Statistical Analysis Plan for Study 1883-306-013

Evaluating the Impact of AGN-190584 on Night Driving Performance

Date: 26 Jul 2021

Version 1.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in protocol amendment 1 for Study 1883-306-013 (approved on 15-Apr-2021).

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.

2.0 Study Design and Objectives

2.1 Objectives and Hypothesis

The objectives are:

- To evaluate night-driving performance in real-world driving conditions in participants with presbyopia treated with AGN-190584 versus vehicle
- To evaluate safety in participants with presbyopia treated with AGN-190584 versus vehicle

The primary efficacy endpoint is overall composite driving performance Z score approximately 1 hour after study intervention instillation. The null and alternative hypotheses for the primary efficacy endpoint are:

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

2.2 Study Design Overview

This is a single-center, randomized, double-masked, crossover, Phase 3b study evaluating the effect of AGN-190584 compared with vehicle when dosed in both eyes on driving

performance under real-world, night-lighting conditions in participants with objective and subjective evidence of presbyopia.

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

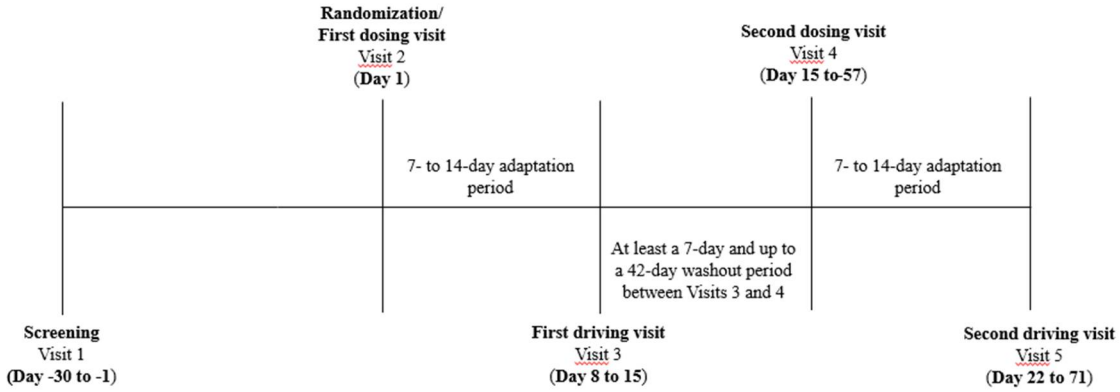
Approximately 54 participants will be enrolled at one study site (Queensland University of Technology, Australia) and approximately 40 participants are expected to complete the study based on an anticipated dropout rate of 25% or less. Participants who prematurely discontinue from the study will not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

The dosing regimen and schedule for this study are as follows:

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

The schema of the study is shown in Figure 2-1.

Figure 2-1 Study Schema



2.3 Treatment Assignment and Blinding

Participants will be randomized to the following study intervention sequences in a 1:1 ratio:

- AGN-190584 followed by vehicle
- vehicle followed by AGN-190584

The identity of study intervention will be masked to the participants and the study center.

2.4 Sample Size Determination

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

3.0 Endpoints

3.1 Primary Endpoint

Primary efficacy endpoint is overall composite driving performance Z score approximately 1 hour after study intervention instillation.

3.2 Other Efficacy Endpoints

- Hazard avoidance
- Road sign recognition
- Road sign recognition distance
- Pedestrian recognition distance
- Lane keeping
- Driving time
- Pupil diameter
- Halometer
- Night-driving experience questionnaire

3.3 Safety Endpoints

- Mesopic/photopic habitual distance visual acuity (HDVA)
- Adverse events (AEs)
- Pregnancy tests for women of childbearing potential (WOCBP)
- Slit-lamp biomicroscopy
- Intraocular pressure (IOP) measurements

4.0 Analysis Populations

The following populations are defined:

Population	Description
Intent-to-Treat (ITT)	The ITT population includes all randomized participants.
Safety	The safety population includes all treated participants who receive ≥ 1 administration of study intervention.

For analyses based on the ITT population, participants will be summarized according to the randomized study intervention. For analyses based on the Safety population, participants will be summarized according to the study intervention they actually receive in each period.

Also, only statistical analyses of safety will be performed by study period as defined in Table 4-1.

Table 4-1 Definition of the Control Period

Period	Start Date	End Date
Period 1	Date of the first dose at Visit 2	• For participants who do not receive the treatment at Visit 4: the end date is the study exit date. • For participants who receive the treatment at Visit 4: the end date is the date when the treatment is received at Visit 4 minus 1 day.
Period 2	Dose date at Visit 4	Study exit date

5.0 Subject Disposition

The total number of participants who were screened, enrolled (randomized), and treated will be summarized. Reasons for exclusion, including screen failure, will be summarized.

