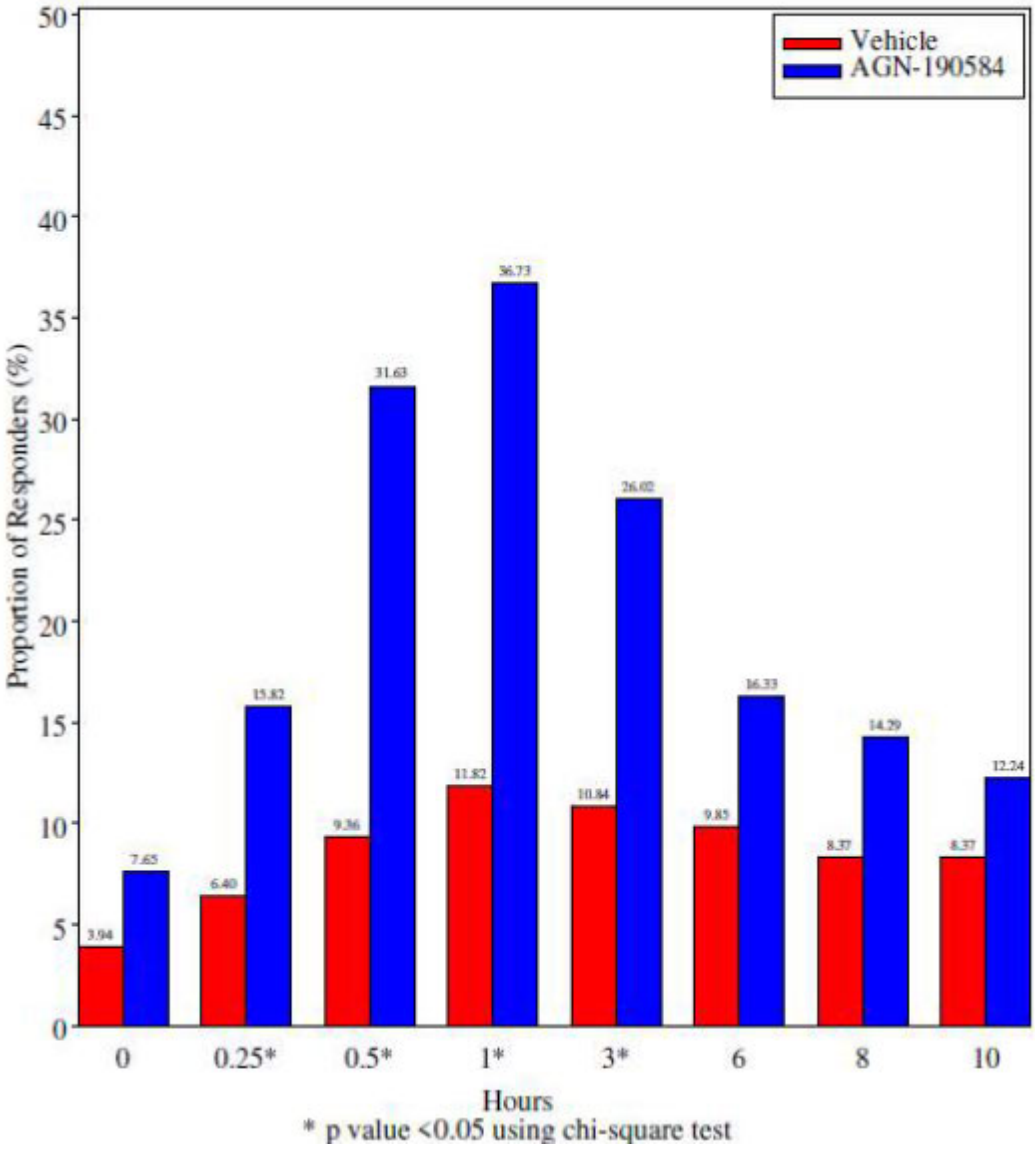
This post-hoc analysis demonstrated an identical outcome to the primary efficacy analysis.

