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Safety and Efficacy of AGN-190584 in Individuals With Presbyopia
The GEMINI 1 Phase 3 Randomized Clinical Trial

George O. Waring IV, MD; Francis W. Price Jr, MD; David Wirta, MD; Cathleen McCabe, MD; Majid Moshirfar, MD; Qiang Guo, PhD; Anu Gore, PhD; Haixia Liu, MD, PhD; Eleonora Safyan, BS; Michael R. Robinson, MD

IMPORTANCE AGN-190584 (Allergan, an AbbVie company) is an optimized topical formulation of pilocarpine hydrochloride, 1.25%, designed for managing presbyopia and enhanced with a proprietary vehicle.

OBJECTIVE To evaluate the efficacy and safety of pilocarpine hydrochloride, 1.25%, in individuals with presbyopia.

DESIGN, SETTING, AND PARTICIPANTS This vehicle-controlled, participant- and investigator-masked, randomized, phase 3 clinical study, GEMINI 1, enrolled individuals with presbyopia, aged 40 to 55 years, at 36 sites in the United States from December 21, 2018, to October 31, 2019. Analysis took place between February 2020 and December 2021.

INTERVENTIONS AGN-190584 or the AGN-190584 formulation vehicle was administered bilaterally, once daily for 30 days.

MAIN OUTCOMES AND MEASURES The proportion of participants with improvement of 3 or more lines in mesopic, high-contrast, binocular distance-corrected near visual acuity (DCNVA) at hours 3 and 6 on day 30 were the primary and key secondary efficacy end points, respectively. Safety measures included adverse events.

RESULTS Of 323 participants who were randomized, 235 (72.8%) were female and 292 (90.4%) were White. The mean (SD) age was 49.6 (3.5) years, and the baseline mean (SD) mesopic DCNVA was 29.2 (6.3) letters. A total of 163 individuals were randomized to AGN-190584 and 160 were randomized to vehicle. GEMINI 1 met its primary and key secondary efficacy end points. On day 30, hour 3, the percentage of participants with improvement of 3 or more lines in mesopic DCNVA was 30.7% (50 of 163) in the AGN-190584 group and 8.1% (13 of 160) in the vehicle group (difference, 22.5% [95% CI, 14.3%-30.8%]; adjusted $P < .001$). At hour 6, those percentages were 18.4% (30 of 163) and 8.8% (14 of 160), respectively (difference, 9.7% [95% CI, 2.3%-17.0%]; adjusted $P = .01$). At hour 8, the between-group difference in 3 or more lines of mesopic DCNVA gains was not statistically significant, but clinically relevant prespecified outcome measures demonstrated AGN-190584 superiority to vehicle in least-squares mean (SE) mesopic DCNVA change from baseline at hour 8 (5.4 [0.51] vs 3.6 [0.52] letters; $P = .009$) and photopic distance-corrected intermediate visual acuity at hour 8 (3.9 [0.44] vs 2.4 [0.45] letters; $P = .01$) and hour 10 (3.5 [0.46] vs 1.7 [0.47] letters; $P = .004$). No participants with mesopic DCNVA improvement of 3 or more lines at hour 3 had losses of more than 5 letters in mesopic, high-contrast, binocular-corrected distance visual acuity. The onset of effect was at 15 minutes. AGN-190584 demonstrated an acceptable safety and tolerability profile.

CONCLUSIONS AND RELEVANCE AGN-190584 demonstrated superiority over vehicle in mesopic DCNVA on day 30, hours 3 and 6, with an acceptable safety profile. AGN-190584 is a safe and efficacious topical therapy for presbyopia through 30 days.

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Visual Abstract

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Supplemental content

Author Affiliations: Waring Vision Institute, Mt Pleasant, South Carolina (Waring); Price Vision Group, Indianapolis, Indiana (Price); Eye Research Foundation, Newport Beach, California (Wirta); The Eye Associates, Bradenton, Florida (McCabe); Hoopes Vision Research Center, Draper, Utah (Moshirfar); John A. Moran Eye Center, University of Utah, Salt Lake City (Moshirfar); AbbVie Inc, Irvine, California (Guo, Gore, Liu, Safyan, Robinson).

Corresponding Author: Michael R. Robinson, MD, Allergan, an AbbVie company, 2525 Dupont Dr, Irvine, CA 92612 (michael.r.robinson@abbvie.com).

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Presbyopia affects approximately 1.8 billion people worldwide[1] (typically individuals aged >40 years) and is a characteristic of the age-related, progressive changes of the crystalline lens, or dysfunctional lens syndrome, which includes stage 1 (mild presbyopia and higher-order aberrations), stage 2 (lens opacity with advancing presbyopia and higher-order aberrations), and cataract with severe presbyopia and higher-order aberrations.[2,3] Presbyopia progressively reduces the eye's ability to focus on near objects, likely resulting from gradual lens thickening and loss of lens elasticity and accommodative ability[4-9] and can impact a person's daily activities, quality of life, and emotional well-being.[10] Advanced and absolute presbyopia also impair intermediate vision as the progressive loss of remaining accommodative ability prevents a wide range of clear vision,[11] and individuals with uncorrected presbyopia reported a significant impact on activities requiring near (reading, writing, and using smartphones) and intermediate (computer work or cooking) vision.[10] Common presbyopia treatments include corrective glasses/lenses[12] and surgery (corneal- or lens-based).[13] There is a need for convenient and noninvasive alternatives for managing presbyopia.