A summary of participant accountability will be provided where the number of participants in each of the following categories will be summarized for each intervention group:

- participants randomized in the study;
- participants who took at least one dose of study drug;

- participants who completed protocol-specified treatment;
- participants who prematurely discontinued study drug and reasons for discontinuation;
- participants in each analysis population, as applicable.

Participant disposition will be summarized by study intervention sequence for the entire study and for Period 1 and Period 2.

6.0 Study Drug Duration

For the safety population, duration of treatment will be summarized by study intervention group. Duration of treatment for each intervention group is defined for each participant as the duration of treatment in Period 1 or Period 2, last dose date minus first dose date in each period +1. Duration of treatment will be summarized using the number of participants treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of participants in each treatment duration interval (1 to 7, 8 to 15, and > 15 days) will be summarized by study intervention group.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, medical history, ophthalmic history and prior and concomitant medications will be summarized by study intervention sequence and in total (e.g., across study intervention sequence) for the ITT population. Categorical variables will be summarized with the number and percentage of participants; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity, race and age (<=50 and > 50 years) when applicable

Demographic parameters will be summarized descriptively by study intervention sequence and in total for the ITT population. Age is calculated from birthdate to the informed consent date in years.

Corrected distance visual acuity (CDVA) and distance-corrected near visual acuity (DCNVA) at baseline will be summarized descriptively by study intervention sequence and in total for the ITT population.

7.2 Medical History

Medical and ophthalmic history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report.

The number and percentage of participants in each medical history category (by MedDRA system organ class and preferred term) will be summarized in total and by study intervention sequence. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Participants reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Ophthalmic history will be summarized similarly. Medical and ophthalmic histories include medical condition prior to Day 1 baseline visit, whether ongoing or resolved.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study

drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug. The number and percentage of participants taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

The number and percentage of participants reporting prior medications will be summarized by drug generic name in total and by study intervention sequence. If a participant took a specific medication multiple times or took multiple medication within the same generic name, the participant will be counted only once for the generic name.

The number and percentage of participants reporting concomitant medications will be summarized by drug generic name by study intervention group. The listings will be provided for prior and concomitant medications.

7.4 Data Collected but Not Analyzed

Iris color assessment, vital signs, ocular surface disease index, National Eye Institute Visual Function questionnaire 25, fluorescein corneal stain, gonioscopy/angle assessment, binocular mesopic and photopic high contrast, BCDVA and DCNVA assessments, manifest refraction and dilated fundoscopic examination results are collected only at Screening and will not be analyzed. Any clinically significant vital sign findings or abnormal pupil dilation findings will be captured as an adverse event and summarized accordingly.

8.0 Efficacy Analyses

8.1 General Considerations

- The primary analysis will be performed after the database is locked and randomization schedule is released.
- Efficacy endpoints will be analyzed using the ITT population. The 95% confidence intervals will be provided for the primary endpoint.

- Baseline for efficacy is defined as the last nonmissing efficacy assessment before the first dose of study intervention in each period or randomization if no study drug is given when applicable.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum.
- Categorical variables will be summarized by number of participants with observed values (n), frequency counts (n1) and percent of participants with observed values.

8.2 Handling of Missing Data

Missing continuous and categorical efficacy data will be analyzed based on observed data. Missing values will be not imputed.

8.3 Primary Efficacy Endpoint and Analyses

8.3.1 Primary Efficacy Endpoint

The night-driving evaluation will be performed approximately 1 hour following study intervention instillation at both driving visits.

The overall composite driving performance Z score for a participant is calculated using the average of Z scores for the following component driving measures: percent hazards hit, percent sign recognition and recognition distance, pedestrian recognition distance, lap duration and percent of time outside of the lane (lane-keeping).

A participant's Z score for a given component driving measure is calculated using the mean and standard deviation from the pooled treatment data. Since a lower percent of hazards hit, lower percentage of time outside of the lane and a shorter lap duration is indicative of better performance, the Z scores of these three components are reversed (e.g., -1 x Z score) before computing the overall driving Z score.

The primary efficacy endpoint is overall composite driving performance Z score approximately 1 hour after study intervention instillation.

8.3.2 Handling of Missing Data for the Primary Efficacy Endpoint

For primary analysis, the missing data will be handled using a MMRM model with the missing at random (MAR) assumption, in which both missingness of data and the correlation of the repeated measurements will be considered.

