Statistical Analysis Plan for Study 2012-201-005 Stage 2

A Multicenter, Vehicle-controlled, Randomized Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of AGN-242428 and AGN-231868 in Participants with Dry Eye Disease

Date: 07 December 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 for Stage 2 of this study as outlined and specified in the 2012-201-005 protocol amendment 3 (approved version dated 19 July 2021). Specifications of tables, figures and data listings are contained in a separate document. Details of the analyses of pharmacokinetic data [redacted] will be documented separately before final database lock.

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 and Hypothesis

This is the first-in-human study to evaluate the safety, tolerability, PK, and efficacy of AGN-242428 and AGN-231868 administered through topical ocular instillation. Data collected from animal studies suggest that both interventions have a good safety profile and the potential to reduce the signs and symptoms of dry eye disease (DED). Data from this study will guide future development of either or both compounds for the treatment of DED.

Table 1. Stage 2 - Study Objectives and Assessments/Endpoints

Objectives	Assessments/Endpoints
Primary	
• To evaluate the safety and tolerability of AGN-242428 and AGN-231868 and their respective vehicles in participants with DED	• AEs, clinical laboratory values, vital signs, ECG findings, IOP, BCVA, slit lamp biomicroscopy, dilated fundus examination, Drop Tolerability Questionnaire score
Secondary	
• To assess the plasma exposure of AGN-242428 and AGN-231868; and tear exposure of AGN-242428, AGN-231868, and lifitegrast in participants with DED following twice daily dosing for up to 6 weeks	• Trough plasma or tear concentration (C_{trough}) and plasma or tear concentration at 0.5 hours post-dose ($C_{0\ 5h}$)
Tertiary/Exploratory	
[redacted]	

2.2 Study Design Overview

This is a Phase 1/2a, multicenter, vehicle-controlled, double-masked, randomized study conducted in 2 consecutive stages in participants with DED. Stage 1 was conducted at 2 sites in the United States and Stage 2 will be conducted at up to approximately 8 sites in the United States.

Stage 1 was planned to evaluate the safety, tolerability, and PK (plasma and tear) of 3 dose strengths of AGN-242428 ([redacted]) and AGN-231868 ([redacted]) in participants with DED.

The AGN-242428 and AGN-231868 dose strengths used in Stage 2 were selected based on safety and tolerability assessed in Stage 1; the highest safe and tolerated dose strength of each intervention (AGN-242428[redacted] and AGN-231868[redacted]) was selected for testing in Stage 2. All participants enrolled in Stage 2 will have DED. In addition, participants will be selected based on their response to the controlled adverse environment (CAE). Only participants with DED who respond to the CAE with an increase in the signs and symptoms of DED will be enrolled in Stage 2.

In Stage 2, [redacted] participants will undergo another assessment of the signs and symptoms of DED with and without the use of the CAE. Only participants who requalify, based on inclusion/exclusion criteria, will be continued in the study.

[redacted] participants will be randomized at baseline, in a 1:1:1:1:1 ratio within each site, to receive AGN-242428, AGN-242428 vehicle, AGN-231868, AGN-231868 vehicle, or Xiidra.

All randomized participants will be administered 1 drop of assigned study intervention in each eye twice daily (approximately 12 hours apart) for 41 days, followed by a single dose administration on Day 42. [redacted] will be assessed on Day 42 with and without the use of the CAE. In addition, [redacted] without the use of the CAE will be assessed on Days 1, 14 and 28.

Assuming no early termination, the duration of participation for each participant in this stage of the study will be approximately 2.5 months (up to 14 days prior to Visit 2 on Day -14 through the last assessment on Day 42).

The Stage 2 schematic for the study is shown in Figure 1.

Figure 1. Study Schematic - Stage 2

2.3 Treatment Assignment and Masking

Participants will be randomized to one of the following study interventions in a 1:1:1:1:1 ratio:

- AGN-242428
- AGN-242428 vehicle
- AGN-231868

- AGN-231868 vehicle
- Xiidra

Randomization will not be stratified. The study eye will be defined as [redacted] at baseline. If both eyes qualify and have [redacted], then study eye will be defined as the eye with [redacted]. If both eyes still qualify, the right eye will be designated as the study eye. Unless otherwise specified, all the applicable assessments will be performed in both eyes.

[redacted] After randomization, the investigator, site staff, and participants will be masked to study intervention.

The AGN-242428, AGN-231868 and their vehicles will be provided in identical single-use vials. Xiidra will be supplied in single-use, commercially available vials that will have the original label overlaid with a new clinical label to prevent unmasking.

[redacted]

2.4 Sample Size Determination

For Stages 1 and 2, the sample size is not based on statistical considerations and is determined empirically. Approximately 322 participants (72 in Stage 1 and 250 in Stage 2) will be enrolled in the study. No participant can be enrolled in more than 1 cohort and/or stage of the study.

3.0 Endpoints

3.1 Safety Endpoints

Safety endpoints are listed as the following:

- adverse events (AEs),
- clinical laboratory values at the Exit/Early Termination visit,
- vital signs at each post-baseline visit,
- electrocardiogram (ECG) findings at the Exit/Early Termination visit,
- intraocular pressure (IOP) at each post-baseline visit,
- best-corrected visual acuity (BCVA) at each post-baseline visit,
- slit-lamp biomicroscopy findings at each post-baseline visit,
- dilated fundus (ophthalmoscopy) examination findings at the Exit/Early Termination visit,
- Drop Tolerability Questionnaire score at each post-baseline visit.