Pilocarpine is a cholinergic muscarinic receptor agonist that has been previously investigated for its ability to improve both depth of focus and accommodation.[14,15] Pilocarpine acts through the M3 muscarinic receptors on the iris sphincter to constrict the pupil and improve depth of focus.[16,17] It also contracts the ciliary muscle to change the lens thickness, stimulating accommodation to allow the eyes to focus on near objects.[17] Previous studies of pilocarpine-based glaucoma treatments have reported adverse events (AEs) including brow ache, headaches, vision blur, and discomfort.[18,19]

Phase 2b, dose-ranging studies (NCT02595528 and NCT02780115) were conducted based on the potential for pilocarpine hydrochloride (0.5%-1.5%) to improve near vision in individuals with presbyopia.[20] Results demonstrated robust efficacy for pilocarpine hydrochloride, 1.0%, with a significant percentage of participants maintaining an improvement of 3 lines or more in near vision for up to 8 hours. The studies also showed that concentrations of pilocarpine hydrochloride, 1.5% or less, had acceptable safety and tolerability profiles.[20] Moreover, results from in vitro and clinical/phase 1 studies showed that combined with a proprietary vehicle, pilocarpine hydrochloride demonstrated rapid equilibration to the tear film's physiologic pH, provided greater tolerability, and reduced vision blur compared with a generic formulation.[21] Based on these results, AGN-190584 (Allergan, an AbbVie company), an optimized formulation of pilocarpine hydrochloride, 1.25%, in a proprietary vehicle, was developed for managing presbyopia. The objective of the phase 3 GEMINI 1 study was to compare the efficacy and safety of AGN-190584 and vehicle in individuals with presbyopia.

Key Points

Question Does AGN-190584 (Allergan, an AbbVie company), an investigational pilocarpine formulation, demonstrate efficacy and safety in managing presbyopia?

Findings In this phase 3 randomized clinical trial, the proportion of participants with improvement of 3 or more lines in mesopic, high-contrast, binocular distance-corrected near visual acuity was statistically significantly higher with AGN-190584 treatment compared with vehicle on day 30, hour 3 (primary end point). AGN-190584 had an acceptable safety profile.

Meaning AGN-190584 was safe and efficacious through 30 days, improving near and intermediate vision on day 30 for up to 10 hours after administration and supporting its use as a treatment for presbyopia.

Methods

Study Design

The GEMINI 1 study was a 30-day, multicenter, double-masked, randomized, vehicle-controlled, parallel-group, phase 3 trial conducted at 36 sites in the United States from December 21, 2018, to October 31, 2019, in compliance with the Declaration of Helsinki.[22] The study protocol (Supplement 1) was approved by an institutional review board or ethics committee at each site. All participants provided written informed consent and were compensated for their time to complete study visits. This study report follows Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Population

Participants (aged 40-55 years) were in good general health with objective and subjective evidence of presbyopia. All eligibility criteria are listed in eTable 1 in Supplement 2. Key inclusion criteria included complaints of poor near vision (without near correction) impacting daily activities[23]; photopic, high-contrast corrected distance visual acuity (CDVA) of 20/25 or better bilaterally; mesopic, high-contrast distance-corrected near visual acuity (DCNVA, measured at 40 cm) of 20/40 to 20/100; photopic, near visual acuity correctable to 20/40 or better bilaterally; and willingness to wear monofocal correction to achieve photopic, binocular CDVA of 20/32 or better during the study. Key exclusion criteria included presence of severe dry eye disease; history of intraocular surgery except photorefractive keratectomy or laser-assisted in situ keratomileusis; history of glaucoma or ocular hypertension; and anisocoria more than 1 mm between pupils under mesopic conditions.

Randomization

Participant randomization (1:1) to AGN-190584 or the AGN-190584 vehicle was stratified by age (≤50 and >50 years), baseline mesopic, high-contrast, binocular DCNVA (20/40 to 20/60 and worse than 20/60), iris color (brown and not brown), and emmetrope status (emmetropes [sphere: −0.50 D to +0.75 D; cylinder: ≤0.75 D] and nonemmetropes). The randomization sequence was computer generated, and an automated interactive electronic response system/method was used to assign participants to study interventions. AGN-190584 and vehicle were provided in identically appearing bottles; both participants and study investigators/staff were masked to the treatment assignment.

Study Intervention and Visits

Participants administered topical AGN-190584 or vehicle bilaterally once daily (in the morning) for 30 days. Study visits were scheduled at screening (1-30 days prebaseline) and days 1 (baseline), 3, 7 (±2), 14 (±2), and 30 (±3)/early exit. On visit days, the study intervention was instilled by designated site personnel at hour 0 (8 AM ± 1 hour).

