Statistical Analysis Plan for Study M21-195

A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia

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Version 1.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for AGN-190584 Study M21-195 with the protocol title of "A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of BID Dosing of AGN-190584 in Subjects with Presbyopia."

Pharmacokinetic analyses are not covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the Linux operating system.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

2.1.1 Objectives

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

2.1.2 Hypotheses

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

The hypotheses for primary endpoint and the secondary endpoints will be tested in a sequential order:

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

2.1.3 Estimands

The details of estimands are listed in Table 1 (Section 9.3.2) for the primary efficacy endpoint and Table 2 (Section 9.4.2) for the key secondary efficacy endpoint.

2.2 Study Design Overview

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

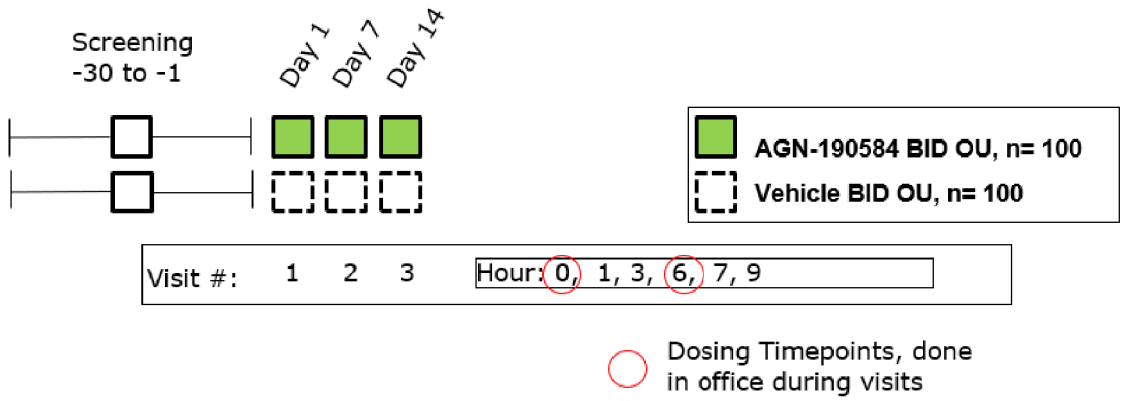
The study consists of the following visits: screening (Days -30 to -1), Day 1 (baseline), Day 7 (± 2 days), and Day 14 (± 2 days). A study schema is shown in Figure 1. Subjects

will receive either AGN-190584 or vehicle dosed twice daily, bilaterally, for 14 days beginning on Day 1. On nonvisit days, subjects will be instructed to instill one drop of the dispensed study treatment in each eye twice daily, with each dose administered 6 hours apart. On visit days, study treatment will be instilled bilaterally by designated site personnel at Hour 0 (8 AM ± 1 hour) and Hour 6 (time measured 6 hours from the time of completion of the Hour 0 study treatment administration). Study procedures on visit days are provided in the Activity Schedule (Protocol Appendix D), and further guidance regarding study procedures is located in the Operations Manual (Protocol Appendix E).

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

The schematic of the study is shown in Figure 1.

Figure 1. Study Schema



BID = twice daily; OU = both eyes

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

2.3 Treatment Assignment and Blinding

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

Randomization will be further stratified by the following stratification factors:

- Age group: ≤ 50 years and > 50 years
- Baseline binocular mesopic DCNVA severity: 20/63 or better, and worse than 20/63; with a maximum of 50% enrolled subjects with baseline binocular mesopic DCNVA of 20/63 or better
- Iris color: brown and nonbrown
- Emmetrope status: emmetrope and nonemmetrope; with a maximum of 25% enrolled subjects with non-emmetrope. A subject will be considered as emmetrope if both eyes of the subject satisfy the 2 criteria based on best cycloplegic distance correction: 1) -0.5D to +0.75D in sphere, inclusively; and 2) ≤ 0.75D in Cylinder.