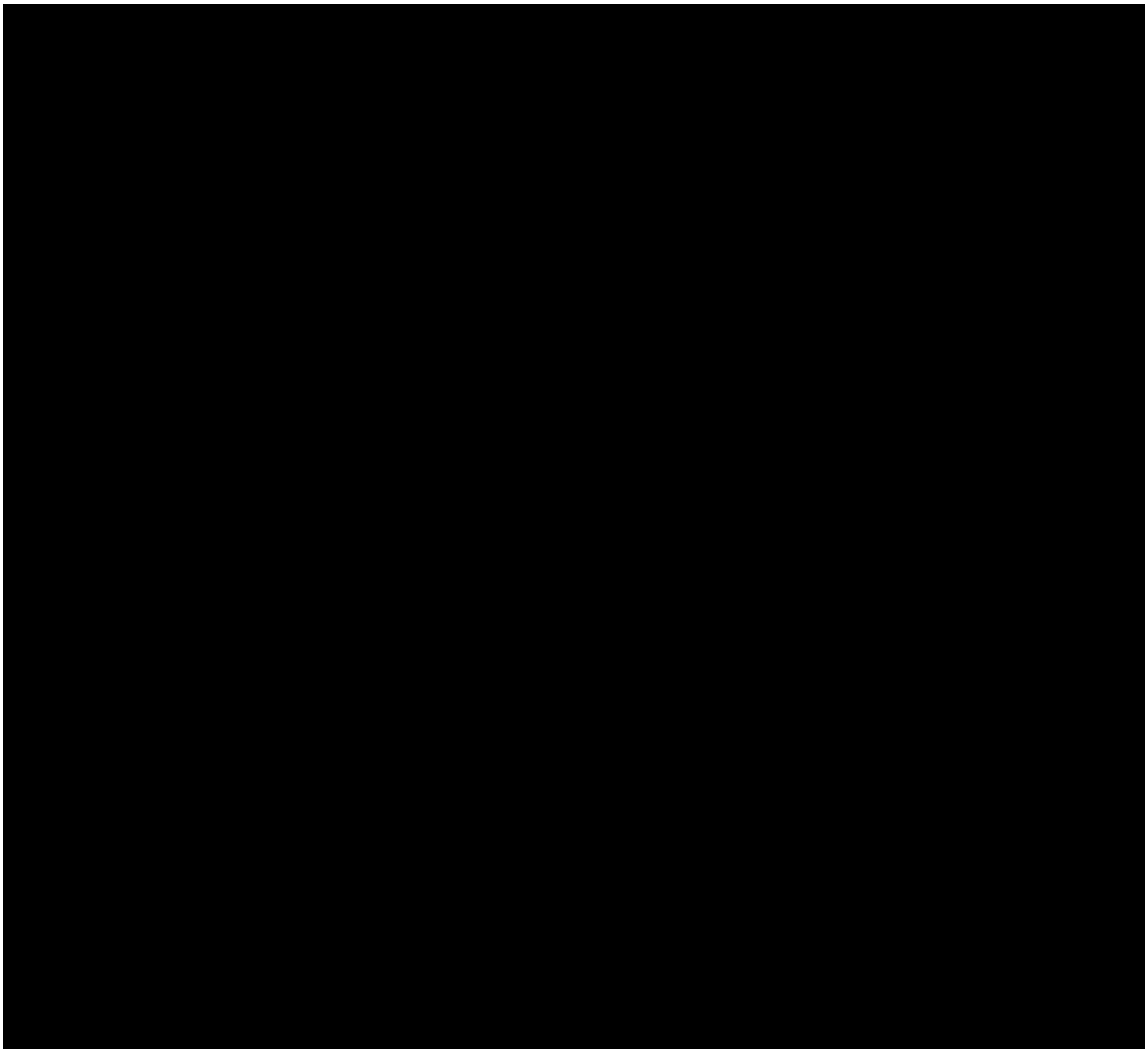
For eye-related endpoints, both eyes will be included in the analysis.

3.2 Secondary endpoints

The secondary endpoints are trough plasma or tear concentration (C_{trough}) and plasma or tear concentration at 0.5 hours post-dose ($C_{0.5h}$). Details of endpoint and analysis will be included in a separate PK SAP.

3.3 Tertiary/Exploratory Efficacy Endpoints

[redacted]



4.0 Analysis Populations

The analysis populations related to the statistical analysis detailed in this document will consist of participants as defined in Table 3. Additional analysis populations, such as PK population and biomarker population will be described separately in other analysis plans. There are a run-in period and a randomized study intervention period in Stage 2.

Table 3. Analysis Populations

Population	Definition
Intent-to-Treat (ITT)	All participants who are randomized. Participants will be summarized according to the randomized study intervention.
Safety	All participants who receive ≥ 1 administration of study intervention for Stage 2. • Safety population in randomized study intervention period includes all participants who receive ≥ 1 administration of randomized study intervention. • The safety analysis will mainly be performed based on safety population in randomized study intervention period. • Participants will be summarized according to the study drug that they actually received. • Unless otherwise specified, study intervention and safety population will refer to the study intervention and safety population in randomized study intervention period in this SAP.

5.0 Subject Disposition

The number of participants who are screened and enter the run-in period for the study will be provided. The number of participants in the study populations (ITT population and Safety population) will be summarized by study intervention group.

The 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 completing the study
- Number and percentage of participants discontinued from the study
- Reasons for discontinuation from the study

In addition, a listing will be provided for participant disposition. A participant is counted as completing the study if he/she has completed all study visits including Day 42 (Exit)

Visit. Participants that exit the study prior to the Day 42 visit will be considered discontinued from the study.

6.0 Study Drug Duration and Compliance

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

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

7.1 Demographics and Baseline Characteristics

Demographic parameters (age [years]; sex; race; ethnicity) will be summarized descriptively by study intervention group for the ITT population.

Baseline characteristics including [redacted] BCVA, IOP values and [redacted] weight, height, and body mass index will be summarized descriptively by study intervention group for the ITT population.

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 participants 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 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).

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?"). The ophthalmic medical history will be summarized in a similar way to medical history.

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 intervention. A concomitant medication is defined as any medication that starts prior to the date of the first dose of study intervention and continues to be taken after the first dose of study intervention or any medication that starts on or after the date of the first dose of study intervention.

The number and percentage of participants taking medications will be summarized by preferred drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications, respectively.

8.4 Efficacy Subgroup Analyses

No subgroup analyses are planned.

9.0 Safety Analyses

9.1 General Considerations

The below general considerations will be applied to safety analyses, unless specified otherwise.

- Safety analyses will be based on safety data using the safety population based on the actual treatment received.

- A participant's actual treatment will be determined by the first dose of study drug.
- In general, baseline is defined as the last non-missing scheduled assessment prior to the first administration of study intervention (non-missing assessment before Day 1 study intervention).
- The change from baseline values at a visit will be computed as the value for the post baseline visit minus the baseline value, unless otherwise indicated.
- Descriptive statistics for continuous variables include the sample size (n, mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum).
- Summary statistics for categorical variables include the sample size (n), frequency count, and percentage.
- AEs and findings from biomicroscopy and ophthalmoscopy examinations will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher, according to the version of the MedDRA coding dictionary used for the study at the time of database lock.

9.2 Adverse Events

AEs will be summarized and presented using primary MedDRA SOCs and preferred terms (PTs). 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 for a participant, the highest severity and level of relationship to investigational product will be reported.

9.2.1 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 drug. Events where the onset date is the same as the study drug start date are assumed to be treatment emergent.

In general, the number and percentage of participants 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 drug within each SOC. The number and percentage of participants experiencing TEAEs will also be summarized by PT for identifying common AEs. TEAEs by PT summaries will be presented in decreasing frequency order on active study drug.

9.2.2 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" 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 eye disorders.

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:

- TEAEs
  - Ocular TEAEs
  - Non-ocular TEAEs
- TEAEs related to study drug
  - Ocular TEAEs related to study drug according to the investigator
  - Non-ocular TEAEs related to study drug according to the investigator
- Severe TEAEs
- Serious TEAEs
  - Ocular serious TEAEs
  - Non-ocular serious TEAEs
- TEAEs leading to withdrawal of study treatment
  - Ocular leading to withdrawal of study treatment
  - Non-ocular leading to withdrawal of study treatment
- TEAEs of special interest
- TEAEs leading to death

- All deaths
- COVID-19 infection.

