Title Page

Protocol Title: A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

Protocol Number: 1883-302-013

Compound Number: AGN-190584

Short Title: Phase 3 efficacy study of AGN-190584 in participants with presbyopia

Sponsor Name: Allergan, Inc.

Legal Registered Address: 2525 Dupont Drive, Irvine, CA 92612, USA

[redacted]

Enter Registry Name	**Phase 3 efficacy study of AGN-190584 in participants with presbyopia**

Approval Date: August 20, 2020

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SAP Version History

This Statistical Analysis Plan (SAP) for study 1883-302-013 is based on the protocol dated March 06, 2020.

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

1. 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 the final protocol amendment 1 of study 1883-302-013 (dated 06 March 2020). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for health economics data will be prepared separately.

Objectives and Endpoints

The objectives of this study are to evaluate the efficacy and safety of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia. Details of the study objectives and corresponding endpoints are described in the table below:

Objectives	Endpoints

To evaluate the efficacy of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia.	• Mesopic and photopic, high contrast DCNVA for each eye and binocularly
	• Mesopic and photopic, high contrast DCIVA for each eye and binocularly
	[redacted]
	• PRO questionnaires:
	  ○ Mesopic and Photopic NVPTQ
	  ○ PICQ
	[redacted]

To evaluate the safety and tolerability of AGN-190584 when administered bilaterally, once daily for 30 days in participants with presbyopia	• AEs • Photopic and mesopic high contrast CDVA for each eye and binocularly • Near Contrast sensitivity • Vital signs (blood pressure and heart rate) • Study drug tolerability and drop comfort assessments • Temporal/supraorbital headache VAS • IOP • Slit-lamp biomicroscopy • Manifest refraction • Dilated funduscopic examination

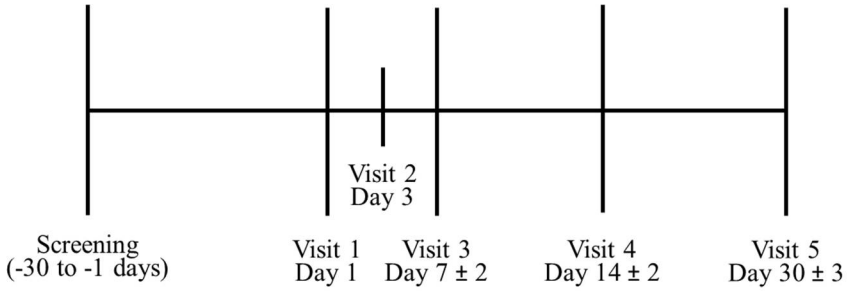
1.1. Study Design

Study 1883-302-013 is a multicenter, double-masked, randomized, vehicle-controlled, parallel group, phase 3 study evaluating the efficacy and safety of AGN-190584 (1.25% pilocarpine) dosed once daily, bilaterally, over a period of 30 days in participants with presbyopia. The study population will consist of adult male and female participants with objective and subjective evidence of presbyopia. Approximately 200 participants per group will be randomized.

Participants will be randomized in a 1:1 ratio to receive either AGN-190584 or vehicle dosed once daily, in each eye, for 30 days. This randomization will be stratified by age (2 groups: ≤ 50 years and > 50 years), baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes. This study consists of the following visits: screening (Days -30 to -1), Day 1 (baseline), and Days 3, 7, 14, and 30.

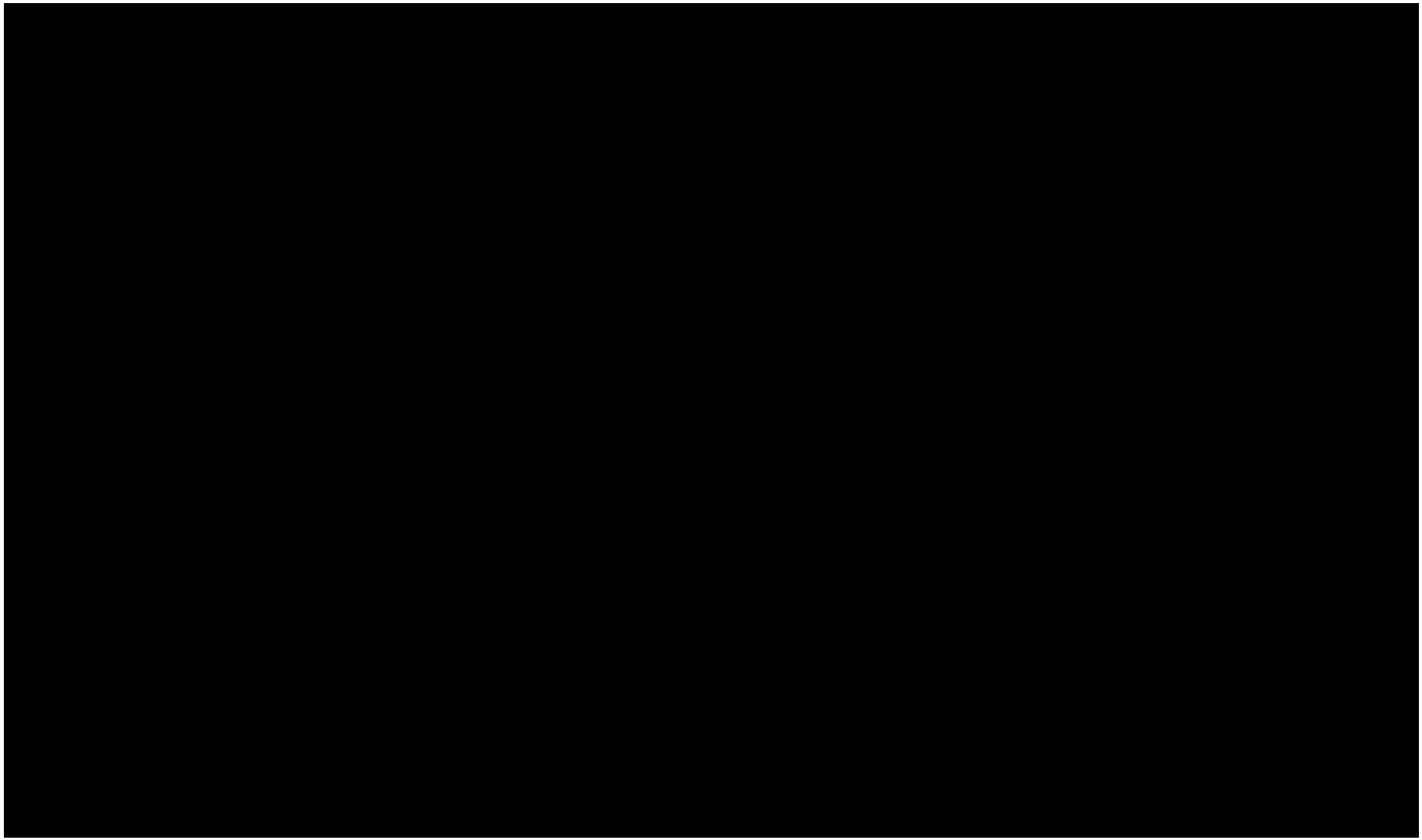
Study interventions, either AGN-190584 or vehicle will be administered as topical eye drop once daily. Following the study schema (Figure 1-1), study intervention will be administered by designated site personnel on visit days and at home by the participant in-between office visits, ideally prior to starting their day. On the day before office visits, the study intervention must be administered no less than 16 hours before the scheduled visit time.