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

2.4 Sample Size Determination

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

Assuming a responder rate of 25% in the AGN-190584 group and 7% in the vehicle group, and a 5% dropout rate, a sample size of 100 subjects per study treatment group will

provide greater than 90% power using chi-square testing at a 2-sided significance level of 5%.

3.0 Endpoints

3.1 Primary Endpoint(s)

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

3.2 Secondary Endpoint(s)

3.2.1 Key Secondary Endpoint

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

3.2.2 Supportive Secondary Endpoints

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

3.3 Additional Efficacy Endpoint(s)

The additional efficacy endpoints are:

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

3.4 Safety Endpoint(s)

The safety measurements will include adverse events (AEs), vital signs (blood pressure and heart rate), mesopic and photopic, high-contrast, binocular CDVA, intraocular pressure (IOP), slit-lamp biomicroscopy, manifest refraction, dilated fundoscopic examination, post-dose tolerability, drop comfort, and pregnancy test.

3.5 Pharmacokinetic Endpoints

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

The analyses of pharmacokinetic endpoints will be covered in a separate analysis plan.

3.6 Patient Reported Outcomes

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

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

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

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

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

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

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

In summary, patient-reported outcomes (PROs) are in the following types:

- Collected at screening visit only for screening purpose, including NEI VFQ-25 and OSDI.
- As additional efficacy endpoints, including NVPTQ, PICQ, and VFA app individual scores (Section 3.3 and Section 9.5)
- As safety endpoints, including the Drop Comfort Questionnaire (Section 3.4 and Section 10.5.8)

- The other PROs including NVPTQ Satisfaction domain, PICQ Impact domain, PGIS, PGIC, and composite scores from VFA app (Appendix A) are not efficacy or safety endpoints. They are not covered in this SAP (Section 11.0).

4.0 Analysis Populations

The following population sets will be used for the analyses.

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

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

5.0 Subject Disposition

The total number of subjects who were screened will be summarized.

Subject disposition will be provided for all screened subjects. The number and percentage of subjects in each of the following categories will be summarized in total and for each treatment group:

- Enrolled (randomized)
  - Never received any study treatment
  - Received randomized study treatment
  - Received study treatment other than randomized
- Treated (took at least one dose of study treatment)
- Completed the study
- Discontinued from the study
- Primary reasons for discontinuation from the study by reason

Primary reasons for study treatment discontinuation will be provided for all treated subjects (the safety population). The number and percentage of subjects will be summarized in total and for each treatment group by reason.

In addition, disposition by investigator will be provided for the ITT population. The number and percentage of subjects in each of the following categories will be summarized in total and for each treatment group by investigator:

- Enrolled (randomized) in the study
- Treated (took at least one dose of study treatment)
- Completed the study
- Discontinued from the study

6.0 Study Treatment Duration

Study treatment duration will be summarized by treatment group for the safety population.

Duration of treatment is defined for each subject as the last dose date minus the first dose date + 1. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

In addition, the number and percentage of subjects in each treatment duration interval ($\geq$ 7 and $\geq$ 14 days) will be summarized.

7.0 Subject Characteristics

Demographics, baseline disease characteristics, medical/ophthalmic history, and prior and concomitant medications will be summarized for the ITT population overall and by treatment group.

Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of nonmissing observations. Continuous variables will be summarized with descriptive statistics (number of

non-missing observations, mean and standard deviation, median, 1st and 3rd quartiles, minimum and maximum.

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include:

- Age

Categorical demographic variables include:

- Age group (≤ 50, > 50 years)
- Sex
- Ethnicity
- Race

Baseline disease characteristics include:

- Baseline binocular mesopic DCNVA severity (20/63 or better, worse than 20/63)
- Iris color (brown, non-brown; and within nonbrown: blue, grey, green, and hazel)
- Emmetrope status (emmetrope, nonemmetrope)

For more details on emmetrope status, see Section 3.14 in Protocol Appendix F.

7.2 Medical History

Medical history including prior procedures data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1 or higher. The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report.

The number and percentage of subjects in each medical history category (by MedDRA primary system organ class and preferred term) will be summarized. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms (PTs) will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or PT).