9.2.3 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
  - Non-ocular TEAEs by SOC and PT
- TEAEs by PT
- TEAEs related to study drug by SOC and PT
  - Ocular TEAEs related to study drug by SOC and PT
  - Non-ocular TEAEs related to study drug by SOC and PT
- TEAEs by SOC, PT, and maximum severity
  - Ocular TEAEs by SOC, PT, and maximum severity
  - Non-ocular TEAEs by SOC, PT, and maximum severity

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

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

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

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

9.2.5 Adverse Events of Special Interest

Summary table by PT will be provided for Adverse Events of Special Interest (AESI) as defined in Appendix B, which will also be provided in a listing.

9.3 Analysis of Laboratory Data

Descriptive statistics for values and changes from the baseline in standard units at each assessment time point will be presented by study intervention group.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or upper-limit PCS criteria listed in Appendix C. The number and percentage of participants who have PCS post-baseline clinical laboratory values will be tabulated by study intervention for all scheduled postbaseline visit. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value.

9.4 Analysis of Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, weight, respiration rate, and temperature) and their changes from baseline at each assessment timepoint will be presented by study intervention group.

Selected vital signs will be considered potentially clinically significant (PCS) if they meet either the lower-limit or upper-limit PCS criteria listed in Appendix C. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study intervention for each postbaseline visit assessments. The percentages will be calculated relative to the number of participants who have available baseline values for those parameters with the change from baseline value criterion or non-PCS baseline values for those vital sign parameters without the change from baseline value criterion and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value.

9.5 Analysis of Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTc) at baseline, Exit visit (pre-CAE and post-CAE) or Early Termination visit, and changes from baseline at the Exit visit will be presented by study intervention group.

ECG values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or upper-limit PCS criteria listed in Appendix C. The number and percentage of participants who have PCS postbaseline ECG values will be tabulated by study intervention for Exit visit (pre-CAE and post-CAE) and Early Termination visit assessments. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value.

9.6 Analysis of Best-corrected Visual Acuity

BCVA will be quantified using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol. Descriptive statistics for BCVA and changes from baseline at each post-baseline visit will be presented by study intervention, and by study eye and nonstudy eye. Change from baseline will also be summarized by study intervention for each eye at each visit in a categorical tabulation as severe (≥ 30 letters decrease from baseline), moderate (≥ 15 and < 30 letters decrease from baseline) and no loss or mild (< 15 letters decrease from baseline).

9.7 Intraocular Pressure

Descriptive statistics for IOP and changes from baseline at each post-baseline visit will be presented by study intervention for each eye.

9.8 Biomicroscopy and Ophthalmoscopy

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 a) the anterior chamber 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; and b) flare: 0=none, +1=faint, +2=moderate, +3= marked and +4=intense).

[redacted] will be summarized using descriptive statistics at all post-baseline visits and pre-/post-CAE when applicable. For Pre-CAE change from baseline, the Day 1 Pre-CAE value prior to the administration of the first administration of study intervention will be used as baseline. For Post-CAE change from baseline, the Day 1 Post-CAE value prior to the administration of the first administration of study intervention will be used as baseline.

The number of participants with biomicroscopy findings of ≥ 2-grade severity increase from baseline will be generated for MedDRA preferred terms recorded on the Ocular Biomicroscopic Exam eCRFs at each post-baseline visit by study intervention for each eye. For findings under other pathology which are not associated with a severity grade, a status change from absent to present will be treated as a 2-grade increase in the analysis. At least 2-grade increase in severity from baseline is defined as a change from no finding to 2 and above, from 0.5 to 2 and above, or from 1 to 3 and above from baseline at any of the follow-up visits. The number and percentage of participants with clinically significant biomicroscopy findings (at least 2-grade increase in severity from baseline) will be tabulated by finding category, and study intervention group.

The ophthalmoscopy findings will be summarized similarly.

9.9 Safety Subgroup Analyses (if applicable)

No safety subgroup analyses are planned.

10.0 Interim Analyses

An interim database lock occurred after completion of Stage 1, and the unmasking and data analyses were performed. This doesn't affect masking of Stage 2. At the end of study, the final database lock will occur.

11.0 Version History

Table 4. SAP Version History Summary

Version	Date	Summary
1.0	07 December 2021	Original version

12.0 Appendices

Appendix A. Protocol Deviations

According to ICH E3 2012 guideline, only important protocol deviations will be reported in CSR. The number and percentage of randomized participants with important protocol deviations will be summarized overall and by study intervention group for participants reported by protocol deviation categories:

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

Appendix B. Definition of Adverse Events of Special Interest

The following adverse events of special interest (AESI) (serious or nonserious) are defined in the protocol and will be summarized by PT terms listed in Table 5:

- AST and/or ALT increased to ≥ 5 ULN
- AST and/or ALT increased to ≥ 3 × ULN AND total bilirubin increased to ≥ 2 × ULN. Typically, all analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period.
- AST and/or ALT increased to ≥ 3 × ULN with symptoms believed to be related to liver injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia > 5%)
- Potential Hy's Law cases:
  - ALT and/or AST ≥ 3 × ULN AND
  - TBL ≥ 2 × ULN AND
  - Alkaline phosphatase < 2 × ULN

Table 5. List of Preferred Terms for Adverse Events of Special Interest

Preferred Term (PT)	PT Code
Aspartate aminotransferase increased	10003481
Alanine aminotransferase increased	10001551
Blood bilirubin increased	10005364
Blood alkaline phosphatase increased	10059570

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The potentially clinically significant criteria for clinical laboratory parameters, vital signs and ECG parameters are provided in the following sections.

Table 6. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Laboratory Group	Parameter	SI Unit	PCS Low Limit	PCS High Limit
Hematology	Eosinophils absolute cell count	10^9/L	—	> 1.5 × ULN
	Hematocrit	%	< 0.8 × LLN	≥ 1.2 × ULN
	Hemoglobin	g/L	< 0.8 × LLN	≥ 1.2 × ULN
	Lymphocytes absolute cell count	10^9/L	< 0.8 × LLN	> 1.2 × ULN
	Neutrophils absolute cell count	10^9/L	< 0.6 × LLN	> 1.6 × ULN
	Platelet count (thrombocytes)	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.8 × LLN	> 1.2 × ULN
	White blood cell count	10^9/L	< 0.7 × LLN	> 1.8 × ULN
Chemistry	Alanine aminotransferase	U/L	—	> 3 × ULN
	Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Alkaline phosphatase	U/L	—	> 3 × ULN
	Aspartate aminotransferase	U/L	—	> 3 × ULN
	Bilirubin, total	µmol/L	—	> 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.3 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.2 × ULN
	Creatinine	µmol/L	—	> 1.8 × ULN
	Glucose, fasting	mmol/L	< 0.8 × LLN	> 1.2 × ULN
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 1.4 × ULN
	Phosphorus	mmol/L	< 0.8 × LLN	> 1.2 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Uric acid (urate)	µmol/L	—	> 1.2 × ULN

