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

Products: AGN-242428 and AGN-231868

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

Study Phase: 1/2a

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Refer to the final page of this protocol for electronic signature and date of approval.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	14 July 2021
Amendment 2	28 April 2020
Amendment 1	18 Dec 2019
Original Protocol	06 May 2019

Amendment 3 (July 2021)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The key changes made in Protocol Amendment 3 are summarized in the table below. Grammatical corrections and minor edits for internal document consistency have also been made and are not specified in the table below.

Section Number and Name	Description of Change	Brief Rationale
Title Page	Update safety contact to sponsor/emergency medical contact Update signatory names/titles	Provide the current contact information and also include a 24 hour emergency number Current signatories
Section 1.2, Figure 1-2	Fixed footnotes in Figure 1-2 to include both footnote 'a' and 'b'	For clarification
Section 1.3, Table 1-2; Section 8	Clarified that after completion of Informed Consent and Inclusion/Exclusion Criteria, for assessments listed with an '#' flexibility in procedure order is allowed; all other assessments will be performed in order listed.	For clarification
Section 1.3, Table 1-2	Added a note to clarify the timing of the collection of used and unused study intervention.	For clarification
Section 1.3, Table 1-2; Section 8.4.3; Section 8.8.1	At the baseline visit (V3), the study eye is not identified at the time of tear collection. Since the process for sample collection is the same, tear samples will be collected, one eye followed by the other, and labelled as OS and OD. The samples will be assigned to biomarker or PK analysis depending on the study eye assignment.	For clarification
Section 8.1.3	Eligibility based on mean of 2 or median of 3 IOP measurements.	Clarification

Amendment 2 (April 2020)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The key changes made in Protocol Amendment 2 are summarized in the table below. Grammatical corrections and minor edits for internal document consistency have also been made and are not specified in the table below.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3.1 Objectives and Endpoints Stage 1, Section 3.2 Objectives and Endpoints Stage 2, Section 4.1 Overall Design, Section 9.4.3.1 Plasma Pharmacokinetic Parameters	Changed "characterize the systemic and tear PK…" to "characterize the plasma and tear PK…" in the study objectives and throughout the protocol.	For clarification.
Section 1.1 Synopsis, Section 4.1 Overall Design	Updated wording to clarify that the planned duration of the study assumes no early termination of the participant.	For clarification.
Section 1.1 Synopsis, Section 1.2 Figures 1-1 and 1-2, Section 1.3 Tables 1-1 and 1-2, Section 4.1 Overall Design Section 10.6 Appendix 6: Study Tabular Summary	Changed Visit 1 Screening period in Stage 1 to 14 days (which changed total Stage 1 duration to approximately 1 month, instead of 22 days) and clarified Visit 1 Screening period in Stage 2.	To facilitate site logistics and clarify screening windows.
Section 1.3 Table 1-1	[redacted]	[redacted]
Section 1.3 Table 1-1	Moved ECG, pregnancy test, drugs of abuse screen, and clinical laboratory tests to immediately follow the physical examination in the SoA for Stage 1.	For clarification that these tests (particularly the fasting blood draws) can be performed right after the physical examination.
Section 1.3 Table 1-2	Updated table notes to reflect that [redacted] measures not being administered when a participant is discontinued due to the use of prohibited medication applies only to the Early Termination visit.	For clarification.
Section 1.3 Tables 1-1 and 1-2	Added that a breathalyzer may be used to evaluate alcohol use as part of the "drugs of abuse screen."	For clarification.
Section 1.3 Tables 1-1 and 1-2, Section 5.1.2 Exclusion Criteria for Stage 1, Section 5.2.2 Exclusion Criteria for Stage 2	Added COVID-19 symptoms and exposure as an exclusion criterion and added more frequent temperature screenings.	To screen for and exclude potential COVID-19 patients.
Section 1.3 Tables 1-1 and 1-2, Section 5.2.1 Inclusion Criteria for Stage 2, Section 5.3.1 Meals and Dietary Restrictions, Section 10.2 Appendix 2: Clinical Laboratory Tests	Changed wording to reflect that fasting is not required for urinalysis in Stage 1 and that no fasting is required in Stage 2.	For clarification of fasting requirements.
Section 1.3 Table 1-2 notes, Section 6.5 Concomitant Therapy, Section 7.2 Participant Discontinuation/ Withdrawal from the Study	Updated procedures for discontinuation due to concomitant therapies. Discontinuation is to be determined by the investigator and/or sponsor rather than required following the use of prohibited medications.	To allow more flexibility for the investigator and sponsor to determine whether a concomitant medication will likely affect the study results.