Gemini 2 (1883-302-013)

Gemini 2 (1883-302-013): Mesopic, High Contrast, Binocular DCNVA: Analysis Of Participants With 3-Line Improvement in DCNVA Without Losing More Than 5 Letters of CDVA (ITT Population)

	Vehicle N=215	AGN-190584 N=212
Day 1, 0.25 Hour		
Responder Rate	3/203 (1.5%)	10/196 (5.1%)
Difference %		3.6%
95% CI		0.1, 7.1
P-value		0.0415
Day 30, 3 Hour		
Responder Rate	22/198 (10.8%)	51/196 (26.0%)
Difference %		15.2%
95% CI		7.7, 22.7
P-value		<0.0001

Figure 11-1 **Proportion of Participants with at Least 3-line Improvement from Baseline at Day 30: Mesopic, High-contrast, Binocular DCNVA (ITT Population)**



Reviewer's Comment:

At Day 30, Hour 3, the proportion of participants with a 3-line, mesopic DCNVA improvement without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction was 26.0% (51/196) in the AGN-190584 group compared with 10.8% (22/203) in the vehicle group. The percent rate difference between groups (95% CI) of 15.2% (7.7, 22.7) was statistically significant (p < 0.0001) in favor of the AGN-190584 group.

Data Quality and Integrity
No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Key Secondary Endpoint
The key secondary efficacy endpoint was the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6.

Gemini 1(1883-301-013): Mesopic, High Contrast, Binocular DCNVA: Analysis of Participants With 3-Line Improvement (ITT Population)

	Vehicle N=160	AGN-190584 N=163
Day 1, 0.25 Hour		
Responder Rate	5/159 (3.1%)	11/161 (6.8%)
Difference %		3.7%
95% CI		(-1.1, 8.4)
P-value		0.1302
Day 30, 6 Hour		
Responder Rate	14/153 (8.8%)	30/163 (18.4%)
Difference %		9.7%
95% CI		(2.3, 17.0)
P-value		0.0114

Gemini 2 (1883-302-013): Mesopic, High Contrast, Binocular DCNVA: Analysis of Participants With 3-Line Improvement (ITT Population)

	Vehicle N=215	AGN-190584 N=212
Day 1, 0.25 Hour		
Responder Rate	3/203 (1.5%)	10/196 (5.1%)
Difference %		3.6%
95% CI		0.1, 7.1
P-value		0.0415
Day 30, 6 Hour		
Responder Rate	20/197 (10.2%)	32/192 (16.7%)
Difference %		6.5%
95% CI		-0.1, 13.1
P-value		0.0548

Reviewer's Comment:
In Gemini 1, At Day 30, Hour 6, the proportion of participants with a 3-line, mesopic DCNVA improvement was 18.4% (30/163) in the AGN-190584 group compared with 8.8% (14/160) in the vehicle group. The percent rate difference between groups (95% CI) of 9.7% (2.3, 17.0) was statistically significant (p = 0.0114) in favor of the AGN-190584 group.

In Gemini 2, analysis of the key secondary efficacy endpoint (proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6) did not achieve statistical significance.

Dose/Dose Response
Not applicable.

Durability/Persistence of Response

Gemini 1(1883-301-013): Mesopic, High Contrast, Binocular DCNVA: Analysis Of Participants With 3-Line Improvement (ITT Population)

	Vehicle N=160	AGN-190584 N=163
Day 30, 0 Hour		
Responder Rate	9/153	7/161
Difference %		-1.5
95% CI		(-6.4, 3.3)
P-value		0.5365
Day 30, 0.25 Hour		
Responder Rate	15/153	28/158
Difference %		7.9
95% CI		(0.3, 15.5)
P-value		0.0431
Day 30, 0.5 Hour		
Responder Rate	15/153	55/158
Difference %		25.0
95% CI		(16.2, 33.8)
P-value		<0.0001
Day 30, 1 Hour		
Responder Rate	24/153	67/161
Difference %		25.9