Laboratory Group	Parameter	SI Unit	PCS Low Limit	PCS High Limit
Urinalysis	Glucose	µmol/L	—	≥ 0.015
	Glucose (alternate units)	—	—	≥ 2+
	pH	—	< 0.9 × LLN	> 1.1 × ULN
	Protein	g/L	—	≥ 1.0
	Protein (alternate units)	—	—	≥ 2+
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal (value provided by the laboratory); PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal (value provided by the laboratory)

Table 7. Potentially Clinically Significant Criteria for Vital Signs Parameters

Parameter	Unit	PCS Category	PCS Criteria	
			Actual Value	Change from Baseline
Sitting Systolic BP	mmHg	High	≥ 180	Increase of ≥ 20
		Low	≤ 90	Decrease of ≥ 20
Sitting Diastolic BP	mmHg	High	≥ 105	Increase of ≥ 15
		Low	≤ 50	Decrease of ≥ 15
Sitting Pulse rate	bpm	High	≥ 120	Increase of ≥ 15
		Low	≤ 50	Decrease of ≥ 15
Weight	kg	High	—	Increase of ≥ 7%
		Low	—	Decrease of ≥ 7%
Respiratory Rate	bpm	High	≥ 28	—
		Low	≤ 8	—
Temperature	°C	High	> 38	—
		Low	< 35	—

BP = blood pressure; bpm = beats/breaths per minute

ECG values meeting *either* the actual value or change from baseline PCS high criteria will be categorized as PCS.

Table 8. Potentially Clinically Significant Criteria for ECG Parameters

Parameter	Unit	PCS High Criteria	
		Actual Value	Change from Baseline
QRS interval	msec	≥ 150	—
PR interval	msec	≥ 250	—
QTcF	msec	> 500	Increase > 60

QTcF = QTc Fridericia

Appendix D. List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AGN	Allergan
ATC	Anatomical therapeutic chemical
BCVA	best corrected visual acuity
CAE	controlled adverse environment
DED	dry eye disease
DMC	data monitoring committee
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
IOP	intraocular pressure
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
ODS	Ocular Discomfort Scale
[redacted]	[redacted]
PCS	potentially clinically significant
PK	pharmacokinetic
PT	preferred term
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
[redacted]	[redacted]
WHO	World Health Organization

Appendix E. Changes to Protocol-planned Analyses

No statistical comparisons/tests among the study intervention groups will be performed for the safety data.

Title Page

Protocol Title:
A Multicenter, Vehicle-controlled, Double-Masked, Randomized Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Exploratory Efficacy of AGN-242428 and AGN-231868 in Participants with Dry Eye Disease

Protocol Number: 2012-201-005 [Stage 1]

Compound Number: AGN-242428 and AGN-231868

Short Title:
Safety, Tolerability, Pharmacokinetics, and Efficacy of AGN-242428 and AGN-231868 in Participants with Dry Eye Disease

Sponsor Name: Allergan Sales LLC

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

Regulatory Agency Identifier Number(s)

Registry	ID
IND	139391, 139392

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List of Tables

SAP Version History

This Safety Statistical Analysis Plan (SAP) for Stage 1 of study 2012-201-005 is based on the protocol amendment 2, dated 27 April 2020.

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

1. Introduction

This SAP provides a technical and detailed elaboration of the statistical analyses of the Stage 1 safety data as outlined and specified in the final protocol of 2012-201-005 (Amendment 2, 27 April 2020). Specifications of tables and data listings are contained in a separate document. A separate SAP will be developed for Stage 2 data.

1.1. Objectives and Endpoints

Table 1-1 Stage 1 Objectives

Stage 1		
Primary Objectives: • To evaluate the safety and tolerability of up to three dose strengths of AGN-242428 and AGN-231868 and their respective vehicles in participants with dry eye disease (DED) • To characterize the plasma and tear pharmacokinetics of AGN-242428 and AGN-231868 in participants with DED following a single bilateral administration; and 13 days of twice daily administration followed by a single administration to both eyes on the final day of administration		
Objective Clinical Category	**Statistical Category**	**Estimand/Variable**
Safety	Primary	• Variables: Adverse events (AEs), clinical laboratory values, vital signs, electrocardiogram (ECG) findings, intraocular pressure (IOP), best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated fundus examination, Drop Tolerability Questionnaire score • Population: Safety Population • Analyses: Descriptive summary
Pharmacokinetics[a]	Primary	• Variables: Systemic and tear pharmacokinetic parameters ▪ Following a single dose administration: area under the plasma or tear concentration versus time curve from time 0 to time of the last measurable concentration ($AUC_{0\text{-tlast}}$) maximum plasma or tear drug concentration (C_{max}), time of maximum plasma or tear drug concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$) ▪ Following repeat dose administration: area under the plasma or tear concentration versus time curve from time 0 to the end of the dosing interval ($AUC_{0\text{-}\tau}$), C_{max}, T_{max}, minimum plasma or tear drug concentration at steady state ($C_{min,ss}$), accumulation index (AI), and $t_{1/2}$ • Population: Pharmacokinetics population • Analyses: Descriptive summary

Note: All estimand attributes explicitly identified for primary estimands only.
[a] Analyses of Pharmacokinetics data will be described in a separate Pharmacokinetic Data Analysis Plan.

1.2. Study Design

Study 2012-201-005 is a Phase 1/2a, multicenter, vehicle-controlled, double-masked, randomized study conducted in 2 consecutive stages in participants with DED. Stage 1 will be conducted at 1 to 2 sites in the United States.

Stage 1

Stage 1 will evaluate the safety, tolerability, and pharmacokinetics (plasma and tear), of a maximum of 3 dose strengths of AGN-242428 ([redacted]) and AGN-231868 ([redacted]) in up to 3 consecutive cohorts (1A, 1B [high dose], and 1C [mid dose]) of participants with DED. There will be 24 participants in each cohort, with participants in each cohort randomized into 1 of 4 intervention arms:

- AGN-242428 (N = 9)
- AGN-231868 (N = 9)
- AGN-242428 vehicle (N = 3)
- AGN-231868 vehicle (N = 3)

All participants will receive 1 drop of the assigned intervention administered by the site staff to the left eye on Day 1 (Visit 2). In the absence of significant study intervention-related safety findings from this administration at the site, on Days 2 to 14, the participants will self-administer a single drop to both eyes, twice daily. On Day 15 (Visit 5), the participants will be administered a single drop to both eyes by the site staff.

The sponsor will decide whether to proceed to the next cohort after DMC review of safety data. If no significant safety or tolerability findings are identified in Cohort 1B, Cohort 1C will not be initiated.

Stage 2

Analysis of Stage 2 data will be discussed in a separate SAP.

No participant can be enrolled in more than 1 cohort and/or stage of the study.

If all doses are well tolerated, the duration of participation for each participant in the study will be as follows:

- For participants in Stage 1: approximately 1 month (Day -14 through collection of the last PK sample on Day 15)

2. Statistical Hypotheses

No hypothesis testing will be performed for Stage 1 safety data.