Section Number and Name	Description of Change	Brief Rationale
[redacted]		
Section 1.3 Tables 1-1 and 1-2, Section 8.1.1 Best-corrected Visual Acuity	Added manifest refraction to the SoA: at all visits in Stage 1 and at Visits 1, 6, and ET in Stage 2.	For clarification of when manifest refraction was required.
Section 5.1.2 Exclusion Criteria for Stage 1, Section 5.2.2 Exclusion Criteria for Stage 2	Added "or anticipated participation during the study" to the exclusion criterion (3.02) prohibiting blood and plasma donation prior to study participation.	For clarification that this criterion applies to blood and plasma donation before and during the study.
Section 5.1.2 Exclusion Criteria for Stage 1	Removed "lissamine green" from exclusion criterion 4.01 in Stage 1, which lists known allergies and sensitivities to study treatments or study diagnostic agents.	Lissamine green is not needed because it is not used in Stage 1.
Section 5.1.2 Exclusion Criteria for Stage 1, Section 5.2.2 Exclusion Criteria for Stage 2, Section 6.5.1 Tables 6-2 and 6-3, Section 6.5.2 Permitted Interventions, Section 6.5.4 Prohibited Interventions During the Study	Excluded flax seed oil, fish oil, and omega-3 supplements from the list of systemic medications that may impact DED or vision.	These medications are not expected to affect the study endpoints so their use should not be prohibited.
Section 6.1.1.2 Dosing Regimen in Stage 2, Section 6.3.2 Masking	Updated wording to clarify that unmasked staff will perform dosing in Stage 2 and that masked staff should not be present during Stage 2 dosing in order to prevent unmasking.	For clarification.
Section 8.1.7 Electrocardiograms	Extended window to perform predose ECG in Stage 2 from 120 minutes to 240 minutes.	To accommodate all other procedures that are required predose in Stage 2.

Section Number and Name	Description of Change	Brief Rationale
[redacted]		

Amendment 1 (December 2019)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The key changes made in Protocol Amendment 1 are summarized in the table below. Grammatical corrections and minor edits for internal document consistency have also been made and are not specified in the table below.

Section Number and Name	Description of Change	Brief Rationale
[redacted]		
Section 1 Synopsis, Section 1.3 Tables 1-1 and 1-2, Section 4.1 Overall Design, Section 4.2.1 Duration of Treatment in Stage 1 and Stage 2, Section 6.1 Table 6-1, Section 6.1.1.1 Dosing Regimen in Stage 1, Section 6.1.1.2 Dosing Regimen in Stage 2, Section 6.3.1 Method of Intervention Assignment, Section 10.6 Appendix 6: Study Tabular Summary	Clarified that twice daily is approximately 12 hours apart dosing.	For clarification.