The following summaries will be provided:

- Medical history: number (%) of subjects with history ongoing at screening
- Medical history: number (%) of subjects with history resolved as of screening
- Ophthalmic medical history: number (%) of subjects with history ongoing at screening
- Ophthalmic medical history: number (%) of subjects with history resolved as of screening

An ophthalmic history will be determined as indicated on the Medical History form of eCRF (marked "OD," "OS," or "OU" to the question of "What was the location of the medical history condition/event?")

7.3 Prior and Concomitant Medications

Medication terms will be coded using the World Health Organization (WHO) Drug Dictionary (Version WHODDMAR21B3G). The version of the dictionary will be noted in the statistical tables and clinical study report.

A prior medication is defined as any medication taken prior to the date of the first dose of study treatment. A concomitant medication is defined as any medication that started prior to the date of the first dose of study treatment and continued to be taken after the first dose of study treatment or any medication that started on or after the date of the first dose of study treatment but not after the last study treatment dose date.

The number and percentage of subjects taking medications will be summarized by preferred drug name based on the WHO Drug Dictionary for both prior and concomitant medications, respectively.

7.4 Protocol Deviations

According to ICH E3 2012 guideline, only important protocol deviations will be reported in CSR.

The number and percentage of randomized subjects with important protocol deviations will be summarized overall and by treatment group for subjects reported by protocol deviation categories.

- Subjects who entered the study even though they did not satisfy the entry criteria
  - Subjects with inclusion criteria not met, overall and by inclusion criteria
  - Subjects with exclusion criteria met, overall and by exclusion criteria
- Subjects developed withdrawal criteria during the study but were not withdrawn
- Subjects received wrong treatment or incorrect dose of study treatment
- Subjects took prohibited concomitant medication
- Subjects with any other important deviations

A listing of subjects with important protocol deviations will be provided.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint (defined in Section 3.1) and the key secondary efficacy endpoint (defined in Section 3.2) will be analyzed based on the ITT population and the following methods will be used to address potential intercurrent events (IE):

- Subjects who prematurely discontinued study treatment before the Day 14 visit will be considered as nonresponders.

- Subjects who die before assessment of the endpoint will be considered as nonresponders for the endpoint.
- Subjects who are lost to follow-up and are missing data for the endpoint will be considered as non-responders for the endpoint.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted for all efficacy endpoints in the ITT population at the end of the study and after the database has been locked. All tests will be 2-sided at an alpha level of 0.05. All confidence intervals (CIs) will be at least 2-sided 95% confidence.

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

Continuous variables will be analyzed using an analysis of covariance (ANCOVA) model that includes treatment, age group, baseline DCNVA severity group, iris color group, and emmetrope status as factors as well as corresponding baseline value as a covariate.

Unless otherwise specified, any mis-stratified subject will be analyzed based on the actual stratum the subject should have been randomized.

"Baseline" refers to the last non-missing observation before the first administration of study treatment or randomization if no study treatment is given. The change from baseline values will be computed as the postbaseline value minus the baseline value.

For descriptive analyses:

- Categorical variables will be summarized with the number and percentage of subjects; unless otherwise stated, percentages will be calculated based on the number of non-missing observations.
- Continuous variables will be summarized with descriptive statistics (number of nonmissing observations, mean and standard deviation, median, 1st and 3rd quartiles, minimum, and maximum.

9.2 Handling of Missing Data

Unless otherwise specified, for the main analyses of primary and secondary efficacy endpoints and the other efficacy endpoints based on the binary data, subjects with missing data will be regarded as nonresponders. Other efficacy endpoints will be analyzed as observed.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint

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

9.3.2 Main Analysis of Primary Efficacy Endpoint

The attributes of the estimand corresponding to the primary efficacy endpoint are summarized in Table 1.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint

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

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

As presented in the estimand for the primary efficacy endpoint in Table 1, the composite strategy will be used to handle the intercurrent events. Subjects with intercurrent events prior to Day 14, Hour 9 will be considered as non-responders for the primary efficacy endpoint. Subjects who have missing data for the primary efficacy endpoint will be categorized as non-responders in the primary analysis.