3. Sample Size Determination

For Stage 1, the sample size is not based on statistical considerations and is determined empirically.

4. Analysis Sets

The analysis set for safety will consist of the population as defined below:

Table 4–1 Analysis Sets

Population	Definition	Study Intervention
Safety	All participants who received at least one administration of study intervention for stage 1	Actual received

5. Statistical Analyses

5.1. General Considerations

The methodologies specified to individual variables are defined as follows:

Table 5-1 Statistical Methodology

Methodology	Description
Categorical descriptives	• Number and percentage of participants in individual categories ○ Participants with ≥ 1 qualifying event counted once per individual category

PCS descriptives	• Number and percentage of participants meeting potentially clinically significant (PCS) criteria
	  ○ Participants with ≥ 1 qualifying event counted once per PCS category
	• Percentage denominator = number of participants with available (non-missing) non-PCS baseline value(s) or available (non-missing) baseline and ≥1 non-missing postbaseline assessment
	  ○ Unevaluable assessments considered missing

Continuous descriptives	• N1, mean, standard deviation (SD), Q1, Q3, median, minimum, maximum • N1 = participants with non-missing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis by visit/timepoint
Supportive data listing	• After table listings, i.e. the listing supports the findings from a table. • Fully defined in the tables, figure, and listing specification document

CFB = change from baseline; PCS = potentially clinically significant; SD = standard deviation.

- An interim database lock will occur after completion of Stage 1. At the end of the study (completion of Stage 2), the final database lock will occur.
- All data will be provided in data listings which will be fully defined in the table, figure, and listing specification document. For these data listings, missing or incomplete dates or missing AE severity or relationship will be listed as is.
- The change from baseline values will be computed as the value for the post baseline visit minus the baseline value, unless otherwise indicated.
- Safety analyses will be based on the observed data. No imputation of missing values will be performed.

- Partial dates will be treated as missing in computations but will be listed in the data listings as they appear on the eCRFs unless otherwise specified. No imputation of missing values will be performed, unless otherwise specified.
- All statistical analysis will be performed using SAS version 9.4 or higher.
- MedDRA will be used to code adverse events and medical history.
- WHO Drug Dictionary will be used to code medications.
- Relative study day is defined as the number of days from the first dose date and will be presented in all data listings where a complete date is presented.
- The baseline for safety parameters will be the last assessment prior to the first administration of study intervention.
- Day 1 is the study day on which study intervention is first administered.
- The end of study for a participant is the last date that he/she participated in the study. The date will be captured on the end of intervention eCRF page.

5.2. Participant Disposition

Number of participants screened for the study will be provided.

For each cohort, summary of study disposition will be provided by study intervention for the following:

- Number of participants randomized
- Number of participants treated
- Number of participants that completed the study
- Number of participants discontinued from the study
- eCRF-reported discontinuation reasons

In addition, a listing will be provided for participant disposition.

Table 5-2 Participant Disposition Summaries

Parameter	Description	Timing	Methodology
Study disposition	Distribution in the Safety Population by study intervention for each cohort.	—	Categorical descriptives/ Supportive data listing

5.3. Primary Endpoint(s) Analysis

Not applicable.

5.4. Secondary Endpoint(s) Analysis

Not applicable.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

5.6. Safety Analyses

Safety analyses will be based on the Safety Population.

Baseline assessments for applicable safety parameters are defined as follows:

Table 5-3 Baseline Definitions

Parameter	Baseline definition
• Clinical laboratory evaluations • Vital signs • ECGs • BCVA • IOP	Last non-missing assessment before the first dose for each participant in Stage 1

5.6.1. Extent of Exposure

Exposure to the study treatment for the Safety Population will be summarized for treatment duration, calculated as last study intervention date - first study intervention date + 1. Descriptive statistics will be presented by cohort and study intervention group.

5.6.2. Adverse Events

An AE will be considered a TEAE if:

- The AE began on or after the first administration of study intervention, or
- The AE was present before the first administration of study intervention, but worsened (increased in severity or became serious) on or after the first dose of study intervention

An AE that occurs after the Exit or Early Termination visits will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

TEAEs will be summarized by cohort and study intervention group using the Safety population.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Listings of all TEAEs, TESAEs, TEAEs leading to discontinuation by participant, and deaths will be presented.

AEs will be coded using MedDRA version 23.0 or newer. Unique participants reporting AEs in the following AE categories will be summarized by cohort and study intervention group for the Safety Population as follows:

Table 5-4 TEAE Summaries

Parameters	Description	Methodology
AE	Overall summary by cohort and study intervention group only for the following categories: • TEAEs • Treatment-related TEAEs • TESAEs • Treatment-related TESAEs • TEAEs leading to study discontinuation • Deaths	Categorical descriptives
TEAEs	Overall summary by cohort and study intervention group and by SOC and PT • Participants categorized overall and within each SOC and PT in decreasing frequency	Categorical descriptives
TEAEs by severity	Overall summary by cohort and study intervention group and by SOC, PT, and severity • Participants categorized overall and within each SOC and PT in decreasing frequency for the most severe occurrence	Categorical descriptives
Treatment-related TEAEs	Overall summary by cohort and study intervention group and by SOC and PT • Participants categorized overall and within each SOC and PT in decreasing frequency	Categorical descriptives
TESAEs	Overall summary by cohort and study intervention group and by SOC and PT[a]	Categorical descriptives[1] Supportive data listing
TEAEs leading to discontinuation	Overall summary by cohort and study intervention group and by SOC and PT[a]	Categorical descriptives[1] Supportive data listing
AESI	Overall summary by cohort and study intervention group and by SOC and PT[a]	Categorical descriptives[1] Supportive data listing

[a] Create summary tables only if at least 5 participants reported SAE, AEs leading to study discontinuation or AESI.

5.6.2.1. Adverse Events of Special Interest

Any report of the following AESIs will be provided in a listing. A summary table will be created only if there are reports by at least 5 participants.

Table 5-5 Adverse Events of Special Interest

Preferred Term (PT)	PT Code
Aspartate aminotransferase increased	10003481
Alanine aminotransferase increased	10001551
Blood bilirubin increased	10005364
Blood alkaline phosphatase increased	10059570

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Parameters

Table 5-6 Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH MCHC	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[a]	BUN Creatinine Glucose (fasting[b]) Total protein Albumin	Potassium Sodium Calcium Cholesterol Chloride	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Total, direct and indirect bilirubin
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)		

[a] In Stage 1, blood samples will be collected following 10-hour fasting period.

[b] Fasting requirement is for Stage 1 only

Descriptive statistics for quantitative clinical laboratory values (in SI units) at Screening, Exit visit, and changes from baseline at Exit/Early Termination visit will be presented by cohort and study intervention group for each clinical laboratory assessment.

Clinical laboratory test values will be considered PCS if they meet either the lower-limit or higher-limit PCS criteria listed in Table 6-5. The number and percentage of participants who have at least one PCS post-baseline clinical laboratory values will be tabulated by cohort and study intervention group at Exit visit. The percentages will be calculated based on the denominator of the number of participants with available non-PCS baseline values and at least one post-baseline value and the numerator of the number of participants with non-PCS baseline value and at least one PCS post-baseline-value.