Section Number and Name	Description of Change	Brief Rationale
Section 1 Synopsis, Section 1.3 Tables 1-1 and 1-2, Section 3.2 Stage 2, Section 5.1.1 Inclusion Criteria for Stage 1, Section 5.2.1 Inclusion Criteria for Stage 2, Section 8.5.9 [redacted]	[redacted]	[redacted]
Section 1.2 Figures 1-1 and 1-2	Revised study flow diagrams for Stages 1 and 2 to reflect changes made to the protocol in this amendment.	For consistency.
Section 1.3 Table 1-1	Revised screening window to Day -10 to Day -1.	To improve logistics.
Section 1.3 Table 1-1 and Table 1-2	Specified that at Early Termination visit, only a single PK sample will be collected.	For clarification to match Section 8.4.1.
Section 1.3 Table 1-2, Section 8 Study Assessments and Procedures	Clarified time of randomization for Stage 2.	To clarify that the participants should be randomized following the [redacted]
[redacted]		
Section 1.3 Table 1-1, Section 10.2 Table 10-1	Removed cotinine testing.	There are no restrictions for use of tobacco during the study.
Section 5.1.2 Exclusion Criteria for Stage 1, Section 5.2.2 Exclusion Criteria for Stage 2, Section 5.3.2 Caffeine, Alcohol, Tobacco, and Cannabis, Section 6.5.1 Table 6-2 and Table 6-3, Section 6.5.4 Prohibited Interventions During the Study	Added exclusion for use of inhalable or ingestible cannabis products or transdermal patches containing THC within 30 days prior to the Screening visit or anticipated use during the study.	Added clarification to accommodate the states where use of cannabis products is legal.
Section 5.1.2 Exclusion Criteria for Stage 1, Section 5.2.2 Exclusion Criteria for Stage 2, Section 6.5.1 Tables 6-2 and 6-3, Section 6.5.4 Prohibited Interventions During the Study	Added exclusion for use of TrueTear within 7 days for Stage 1 or 14 days for Stage 2 prior to the Screening visit or anticipated use during the study.	This medication may affect the study endpoints so the use should not be permitted.
Section 5.3.2 Caffeine, Alcohol, Tobacco, and Cannabis	Added specific visits.	For clarification.
Section 6.1 Study Intervention(s) Administered, Section 6.3.2 Masking	Updated packaging for study interventions in Stage 2.	To update the packaging for study interventions in Stage 2.

Section Number and Name	Description of Change	Brief Rationale
Section 6.2 Preparation/Handling/Storage/ Accountability	Clarified instructions for storage and accountability.	For clarification.
Section 6.3.2 Masking	Clarified that there will be unmasked pharmacy staff in Stage 1.	For clarification.
Section 8.1.1 Best-corrected Visual Acuity	Removed language regarding low luminance BCVA measurements.	Only normal luminance BCVA will be performed.
Section 8.1.7 Electrocardiograms	Clarified that sites will transmit ECG data to the central reader after interpretation of the results is performed by a qualified physician or designee at the site.	For clarification.
Section 8.1.8 Clinical Safety Laboratory Assessments	Adjusted the language on capturing local lab data in EDC.	For clarification.
Section 8.1.11 Suicidal Risk Monitoring	Removed section stating this is not applicable.	As this is not applicable, removed unnecessary section.
Section 8.4.1 Pharmacokinetic Blood Draw Schedule, Section 8.4.3 Pharmacokinetic Tear Sampling Schedule, Section 8.8.1 Tears	Removed requirement for "atomic clocks."	To allow for use of other precise systems such as pyramid system clocks.
Section 1.3 Table 1-1, Section 8.4.3 Pharmacokinetic Tear Sampling Schedule	Removed predose tear sampling for PK analysis from Visits 2 and 4 in Stage 1.	The samples collected at predose on these visits will be used for biomarker assay optimization instead of PK.
[redacted]		
[redacted]		
Section 10.9 Appendix 9: Study Schedule Supplement	Removed this appendix.	Removed this appendix as it is a duplication of the information in the SoA.

Table of Contents

Title Page 1
Protocol Amendment Summary of Changes Table 2
Table of Contents 9
List of Tables 14
List of Figures 15
1. Protocol Summary 16
   1.1. Synopsis 16
   1.2. Schema 19
   1.3. Schedule of Activities (SoA) 22
2. Introduction 32
   2.1. Study Rationale 33
   2.2. Background 33
      2.2.1. AGN-242428 34
         2.2.1.1. Pharmacology 34
         2.2.1.2. Pharmacokinetics 34
         2.2.1.3. Toxicology 34
         2.2.1.4. Clinical Experience 35
      2.2.2. AGN-231868 35
         2.2.2.1. Pharmacology 35
         2.2.2.2. Pharmacokinetics 36
         2.2.2.3. Toxicology 36
         2.2.2.4. Clinical Experience 36
   2.3. Benefit/Risk Assessment 37
3. Objectives and Endpoints 38
   3.1. Stage 1 38
   3.2. Stage 2 39
4. Study Design 40
   4.1. Overall Design 40
   4.2. Scientific Rationale for Study Design 41
      4.2.1. Duration of Treatment in Stage 1 and Stage 2 41
      4.2.2. Cohorts in Stage 1 41
      4.2.3. Dose Selection for Stage 2 42
      4.2.4. Controlled Adverse Environment 42
      4.2.5. [redacted] 43
   4.3. Justification for Dose 43
      4.3.1. AGN-242428 43
      4.3.2. AGN-231868 43
   4.4. End of Study Definition 44