Outcome Measures

The primary efficacy end point was the proportion of participants gaining 3 or more lines in mesopic (10-11 lux at the target), high-contrast, binocular DCNVA on day 30, hour 3. The key secondary efficacy end point was the proportion of participants gaining 3 or more lines in mesopic, high-contrast, binocular DCNVA on day 30, hour 6. Other prespecified efficacy end points included the proportion of participants gaining 3 or more lines in mesopic, high-contrast, binocular DCNVA on day 30, hours 8 and 10; change from baseline in mesopic, high-contrast, binocular DCNVA letters on day 30, hours 0.25 and 0.5; proportion of participants achieving 20/40 or better in photopic (>251 lux at the target), high-contrast, binocular DCNVA on day 30, hours 1 and 3; change from baseline in photopic, high-contrast, binocular distance-corrected intermediate visual acuity (DCIVA; measured at 66 cm) letters on day 30, hour 3; and mean change from baseline on day 30, hour 3 in patient-reported outcomes of mesopic Near Vision Presbyopia Task-based Questionnaire performance and satisfaction scores, and Presbyopia Impact and Coping Questionnaire coping and impact scores. The Near Vision Presbyopia Task-based Questionnaire and Presbyopia Impact and Coping Questionnaire patient-reported outcome instruments were recently developed in accord with US Food and Drug Administration (FDA) standards and validated by the study sponsor.[24,25]

Preplanned safety outcome measures included AEs; photopic and mesopic, high-contrast, binocular CDVA; biomicroscopy and ophthalmoscopy findings; intraocular pressure; and vital signs. The timing of assessments is provided in the eMethods in Supplement 2.

Statistical Analysis

Sample size calculations were considered for both the primary and key secondary efficacy end points; the calculation requiring the larger sample size, ie, for the key secondary efficacy end point, was used. Assuming proportions of participants gaining 3 or more lines in mesopic DCNVA of 15% with AGN-190584 and 3.6% with vehicle at day 30, hour 6, and 10% dropout, a sample size of approximately 150 participants per group was planned to provide 90% power at a 2-sided significance level of .05.

The intent-to-treat population (all randomized participants) was used for efficacy analyses. The primary and key secondary efficacy end points were tested using the Pearson χ^2 test. Point estimates of between-group differences (AGN-190584–vehicle) with a 2-sided 95% CI were provided; missing data were imputed as 3-line gain failures.

Analyses of other secondary efficacy end points used observed data. End points assessing proportions of participants were analyzed with the Pearson χ^2 test; end points assessing change from baseline in DCNVA and DCIVA were analyzed using a mixed-effects model for repeated measures including treatment, visit, treatment-by-visit interaction, 4 stratification factors as fixed factors, and baseline value and baseline value-by-visit interactions as covariates under the assumption of missing at random. An unstructured covariance matrix was used for repeated measures. Patient-reported outcomes were analyzed using analysis of covariance including factors of treatment and 4 stratification factors and corresponding baseline score as a covariate. A graphical approach for structured hypotheses (eFigure 1 in Supplement 2) was used to control the overall familywise error rate at $\alpha = .05$ for the primary and secondary efficacy end points. *P* values were calculated as adjusted values where indicated.

The safety population included all participants who received 1 or more administrations of study intervention. Analyses using this population were based on the actual study intervention received. Participants self-identified their sex and race and ethnicity on a checklist; these data were required by the regulatory agency and summarized with descriptive statistics. Analysis took place between February 2020 and December 2021.

Results

Disposition, Demographics, and Baseline Characteristics

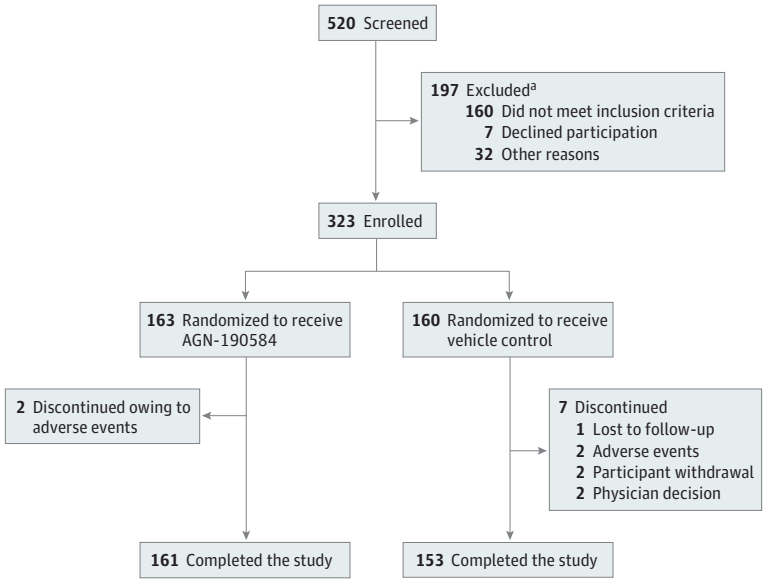
Of 520 participants screened, 323 were randomized to either AGN-190584 (n = 163) or vehicle (n = 160). Of those randomized, 98.8% (161 of 163) and 95.6% (153 of 160) completed the study, respectively (**Figure 1**).

The intent-to-treat population included 88 male individuals (27.2%) and 235 female individuals (72.8%); the mean (SD) age was 49.6 (3.5) years, and 185 (57.3%) participants were 50 years or younger. Most participants were White (292 [90.4%]) and not Hispanic or Latino (266 [82.4%]). Demographics and baseline characteristics were balanced between groups (**Table 1**).