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

If the proportions of subjects with reported IEs are considered unbalanced between the treatment groups and are higher in the vehicle group than in the AGN-190584 group, the subjects with IEs will not be considered as nonresponders for the primary efficacy analysis.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

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

In addition, the following sensitivity analyses with respect to missing data handling approaches will be conducted to explore the robustness of the primary efficacy analysis results:

- Observed data without imputation: The comparison between AGN-190584 and vehicle for the primary efficacy endpoint will be made using the Pearson's chi-square test based on observed data without imputation.
- Last observation carried forward (LOCF): Missing data for the primary efficacy endpoint at Day 14, Hour 9 will be imputed using a time matched LOCF, and the comparison between AGN-190584 and Vehicle for the primary efficacy endpoint will be conducted based on the data after imputation.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoint

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

9.4.2 Main Analyses of Key Secondary Efficacy Endpoint

The attributes of the estimand corresponding to the key secondary efficacy endpoint are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Key Secondary Efficacy Endpoint

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

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

As presented in the estimand for the key secondary efficacy endpoint in Table 2, the composite strategy will be used to handle the intercurrent events. Subjects with intercurrent events prior to Day 14, Hour 9 will be considered as non-responders for the key secondary efficacy endpoint. Subjects who have missing data for the key secondary efficacy endpoint will be categorized as non-responders in the primary analysis.

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

If the proportions of subjects with reported IEs are considered unbalanced between the treatment groups and are higher in the vehicle group than in the AGN-190584 group, the subjects with IEs will not be considered as nonresponders for the key secondary efficacy analysis.

9.4.3 Sensitivity and Supplementary Analyses for Key Secondary Efficacy Endpoint

Similar as for the primary efficacy endpoint, a 2-sided 95% confidence interval using Wilson-Newcombe method will be presented for the key secondary efficacy endpoint.

In addition, the following sensitivity analyses with respect to missing data handling approaches will be conducted to explore the robustness of the key secondary efficacy analysis results:

- Observed data without imputation: The comparison between AGN-190584 and vehicle for the key secondary efficacy endpoint will be made using the Pearson's chi-square test based on observed data without imputation.
- Last observation carried forward (LOCF): Missing data for the key secondary efficacy endpoint at Day 14, Hour 9 will be imputed using a time matched LOCF, and the comparison between AGN-190584 and vehicle for the key secondary efficacy endpoint will be conducted based on the data after imputation.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

Supportive Secondary Endpoints:

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

The same analysis method as described in Section 9.3.2 for the primary efficacy endpoint will be applied for the above supportive secondary endpoints. The comparison of the proportions between AGN-190584 and vehicle will be made using the Pearson's chi-square test. The treatment difference will be provided with a 2-sided 95% CI using the normal approximation based on the pooled variance without continuity correction.

9.5 Additional Efficacy Endpoints and Analyses

The additional efficacy endpoints are:

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

- Change from baseline in reading speed (words per minute)
- Change from baseline in median contrast level (%) based on the original value

The PRO scoring algorithms for the NVPTQ, PICQ, and VFA app are provided in Appendix A.

The additional efficacy endpoints will be analyzed using an ANCOVA model that includes treatment, age group, baseline DCNVA severity group, iris color group, and emmetrope status as factors as well as corresponding baseline PRO score as a covariate.

The same analysis will be applied for these PRO scores at other visits/timepoints.

Additionally, for the PRO domain mesopic NVPTQ Performance score at Day 14 Hour 9 and the PRO domain PICQ Coping score at Day 14 Hour 3, the cumulative distribution function (CDF) curves representing the cumulative proportion of subjects with any particular level of change from baseline in a PRO domain will be presented by treatment group.