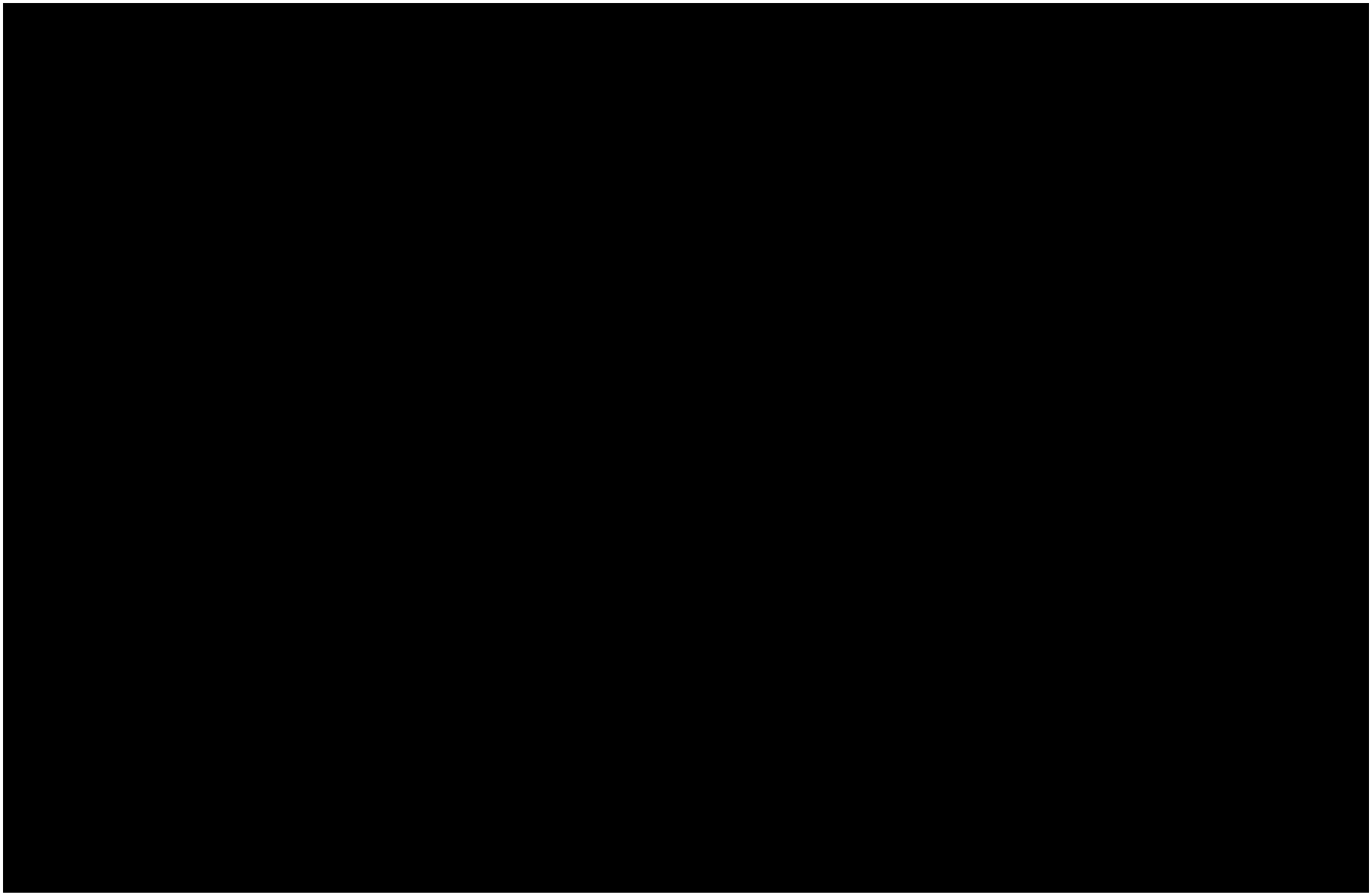
Figure 1-1 Study Schema



The schedule of activities for Study 1883-302-013 is presented in Table 1-1 and Table 1-2.