5. Study Population 45
5.1. Stage 1 45
5.1.1. Inclusion Criteria for Stage 1 45
5.1.2. Exclusion Criteria for Stage 1 47
5.2. Stage 2 50
5.2.1. Inclusion Criteria for Stage 2 50
5.2.2. Exclusion Criteria for Stage 2 53
5.3. Lifestyle Considerations 56
5.3.1. Meals and Dietary Restrictions 56
5.3.2. Caffeine, Alcohol, Tobacco, and Cannabis 56
5.3.3. Activity 56
5.4. Screen Failures 57

6. Study Intervention 58
6.1. Study Intervention(s) Administered 58
6.1.1. Dosing Regimen 59
6.1.1.1. Dosing Regimen in Stage 1 59
6.1.1.2. Dosing Regimen in Stage 2 59
6.1.1.3. [redacted] Medications and Administration 60
6.2. Preparation/Handling/Storage/Accountability 60
6.3. Measures to Minimize Bias: Randomization and Masking 60
6.3.1. Method of Intervention Assignment 60
6.3.2. Masking 61
6.4. Study Intervention Compliance 62
6.5. Concomitant Therapy 63
6.5.1. Prohibited Interventions and Washout Before the Study 64
6.5.2. Permitted Interventions 65
6.5.3. Rescue Medicine 66
6.5.4. Prohibited Interventions During the Study 67
6.6. Dose Modification 68
6.7. Intervention after the End of the Study 69

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 70
7.1. Discontinuation of Study Intervention 70
7.2. Participant Discontinuation/Withdrawal from the Study 71
7.3. Lost to Follow-up 71

8. Study Assessments and Procedures 73
8.1. Safety Assessments 74
8.1.1. Best-corrected Visual Acuity 74
8.1.2. Slit lamp Biomicroscopy 74
8.1.2.1. Eyelid/Eyelid Margins/Lashes 74
8.1.2.2. Conjunctiva 75

8.1.2.3. Cornea 75
8.1.2.4. Anterior Chamber 76
8.1.2.5. Iris/Pupil 77
8.1.3. Intraocular Pressure 77
8.1.4. Dilated Fundus Exam 77
8.1.4.1. Lens 77
8.1.4.2. Vitreous 78
8.1.4.3. Fundus 78
8.1.4.4. Optic Nerve 78
8.1.5. Physical Examinations 78
8.1.6. Vital Signs 78
8.1.7. Electrocardiograms 79
8.1.8. Clinical Safety Laboratory Assessments 79
8.1.9. Pregnancy Test (WOCBP Only) 80
8.1.10. Other Assessments 80
8.2. Adverse Events and Serious Adverse Events 81
8.2.1. Time Period and Frequency for Collecting AE and SAE Information 81
8.2.2. Method of Detecting AEs and SAEs 81
8.2.3. Follow-up of AEs and SAEs 81
8.2.4. Regulatory Reporting Requirements for SAEs 82
8.2.5. Pregnancy 82
8.2.6. AEs of Special Interest 83
8.2.7. Medication Errors 83
8.3. Treatment of Overdose 83
8.4. Pharmacokinetics 83
8.4.1. Pharmacokinetic Blood Draw Schedule 83
8.4.2. Pharmacokinetic Blood Sampling Procedure 84
8.4.3. Pharmacokinetic Tear Sampling Schedule 85
8.4.4. Pharmacokinetic Tear Sampling Procedure 86
8.4.5. Pharmacokinetic Sample Bioanalysis 86

[redacted]

[redacted]