9.6 Exploratory Efficacy Endpoints and Analyses

Exploratory efficacy endpoints are not defined in the protocol and will be included for exploratory analyses:

- Change from baseline in mesopic near pupil diameter
- Change from baseline in mesopic distance pupil diameter
- Change from baseline in photopic near pupil diameter
- Change from baseline in photopic distance pupil diameter

Descriptive statistics for pupil diameter (mesopic near, mesopic distance, photopic near and photopic distance) and changes from baseline values at each assessment timepoint will be presented by treatment group and by eye (dominant and non-domninant).

Additionally, similar analysis methods as described for primary (Section 9.3.2) and secondary efficacy endpoints (Section 9.4.2) will be used for the following exploratory efficacy endpoints based on observed data.

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

9.7 Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the primary and key secondary endpoints for the following subgroups:

- Age group (≤ 50, > 50 years)
- Sex (male, female)
- Race (white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple.)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline binocular DCNVA (20/63 or better, worse than 20/63)
- Iris color (brown, non-brown)
- Emmetrope status (emmetropes, non-emmetropes)

Descriptive summary statistics and 95% confidence intervals will be provided; no statistical hypothesis test will be performed. For any subgroup with < 10 subjects in a treatment group, only descriptive summary statistics will be provided.

10.0 Safety Analyses

10.1 General Considerations

The safety measurements will include AEs; vital signs (blood pressure and heart rate); mesopic and photopic, high-contrast, binocular CDVA; IOP; slit lamp biomicroscopy; manifest refraction; dilated fundoscopic examination; post-dose tolerability (for subjects reporting specific ocular symptoms), drop comfort; and pregnancy test.

Safety data will be summarized using the Safety population based on the treatment actually received, regardless of the treatment randomized. A subject's actual treatment will be determined by the first dose of study drug.

AEs and findings from biomicroscopy and ophthalmoscopy examinations will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the tables/listings and in the clinical study report.

10.2 Adverse Events

AEs will be summarized and presented using primary MedDRA SOCs and PTs. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times for a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of study treatment. Events where the onset date is the same as the study treatment start date are assumed to be treatment emergent.

In general, the number and percentage of subjects experiencing TEAEs will be summarized overall, as well as by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in decreasing frequency order on active study treatment within each SOC. The number and percentage of subjects experiencing TEAEs will also be summarized by PT regardless of the SOC. TEAEs by PT summaries will be presented in decreasing frequency order on active study treatment.

10.2.2 Adverse Event Overview

Adverse events will be classified into ocular AEs and non-ocular AEs. An ocular AE will be determined as indicated on the AE form of eCRF (marked "OD" and/or "OS" to the question of "what was the location of the adverse event?"), and thus are not limited to AEs with primary SOC of eye disorders.

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- TEAEs
  - Ocular TEAEs
  - Nonocular TEAEs
- TEAEs with reasonable possibility of being related to study treatment according to the investigator
  - Ocular TEAEs with reasonable possibility of being related to study treatment according to the investigator
  - Nonocular TEAEs with reasonable possibility of being related to study treatment according to the investigator

- Severe TEAEs
- Serious TEAEs
  - Ocular serious TEAEs
  - Nonocular serious TEAEs
- TEAEs leading to withdrawal of study treatment
  - Ocular leading to withdrawal of study treatment
  - Nonocular leading to withdrawal of study treatment
- TEAEs leading to death
- Adverse events of special interest (AESIs) within the following 2 categories (AESIs will be based on the search criteria in Appendix B):
  - Headache AESIs
  - Visual disturbance AESIs
- All deaths
- COVID-19 Infection

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized for each of the following AE categories:

- TEAEs by SOC and PT
  - Ocular TEAEs by SOC and PT
  - Nonocular TEAEs by SOC and PT
- TEAEs by PT
- TEAEs with reasonable possibility of being related to study treatment by SOC and PT
  - Ocular TEAEs with reasonable possibility of being related to study treatment by SOC and PT
  - Nonocular TEAEs with reasonable possibility of being related to study treatment by SOC and PT
- TEAEs by SOC, PT, and maximum severity

Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise.

If the same adverse event occurs multiple times for a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Treatment Discontinuation

SAEs (including deaths) and AEs leading to study treatment discontinuation will be summarized by SOC and PT and in listing format.