Table 1-1 Schedule of Visits and Procedures: Screening to Visit 3





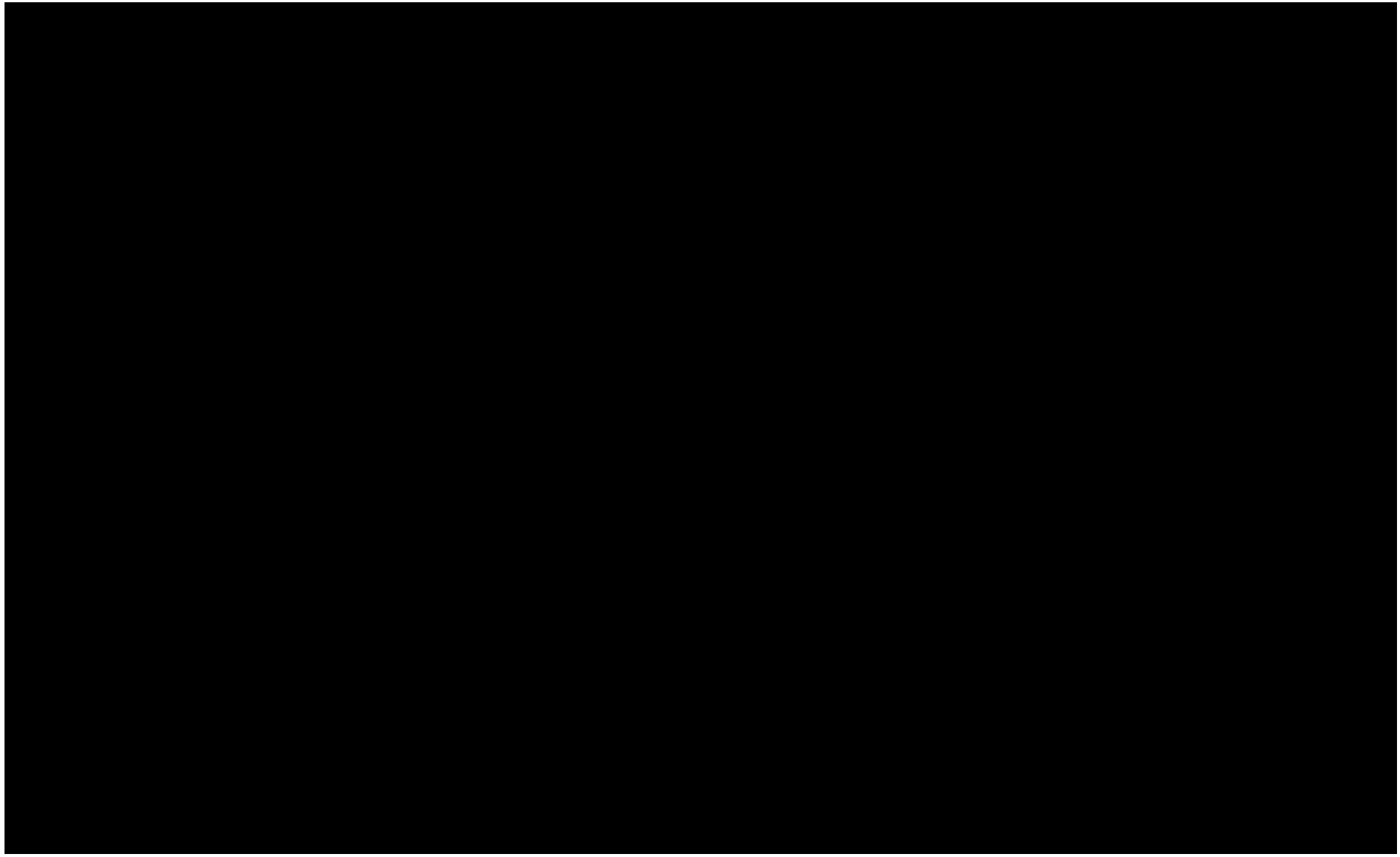