8.3.3 Primary Efficacy Analysis

Primary efficacy endpoint (overall composite driving performance Z score approximately 1 hour after study intervention instillation) will be analyzed using a linear mixed-effects model with repeated measures (MMRM).

The model will use overall composite driving performance Z score approximately 1 hour after study intervention instillation as dependent variable, include study intervention group (AGN-190584, vehicle), study intervention sequence (Sequence 1: AGN-190584 followed by vehicle, Sequence 2: vehicle followed by AGN-190584), and study period (Period 1, Period 2) as fixed effects and participant nested within sequence of testing as a random effect. The covariance structure to model the within-participant correlation error structure will be unstructured. If the unstructured covariance matrix results in a lack of convergence, compound symmetry covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom.

The least-square (LS) mean and 95% CI will be provided for each study intervention (AGN-190584, or vehicle) in overall composite driving performance driving Z score.

The comparison between the two study interventions (AGN-190584 vs. vehicle) will be performed by providing LS mean and 95% CI for the between-group difference in the overall composite driving performance Z score. Noninferiority of AGN-190584 will be concluded if the lower bound of the 95% CI of the least square mean difference between AGN-190584 and vehicle is greater than -0.25.

8.3.4 Additional Analyses of the Primary Efficacy Endpoint

The primary endpoint will also be summarized by descriptive statistics. The observed data will be used, and no imputation will be performed.

8.4 Other Efficacy Analyses

The other effectiveness analyses will be performed using the ITT population for all variables listed in Table 8-1

The continuous efficacy endpoints will be summarized by descriptive statistics. The number and percentage of participants reporting each response will be provided for the 12 questions in the night-driving experience questionnaire. The denominator will be the number of the participants with a non-missing response for the specific question. The results will be presented by study intervention group. The results for "AGN-190584" group will be based on Period 1 data for study intervention sequence "AGN-190584 followed by vehicle", and Period 2 data for study intervention sequence "vehicle followed by AGN-190584". The results for "vehicle" group will be based on Period 2 data for study intervention sequence "AGN-190584 followed by vehicle", and Period 1 data for study intervention sequence "vehicle followed by AGN-190584".

The other efficacy analysis results will be deemed supportive. No hypotheses will be tested on the other efficacy endpoints, and no multiplicity adjustment will be performed.

Table 8-1 Other Effectiveness Analyses

Endpoint	Description	Derivation	Methodology
Hazard avoidance	Percentage of hazards hit for each participant	Calculated from the reported total number of hazards and the number of hazards hit.	Continuous descriptive statistics
Sign recognition	Percentage of sign recognition for each participant	Calculated from the reported total number of signs and the number of signs correctly identified	Continuous descriptive statistics
Sign recognition distance	Recognition distance in meters to one specific sign	Reported distance	Continuous descriptive statistics
Lane-keeping	Percentage of time outside of the lane (lane-keeping)	Calculated post-testing from the reported total driving time and reported time outside of lane. Lane crossings where the participant is responding to a hazard on the road are not included.	Continuous descriptive statistics
Pedestrian recognition distance	Distance for pedestrian recognition	Reported distance	Continuous descriptive statistics
Driving time	The time to complete the road course	Reported time (min, sec) converted to seconds	Continuous descriptive statistics
Pupil diameter	Measured before dosing, after dosing at driving test visit in each eye	Reported value	Continuous descriptive statistics
Halometer	The area of the halo surrounding the LED glare source	Reported value	Continuous descriptive statistics
Night-driving experience questionnaire	12 questions to evaluate the participants' night driving experience	Reported responses to each question	Ordinal descriptive statistics and response frequencies

8.5 Efficacy Subgroup Analyses

No efficacy subgroup analyses will be performed for this study.

9.0 Safety Analyses

9.1 General Considerations

- The safety endpoints will be analyzed with descriptive statistics using the safety population.
- The safety results will be presented by study intervention group.
- The results for "AGN-190584" group will be based on Period 1 data for study intervention sequence "AGN-190584 followed by vehicle", and Period 2 data for study intervention sequence "vehicle followed by AGN-190584".
- The results for "vehicle" group will be based on Period 2 data for study intervention sequence "AGN-190584 followed by vehicle", and Period 1 data for study intervention sequence "vehicle followed by AGN-190584".
- For each study period, the baseline for safety parameters will be the last assessment prior to the first administration of study intervention in the period unless specified otherwise.
- For each study period, the change from baseline values will be computed as the postbaseline value minus the baseline value (defined above) for that study period.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum.
- Categorical variables will be summarized by number of participants with observed values (n), frequency counts (n1) and percent of participants with observed values.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) 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 AE tables and in the clinical study report.