Efficacy (Intent-to-Treat Population)

The proportion of participants with an improvement of 3 or more lines of mesopic, high-contrast, binocular DCNVA was higher with AGN-190584 than vehicle on day 30 from hours 0.25 to 6 ($P < .05$), and comparable in both groups at hours 8 and 10 (**Figure 2**A). On day 30, hour 3, the percentage of participants with an improvement of 3 lines or more was 30.7% (50 of 163) in the AGN-190584 group and significantly higher compared with 8.1% (13 of 160) in the vehicle group (difference, 22.5% [95% CI, 14.3%-30.8%]; $P < .001$ after multiplicity adjustment). At hour 6, 18.4% (30 of 163) and 8.8% (14 of 160) of participants had improvement of 3 or more lines with AGN-190584 and vehicle, respectively (difference, 9.7% [95% CI, 2.3%-17.0%]; adjusted $P = .01$). Preplanned subgroup analyses showed a clinically significant proportion of participants treated with AGN-190584 with gains of 3 or more lines in mesopic DCNVA at day 30, hours 3 and 6, in all evaluated subgroups based on age, baseline binocular DCNVA, iris color, and emmetrope status (eTable 2 in Supplement 2).

Figure 1. Participant Disposition



The adverse events leading to study discontinuation were bradycardia (n = 1) and dyschromatopsia and bilateral visual field defect (n = 1) in the AGN-190584 group and corneal abrasion (n = 1) and headache and migraine (n = 1) in the vehicle group.

[a] Participants could fail screening owing to multiple reasons.

Table 1. Participant Demographics and Characteristics at Baseline (Intent-to-Treat Population)

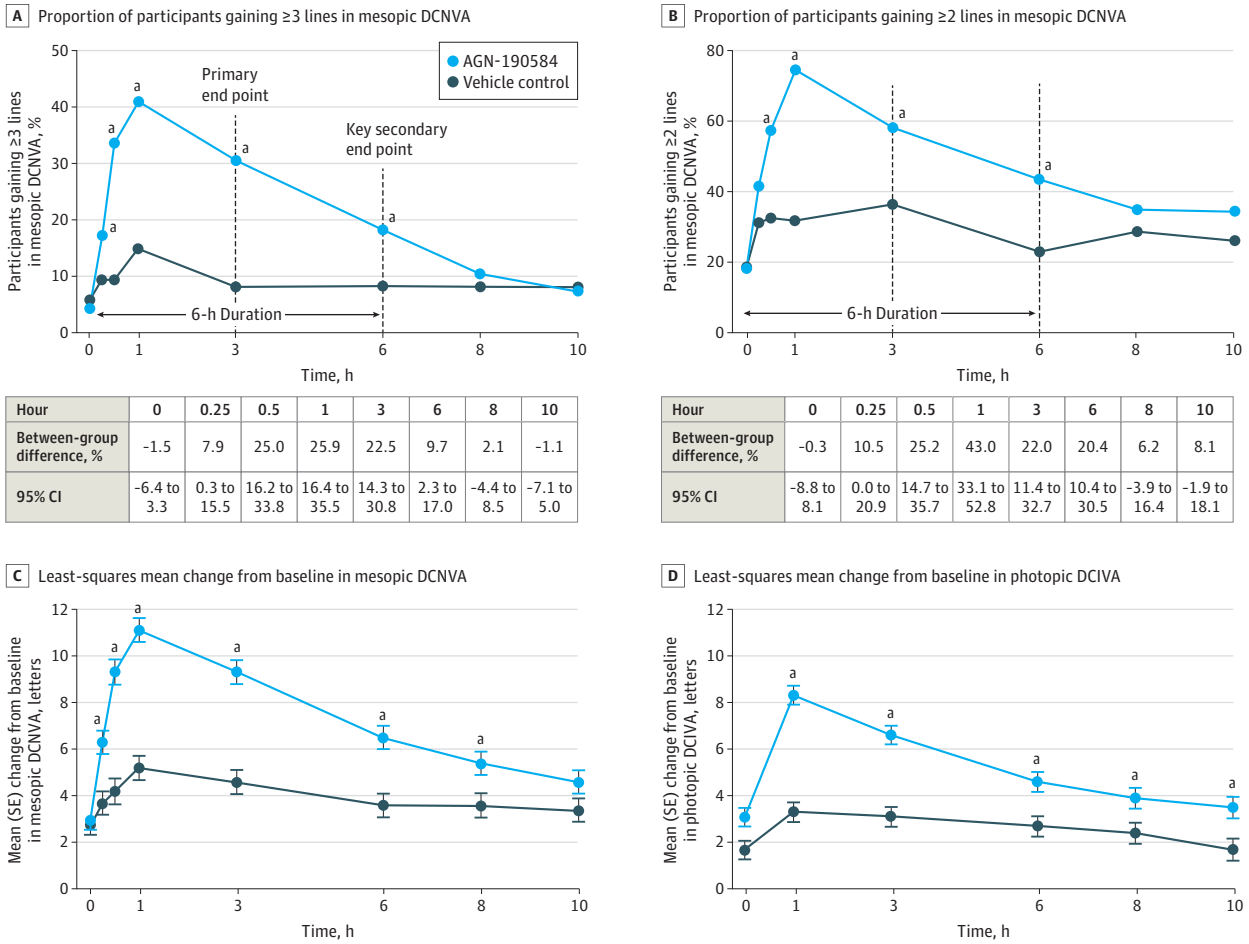
Parameter	No. (%) AGN-190584 (n = 163)	Vehicle (n = 160)	Total (N = 323)
Age, y			
Mean (SD) [range]	49.5 (3.8) [40-55]	49.7 (3.2) [41-55]	49.6 (3.5) [40-55]
≤50	92 (56.4)	93 (58.1)	185 (57.3)
>50	71 (43.6)	67 (41.9)	138 (42.7)
Sex			
Male	50 (30.7)	38 (23.8)	88 (27.2)
Female	133 (69.3)	122 (76.3)	235 (72.8)
Race and ethnicity			
American Indian or Alaska Native	0	2 (1.3)	2 (0.6)
Asian	2 (1.2)	1 (0.6)	3 (0.9)
Black or African American	13 (8.0)	12 (7.5)	25 (7.7)
Hispanic or Latino	31 (19.0)	26 (16.3)	57 (17.6)
Native Hawaiian or other Pacific Islander	0	0	0
Not Hispanic or Latino	132 (81.0)	134 (83.8)	266 (82.4)
White	148 (90.8)	144 (90.0)	292 (90.4)
Multiple[a]	0	1 (0.6)	1 (0.3)
Iris color			
Brown	78 (47.9)	77 (48.1)	155 (48.0)
Not brown	85 (52.1)	83 (51.9)	168 (52.0)
Emmetrope status			
Emmetrope	125 (76.7)	123 (76.9)	248 (76.8)
Nonemmetrope	38 (23.3)	37 (23.1)	75 (23.2)
Mesopic, high-contrast, binocular DCNVA			
Mean (SD) [range], letters	29.2 (6.6) [18-45]	29.1 (6.0) [19-49]	29.2 (6.3) [18-49]
20/40 to 20/60	66 (40.5)	62 (38.8)	128 (39.6)
Worse than 20/60	97 (59.5)	98 (61.3)	195 (60.4)
Photopic, high-contrast, binocular CDVA, mean (SD) [range], letters[b]	60.1 (4.3) [45-70]	60.0 (3.9) [49-68]	NA
Photopic, high-contrast, binocular DCIVA, mean (SD) [range], letters	53.4 (7.2) [30-73]	53.4 (6.9) [18-69]	NA