8.7. Genetics 94
[redacted]
8.9. Medical Resource Utilization and Health Economics 96
9. Statistical Considerations 97
9.1. Statistical Hypotheses 97
9.2. Sample Size Determination 97
9.3. Populations for Analyses 97
9.4. Statistical Analyses 97
[redacted]
9.4.2. Safety Analyses 98
9.4.2.1. Adverse Events 98
9.4.2.2. Clinical Laboratory Assessments 99
9.4.2.3. Vital Signs 99
9.4.2.4. Electrocardiograms 100
9.4.2.5. Best-corrected Visual Acuity 100
9.4.2.6. Intraocular Pressure 100
9.4.2.7. Biomicroscopy 100
9.4.3. Pharmacokinetics Analyses 100
9.4.3.1. Plasma Pharmacokinetic Parameters 100
9.4.3.2. Tear Pharmacokinetic Parameters 101
9.4.3.3. Statistical Analyses of Pharmacokinetic Data 102
9.4.4. Other Analyses 102
9.4.4.1. Subgroup Analyses 102
9.5. Interim Analyses 102
10. Supporting Documentation and Operational Considerations 103

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 104
10.1.1. Regulatory and Ethical Considerations 104
10.1.2. Financial Disclosure 104
10.1.3. Informed Consent Process 105
10.1.4. Data Protection 105
10.1.5. Posting Clinical Study Data 105
10.1.6. Data Quality Assurance 106
10.1.7. Source Documents 106
10.1.8. Study and Site Closure 106
10.1.9. Publication Policy 107
10.1.10. Compliance with Protocol 107
10.1.11. Data Monitoring Committee 108
10.2. Appendix 2: Clinical Laboratory Tests 109
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 110
Definition of AE 110
Definition of SAE 113
Recording and Follow-up of AEs and/or SAEs 115
Reporting of SAEs 117
10.4. Appendix 4: Abbreviations 118
10.5. Appendix 5: Standard Discontinuation Criteria 120
10.6. Appendix 6: Study Tabular Summary 121
10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information 124
Definitions: 124
Contraception Guidance: 124
Pregnancy Testing: 126
Collection of Pregnancy Information: 126
10.8. Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments 127
11. References 128

List of Tables

Table 1-1 Schedule of Activities – Stage 1 22
Table 1-2 Schedule of Activities – Stage 2 25
Table 6-1 Study Interventions 58
Table 6-2 Stage 1: Required Washout Intervals for Prohibited Medications or Interventions Prior to the Screening Visit 64
Table 6-3 Stage 2: Required Washout Intervals for Prohibited Medications or Interventions Prior to the Screening Visit 65
Table 8-1 Erythema Grading Scale (Eyelid/Eyelid Margins/Lashes) 74
Table 8-2 Edema Grading Scale (Eyelids) 74
Table 8-3 Allergan Bulbar Hyperemia Grading Guide Photo Descriptions (Conjunctiva) 75
Table 8-4 Grading Scale for the Presence and Severity of Edema (Conjunctiva) 75
Table 8-5 Grading Scale for the Presence and Severity of Subconjunctival Hemorrhage (Conjunctiva) 75
Table 8-6 Edema Grading Scale (Cornea) 76
Table 8-7 Grading Scale for Superficial Punctate Keratopathy (Cornea) 76
Table 8-8 Settings for Measurements of Cells and Flare in the Anterior Chamber 76
Table 8-9 Grading Scale for Cells in the Anterior Chamber 76
Table 8-10 Grading Scale for Flare in the Anterior Chamber 77
Table 8-11 Grading Scale for Cataract Assessment 78
Table 8-12 Blood Sampling Schedule for Pharmacokinetics – Stage 1 83
Table 8-13 Blood Sampling Schedule for Pharmacokinetics – Stage 2 84
Table 8-14 Tear Sampling Schedule for Pharmacokinetics – Stage 1 85
Table 8-15 Tear Sampling Schedule for Pharmacokinetics – Stage 2 85
[redacted]
Table 9-1 Analysis Populations 97
Table 10-1 Protocol-required Safety Laboratory Assessments 109
Table 10-2 Highly Effective Contraceptive Methods 125

List of Figures

Figure 1-1 Study Flow Diagram – Stage 1 20
Figure 1-2 Study Flow Diagram – Stage 2 21

[redacted]

[redacted]

1. Protocol Summary

1.1. Synopsis

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

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

Study Phase: 1/2a

Study Rationale:

This is the first-in-human study to evaluate the safety, tolerability, pharmacokinetics (PK), and exploratory 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 the future development of either or both of these compounds for the treatment of DED.