10.2.5 Adverse Events of Special Interest

Adverse events of special interest in the following categories will be based on the search criteria in Appendix B:

- Headache AESIs
- Visual disturbance AESIs

The following treatment-emergent AESIs will be summarized overall and by PT:

- Headache AESIs
  - Headache AESIs with reasonable possibility of being related to study treatment
  - Headache AESIs with no reasonable possibility of being related to study treatment
- Visual disturbance AESIs

For each of the above categories of AESIs, descriptive summaries will be presented by treatment group for the following parameters:

- Any AESI
- Severity (mild, moderate, severe)

- Duration (days)
- Duration category (1 day, 2 to 5 days, 6 to 20 days, > 20 days)
- Onset day category (Day 1, Day 2 to Day 10, > Day 10)
- Pattern (continuous, intermittent)
- Outcome (recovered/resolved, recovered/resolved with sequelae, rot recovered/not resolved, fatal, unknown)
- Concomitant medication or therapy (yes, no)
    - Yes, Outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown)
    - No, Outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown)
- Discontinuation from the study treatment
- Ongoing at exit

In addition, concomitant medications or therapy started on or after the first study treatment date for the indication of headache AESIs will be summarized by preferred drug name and by treatment group.

The following listings will be provided:

- Headache AESIs: with reasonable possibility of being related to study treatment
- Headache AESIs: with no reasonable possibility of being related to study treatment
- Visual disturbance AESIs.

10.2.6 Headache Assessment

Whenever a headache AE is reported after the initial dosing at Day 1, the subject will be followed up with a supplemental headache assessment form to further assess the headache. Severity score will be assessed using a visual analog scale (VAS) (0 – 100 for No pain – Worst possible pain):

- Overall headache/migraine severity score (0 – 100)
- Temporal headache/browache severity score (0 – 100)
- Supraorbital headache/browache severity score (0 – 100)

The number and percentage of subjects who had any of the above 3 VAS assessments will be summarized by treatment group for overall/temporal/supraorbital, respectively. In addition, the total number of assessments of overall headache/migraine, temporal headache/browaches, and supraorbital headache/browache will be summarized by treatment group.

In addition to the severity scores, the following information will be assessed for overall headache/migraine:

- Onset after the first or second dose of study medication (after first dose, after second dose, both, unsure)
- Intermittent status (yes, no)
- Onset time after taking the study medication (0-1 hour, > 1-2 hours, > 2-4 hours, > 4-6 hours, > 6 hours)
- How long did the headache/migraine last? (0-1 hour, > 1-2 hours, > 2-4 hours, > 4-6 hours, > 6 hours)

All headache assessments for TEAEs will be summarized using descriptive statistics by treatment group. The percentages will be based on the total number of assessed events by treatment group, whenever applicable. For intermittent status, only the category of "Yes" will be summarized.

Additionally, similar summaries will be provided for the following 2 subsets:

- Supplemental headache assessments for TEAEs with reasonable possibility of being related to study treatment
- Supplemental headache assessments for TEAEs with no reasonable possibility of being related to study treatment

10.3 Analysis of Laboratory Data

Urine pregnancy test will be performed at Screening, Day 1, and Day 14 for women of childbearing potential only.

10.4 Analysis of Vital Signs

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

10.5 Other Safety Analyses

10.5.1 Mesopic, High-Contrast, Binocular CDVA

Mesopic, high-contrast, binocular CDVA is assessed at each visit.

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

10.5.2 Photopic, High-Contrast, Binocular CDVA

Photopic, high-contrast, binocular CDVA is assessed at each visit.

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

10.5.3 Intraocular Pressure

IOP is measured for each eye using the Goldmann applanation tonometer at Hour 0, Hour 1, and Hour 7 (1 hour after the second dose) at each visit.

Tabulations will be based on the eye with a greater magnitude of change from baseline assessed at each assessment time point of a visit. In case of both eyes have same magnitude change in different directions, the decrease change from baseline will be

chosen. Descriptive statistics for IOP and changes from baseline at each assessment timepoint will be presented by treatment group.