Abbreviations:
CDVA, corrected-distance visual acuity; DCIVA, distance-corrected intermediate visual acuity; DCNVA, distance-corrected near visual acuity; NA, not analyzed.

[a] Participants who reported more than 1 race were only included in the multiple category.

[b] Analyzed for the safety population; AGN-190584: n = 163 and vehicle: n = 159.

Figure 2. High-Contrast, Binocular Visual Outcomes at Day 30



Hour	0	0.25	0.5	1	3	6	8	10
Between-group difference, %	-1.5	7.9	25.0	25.9	22.5	9.7	2.1	-1.1
95% CI	-6.4 to 3.3	0.3 to 15.5	16.2 to 33.8	16.4 to 35.5	14.3 to 30.8	2.3 to 17.0	-4.4 to 8.5	-7.1 to 5.0

Hour	0	0.25	0.5	1	3	6	8	10
Between-group difference, %	-0.3	10.5	25.2	43.0	22.0	20.4	6.2	8.1
95% CI	-8.8 to 8.1	0.0 to 20.9	14.7 to 35.7	33.1 to 52.8	11.4 to 32.7	10.4 to 30.5	-3.9 to 16.4	-1.9 to 18.1

Mesopic and photopic conditions were defined as lighting 10 to 11 lux and 251 lux or more, respectively, measured at the target. DCIVA indicates distance-corrected intermediate visual acuity; DCNVA, distance-corrected near visual acuity.

[a] $P < .05$.

Peak efficacy was observed at hour 1, when 41.6% (67 of 161) of participants treated with AGN-190584 had DCNVA improvement of 3 lines or more (Figure 2A). In a post hoc analysis, no participants with DCNVA improvement of 3 lines or more had a loss of more than 5 letters in mesopic, high-contrast, binocular CDVA on day 30, hour 3. The proportion of participants with improvement of 2 lines or more in mesopic, high-contrast, binocular DCNVA was also greater with AGN-190584 than vehicle on day 30 from hours 0.5 to 6 ($P < .001$; Figure 2B).

Other preplanned analyses demonstrated a longer duration of effect of AGN-190584. Change from baseline in mesopic, high-contrast, binocular DCNVA was greater with AGN-190584 than vehicle on day 30 from 0.25 to 8 hours ($P \leq .01$). The least-squares mean (SE) change from baseline with AGN-190584 vs vehicle was 6.3 (0.49) vs 3.7 (0.50) letters at hour 0.25 ($P < .001$); 9.3 (0.54) vs 4.2 (0.55) letters at hour 0.5 ($P < .001$); 11.1 (0.51) vs 5.2 (0.52) letters at hour 1 ($P < .001$); 9.3 (0.51) vs 4.6 (0.52) letters at hour 3 ($P < .001$); 6.5 (0.50) vs 3.6 (0.51) letters at hour 6 ($P < .001$); and 5.4 (0.51) vs 3.6 (0.52) letters at hour 8 ($P = .009$) (Figure 2C). Change from baseline in photopic DCIVA on day 30 was greater with AGN-190584 than vehicle up to 10 hours ($P \leq .01$). The least-squares mean (SE) change from baseline in photopic DCIVA with AGN-190584 vs vehicle was 8.3 (0.41) vs 3.3 (0.42) letters at hour 1 ($P < .001$); 6.6 (0.41) vs 3.1 (0.42) letters at hour 3 ($P < .001$); 4.6 (0.43) vs 2.7 (0.44) letters at hour 6 ($P = .001$);3 .9 (0.44) vs 2.4 (0.45) letters at hour 8 ($P = .01$); and 3.5 (0.46) vs 1.7 (0.47) letters at hour 10 ($P = .004$) (Figure 2D).