Objectives and Endpoints:

Objectives	Assessments/Endpoints
Stage 1	
Primary	
• To evaluate the safety and tolerability of AGN-242428 and AGN-231868 and their respective vehicles in participants with DED	• 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
• To characterize the plasma and tear PK of AGN-242428 and AGN-231868 in participants with DED following a single bilateral dose and 13 days of twice daily administration followed by a single dose administration to both eyes	• The PK parameters to be calculated 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 ($t_{1/2}$) • The PK parameters to be calculated 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 $t_{1/2}$

Objectives	Assessments/Endpoints
Stage 2	
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 postdose ($C_{0\ 5h}$)
[redacted]	

[a] The exact statistical comparisons will be described in detail in the statistical analysis plan and will include, but will not be limited to, assessments of changes from baseline and responder analyses.

Overall Study Design:

This will be a Phase 1/2a, multicenter, vehicle-controlled, double-masked, randomized study conducted in 2 consecutive stages in participants with DED.

Stage 1 will evaluate the safety, tolerability, and PK (plasma and tear) of a maximum of 3 dose levels of AGN-242428 ([redacted]) and AGN-231868 ([redacted]) in participants with DED. Participants in Cohort 1A will be randomized 3:3:1:1 to receive 1 drop of [redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles (4 dosing arms total) to the left eye on Day 1. In the absence of significant study intervention-related safety findings, starting on Day 2, participants will administer 1 drop of the same randomized study intervention twice daily (approximately every 12 hours) to both eyes for an additional 13 days (through Day 14), followed by a single dose administration to both eyes on Day 15. The sponsor will decide whether to proceed to Cohort 1B after review of Cohort 1A data by the data monitoring committee (DMC). The DMC will be masked to the interventions but can request to be unmasked at any time.

Participants in Cohort 1B will be randomized 3:3:1:1 to receive [redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles. The same dosing regimen used in Cohort 1A will be applied in Cohort 1B. If any significant safety findings are identified during dosing in Cohort 1B, the DMC can recommend proceeding to Cohort 1C. In Cohort 1C, participants will be randomized 3:3:1:1 to receive [redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles. The same dosing regimen used in the previous cohorts will be applied in Cohort 1C. If no significant safety or tolerability findings are identified in Cohort 1B (high dose), Cohort 1C (mid dose) will not be initiated. It is possible that only 1 of the 2 tested experimental interventions (AGN-242428 or AGN-231868) and corresponding vehicle will proceed to the next cohort following DMC review of safety data.

After the sponsor's determination of adequate safety and tolerability of the interventions in Stage 1, Stage 2 will begin. The AGN-242428 and AGN-231868 doses will be selected based on safety and tolerability assessed in Stage 1; ie, the highest safe and tolerated dose of each intervention will be selected for testing in Stage 2. It is possible that only 1 experimental intervention (AGN-242428 or AGN-231868) will have acceptable safety to proceed to 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.

[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] requalified 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 to be administered as 1 drop in each eye twice daily (approximately 12 hours apart) for 41 days followed by a single dose administration to both eyes on Day 42. [redacted]

Number of Participants:

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. Participants withdrawn due to adverse events (AEs) will not be replaced. Participants who are withdrawn for other reasons may be replaced at the discretion of the sponsor if deemed necessary. No participant can be enrolled in more than 1 cohort and/or stage of the study.

Number of Sites:

Stage 1 will be conducted at 1 to 2 sites in the United States and Stage 2 will be conducted at up to approximately 8 sites in the United States.