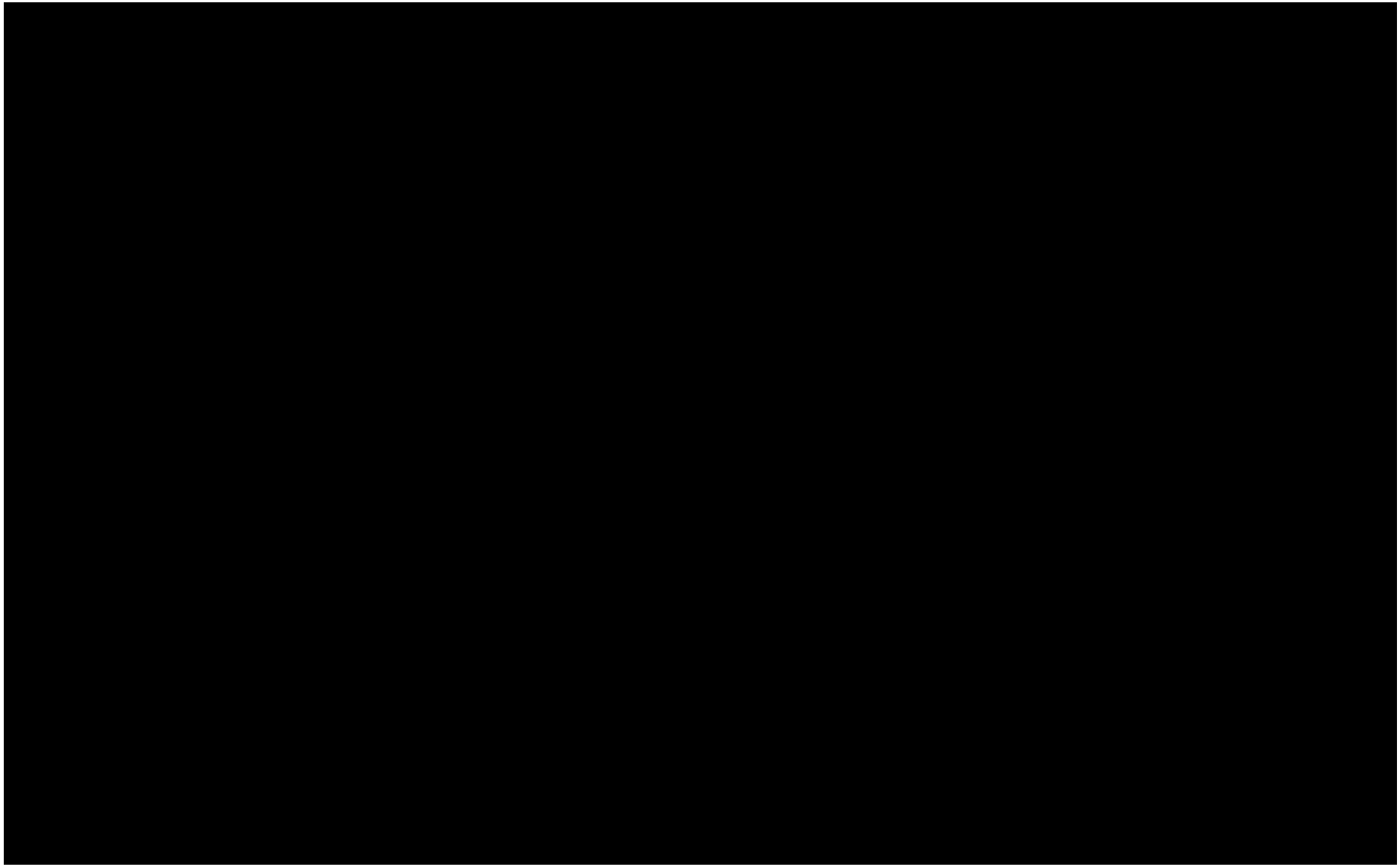
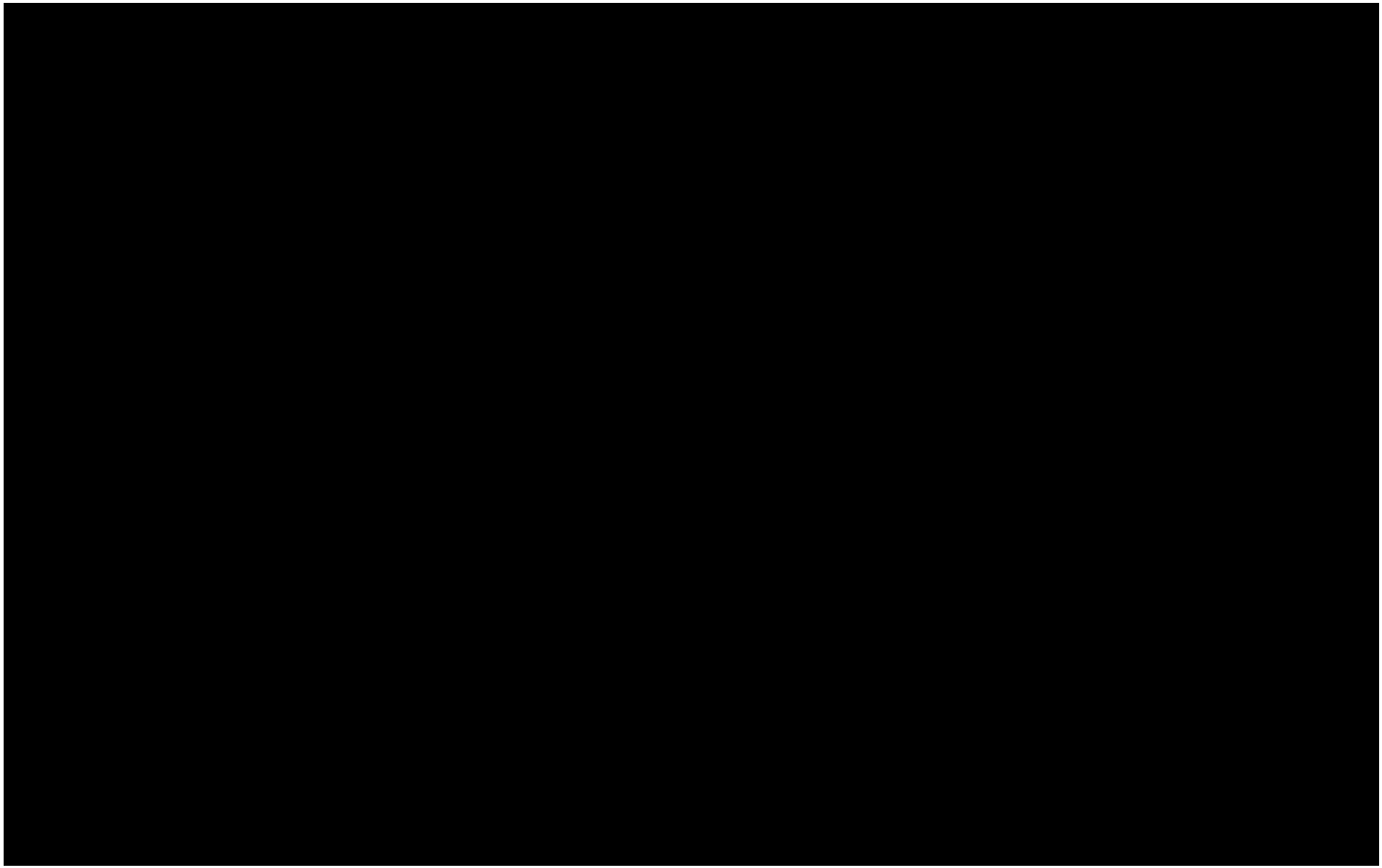
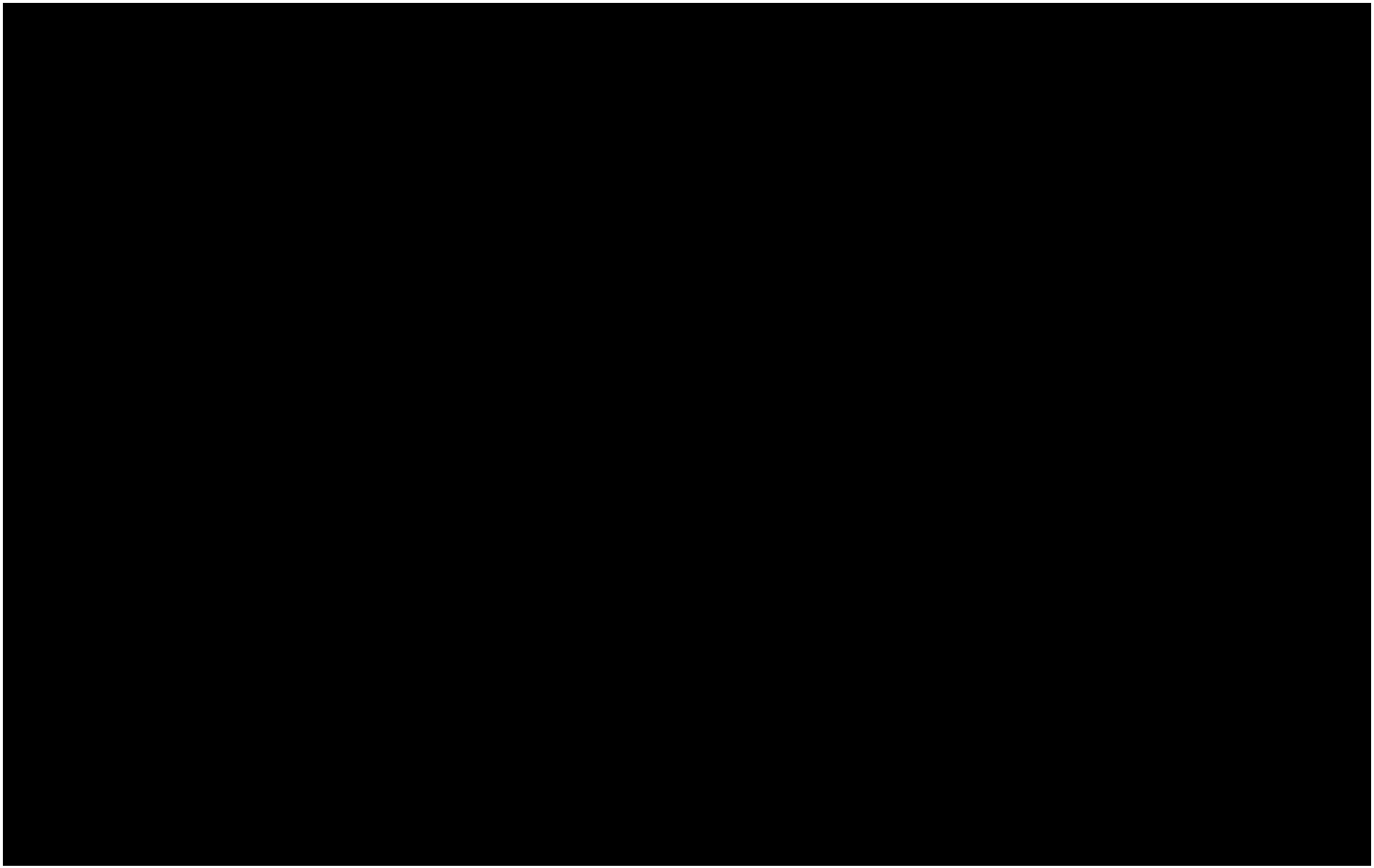