95% CI		(16.4, 35.5)
P-value		<0.0001
Day 30, 3 Hour		
Responder Rate	13//153	50/163
Difference %		22.5
95% CI		(14.3, 30.8)
P-value		<0.0001
Day 30, 6 Hour		
Responder Rate	14/153	30/161
Difference %		9.7
95% CI		(2.3, 17.0)
P-value		0.0114
Day 30, 8 Hour		
Responder Rate	13/153	17/161
Difference %		2.1
95% CI		(-4.4, 8.5)
P-value		1.0000
Day 30, 10 Hour		
Responder Rate	13/152	12/160
Difference %		-1.1
95% CI		(-7.1, 5.0)
P-value		1.0000

Reviewer's Comment:
At Day 30 the treatment effect seems to peak at 0.5 hour, 1 hour, and 3 hour timepoints. By Hour 6 there is definitely a decrease in treatment effect, and at the 8 Hour and 10 Hour timepoints there is definitely no effect of the drug.

Gemini 2 (1883-302-013): Mesopic, High Contrast, Binocular DCNVA: Analysis Of Participants With 3-Line Improvement (ITT Population)

	Vehicle N=215	AGN-190584 N=212
Day 30, 0 Hour		
Responder Rate	8/199	15/193
Difference %		4.0
95% CI		(-1.7, 9.8)
P-value		0.1653
Day 30, 0.25 Hour		
Responder Rate	13/196	31/193
Difference %		9.4
95% CI		(3.2, 15.7)
P-value		0.0033
Day 30, 0.5 Hour		
Responder Rate	19/197	62/193
Difference %		22.5
95% CI		(14.7, 30.3)
P-value		<0.0001
Day 30, 1 Hour		
Responder Rate	24/198	72/193
Difference %		25.2
95% CI		(17.0, 33.4)
P-value		<0.0001
Day 30, 3 Hour		
Responder Rate	22/198	54/193
Difference %		16.7
95% CI		(9.1, 24.3)
P-value		<0.0001
Day 30, 6 Hour		
Responder Rate	20/197	32/192
Difference %		6.5
95% CI		(-.01, 13.1)
P-value		0.0548

Day 30, 8 Hour		
Responder Rate	17/197	28/193
Difference %		5.9
95% CI		(-0.5, 12.2)
P-value		0.0693
Day 30, 10 Hour		
Responder Rate	17/195	24/191
Difference %		3.8
95% CI		(-2.3, 10.1)
P-value		0.2200

Reviewer's Comment:
Gemini 2 shows similar treatment effects at Day 30. At Day 30 the treatment effect seems to peak at 0.5 hour, 1 hour, and 3 hour timepoints. By Hour 6 there is definitely a decrease in treatment effect, and at the 8 Hour and 10 Hour timepoints there is definitely no effect of the drug.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Studies Gemini 1 and Gemini 2, demonstrated efficacy in their primary endpoints, i.e., the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3.

7.1.2. Secondary and Other Endpoints

See Section 6.1.2.

7.1.3. Subpopulations

Subgroup analyses for mesopic, high-contrast, binocular DCNVA at Day 30, Hour 3 (primary efficacy endpoint) and Hour 6 (key secondary efficacy endpoint) included age group (≤ 50 and > 50 years), baseline binocular DCNVA (20/40 to 20/60, inclusive, and worse than 20/60), iris color (brown and nonbrown), and emmetrope status (emmetropes and non-emmetropes).

Gemini 1

Age subgroup analyses (≤ 50 and > 50 years) showed that the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within both age subgroups at Day 30, Hours 3 and 6.

Baseline DCNVA subgroup analyses (20/40 to 20/60 and worse than 20/60) showed the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within both baseline DCNVA subgroups at Day 30, Hours 3 and 6.

Iris color (brown and nonbrown) subgroup analyses of the primary and key secondary efficacy endpoints showed the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within both iris color subgroups at Day 30, Hours 3 and 6.

Emmetrope status (emmetrope and non-emmetrope) subgroup analyses showed the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within the emmetropes and non-emmetrope subgroups at Day 30, Hours 3 and 6.

Gemini 2

Age subgroup analyses (≤ 50 and > 50 years) for the primary and key secondary efficacy endpoints demonstrated that the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within both age subgroups at Day 30, Hour 3 (without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction) and Hour 6. In addition, within the AGN-190584 group, both subgroups showed a similar percentage of 3-line responders at Day 30, Hours 3 and 6.