9.2.1 Treatment-Emergent Adverse Events

An AE will be considered a treatment emergent adverse events (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE. Per the AE/SAE training manual, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those AEs with recorded onset date on or after the date of the first study intervention and within 30 days after the last dose of study intervention.

An AE will be considered a treatment emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any serious adverse event (SAE) criterion.

9.2.2 Adverse Event Overview

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

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

- Any treatment-emergent AE (ocular and non-ocular)
- Any treatment-emergent AE with reasonable possibility of being related to study drug according to the investigator (ocular and non-ocular)
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
- Any treatment-emergent AE: headache of special interest
- Any treatment-emergent AE: visual disturbance of special interest
- All deaths

Overall summary of TEAEs will be provided by study intervention group on a per-participant level.

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

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT. Specific adverse events will be counted once for each participant for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a participant, the highest severity and level of relationship to investigational product will be reported.

Nonocular TEAEs will also be summarized by SOC and PT.

Ocular TEAEs will be summarized by preferred term and maximum relationship to study drug assessed by investigator.

9.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All the SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and presented in listing format. The listing will indicate if an AE is ocular or nonocular. All nonocular SAEs (including deaths) and nonocular AEs leading to study drug discontinuation will be summarized by SOC and PT.

9.2.5 Adverse Events of Special Interest

Headache of special interest and visual disturbance of special interest are the adverse events of special interest. List of PT for AEs of special interest is provided in Appendix B. The TEAEs of special interest will be summarized by study intervention group.

A similar summary will be provided for visual disturbance TEAEs of special interest. The definition of these adverse events of special interest is described in Appendix B. The list of preferred terms used for the analysis will be reviewed and finalized prior to database lock.

9.3 Vital Signs

Vital signs are collected only at screening and data will not be analyzed.

9.4 Pregnancy

Positive test results for women of childbearing potential will be listed.

9.5 Ocular Safety Analyses

9.5.1 Slit-lamp Biomicroscopy and Ophthalmoscopy

All biomicroscopy and ophthalmoscopy examinations findings will be coded using the MedDRA dictionary.

The number and percentage of participants with biomicroscopy or ophthalmoscopy findings of greater than 1-grade severity increase from baseline for findings with a severity grade, or a positive status change from absence at baseline to presence at postbaseline (not associated with a severity grade), will be summarized by preferred term and study intervention group.

9.5.2 Mesopic and Photopic Binocular HDVA

Binocular HDVA will be tested using logMAR charts at 4 m under 2 lighting conditions: mesopic luminance (10 to 11 lux) and photopic luminance (≥ 251 lux) under normal room lighting. Testing will be conducted with the optimal distance refractive correction. Forced choice letter-by-letter scoring will be used for each test and the total number of correct letters or the highest value (number) of the grid identified (as applicable) will be collected for each eye.

The total number of correct letters or the highest value (number) of the grid identified (as applicable) will be summarized by study intervention group, at the participant level for the screening test, before dosing at each driving test visit, and after dosing at each driving test visit for each lighting condition. The change at each driving test (post dosing assessment

minus pre dosing assessment) will also be summarized by study intervention group, at the participant level.

9.5.3 Intraocular Pressure

Intraocular pressure (IOP) will be measured for each eye, IOP change from baseline will be calculated for each eye and the summary will be based on the eye with greater decrease from baseline.

10.0 Interim Analyses

No interim analysis is planned for this study.

10.1 Data Monitoring Committee

Data monitoring committee is not required for this study.

11.0 Overall Type-I Error Control

There is only 1 statistical hypothesis on primary endpoint in this study. No multiplicity adjustment will be performed.

12.0 Version History

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1		Not Applicable	Original version

13.0 References

14.0 Appendices

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest (*if applicable*)

Table 14-1 List of Preferred Terms for AEs of Special Interest[1]

Area of Safety Interest	*Preferred Term*
Headache of special interest	*Headache*
	Migraine
	Migraine with aura
	Sinus headache
	Other PT related to headache of special interest
Visual Disturbance of Special Interest	*Dyschromatopsia*
	Glare
	Halo vision
	Metamorphopsia
	Photophobia
	Photopsia
	Pseudomyopia
	Vision blurred
	Visual acuity reduced
	Visual field defect
	Visual impairment
	Other PT related to vision impairment of special interest

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

Appendix C. List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
BCDVA	distance-corrected distance visual acuity
DCNVA	distance-corrected near visual acuity
HDVA	habitual distance visual acuity
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment emergent serious adverse event
WOCBP	women of childbearing potential

Appendix D. Changes to Protocol-planned Analyses

There are no changes from the protocol-planned analyses.