Table 1-2 Schedule of Visits and Procedures: Visit 4 to Visit 5/Early Exit







2. Statistical Hypotheses

For the primary efficacy analysis, the null hypothesis is that there is no difference between AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days in the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA without losing more than 5-letters of mesopic, high contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3. The alternative hypothesis is that there is a difference between AGN-190584 ophthalmic solution and vehicle.

For the key secondary efficacy analysis, the null hypothesis is that there is no difference between AGN-190584 ophthalmic solution and vehicle dosed bilaterally, once daily for 30 days in the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The alternative hypothesis is that there is a difference between AGN-190584 ophthalmic solution and vehicle.

The hypotheses will be tested using chi-square tests at a significance level of 5%.

3. Sample Size Determination

The primary efficacy parameter is the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA without losing more than 5-letters of mesopic, high contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3. The key secondary efficacy parameter is the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The sample size calculation is based on the key secondary efficacy parameter.

The vehicle group intervention effect and AGN-190584 effect are assumed to be 8.8% and 18.4%, respectively, as observed in the Phase 3 study 1883-301-013. Two hundred (200) participants will be required in each study intervention group to detect the above difference with a power of 80% or greater at the 2-sided 5% significance level.

4. Populations for Analysis

Two analysis populations were defined for this study as follows:

- The intent-to-treat (ITT) population will consist of all randomized participants. The analysis using the ITT population will be based on the study intervention assigned.
- The safety population will consist of all participants who received at least 1 administration of study intervention. The analysis using the safety population will be based on the actual study intervention received.

5. Statistical Analyses

5.1. General Considerations

- Efficacy endpoints will be analyzed using the ITT population, and the safety endpoints will be analyzed using the safety population.
- The baseline for efficacy and safety will be the last non-missing assessment prior to the first administration of study intervention. For participants who were randomized but not treated, the baseline value will be the assessment collected on or prior to the randomization date, whichever is later.
- The change from baseline values will be computed as the postbaseline value minus the baseline value.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max).
- Categorical variables will be summarized by number of participants with observed values or events (n), frequency count (n1) and percentage of participants with observed values or events.
- All statistical hypothesis tests will be performed at the 2-sided 5% significance level, unless stated otherwise. All confidence intervals will be at least 2-sided 95% confidence intervals.
- In general, statistical analyses will be performed using SAS version 9.4 or higher. MedDRA version 22.1 or higher will be used to code adverse events, biomicroscopy, and medical history. WHODRUG Enhanced B2 will be used to code medications.

To control the overall Type 1 error rate in the efficacy analysis, a gatekeeping testing strategy will be used. All secondary efficacy endpoints will be tested only if the primary efficacy endpoint is statistically significant and the testing procedures are described in the graphical procedure in Figure 5-1.

For primary and key secondary analyses, participants with missing data will be regarded as non-responders. Analyses for other secondary efficacy endpoints will be based on observed data only.

Per confirmation of the site, DCNVA measurements were not conducted correctly for participants at investigator site 051 at screening visit and baseline visit (Day 1 Hour 0). In error, the participants were corrected for near vision rather than distance vision when these

measurements were taken. Therefore, it is decided to exclude all participants from this site from efficacy analyses. These participants will be included in all safety analyses.

5.2. Participant Disposition

The number of participants screened for the study will be provided.

Summary of study disposition post randomization will be provided by study intervention group as randomized for the following:

- Number of participants randomized; this frequency count will be used as the denominator to calculate the percentages described below
- Number and percentage of participants treated
- Number and percentage of participants who completed the study
- Number and percentage of participants who discontinued the study
- Reasons for discontinuation from the study

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The primary efficacy parameter will be the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA without losing more than 5-letters of mesopic, high contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3.

5.3.2. Main Analytical Approach

The primary efficacy parameter will be analyzed using a chi-square test with 2-sided 95% confidence interval based on the normal approximation based on pooled variance without continuity correction.

5.3.3. Sensitivity Analysis

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

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Secondary Analysis

The key secondary efficacy endpoint will be the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA at Day 30, Hour 6. The key secondary efficacy parameter will be analyzed in the same way as the primary efficacy parameter.

5.4.2. Other Secondary Analyses

Other secondary efficacy endpoints include:

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

All secondary endpoints related to proportion of participant gaining 3 lines or more or achieving 20/40 better (endpoints 1, 3, 6 and 8) will be analyzed with the same analysis method as the primary efficacy parameter.

Timepoints are defined as scheduled measurement times made for each visit. Change from baseline in mesopic, high contrast, binocular DCNVA letters (endpoints 2 and 7) will be analyzed using mixed-effects model with repeated measures (MMRM) by timepoint that includes treatment, visit, treatment by visit interaction, age group, baseline DCNVA severity, iris color, and emmetropes/non-emmetropes as factors as well as baseline DCNVA value, and baseline DCNVA value by visit interaction as covariates under the assumption of missing at random (MAR). An unstructured covariance matrix will be used as the covariance structure for

repeated measurements. A sensitivity analysis will be implemented with the missing data imputed with the average outcome of the vehicle arm under the assumption of missing not at random (MNAR). Change from baseline in photopic, high contrast, binocular DCIVA letters (endpoints 4) will be analyzed with the similar way as change from baseline in mesopic, high contrast, binocular DCNVA letters. Baseline DCIVA will be included as the covariate instead of baseline DCNVA.

NVPTQ and PICQ scoring algorithms are provided in Appendix 4. Change from baseline in the mesopic NVPTQ Performance score, Mesopic NVPTQ Satisfaction score, PICQ Coping score, and PICQ Impact score (endpoints 4, 9, 10 and 11) will be analyzed using an analysis of covariance (ANCOVA) model that includes treatment, age group, baseline DCNVA severity, iris color, emmetropes/non-emmetropes as factors as well as baseline PRO score as covariate. Also, the cumulative distribution function (CDF) curves will be presented for each of the change from baseline PRO domain scores. The CDF curves (one per domain score for a total of four) represent the cumulative proportion of patients with any particular level of CFB in PRO domain scores at Day 30 Hour 3, by treatment arm. Curves will be produced with a vertical line drawn at the responder threshold.