Baseline DCNVA subgroup analyses (20/40 to 20/60 and worse than 20/60) of the primary and key secondary efficacy endpoints demonstrated that the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within both baseline DCNVA subgroups at Day 30, Hour 3 (without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction) and Hour 6. In addition, within the AGN-190584 group, both subgroups showed a similar percentage of 3-line responders at Day 30, Hours 3 and 6.

Iris color (brown and nonbrown) subgroup analyses of the primary and key secondary efficacy endpoints demonstrated that the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within both iris color subgroups at Day 30, Hour 3 (without losing more than 5 letters of mesopic, high-contrast,

binocular CDVA with the same refractive correction) and Hour 6. In addition, within the AGN-190584 group, both subgroups showed evidence of efficacy at Day 30, Hours 3 and 6, and the proportion of responders was higher in the brown iris color subgroup, compared with the nonbrown subgroup, at both of these timepoints.

Emmetrope status (emmetrope and non-emmetrope) subgroup analyses of the primary and key secondary efficacy endpoints demonstrated that the proportion of participants in the AGN-190584 group with a 3-line, mesopic DCNVA improvement was numerically greater than vehicle within the emmetrope and non-emmetrope subgroups at Day 30, Hour 3 (without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction) and Hour 6. In addition, within the AGN-190584 group, both subgroups showed broadly similar evidence of efficacy at Day 30, Hours 3 and 6.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 6.1.2.

7.2. Integrated Assessment of Effectiveness

The data contained in this submission establishes the efficacy of pilocarpine ophthalmic solution 1.25% dosed OU QD for the treatment of presbyopia in adults.

8. Review of Safety

8.1. Safety Review Approach

The two studies which provide the main support for safety and efficacy were: Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013).

In addition, on 6/16/21 (SDN-7) at 120 day Safety Update was submitted. Since the initial submission, there have been no follow-up reports received during the 120-day safety reporting period for any of the completed studies. In addition, there are no new safety data from the completed clinical studies evaluating Pilocarpine HCl 1.25% and there are no ongoing clinical trials. Therefore, this safety update discusses clinical and nonclinical literature relevant to the safety of pilocarpine, covering the time period from 8/22/20-3/31/21 based on a literature review of pilocarpine. No new clinically significant safety information relevant to the use of

pilocarpine was identified from this literature review, and the reported safety information is consistent with the information presented in the original NDA.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Gemini 1 (1883-301-013): Extent of Exposure (Safety Population)

	Vehicle N=159	AGN-190584 N=163
Treatment Duration (Days)		
>= 7 Days	155	161
>= 14 Days	153	161
>= 21 Days	153	161
>= 28 Days	143	153
Mean (sd)	28.8 (5.1)	29.3 (3.2)
Min, Max	1, 39	3, 39

Gemini 2 (1883-302-013): Extent of Exposure (Safety Population)

	Vehicle N=215	AGN-190584 N=212
Treatment Duration (Days)		
>= 7 Days	213	209
>= 14 Days	210	208
>= 21 Days	209	207
>= 28 Days	193	193
Mean (sd)	29.0 (4.1)	29.2 (4.4)
Min, Max	1, 46	1, 43

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database:

Pilocarpine in concentrations between 0.5% and 8% have been marketed for over 100 years for the reduction of elevated intraocular pressure. The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

AEs were classified by MedDRA system organ class (SOC) 22.1.

8.3.3. Routine Clinical Tests

See section 8.4.6.

8.4. Safety Results

8.4.1. Deaths

No deaths in either Study Gemini 1 or Gemini 2.

8.4.2. Serious Adverse Events

Gemini 1(1883-301-013)
No serious TEAEs were reported in the safety population. One 46-year-old, female participant (b) (6) had a serious adverse event (porphyria) during screening, which was moderate in intensity and resolved. This participant was not enrolled or included in the safety population; thus, a narrative was not prepared.