The proportion of participants achieving 20/40 or better photopic, high-contrast, binocular DCNVA was greater with AGN-190584 than vehicle on day 30 from 0.5 to 3 hours ($P \leq .02$). The proportion with AGN-190584 vs vehicle was 84.2% (133 of 158) vs 70.6% (108 of 153) at hour 0.5 ($P = .004$); 92.5% (149 of 161) vs 73.9% (113 of 153) at hour 1 (adjusted $P = .01$); and 84.5% (136 of 161) vs 71.9% (110 of 153) (adjusted $P = .02$) at hour 3. The distribution of DCNVA (Snellen equivalent) at hours 0, 3, and 6 is provided in eTable 3 in Supplement 2.

Change from baseline in mesopic Near Vision Presbyopia Task-based Questionnaire performance, Near Vision Presby-

Table 2. Summary of Primary and Secondary Efficacy End Points

End point	No./total No. (%)		AGN-190584 vs vehicle, difference (95% CI)	*P* value	Adjusted *P* value
	AGN-190584	Vehicle			
P1: proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA at day 30, hour 3[a]	50/163 (30.7)	13/160 (8.1)	22.5 (14.3 to 30.8)	<.001	<.001
KS: proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA at day 30, hour 6[a]	30/163 (18.4)	14/160 (8.8)	9.7 (2.3 to 17.0)	.01	.01
S1: proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA at day 30, hour 8[b]	17/161 (10.6)	13/153 (8.5)	2.1 (−4.4 to 8.5)	.53	>.99
S2: change in mesopic, high-contrast, binocular DCNVA from baseline to day 30, hour 0.5, LS mean (SE), letters	9.3 (0.54)	4.2 (0.55)	LS mean difference, 5.1 (3.7 to 6.5)	<.001	.01
S3: proportion of participants achieving 20/40 or better photopic, high-contrast, binocular DCNVA at day 30, hour 1[b]	149/161 (92.5)	113/153 (73.9)	18.7 (10.6 to 26.7)	<.001	.01
S4: change in photopic, high-contrast, binocular DCIVA from baseline to day 30, hour 3, LS mean (SE), letters	6.6 (0.41)	3.1 (0.42)	LS mean difference, 3.5 (2.4 to 4.6)	<.001	.01
S5: change in mesopic NVPTQ performance score from baseline to day 30, hour 3, LS mean (SE)	1.4 (0.11)	0.6 (0.11)	LS mean difference, 0.8 (0.6 to 1.1)	<.001	.01
S6: proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA at day 30, hour 10[b]	12/160 (7.5)	13/152 (8.6)	−1.1 (−7.1 to 5.0)	.73	>.99
S7: change in mesopic, high-contrast, binocular DCNVA from baseline to day 30, hour 0.25, LS mean (SE), letters	6.3 (0.49)	3.7 (0.50)	LS mean difference, 2.6 (1.3 to 3.9)	<.001	.01
S8: proportion of participants achieving 20/40 or better photopic, high-contrast, binocular DCNVA at day 30, hour 3[b]	136/161 (84.5)	110/153 (71.9)	12.6 (3.5 to 21.6)	.007	.02
S9: change in mesopic NVPTQ satisfaction score from baseline to day 30, hour 3, LS mean (SE)	1.4 (0.1)	0.6 (0.11)	LS mean difference, 0.8 (0.5 to 1.1)	<.001	.01
S10: change in PICQ coping score from baseline to day 30, hour 3, LS mean (SE)	−1.0 (0.07)	−0.5 (0.07)	LS mean difference, −0.5 (−0.6 to −0.3)	<.001	.01
S11: change in PICQ impact score from baseline to day 30, hour 3, LS mean (SE)	−0.7 (0.06)	−0.4 (0.06)	LS mean difference, −0.3 (−0.4 to −0.1)	.001	.01

Abbreviations: DCNVA, distance-corrected near visual acuity; KS, key secondary efficacy end point; LS, least-squares; NVPTQ, Near Vision Presbyopia Task-based Questionnaire; P1, primary efficacy end point; PICQ, Presbyopia Impact and Coping Questionnaire; S, secondary efficacy end point.

[a] Missing data were imputed as failure to achieve gain of 3 or more lines in DCNVA.

[b] Based on observed data for all participants with data at baseline and the time point.

opia Task-based Questionnaire satisfaction, Presbyopia Impact and Coping Questionnaire coping, and Presbyopia Impact and Coping Questionnaire impact scores (**Table 2**) were significant at day 30, hour 3, favoring AGN-190584 (adjusted *P* = .01). Table 2 summarizes all efficacy end points.

Pupil diameter of the nondominant eye (near vision) decreased with AGN-190584 under both mesopic and photopic conditions. At peak efficacy, the decrease from baseline was 42.3% (-1.5 mm from 3.5 mm at baseline) with AGN-190584 under photopic conditions and 52.1% (-2.4 mm from 4.6 mm at baseline) under mesopic conditions. No obvious change was observed in eyes receiving vehicle under either condition (eFigure 2 in Supplement 2).