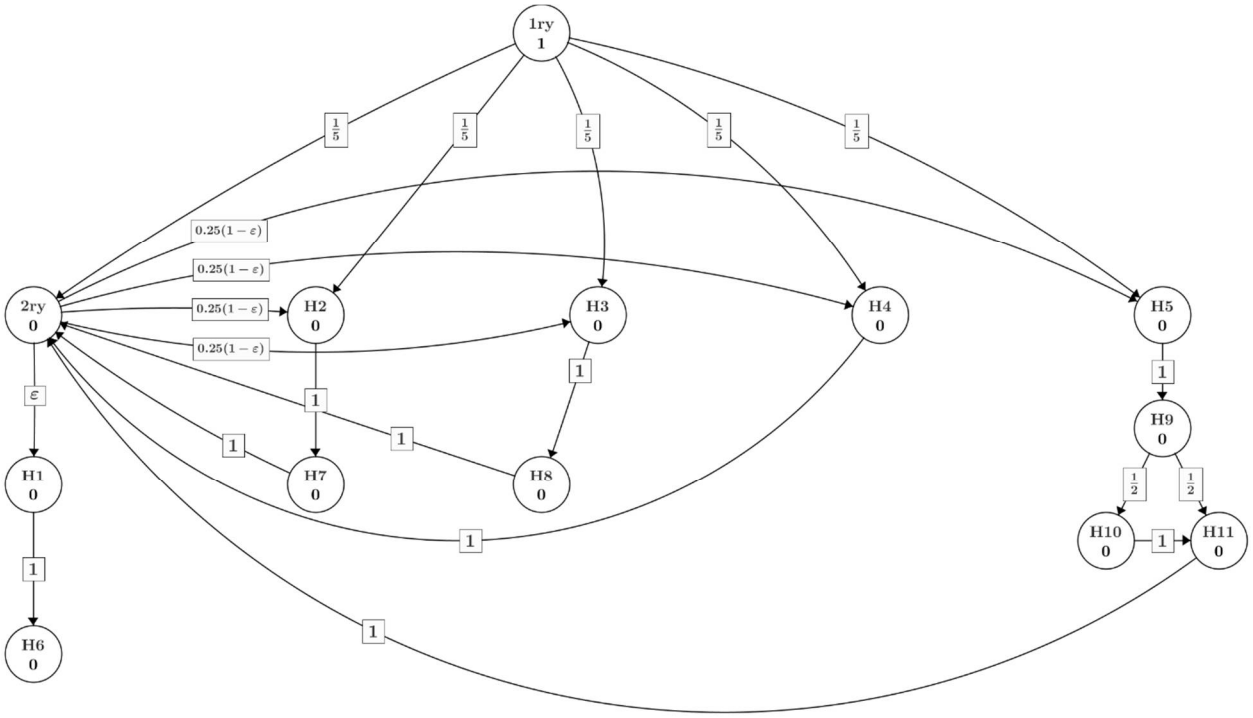
5.4.3. Multiplicity Adjustment

The graphical procedure displayed in Figure 5-1 will be employed to control the overall familywise error rate at α=0.05 for the following hypotheses testing. Let 1ry, 2ry, H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, and H11 represent the treatment effect comparisons of AGN-190584 with vehicle. Details of the hypotheses and corresponding efficacy parameters are described in Table 5-1.

Table 5-1 Hypotheses and Corresponding Efficacy Parameters

Hypothesis	Efficacy Parameter
1yr	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA without losing more than 5-letters of mesopic, high contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3
2ry	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 6
H1	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 8
H2	Change from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.5
H3	Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 1
H4	Change from baseline in photopic, high contrast, binocular DCIVA letters at Day 30, Hour 3
H5	Change from baseline in Mesopic NVPTQ Performance score at Day 30, Hour 3
H6	Proportion of participants gaining 3-lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 10
H7	Change from baseline mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.25
H8	Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 3
H9	Change from baseline in Mesopic NVPTQ Satisfaction score at Day 30, Hour 3
H10	Change from baseline in PICQ Coping score at Day 30, Hour 3
H11	Change from baseline in PICQ Impact score at Day 30, Hour 3

Figure 5-1 Graphical Testing Procedure



Specifically, 2ry, H2, H3, H4 and H5 will be tested at a=0.01 separately. If 2ry, H2, H3, H4 or H5 is rejected, H7, H8 or H9 will then be tested. If H9 is rejected, H10 and H11 will then be tested. H1 and H6 will be tested only if all other endpoints are significant.

[redacted]

5.6. Safety Analyses

The safety analyses will be performed using the safety population. The safety parameters will include AEs, vital signs (blood pressure and heart rate), mesopic and photopic, high contrast, CDVA, for each eye and binocularly, study intervention tolerability and drop comfort assessments, temporal/supraorbital headache assessment using VAS, IOP, slit-lamp biomicroscopy and near contrast sensitivity. For each safety parameter, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

5.6.1. Extent of Exposure

The exposure to study intervention, calculated as (last study intervention date - first study intervention date + 1), will be summarized using descriptive statistics by treatment for the safety population.

5.6.2. 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) after the first administration of study intervention. However, an AE that occurs more than 30 days after the last administration of study intervention will not be counted as a TEAE.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by descending percentage in any group, by SOC and PT, and further categorized by severity and causal relationship to the study intervention. If more than 1 AE is coded to the same PT for the same participant, the participant will be counted only once for that PT using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The incidence of common (≥ 5% of participants in any treatment group) TEAEs will be summarized by SOC, PT, and treatment group.

The total number of TEAEs by severity will be summarized by treatment group. The total number of TEAEs as well as headache of special interest by causal relationship to the study intervention will be summarized by treatment group. The number and percentage of participants reporting study intervention related TEAEs will be tabulated by SOC and PT.

An ocular AE is defined as the location of AE occurring in the eye. Ocular and nonocular headache of special interest will be summarized.

A TESAE is defined as an SAE that is also a TEAE. The number and percentage of participants who have TESAEs will be summarized by PT and treatment group. In addition, the incidence of on-therapy SAEs that lead to death will be summarized separately by PT for each treatment group.

Summary tables will be provided for TEAEs leading to discontinuation and TESAEs. Listings of all TEAEs, SAEs, and AEs leading to discontinuation by participant will be presented.

5.6.3. 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.

5.6.4. Mesopic, High Contrast, Binocular CDVA

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

5.6.5. Photopic, High Contrast, Binocular CDVA

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

5.6.6. Study Intervention Tolerability and Drop Comfort Assessments

Ocular tolerability assessment will be performed at each visit. Symptoms of blurred vision, foreign body sensation, pain, burning/stinging, tearing, and itching will be assessed using a 5-point scale (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe) for the severity and a 3-point scale (<1 min, 1 to 5 min, and >5 min) for the duration. Drop comfort will be assessed using a 6-point scale (soothing, very comfortable, comfortable, uncomfortable, very uncomfortable, and intolerable). For the severity, duration, and drop comfort, the number and percentage of participants in each category will be tabulated for each time point by treatment group.

5.6.7. Temporal/Supraorbital Headache Visual Analog Scale

Temporal and supraorbital headache will be separately assessed for each eye using a VAS at each visit. The reported values and the changes from baseline will be summarized using descriptive statistics for each time point for each eye by treatment group.

5.6.8. Intraocular Pressure

IOP is measured for each eye using the Goldmann applanation tonometer at each visit. Tabulations will be based on the worst change (greater increase from baseline) between 2 eyes assessed at each visit. Descriptive statistics for IOP and changes from baseline at each assessment timepoint will be presented by treatment group.

5.6.9. 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 lids/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 participants with clinically significant biomicroscopy findings will be tabulated by finding category, assessment timepoint and treatment group. A clinically significant finding is defined as more than one severity grade increase (worsening) from baseline 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).

5.6.10. Near Contrast Sensitivity

Near contrast sensitivity assessment is conducted under photopic conditions. A Pelli-Robson contrast sensitivity chart is used. The logarithmic contrast sensitivity value of the last triplet of which at least 2 letters are correct read is marked as contrast sensitivity. Descriptive statistics for near contrast sensitivity and changes from baseline at each assessment timepoint will be presented by treatment group.