Gemini 2 (1883-302-013)
No serious TEAEs were reported in the AGN-190584 group. Two participants in the vehicle group had serious TEAEs of dysphagia and Guillain-Barre syndrome.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Gemini 1 (1883-301-013): Discontinuations

Subject Number	Group	Description
Participant (b) (6)	AGN-190584	44 yo WF discontinued from the study for a TEAE of bradycardia, which was of mild intensity, unrelated to treatment, and unresolved at study exit.
Participant (b) (6)	AGN-190584	Discontinued from the study for TEAEs of

		dyschromatopsia (unrelated to treatment) and bilateral visual field defect (related to treatment) which were of mild intensity and resolved by study exit.
Participant (b) (6)	Vehicle	46 yo WF discontinued from the study for TEAEs of headache and migraine, which were moderate in intensity, related to treatment and resolved by study exit.

Reviewer's Comment:
In Gemini 1, discontinuations from the study due to TEAEs occurred for 2 participants (1.2%) in the AGN-190584 group and 1 participant (0.6%) in the vehicle group.

Gemini 2 (1883-302-013): Discontinuations

Subject Number	Group	Description
Participant (b) (6)	AGN-190584	53 yo WF was discontinued from the study on Day 8 for TEAEs of headache and vision blurred in both eyes that began on Day 1 and lasted 11 days. Both TEAEs were moderate, related to study treatment, and recovered/resolved.
Participant (b) (6)	AGN-190584	53 yo WF was discontinued from the study on Day 2 for a TEAE of headache (described by the investigator as dull headache) that began on Day 2 and lasted 3 days. The TEAE was moderate, related to study treatment, and recovered/resolved.
Participant (b) (6)	AGN-190584	51 yo WF was discontinued from the study on Day 3 for TEAEs of photopsia and vitreous detachment in the left eye that began on Day 3. The photopsia (described by the investigator as flashing lights) was deemed severe and treatment related, and it recovered/resolved after 16 days. The vitreous detachment (described by the investigator as posterior vitreous detachment) was deemed moderate and treatment related, and it was ongoing at the time of discontinuation. This participant also had TEAEs of glare and vision blurred which were mild and resolved by study exit.
Participant (b) (6)	Vehicle	40 yo WF discontinued from the study for a serious TEAE of dysphagia, which was severe and unrelated to study treatment.

Reviewer's Comment:
In Gemini 2, discontinuations from the study due to TEAEs occurred for 3 participants (1.4%) in the AGN-190584 group and 1 participant (0.5%) in the vehicle group.

8.4.3 Treatment Emergent Adverse Events and Adverse Reactions

Gemini 1(1883-301-013): Ocular Treatment Emergent AEs

	Vehicle N=159	AGN-190584 N=163
Headache	6	7
Visual impairment	1	7
Conjunctival hyperemia	4	4
Vision blurred	2	4
Eye irritation	1	4
Eye pain	1	4
Lacrimation increased	0	4
Dry eye	3	2
Asthenopia	0	2
Photophobia	0	2
Punctate keratitis	5	1
Vital dye staining cornea present	2	1
Meibomian gland dysfunction	1	1
Chalazion	0	1
Dyschromatopsia	0	1
FBS in eyes	0	1
Glare	0	1
Lacrimation decreased	0	1
Migraine with aura	0	1
Paranasal sinus discomfort	0	1
Visual field defect	0	1
Vitreous floaters	0	1
Conjunctival disorder	1	0
Conjunctival hemorrhage	1	0
Conjunctival edema	1	0
Eye pruritis	1	0

Reviewer's comment:
For Gemini 1, the TEAEs were reported for 35.0% (57/163) of participants in the AGN-190584 group compared with 23.3% (37/159) of participants in the vehicle group. The TEAEs reported for at least 2 participants (≥ 1%) in either treatment group, in order of descending incidence, were: headache, visual impairment, conjunctival hyperemia, vision blurred, eye irritation, eye pain, lacrimation increased, nausea, dry eye, asthenopia, photophobia, and hypertension in the AGN-190584 group; and headache, punctate keratitis, conjunctival hyperemia, dry eye, vision blurred, and vital dye staining cornea present in the vehicle group.