A supportive listing of participants with postbaseline PCS values will be provided, including the participant number and baseline and postbaseline values, for the safety population. A listing of conversion factors to convert SI units to conventional units will be provided.

Table 5-7 Clinical Laboratory Summaries

Endpoint	Description	Timing	Methodology
PCS values[a]	Summary by laboratory category, laboratory test, and PCS criteria • Participants with baseline PCS values excluded from analysis • Parameters and PCS criteria specified in Sections 6.5.2.2 and 6.5.2.1, respectively	Screening[b], Exit[c]	PCS descriptives/ Supportive data listing
Descriptives	Summary by laboratory category and laboratory test in SI and /or CV units and analysis visit • Parameters specified in Section 6.5.2.2	Screening[b], Exit[c]	CFB descriptives

[a] Participants who report ≥ 1 postbaseline PCS value and all clinical laboratory for those participants will be listed.
[b] Visit will be used as baseline for change from baseline summaries.
[c] Exit: Final or early termination visit.

5.6.3.2. Potential Hy's Law

Potential Hy's Law criteria will be listed for the Safety Population as follows:

Table 5-8 Potential Hy's Law Summaries

Parameter	Description	Timing	Methodology
Potential Hy's Law within 24-hour window	Postbaseline assessment of the following laboratory parameters based on blood draws collected within a 24-hour period: • ALT or AST ≥ 3 × ULN • TBL ≥ 2 × ULN • ALP < 2 × ULN	Study Intervention Period	Supportive data listing

5.6.3.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, weight, respiration rate, and temperature) at Screening, Baseline (Day 1) and changes from baseline values at each visit and at the Exit/Early Termination visit will be presented by cohort and study intervention group.

Vital sign values will be considered PCS if they meet either the lower-limit or higher-limit PCS criteria listed in Table 6-6. The number and percentage of participants who have at least one PCS post-baseline vital sign value will be tabulated by cohort and study intervention group. The percentages will be calculated based on the denominator of the number of participants with available baseline values or non-PCS baseline values (respiratory rate and temperature) and at least one post-baseline value and the numerator of the number of participants with non-PCS baseline value and at least one PCS post-baseline value.

A supportive listing of participants with postbaseline PCS values will be provided, including the participant number and baseline and postbaseline values, for the safety population.

Table 5-9 Vital Signs Summaries

Endpoint	Description	Timing	Methodology
PCS values[a]	Summary by parameter and PCS criteria • Denominator: available baseline or non-PCS baseline (respiratory rate or temperature) and at least one end-of-study or postbaseline values • Parameters and PCS criteria specified in Sections 6.5.3.2 and 6.5.3.1 respectively	Blood pressure, pulse rate, temperature: Day 1[b], Day 2, Day 8, Exit[c] Respiration rate, weight: Screening [b], Exit[c]	PCS descriptives/ Supportive data listing[a]
Descriptives	Summary by parameter and analysis visit • Parameters specified in Section 6.5.3.2	Blood pressure, pulse rate, temperature: Screening, Day 1[b], Day 2, Day 8, Exit[c] Respiration rate, weight: Screening[b], Exit[c]	CFB descriptives

[a] Participants who report ≥ 1 postbaseline PCS value and all vital signs will be listed.
[b] Visit will be used as baseline for change from baseline summaries.
[c] Exit: Final or early termination visit.

5.6.3.4. Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) at Baseline and Exit/Early Termination visits, and changes from baseline values at Exit/Early Termination visit will be presented by cohort and study intervention group.

The QTc will be calculated using the Fridericia correction (if the vendor does not provide). QTcF are derived as follows:

Table 5-10 Derivations of QTcF

Parameter	Derivation if RR available	Derivation if RR unavailable
QTcF (QTc Fridericia)	$\frac{QT}{\text{cubic root of RR}}$	$\frac{QT}{\text{cubic root of 60/HR}}$

ECG parameter values will be considered PCS if they meet either the lower-limit or higher-limit PCS criteria listed in Table 6-7. The number and percentage of participants who have at least one PCS post-baseline ECG values will be tabulated for all participants by cohort and study intervention group. The percentages will be calculated based on the denominator of the number of participants with available non-PCS baseline values and at least one post-baseline value and the numerator of the number of participants with non-PCS baseline value and at least one PCS post-baseline value.

A supportive listing of participants with postbaseline PCS values will be provided, including the participant number and baseline and postbaseline values, for the safety population.

Table 5-11 ECG Summaries

Endpoint	Description	Timing	Methodology
PCS values	Summary by parameter and PCS criteria • Participants with baseline PCS values excluded from analysis • Parameters and PCS criteria specified in Sections 6.5.4.2 and 6.5.4.3, respectively.	Screening[b], Exit[c]	PCS descriptives/ Supportive data Listing[a]
Descriptives	Summary by parameter and analysis visit • Parameters specified in Section 6.5.4.3	Screening[b], Exit[c]	CFB descriptives

[a] Participants who report ≥ 1 postbaseline PCS value and all ECG will be listed.
[b] Visit will be used as baseline for change from baseline summaries.
[c] Exit: Final or early termination visit.

5.6.3.5. Physical Exam

Abnormalities in PEs during Stage 1 of the study will be captured in medical history or AE data panels. Therefore, there will be no separate analyses for physical examination.

5.6.3.6. Best-corrected Visual Acuity

BCVA will be measured in each eye using the ETDRS chart. Descriptive statistics for BCVA at Screening, Baseline (Day 1), and changes from baseline at each postbaseline visit will be presented by cohort, and study intervention group for each eye. Vision loss will also be

summarized by study intervention group for each eye at each visit in a categorical tabulation as severe (≥ 30 letters decrease from baseline), moderate (≥ 15 and < 30 letters decrease from baseline) and no loss or mild (< 15 letters decrease from baseline).

Table 5-12 BCVA Summaries

Parameter	Description	Timing	Methodology
Vision loss	• Severe vision loss (>= 30 letters decrease from baseline) • Moderate vision loss (>= 15 and < 30 letters decrease from baseline) • No loss or mild vision loss (<15 letters decrease from baseline)	Treatment Period	Categorical descriptives
BCVA	Raw values and change from baseline	Treatment Period	CFB descriptives

5.6.3.7. Intraocular Pressure

IOP will be measured in each eye using the Goldmann applanation tonometer. At least 2 measurements will be taken for each eye. If the 2 independent measurements differ by ≤ 2 mm Hg, a third measurement is not required, and the 2 measurements will be recorded. If the first 2 measurements differ by > 2 mm Hg, a third measurement must be made, and all 3 measurements will be recorded. The mean of the 2 (or 3) measures will be used as the IOP value. If, for any reason, only a single measurement is obtained, then this measurement will be used as the IOP value.