10.5.4 Slit Lamp Biomicroscopy

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

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

10.5.5 Manifest Refraction

Both mesopic manifest refraction (distance and near) and photopic manifest refraction (distance and near) will be assessed in each eye at Screening. If a subject loses ≥ 1 line (≥ 5 letters) of CDVA or DCNVA compared with Hour 0 of the same study visit at Hour 1 after dosing, a manifest refraction should be repeated under the same lighting conditions.

Manifest refraction assessments will be listed.

10.5.6 Dilated Fundoscopic Examination

Dilated fundoscopic examination will be performed in each eye at Screening and at Hour 9 on Day 14/early exit.

Findings from dilated fundoscopic examination will be listed.

10.5.7 Post-DoseTolerability

Post-dose tolerability will be assessed after each dose at each visit in all subjects who report any of the following ocular symptoms after drop instillation:

- blurred vision/vision disturbance
- foreign body sensation/grittiness
- pain
- burning/stinging/irritation
- tearing/watery eyes/discharge
- itching

These subjects will rate each of these symptoms using a 5-point scale (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe) for severity and a 3-point scale (< 1 min, 1 to 5 min, and > 5 min) for duration. The number and percentage of subjects who report each category of severity and duration will be tabulated for each time point by treatment group.

10.5.8 Drop Comfort

Drop comfort will be assessed in all subjects after each dose at each visit.

Subjects will rate the overall comfort of the treatment drops using a 6-point scale (soothing, very comfortable, comfortable, uncomfortable, very uncomfortable, and intolerable). The number and percentage of subjects who report each category will be tabulated for each time point by treatment group.

10.6 Safety Subgroup Analyses

Ocular TEAEs will be summarized by preferred term for each of the following subgroups:

- Age group (≤ 50, > 50 years)

- Sex (male, female)
- Race (white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple.)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

11.0 Other Analyses

Plasma concentrations of AGN-190584 will be assessed at selected sites in approximately 10% of all enrolled subjects. Details of the statistical analyses of PK data will be described in the PK analysis plan finalized before database lock.

Additional PRO exploratory analyses other those described in Section 9.5 will be described in a separate analysis plan (Appendix A).

12.0 Interim Analyses

Not applicable.

12.1 Data Monitoring Committee

Not applicable.

13.0 Overall Type-I Error Control

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

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

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

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

14.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	19 NOV 2021	Original version

15.0 References

Appendix A. PRO Scoring Algorithm

The NVPTQ and the PICQ scoring algorithms can be found in:

- Scoring Algorithms for Presbyopia Patient-Reported Outcome Instruments
  December 9, 2019 by Outcometrix

VFA app coping behavior metric scores and candidate composite scores can be found in:

- Psychometric Evaluation of the Visual Function Assessment Scores in Presbyopia Final Psychometric Analysis Plan
  June 17, 2021 by RTI Health Solutions

Appendix B. Definition of Adverse Events of Special Interest

AESIs will be identified using the following search criteria[1]:

Area of Safety Interest	Search Criteria – Preferred Term (PT)	PT Code
Headache	Headache	10019211
	Migraine	10027599
	Migraine with aura	10027607
	Sinus headache	10040744
	Other PT(s) related to headache of special interest	(TBD)
Visual disturbance	Dyschromatopsia	10013892
	Glare	10052128
	Halo vision	10019099
	Metamorphopsia	10063341
	Photophobia	10034960
	Photopsia	10034962
	Pseudomyopia	10075919
	Vision blurred	10047513
	Visual acuity reduced	10047531
	Visual field defect	10047555
	Visual impairment	10047571
	Other PT(s) related to visual disturbance of special interest	(TBD)

1. The final list of PTs to be used will be reviewed and finalized prior to database lock.

Appendix C. List of MedDRA Preferred Terms for COVID-19 Infection

Area of Safety Interest	Search Criteria
COVID-19 Infection	MedDRA 24.1 COVID-19 SMQ 20000237 (narrow search)