Gemini 2 (1883-302-013): Ocular Treatment Emergent AEs

	Vehicle N=215	AGN-190584 N=212
Conjunctival hyperemia	11	15
Vision blurred	1	13
Eye pain	3	12
Eye irritation	1	5
Punctate keratitis	6	3
FBS in eyes	2	3
Visual acuity reduced	1	3
Visual impairment	0	3
Lacrimation increased	2	2
Abnormal sensation in eye	0	2
Vitreous floaters	0	2
Keratitis	2	1
Cataract	0	1
Conjunctival edema	0	1
Dry eye	0	1
Eyelid margin crusting	0	1
Glare	0	1
Halo vision	0	1
Metamorphopsia	0	1
Photopsia	0	1
Psuedomyopia	0	1
Swelling of eyelid	0	1
Vitreous degeneration	0	1
Vitreous detachment	0	1
Eye discharge	2	0
Chalazion	1	0
Corneal cyst	1	0
Eye pruritis	1	0
Eyelid edema	1	0
Lacrimal disorder	1	0
Lacrimation decreased	1	0

Reviewer's comment:
For Gemini 2, the TEAEs reported in the AGN-190584 group (34.4%, 73/212), compared with the vehicle group (23.7%, 51/215). The TEAEs reported for at least 1% of participants in either treatment group, in order of descending incidence, were: headache, conjunctival hyperemia, vision blurred, eye pain, eye irritation, punctate keratitis, foreign body sensation in eyes, visual

acuity reduced, visual impairment, and nausea in the AGN-190584 group; and conjunctival hyperemia, headache, punctate keratitis, eye pain, and nasopharyngitis in the vehicle group.

Gemini 1(1883-301-013): Non-Ocular Treatment Emergent AEs reported in more than 1 subject

	Vehicle N=159	AGN-190584 N=163
Nausea	0	4
Headache	9	16
HTN	1	2

Gemini 2 (1883-302-013): Non-Ocular Treatment Emergent AEs reported in more than 1 subject

	Vehicle N=215	AGN-190584 N=212
Nausea	0	3
Nasopharyngitis	3	1
Headache	9	23
Dizziness	0	2
Sinus headache	1	1
Cough	1	1

Reviewer's comment:
Headache and nausea were the only non-ocular TEAEs were reported in 1% or more of subjects in either treatment group in the Gemini 1 or Gemini 2 study.

8.4.4. Laboratory Findings

Clinical laboratory data collection was not part of the study protocols.

8.4.5. Vital Signs

Gemini 1(1883-301-013)
Vital signs data (diastolic blood pressure, systolic blood pressure, and heart rate) at baseline, Day 1, Day 7, Day 14m and Day 30. No clinically significant changes in vital signs data occurred in any treatment group.

Gemini 2 (1883-302-013)
Vital signs data (diastolic blood pressure, systolic blood pressure, and heart rate) at baseline, Day 1, Day 7, Day 14m and Day 30. No clinically significant changes in vital signs data occurred in any treatment group.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Adverse Events of Special Interest: Headaches and Visual Impairment

The following adverse events of special interest were identified and analyzed after database lock as additional safety variables:

- Headache TEAEs with preferred terms of headache, migraine, migraine with aura, and sinus headache
- Vision impairment TEAEs with preferred terms of vision blurred, visual impairment, and visual field defect
    - Visual acuity reduced was also identified as a preferred term of interest; however, it was not reported by any participant in any group

Headaches

Headache adverse events of special interest were TEAEs with the following preferred terms: headache, migraine, migraine with aura, and sinus headache.

Gemini 1

A total of 20 (12.3%) participants reported treatment-related headache TEAEs of special interest in the AGN-190584 group (19 participants with the preferred term headache and 1 participant with the preferred term migraine with aura) compared with 10 (6.3%) participants in the vehicle group (all 10 participants with the preferred term headache and 1 of those 10 also with the preferred term migraine). The duration of the treatment-related headaches was varied in the AGN-190584 group with approximately half lasting 1 day or less and others lasting most of the study duration, while most headaches in the vehicle group lasted 1 day or less (median = 1.0 day). All treatment-related headaches in both groups recovered or resolved without treatment, and almost all were mild. In the AGN-190584 group, 1 participant reported moderate headache and 1 participant reported severe headache; both continued in the study. In the vehicle group, 1 participant reported moderate events of headache and migraine, and discontinued from the study.