Descriptive statistics for IOP at Screening, Baseline (Day 1), and changes from baseline and number of participants reporting IOP > 21 mm Hg at each postbaseline visit will be presented by cohort and study intervention group for each eye.

Table 5-13 IOP Summaries

Parameter	Description	Timing	Methodology
IOP category	IOP > 21 mmHg (raw value)	Treatment period	Categorical descriptives
IOP	Raw values and change from baseline	Treatment period	CFB descriptives

5.6.3.8. Biomicroscopy

Slit-lamp biomicroscopy exam will be performed in each eye.

The number of participants with biomicroscopy findings of any severity increase from baseline at one or more visits will be generated for each MedDRA preferred terms by cohort and study

intervention group for each eye. For findings under "other pathology" which are not associated with a severity grade, a status change from absent to present will be treated as an increase of severity in the analysis.

Table 5-14 Biomicroscopy

Parameter	Description	Timing	Methodology
Biomicroscopy	Any severity increase from baseline for each eye	Treatment period	Categorical descriptives

5.6.3.9. Dilated Fundus Examination

Lens, vitreous, fundus, and optic nerve will be evaluated for pathology. If pathology is present, it will be recorded.

Cup/disc ratio will be reported using 0.0 to 1.0 scale according to an Armaly chart. Lens status will be assessed as phakic, pseudophakic, or aphakic. Cataract assessment for presence and severity of nuclear, cortical and posterior subcapsular cataract lens opacities will be evaluated. Each type of cataract severity and change from baseline will be evaluated. These data will be presented as listings only.

Table 5-15 Dilated Fundus Examination

Parameter	Description	Timing	Methodology
Dilated Fundus Examination	Listing for the following data: • Cup/disc ratio • Lens status • Cataract assessment	Treatment period	Listing

5.6.3.10. Drop Tolerability Questionnaire Score

Participants will be asked to rate the acute overall tolerability attributes of study interventions on an 8-question VAS Drop Tolerability Questionnaire. Descriptive statistics for each question at Baseline (Day 1), and changes from baseline at each postbaseline visit will be presented by cohort and study intervention group.

Table 5-16 Drop Tolerability Questionnaire Score

Parameter	Description	Timing	Methodology
Drop Tolerability Questionnaire VAS score	Raw values and change from baseline	Treatment period	CFB descriptives

5.7. Other Analyses

5.7.1. Other Variables and/or Parameters

5.7.1.1. Pharmacokinetic Analyses

Pharmacokinetic blood and tear (both eyes) sampling times and plasma and tear concentrations of AGN-242428 and AGN-231868 will be listed for the Safety Population. PK analyses will be described in the PK data analysis plan.

5.7.2. Subgroup Analyses

No subgroup analysis is planned for this study.

5.8. Interim Analyses

There is no interim analysis planned.

There are 2 database locks planned. The first database lock will take place after completion of Stage 1. At this time, the data for Stage 1 will be unmasked and topline data analyses will be performed. A topline report will be created in lieu of an interim CSR.

5.8.1. Data Monitoring Committee

The DMC will be composed of the sponsor's internal members who will be masked to the interventions. However, data can be unmasked at the DMC's discretion at any time.

In Stage 1, at the end of each cohort, the DMC will review the safety data and provide a recommendation on whether the study can proceed to the next cohort. In Stage 1, it is possible that only 1 of the interventions will proceed to the next cohort and/or to Stage 2.

All details of the committee membership, procedures for safety review, frequency of review, and communication between the safety review committee and other information will be detailed in the DMC charter.

6. Supporting Documentation

Additional study population, baseline characteristics, and pre-defined safety criteria can be found in Section 6.3.

6.1. Appendix 1: List of Abbreviations

Table 6-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
AESI	adverse event of special interest
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ALP	alkaline phosphatase
AUC	area under the curve
AUC0-tlast	area under the plasma or tear concentration versus time curve from time 0 to time of the last measurable concentration
AUC0-τ	area under the plasma or tear concentration versus time curve from time 0 to the end of the dosing interval
BCVA	best-corrected visual acuity
BID	twice daily
BP	Blood pressure
bpm	beats/breaths per minute
BUN	blood urea nitrogen
CAE	controlled adverse environment
CFB	change from baseline
Cmax	maximum plasma or tear drug concentration
Cmin,ss	minimum plasma or tear drug concentration at steady state
CRF	case report form
CSR	Clinical Study Report
DED	dry eye disease
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
hCG	human chorionic gonadotropin
ICH	International Council on Harmonization
IND	investigational new drug
IOP	intra-ocular pressure
LD	last day of the month
LLN	lower limit of normal
MedDRA	Medication Dictionary for Regulatory Activities
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MM	available start date month

Abbreviation/Term	Definition
MSP	medical safety physician
NA	not applicable
[redacted]	[redacted]
OD	right eye
[redacted]	[redacted]
OS	left eye
[redacted]	[redacted]
OTC	over-the-counter
PE	physical examination
PCS	potentially clinically significant
PK	pharmacokinetic
PT	Preferred Term
QTc	QT Interval Corrected for Heart Rate
QTcF	QT Interval Corrected for Heart Rate Using the Fridericia Formula ($Qtcf = QT/(RR)^{1/3}$)
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SI	Le Système International d'Unités (International System of Units)
SOC	System Organ Class
SoA	schedule of activities
$t_{1/2}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
THC	tetrahydrocannabinol
ULN	upper limit of normal
[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
YYYY	available start date year

6.2. Appendix 2: Changes to Protocol-planned Analyses

There are no changes from the protocol-planned analyses.

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographics

Demographics will be summarized descriptively by cohort and study intervention group for the Safety Population, as follows:

Table 6-2 Demographic Summaries

Parameter	Description	Timing	Methodology
Age	Age (years)	—	Categorical descriptives
Sex, race, and ethnicity	eCRF categories	—	Categorical descriptives

Demographic and baseline characteristics will be provided in a listing.

6.3.2. Baseline and Disease Characteristics

Baseline characteristics will be summarized descriptively by cohort and study intervention group for each eye for the Safety Population as follows:

Table 6-3 Baseline and Disease Characteristics Summaries

Parameter	Description	Timing	Methodology
Baseline characteristics	• Height (m) • Weight (kg) • Body mass index (BMI) ○ Weight (kg) / height (m)^2	Last assessment before the first dose date of the study intervention	Continuous descriptives
Disease characteristics	[redacted] • BCVA	Last assessment before the first dose of the study intervention [Screening, Day 1]	Continuous descriptives

6.3.3. Protocol Deviations

A data listing of any significant protocol deviations will be provided for the Safety Population.

6.3.4. Medical and Ophthalmic History

Participants' medical and ophthalmic history, encompassing abnormalities and surgeries data, will be coded using the MedDRA, version 23.0 or higher. Reported medical events, ophthalmic

events and surgical history will be summarized using MedDRA SOC and PT by cohort and study intervention group for the Safety Population. Medical history includes prior medical history (prior to Day 1, first dose date) and still ongoing.