[redacted]

5.8. Interim Analyses

No interim analysis is planned for this study.

5.8.1. Data Monitoring Committee

Data monitoring committee is not required for this study.

6. Supporting Documentation

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
bpm	beats per minute
CDF	cumulative distribution function
CDVA	corrected distance visual acuity
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
eCRF	electronic case report form
ID	identification
IOP	intraocular pressure
ITT	intent-to-treat
IxRS	interactive electronic response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury
MMRM	mixed model repeated measure
MNAR	missing not at random
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
NVPTQ	Near Vision Presbyopia Task-based Questionnaire
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
PCS	potentially clinically significant
[redacted]	
PICQ	Presbyopia Impact and Coping Questionnaire
[redacted]	
PRO	patient reported outcomes

PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
VAS	visual analog scale
WHO DDE	World Health Organization Drug Dictionary Enhanced
WOCBP	women of childbearing potential

6.2. Appendix 2: Changes to Protocol-Planned Analyses

The primary efficacy endpoint will be the proportion of participants gaining 3 lines or more from baseline in mesopic, high contrast, binocular DCNVA without losing more than 5-letters of mesopic, high contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3.

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographics

Demographic parameters (age; age groups of ≤ 50 years and > 50 years; sex; race; ethnicity) will be summarized descriptively by treatment group for the ITT populations.

6.3.2. Baseline Characteristics

Baseline binocular DCNVA (2 groups: 20/40 to 20/60 inclusively, and worse than 20/60), iris color (brown and non-brown), and emmetropes/non-emmetropes will be summarized descriptively with frequency and percentage by treatment group for the ITT population.

6.3.3. Protocol Deviations

Unique participants reporting significant protocol deviations will be summarized in total and by treatment group for all randomized participants.

6.3.4. Medical History

Medical and surgical history will be summarized by treatment group for the Safety Population. Medical history includes prior medical history (prior to Day 1, first dose date) and still ongoing.

6.3.5. Ophthalmic Medical History

Ophthalmic medical and surgical history will be summarized by treatment group for the Safety Population. Ophthalmic medical history includes prior medical history (prior to Day 1, first dose date) and still ongoing.

6.3.6. Prior/Concomitant medications

Prior medication is defined as any medications taken prior to the start of study intervention. *Concomitant medication* is defined as any medication taken on or after the start of study intervention regardless of the start date of the medication.

The number and percentage of participants with prior and concomitant medication use will be summarized by treatment group and Anatomical Therapeutic Chemical code for the safety population. If a participant took a specific medication multiple times or took multiple medications within the same therapeutic class, the participant will be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc.) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be

reviewed during the course of the study and may be pooled under a single coded drug name for analyses. No statistical comparisons will be performed.

6.4. Appendix 4: PRO Scoring Algorithm

6.4.1. NVPTQ Performance Domain Score

To account for the impact of squinting on performance, the responses to the pair of performance and squinting items on each task is combined into a new testlet variable informed by a series of item response theory models. For performance and squinting, this new testlet variable is created by combining all possible response categories according to Table 1.

Table 1 Testlet variable values based on combining performance item responses and squinting item responses

Squinting / Performance	Yes, but I still could not read any of the text (2)	Yes, and squinting helped me read some or all of the text (1)	No, I did not squint (0)
I could not read any of the text due to problems seeing up close (0)	0	0	0
Poor (1)		0	1
Fair (2)		1	2
Good (3)		2	3
Very Good (4)		3	4
Excellent (5)		4	5

Note. The values in parentheses are the raw values corresponding to the item response. These are the variable values in the ADaM datasets.

If the response to either the performance or squinting item within a task is missing, then the corresponding testlet is assigned a missing value. Because the four tasks are highly related, there is no limit on the number of missing testlet scores to be able to calculate the performance domain score. The performance domain score is calculated as the average of the non-missing testlet values as follows:

NVPTQ Performance Score = (Book testlet + Newspaper testlet + Menu testlet + Nutrition Label testlet) / (# testlets with non-missing responses)

The NVPTQ Performance Score ranges from 0 to 5, with 0 corresponding to poorest performance and 5 corresponding to best performance. Thus, higher scores correspond to better outcomes This algorithm puts the performance score on the original performance item response metric, which also ranges from 0 to 5, so the performance item responses can be referenced when interpreting the score. Individual-level score changes of 0.75 points or greater can be considered clinically meaningful; i.e., an individual whose NVPTQ Performance Score increases by at least 0.75 points from baseline can be considered a responder.

6.4.2. NVPTQ Satisfaction Domain Score

To account for the impact of squinting on satisfaction, the responses to the pair of satisfaction and squinting items on each task is combined into a new testlet variable informed by a series of item response theory models. For satisfaction and squinting, this new testlet variable is created by combining all possible response categories according to Table 2.

Table 2 Testlet variable values based on combining satisfaction item responses and squinting item responses

Squinting / Satisfaction	Yes, but I still could not read any of the text (2)	Yes, and squinting helped me read some or all of the text (1)	No, I did not squint (0)
Very dissatisfied (0)	0	0	0
Dissatisfied (1)		0	1
Neither satisfied nor dissatisfied (2)		1	2
Satisfied (3)		2	3
Very satisfied (4)		3	4

Note. The values in parentheses are the raw values corresponding to the item response. These are the variable values in the ADaM datasets.

If the response to either the satisfaction or squinting item within a task is missing, then the corresponding testlet is assigned a missing value. Because the four tasks are highly related, there is no limit on the number of missing testlet scores to be able to calculate the satisfaction domain score. The satisfaction domain score is calculated as the average of the non-missing testlet values as follows:

NVPTQ Satisfaction Score = (Book testlet + Newspaper testlet + Menu testlet + Nutrition Label testlet) / (# testlets with non-missing responses)

The NVPTQ Satisfaction Score ranges from 0 to 4, with 0 corresponding to greatest dissatisfaction and 4 corresponding to greatest satisfaction . Thus, higher scores correspond to better outcomes. This algorithm puts the satisfaction score on the original satisfaction item response metric, which also ranges from 0 to 4, so the satisfaction item responses can be referenced when interpreting the score. Individual-level score changes of 1.00 points or greater can be considered clinically meaningful; i.e., an individual whose NVPTQ Satisfaction Score increases by at least 1.00 points from baseline can be considered a responder.

6.4.3. PICQ Coping Score

The coping domain consists of the following 8 items:

- Item 1: Normal-sized text
- Item 2: Small-sized text
- Item 3: Information on a computer
- Item 4: Information on a cell phone
- Item 5: Increase font size
- Item 6: Use glasses to read close
- Item 12: Hold reading materials farther out or closer
- Item 13: Squint to read

Each of these items includes response categories ranging from 0, corresponding to “Never”, to 4, corresponding to “All of the time.” Items 3, 4, 5, and 6 include additional response categories, labeled with values of 9 or 10, to indicate that the question is not applicable because the participant did not use the object being evaluated (e.g., “I did not use a computer over the past 7 days”) or because the participant did not have the opportunity to change his behavior (e.g., “I permanently increased the font size on my computer, tablet, or cell phone prior to the past 7 days”). Responses in these “not applicable” categories labeled 9 or 10 are assigned missing values.