Gemini 2

More participants reported treatment-related headache TEAEs of special interest in the AGN-190584 group (13.2%, 28 participants with the preferred term headache and 1 participant with the preferred term sinus headache), compared with the vehicle group (2.3%, 5 participants with the preferred term headache and 1 participant with the preferred term migraine with aura). The durations of the treatment-related headaches of special interest were varied in the AGN-190584 group with just over half lasting 1 day or less (median = 1.0 day) and others lasting most of the study duration, while most treatment-related headaches of special interest in the vehicle group lasted a few days or less (median = 3.0 days). All treatment-related headaches of special interest in both groups recovered or resolved and most were mild. In the AGN-190584

group, 6 participants reported a treatment-related headache of special interest of moderate severity, which all resolved by study exit; 4 of these participants continued in the study and 2 discontinued from the study. In the vehicle group, 1 participant reported a treatment-related headache of special interest (migraine with aura) of moderate severity, which resolved by study exit; this participant continued in the study.

Vision Impairment

Vision impairment events of special interest were TEAEs with the following preferred terms: vision blurred, visual impairment, and visual field defect. Each of these preferred terms was analyzed separately. The preferred term visual acuity reduced would also have been included as a preferred term of interest; however, it was not reported in this study.

Gemini 1

A total of 4 (2.5%) participants reported vision blurred TEAEs of special interest in the AGN-190584 group compared with 2 (1.3%) participants in the vehicle group. The duration of the vision blurred TEAEs was similarly varied in both groups and all were mild and recovered or resolved without treatment.

Gemini 2

More participants reported vision blurred TEAEs of special interest in the AGN-190584 group (6.1%), compared with the vehicle group (0.5%). About half of the vision blurred TEAEs lasted for most of the study, while the rest were shorter in duration; almost all were transient, lasting either < 15 minutes or 15 minutes to 2 hours after dosing. Almost all vision blurred TEAEs were mild, related to treatment, had no impact on daily activities, and recovered or resolved by study exit. One participant was discontinued from the study for TEAEs of vision blurred and headache.

Reviewer's Comment:

The following TEAEs of special interest were examined: headache TEAEs with preferred terms of headache, migraine, migraine with aura, and sinus headache; and vision impairment TEAEs with preferred terms of vision blurred, visual impairment, and visual field defect. Findings indicated that all TEAEs of special interest were numerically more common in the AGN-190584 group compared with the vehicle group.

8.6. Additional Safety Explorations

8.6.1. Pediatrics and Assessment of Effects on Growth

Pilocarpine ophthalmic solution in multiple concentrations including those at least 4 times the concentration proposed in this application has been used in children for the treatment of elevated intraocular pressure for many decades. The safety profile in children is the same as the safety profile in adults.

The Applicant requested a full waiver for pediatric subjects 0 to 17 years of age because studies are impossible or highly impracticable. Presbyopia is included on the automatic waiver list as a condition that is rare in pediatric patients.

At the PeRC meeting on 8/24/21 Perc agreed with granting the full waiver for pediatric subjects 0 to 17 years of age because studies would be impossible or highly impractical as there are too few patients to study.

8.6.2. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Pilocarpine is a non-narcotic and does not have abuse potential.

9. Advisory Committee Meeting and Other External Consultations

There were no issues identified in the review of the application that were thought to benefit from an Advisory Committee discussion.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The application for NDA 214028 Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% for the treatment of presbyopia in adults is recommended for approval with the attached labeling in Appendix 13.3 of this review.

10.2. Nonprescription Drug Labeling

N/A.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12.Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13.Appendices

13.1. References

No additional literature references were identified that were contrary to the literature refences submitted in the application.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Gemini 1 (1883-301-013)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in S: Not applicable Sponsor of covered study: Not applicable		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Gemini 2 (1883-302-013)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in S: Not applicable Sponsor of covered study: Not applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Labeling

The application for NDA 214028 Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% for the treatment of presbyopia in adults is recommended for approval with the attached labeling submitted 10/27/2021.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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10/28/2021 07:46:21 AM

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