Table 6-4 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history	Abnormalities and surgeries	—	Categorical descriptives
Ophthalmic history	Abnormalities and surgeries	—	Categorical descriptives

SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose strength group.

6.3.5. Prior/Concomitant Medications (Including Dictionary)

The medication data will be coded using the WHO Drug Dictionary Enhanced, version MAR 2017 or newer. Prior medication is defined as any medication taken prior to the start of study intervention regardless of stop date of the medication. Concomitant medication is defined as any medication taken after the start of study intervention regardless of the start date of the medication.

Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical code (4th level, or most specific level available if 4th level is unavailable).

Medications data along with prior or concomitant medication flag will be listed for the Safety Population.

6.3.6. Potentially Clinically Significant Criteria for Safety Endpoints

The potentially clinically significant criteria for clinical laboratory parameters, vital signs, and ECG parameters are provided in the following sections.

6.3.6.1. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Laboratory assessments values meeting any of the following PCS low or PCS high criteria will be categorized as PCS:

Table 6-5 Clinical Laboratory PCS Criteria

Laboratory Group	Parameter	SI Unit	PCS Low Limit	PCS High Limit
Hematology	Eosinophils absolute cell count	10^9/L	—	> 1.5 × ULN
	Hematocrit	%	< 0.8 × LLN	≥ 1.2 × ULN
	Hemoglobin	g/L	< 0.8 × LLN	≥ 1.2 × ULN
	Lymphocytes absolute cell count	10^9/L	< 0.8 × LLN	> 1.2 × ULN
	Neutrophils absolute cell count	10^9/L	< 0.6 × LLN	> 1.6 × ULN
	Platelet count (thrombocytes)	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.8 × LLN	> 1.2 × ULN
	White blood cell count	10^9/L	< 0.7 × LLN	> 1.8 × ULN
Chemistry	Alanine aminotransferase	U/L	—	> 3 × ULN
	Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Alkaline phosphatase	U/L	—	> 3 × ULN
	Aspartate aminotransferase	U/L	—	> 3 × ULN
	Bilirubin, total	µmol/L	—	> 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.3 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.2 × ULN
	Creatinine	µmol/L	—	> 1.8 × ULN
	Glucose, fasting	mmol/L	< 0.8 × LLN	> 1.2 × ULN
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 1.4 × ULN
	Phosphorus	mmol/L	< 0.8 × LLN	> 1.2 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Uric acid (urate)	µmol/L	—	> 1.2 × ULN
Urinalysis	Glucose	µmol/L	—	≥ 0.015
	Glucose (alternate units)	—	—	≥ 2+
	pH	—	< 0.9 × LLN	> 1.1 × ULN
	Protein	g/L	—	≥ 1.0
	Protein (alternate units)	—	—	≥ 2+
	Specific gravity	—	—	> 1.1 × ULN

6.3.6.2. Potentially Clinically Significant Criteria for Vital Signs

Vital sign values meeting *both* the actual value and change from baseline PCS criteria will be categorized as PCS:

Table 6-6 Vital Sign PCS Criteria

Parameter	Unit	PCS Category	PCS Criteria	
			Actual Value	Change from Baseline
Sitting Systolic BP	mmHg	High	≥ 180	Increase of ≥ 20
		Low	≤ 90	Decrease of ≥ 20
Sitting Diastolic BP	mmHg	High	≥ 105	Increase of ≥ 15
		Low	≤ 50	Decrease of ≥ 15
Sitting Pulse rate	bpm	High	≥ 120	Increase of ≥ 15
		Low	≤ 50	Decrease of ≥ 15
Weight	kg	High	—	Increase of ≥ 7%
		Low	—	Decrease of ≥ 7%
Respiratory Rate	bpm	High	≥ 28	—
		Low	≤ 8	—
Temperature	°C	High	> 38	—
		Low	< 35	—

6.3.6.3. Potentially Clinically Significant Criteria for ECG Parameters

ECG values meeting *either* the actual value or change from baseline PCS high criteria will be categorized as PCS:

Table 6-7 ECG PCS Criteria

Parameter	Unit	PCS High Criteria	
		Actual Value	Change from Baseline
QRS interval	msec	≥ 150	—
PR interval	msec	≥ 250	—
QTcF	msec	> 500	Increase > 60

6.4. Data Handling Conventions

6.4.1. Study Intervention Conventions

6.4.1.1. Analysis Days

Study days are defined as follows:

Table 6-8 Analysis Day Definitions

Term	Description

Study Day	Relative to study intervention start date
	If analysis date ≥ intervention start date:
	• Day = analysis date – study intervention start date + 1
	  ○ Day 1 = study intervention start date
	If analysis date < intervention start date:
	• Day = analysis date – study intervention start date
	  ○ Day -1 = day before study intervention start date
	  ○ There is no Day 0

6.4.1.2. Analysis Window

Table 6-9 Analysis Visit Definitions for Stage 1

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Visit 2/Baseline	Day 1	Day 1
Visit 3	Day 2	Days [2, 5]
Visit 4	Day 8	Days [6, 11]
Visit 5	Day 15	Day 12 to study exit day

6.4.1.3. Missing/Incomplete Intervention End Date

If the investigator is unable to provide the study intervention end date, study intervention end date will be imputed to the last available dosing record date.

6.4.2. Repeated or Unscheduled Assessments

If postbaseline assessments are repeated or if unscheduled assessments occur, the last postbaseline assessment will be used as the postbaseline assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the supportive data listings.

6.4.3. Missing Date Imputation

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6-10 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[a]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[a]
6	—	Yes	—	No[a]
7	—	—	Yes	No[a]
8	—	—	—	Yes

[a] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6-11 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

6.4.3.1. Missing/Incomplete AE Start Date

Imputation of dates with missing day and/or month is only applied to TEAEs. If adequate information is available, no imputation is needed. TEAE start dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan or the initial study intervention administration date if they have the same year, whichever is later (because TEAE onset is not expected prior to administration of study intervention)
- If day is missing but the month and year are available, then the imputed day will be the first day of the month or the initial injection date if they have the same month and year, whichever is later.

6.4.3.2. Missing/Incomplete Medication Start Date

Medication start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date – 1
- Complete end date

6.4.3.3. Missing/Incomplete AE/Medication End Date

Imputation of dates with missing day and/or month is only applied to TEAEs when AE duration is calculated. If adequate information is available, no imputation is needed. TEAE end dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be 31 Dec or the study exit date if they have the same year, whichever is earlier

If day is missing but the month and year are available, then the imputed day will be the last day of the month or the study exit date if they have the same month and year, whichever is earlier.

6.4.4. Safety Endpoint Conventions

6.4.4.1. Adverse Events

6.4.4.1.1. Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

Table 6-12 Missing AE Severity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Severity	Mild	AEs before the first dose of the study intervention in the study
	Severe	AEs on or after the first dose of the study intervention in the study
Relationship	NA	AEs before the first dose of the study intervention in the study
	Related	AEs on or after the first dose of the study intervention in the study

7. References

Not applicable.