Safety

The safety population included 322 participants; 1 participant was excluded from the vehicle group because no treatment doses were administered. Overall, 35.0% (57 of 163) and 23.3% (37 of 159) of participants in the AGN-190584 and vehicle groups, respectively, reported 1 or more treatment-emergent AEs; all reported treatment-emergent AEs are listed in eTable 4 in Supplement 2. **Table 3** shows the treatment-emergent AEs reported in 2% or more of participants in either treatment group, with headache being the most common (possibly because participants were prompted/asked to rate temporal/supraorbital headaches per a visual analog scale). In the AGN-190584–treated group, 87% (20 of 23) of headaches were considered mild and none required treatment; no participants discontinued the study owing to headaches. No deaths or serious treatment-emergent AEs occurred during the treatment period.

Discussion

In this study, AGN-190584 met the primary and key secondary efficacy end points: statistically significant differences in

the proportion of participants achieving an improvement of 3 or more lines in mesopic, high-contrast, binocular DCNVA were observed on hours 3 and 6, respectively, on day 30, favoring AGN-190584. Mesopic lighting conditions were used for these outcomes because patients with presbyopia have the most difficulty with reading in dim lighting. Additionally, no participant with an improvement of 3 lines or more in mesopic DCNVA at hour 3 on day 30 lost more than 5 letters in CDVA. The rapid onset of action (15 minutes) and duration of effect (≥6 hours) of AGN-190584 were maintained through day 30. The secondary efficacy end point of functional vision (achieving 20/40 or better photopic, high-contrast, binocular DCNVA), which allows participants to read 6-point fonts from a distance of 14 inches (approximately 35 cm),[26] was also met.

Analyses of patient-reported outcome end points demonstrated significant treatment benefits of AGN-190584. Participants receiving AGN-190584 reported greater ability and satisfaction regarding near-vision reading, and a clinically meaningful reduction in use of presbyopia coping mechanisms, compared with participants receiving vehicle. The end point of improvement of 2 lines or more in mesopic, high-contrast, binocular DCNVA was not prespecified but was included because improvement of 2 lines or more was considered clinically meaningful to participants[27]; improvement of 3 lines or more was used for the prespecified primary and secondary end points, per FDA requirement.[28]

Presbyopia and vision impairment have been associated with poor quality of life.[29-33] Presbyopia can hinder daily living activities, hobbies, and social interactions and cause psychological distress.[31] Near vision is used for daily activities such as reading newspapers, smartphones, prescription labels on medications, and menus, while intermediate vision is used for social interactions, computer work, and cooking.[34] Commonly used presbyopia treatment options are over-the-counter unifocal reading glasses that primarily correct near vision and multifocal glasses that often have a narrow range for intermediate distance correction. For both options, correction at all viewing distances is limited. AGN-190584 improved near vision and demonstrated improvement in DCIVA through 10 hours on day 30. The mechanism of action of AGN-190584 is through dynamic pupil modulation, in which the iris sphincter is contracted to reduce the pupil size to an optimal range.[20] Pupil size reduction increases depth of focus and allows for a greater range of uninterrupted near and intermediate vision that cannot be achieved using eyeglasses.

Treatment with AGN-190584 was well tolerated, with most treatment-related ocular AEs reported as mild in intensity. Participants in both treatment groups had no clinically significant changes in photopic or mesopic, high-contrast, binocular CDVA, biomicroscopy or ophthalmoscopy findings, intraocular pressure, and vital signs. Headache associated with use of pilocarpine eye drops for glaucoma treatment has led to participant discontinuations in clinical studies.[35-38] In GEMINI 1, no discontinuations from the study were due to headache, and the risk of headache (AGN-190584, 14.1%; vehicle, 9.4%) appeared lower than that previously seen with other ocular pilocarpine formulations (>20%),[35,37,38] despite being prompted. Furthermore, 87% of headaches that were related to AGN-190584 were mild and transient, requiring no treatment. Overall, AGN-190584 demonstrated an acceptable safety profile and did not impair distance vision; the overall benefit-risk supports the use of AGN-190584 for presbyopia management, and AGN-190584 recently became the first FDA-approved pharmacologic therapy for presbyopia.

Table 3. Treatment-Emergent Adverse Events Reported in >2% of Participants in Either Treatment Group

System organ class preferred term	No. (%) AGN-190584 (n = 163)	No. (%) Vehicle (n = 159)
Eye disorders		
Visual impairment	7 (4.3)	1 (0.6)
Conjunctival hyperemia	4 (2.5)	4 (2.5)
Vision blur	4 (2.5)	2 (1.3)
Eye irritation	4 (2.5)	1 (0.6)
Eye pain	4 (2.5)	1 (0.6)
Lacrimation increased	4 (2.5)	0
Punctate keratitis	1 (0.6)	5 (3.1)
Nervous system disorders		
Headache[a]	23 (14.1)	15 (9.4)
Gastrointestinal disorders		
Nausea	4 (2.5)	0

[a] Participants were asked to provide a subjective rating of temporal/supraorbital headaches using a visual analog scale, which may have prompted reports of headaches as an adverse event.