Because of the similarity of the content of certain item pairs, two new testlet variables are created prior to scoring. The testlet variable for Item 1 and Item 2 is calculated by computing the mean of the non-missing responses to the two items. The testlet variable for Item 3 and Item 4 is calculated by computing the mean of the non-missing responses to the two items. If either item in the testlet pair has a missing value, the testlet value is assigned the value of the non-missing item. If both items in the testlet pair have missing values, then the testlet is assigned a missing value.

Items 1&2 Testlet = (Item 1 + Item 2)/ # non-missing responses to Item 1 and Item 2

Items 3&4 Testlet = (Item 3 + Item 4) /# non-missing responses to Item 3 and Item 4

After the testlet variables have been created, the coping domain score is calculated as the mean of the non-missing values to the coping testlets and single coping items. Because the coping items are well-related and internally consistent, and because missing data are expected for some items due to the "not applicable" response categories, there is no limit on the number of missing item responses to be able to calculate the coping domain score.

PICQ Coping Score = (Item 1&2 Testlet + Item 3&4 Testlet + Item 5 + Item 6 + Item 12 + Item 13) /# non-missing responses to the 6 components of the coping score

The PICQ Coping Score ranges from 0 to 4, with 0 corresponding to least amount of coping and 4 corresponding to the greatest amount of coping. Thus, higher scores correspond to poorer outcomes. This algorithm puts the coping score on the original item response metric, which also ranges from 0 to 4, so the coping item responses can be referenced when interpreting the score. Individual-level score changes of 1.00 points or greater can be considered clinically meaningful; i.e., an individual whose PICQ Coping Score decreases by at least 1.00 points from baseline can be considered a responder.

6.4.4. PICQ Impact Score

The impacts domain consists of the following 6 items:

- Item 9: Rely on others
- Item 15: Rest eyes
- Item 16: Feel older
- Item 17: Feel self-conscious
- Item 19: Take longer to complete a task
- Item 20: Inconvenient

The first five impacts items include response categories ranging from 0, corresponding to "Never", to 4, corresponding to "All of the time." Item 20 uses response categories ranging from 0, corresponding to "Not at all", to 4, corresponding to "Extremely." Item 9 includes an additional response category, labeled with a value of 9, to indicate that the question is not applicable because the subject did not have the opportunity to experience the impact (i.e., "Never because I used or did something to help"). Responses in this "not applicable" category are assigned missing values.

Because of the similarity of the content of Item 16 and Item 17, a new testlet variable is created prior to scoring by computing the mean of the non-missing responses to the two items. If either

item in the testlet pair has a missing value, the testlet is assigned the value of the non-missing item. If both items in the testlet pair have missing values, then the testlet is assigned a missing value.

Items 16&17 Testlet = (Item 16 + Item 17) /# non-missing responses to Item 16 and Item 17

After the testlet variable has been created, the impacts domain score is calculated as the mean of the non-missing values to the impacts testlet and single impacts items. Because the impacts items are well-related and internally consistent, and because missing data are expected for some items due to the "not applicable" response categories, there is no limit on the number of missing item responses to be able to calculate the impacts domain score.

PICQ Impacts Score = (Item 9 + Item 15 + Items 16&17 Testlet + Item 19 + Item 20) /# non-missing responses to the 5 components of the impacts score

The PICQ Impacts Score ranges from 0 to 4, with 0 corresponding to least amount of impacts and 4 corresponding to the greatest amount of impacts. Thus, higher scores correspond to poorer outcomes. This algorithm puts the impacts score on the original item response metric, which also ranges from 0 to 4, so the impacts item responses can be referenced when interpreting the score. Individual-level score changes of 1.00 points or greater can be considered clinically meaningful; i.e., an individual whose PICQ Impacts Score decreases by at least 1.00 points from baseline can be considered a responder.

6.5. Data handling convention

6.5.1. Visit Time Windows

For ITT and safety by-visit analyses, all follow-up visits or the exit visit, participants will be reassigned with the visit number based on the number of days from the first dose date according to the following windows corresponding to relevant analysis.

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Statistical Analyses Window
Pretreatment	Baseline	Day 1 (Visit 1)	Treatment Day ≤ 1, pre-dose/randomization
Treatment	Day 1	Day 1 (Visit 1)	Treatment Day 1, post dose/randomization
	Day 3	Day 3 (Visit 2)	Treatment Day [2, 4]
	Day 7	Day 7 (Visit 3)	Treatment Day [5, 10]

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Statistical Analyses Window
	Day 14	Day 14 (Visit 4)	Treatment Day [11, 21]
	Day 30	Day 30 (Visit 5)	Treatment Day [22, 45]

If multiple assessments were taken within an analysis window, the assessment obtained on the day closest to the target day will be used; in the case of a tie, the assessment obtained on the later day will be used in the analysis.

6.5.2. Missing Date of the Last Dose of Study Intervention

When the date of the last dose of study intervention is missing for a participant in the safety population, all efforts should be made to obtain the date from the investigator. If the data is still missing after all efforts have been made, the last available dosing record date will be used as the last dose date.

6.5.3. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If the severity of a TEAE is missing, the maximum severity will be assigned to the event for the summarization by severity. The value will be displayed as missing in the data listing.

6.5.4. Missing Causal Relationship to Study Drug for Adverse Events

If the relationship to the study intervention is missing for a TEAE, the event will be considered related to the study intervention for the summarization. The value will be displayed as missing in the data listing.

6.5.5. Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing):

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study intervention, the date of the first dose of study intervention will be assigned to the missing start date.
- If the stop date is before the date of the first dose of study intervention, the stop date will be assigned to the missing start date.

6.5.6. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

6.5.6.1. Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day.

6.5.6.2. Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study intervention is missing, impute it as descripted in Section 6.5.3. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study intervention, the month and day of the last dose of study intervention will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the last dose of study intervention, *December 31* will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last dose of study intervention, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study intervention, the day of the last dose of study intervention will be assigned to the missing day.
- If either the year of the incomplete stop date is before the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study intervention, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete stop date is after the year of the date of the last dose of study intervention or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study intervention, the first day of the month will be assigned to the missing day.

7. References

Not Applicable.

Electronic Signatures

User	Date	Justification
[redacted]	21-Aug-2020 16:48:35 (GMT)	Subject Matter Expert Approval
	20-Aug-2020 23:42:57 (GMT)	Manager Approval
	20-Aug-2020 22:44:05 (GMT)	Document Originator Approval
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