Compared with commercially available pilocarpine eye drops used for glaucoma, AGN-190584 is better tolerated, likely owing to its proprietary vehicle that equilibrates to the ocular surface pH within 1 minute[21] (rising from approximately 4, needed to ensure drug stability,[39,40] to approximately 7) to mitigate AEs (eg, stinging and vision blur). Results from in vitro and clinical/phase 1 studies showed that the proprietary vehicle of AGN-190584 allowed pilocarpine to achieve faster equilibration to the tear film's physiologic pH, compared with a commercially available generic pilocarpine formulation (pH of approximately 4) that did not reach physiologic pH (approximately 7) in simulated tears, even after 10 minutes.[21] Previous studies using a generic pilocarpine formulation have reported that up to 67% of participants had vision blur lasting less than 20 minutes[36] and 11% reported burning or stinging.[35] In GEMINI 1, vision blur, eye irritation, and eye pain each occurred in only 2.5% of participants treated with AGN-190584. Bioavailability of pilocarpine is increased with the AGN-190584 formulation because of the rapid shift of the drug to a predominantly nonionized form at a pH of approximately 7 that facilitates transcorneal drug penetration. This leads to faster pupillary constriction[41] and improved aqueous humor dynamics[39] compared with a low-pH pilocarpine formulation.

Limitations

Although the primary end point was assessed under mesopic conditions, the effects of pilocarpine on night vision were not evaluated. A separate clinical trial (NCT04837482) specifically designed to determine the impact of AGN-190584 on night driving performance is underway. Once-daily dosing was

evaluated, but more frequent use of AGN-190584 may be needed for adequate reading vision throughout the day; this may be evaluated in future clinical trials. Also, near visual acuity improvements with pilocarpine were not directly compared with those obtained by spectacle correction for near visual acuity.

Conclusions

AGN-190584 applied bilaterally once daily was statistically superior in efficacy compared with vehicle in increasing the proportion of participants with improvement of 3 lines or more in mesopic DCNVA at hours 3 and 6 (but not at hour 8) on day 30, while being safe and well tolerated through 30 days. Achievement of 3-line gains is a rigorous efficacy end point that was required by the FDA. Other efficacy analyses, including change from baseline in mesopic DCNVA and photopic DCIVA letters, demonstrated a duration of AGN-190584 effect out to 8 and 10 hours. The primary and key secondary efficacy end points were met, with AGN-190584 improving functional near and intermediate vision for 30 days without compromising distance vision in individuals with presbyopia.

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Concept and design: Waring, Moshirfar, Gore, Liu, Robinson.
Acquisition, analysis, or interpretation of data: Price, Wirta, McCabe, Moshirfar, Guo, Gore, Liu, Safyan, Robinson.
Drafting of the manuscript: Gore, Liu, Robinson.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Guo, Robinson.
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Supervision: Waring, Wirta, McCabe, Moshirfar, Gore, Safyan, Robinson.

Conflict of Interest Disclosures: Dr Waring reported personal fees from Allergan (an AbbVie company) during the conduct of the study and outside the submitted work. Dr Price reported grants from AbbVie, Alcon, Aerie Pharmaceuticals, Kala Pharmaceuticals, Allergan (an AbbVie company), and EyePoint; ownership interests in Staar Surgical, RxSight, and Strathspey Crown; and personal fees from Haag-Streit and Gebauer outside the submitted work. Dr Wirta has consulted for Allergan (an AbbVie company) and Eyenovia and has received grant support from Aerpio, Allergan (an AbbVie company), Annexon, Dompe, Eyenovia, Mallinckrodt, Nicox, Novaliq, Novartis, SilkTech, and Santen. Dr McCabe reported personal fees from Allergan (an AbbVie company) during the conduct of the study; personal fees from Bausch and Lomb, Alcon, Visus, Surface Pharma, Johnson and Johnson Vision, and Zeiss outside the submitted work. Drs Gore and Robinson reported a patent to 10,610,518 on presbyopia treatments issued. Ms Safyan and Drs Guo, Gore, Liu, and Robinson are full-time employees of AbbVie Inc and may hold AbbVie stock. No other disclosures were reported.

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Invited Commentary

Clinical Trial Design—The Best Approach Is Often the Simple One

Kevin K. Ma, MD; Jennifer Rose-Nussbaumer, MD

The well-known painter Hans Hofmann's timeless quote, "The ability to simplify means to eliminate the unnecessary so that the necessary may speak," certainly applies to randomized clinical trial design.[1(p118)] In this edition of *JAMA Ophthalmology*, Waring et al[2] report the results of their phase 3, vehicle-controlled, double-blind, randomized clinical trial of AGN-190584 in individuals with presbyopia. The authors are to be congratulated on their work on this important question, as presbyopia is estimated to affect approximately 1.8 billion individuals worldwide and can lead to a substantial decrease in quality of life and impaired productivity.[3] A new pharmacologic treatment for presbyopia could provide a convenient and reversible alternative to corrective lenses while avoiding the risks of surgery. Overall, the outcome of their study suggests that pilocarpine can be used, with minimal adverse effects, to improve near vision in patients with distance-corrected presbyopia.

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Although the results are promising, the complexity of the study design makes them less compelling than they may have been. The participants were randomized using an elaborate stratification scheme including characteristics with small effects on prognosis, such as age (inclusion criteria, narrow range for age: 40-55 years), emmetrope status (monofocal distance