Intervention Groups and Study Duration:

Stage 1

Stage 1 includes up to 3 consecutive cohorts, with 24 participants in each cohort. Participants in each cohort will be randomized into 4 groups in a 3:3:1:1 ratio, as follows:

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

Stage 2

[redacted] 250 participants who requalify at the Baseline visit will be randomized into 5 groups, in a 1:1:1:1:1 ratio within each site, as follows:

- AGN-242428 (N = 50)
- AGN-242428 vehicle (N = 50)
- AGN-231868 (N = 50)
- AGN-231868 vehicle (N = 50)
- Xiidra (N = 50)

Assuming no early termination, the duration of participation for each participant in the study will be as follows:

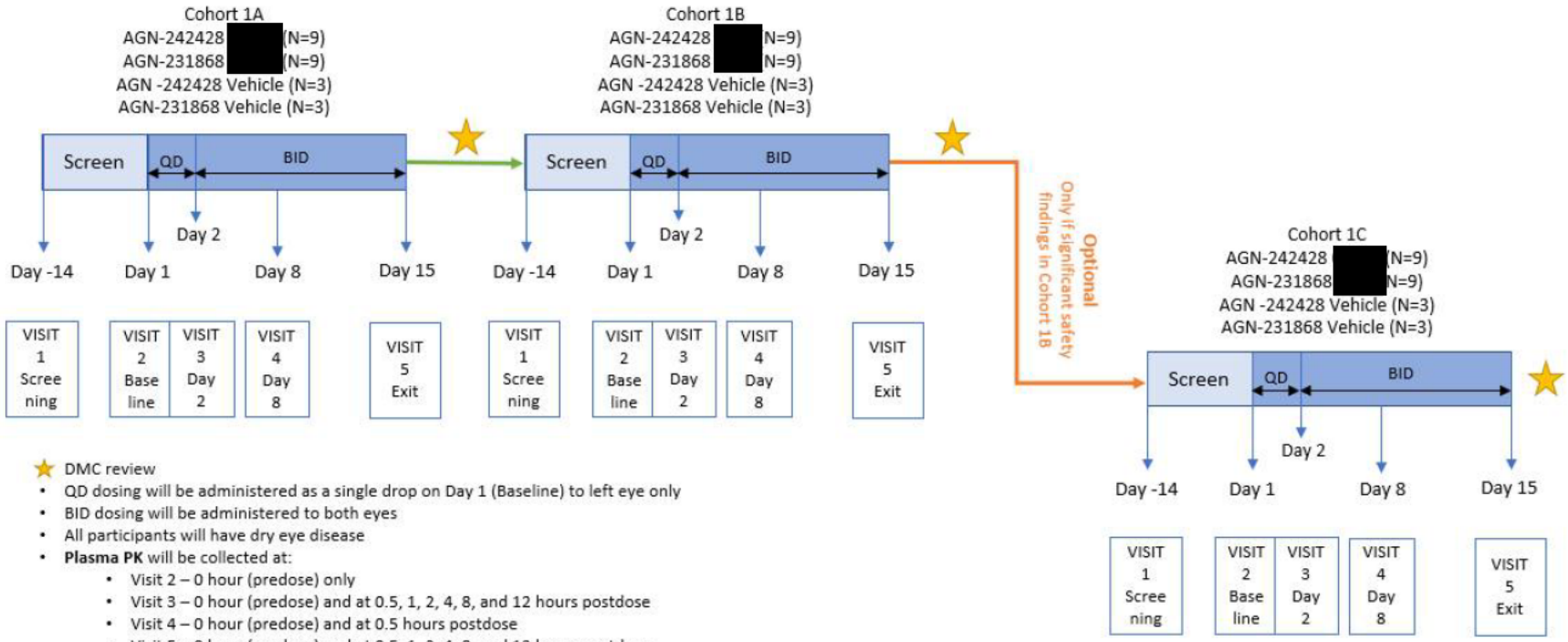
- Stage 1: approximately 1 month (Day -14 through collection of the last PK sample on Day 15)
- Stage 2: approximately 2.5 months (up to 14 days prior to Visit 2 on Day -14 through the last assessment on Day 42)

Data Monitoring Committee: Yes

1.2. Schema

Study flow diagrams for Stages 1 and 2 of the study are presented in Figure 1-1 and Figure 1-2.

Figure 1-1 Study Flow Diagram – Stage 1

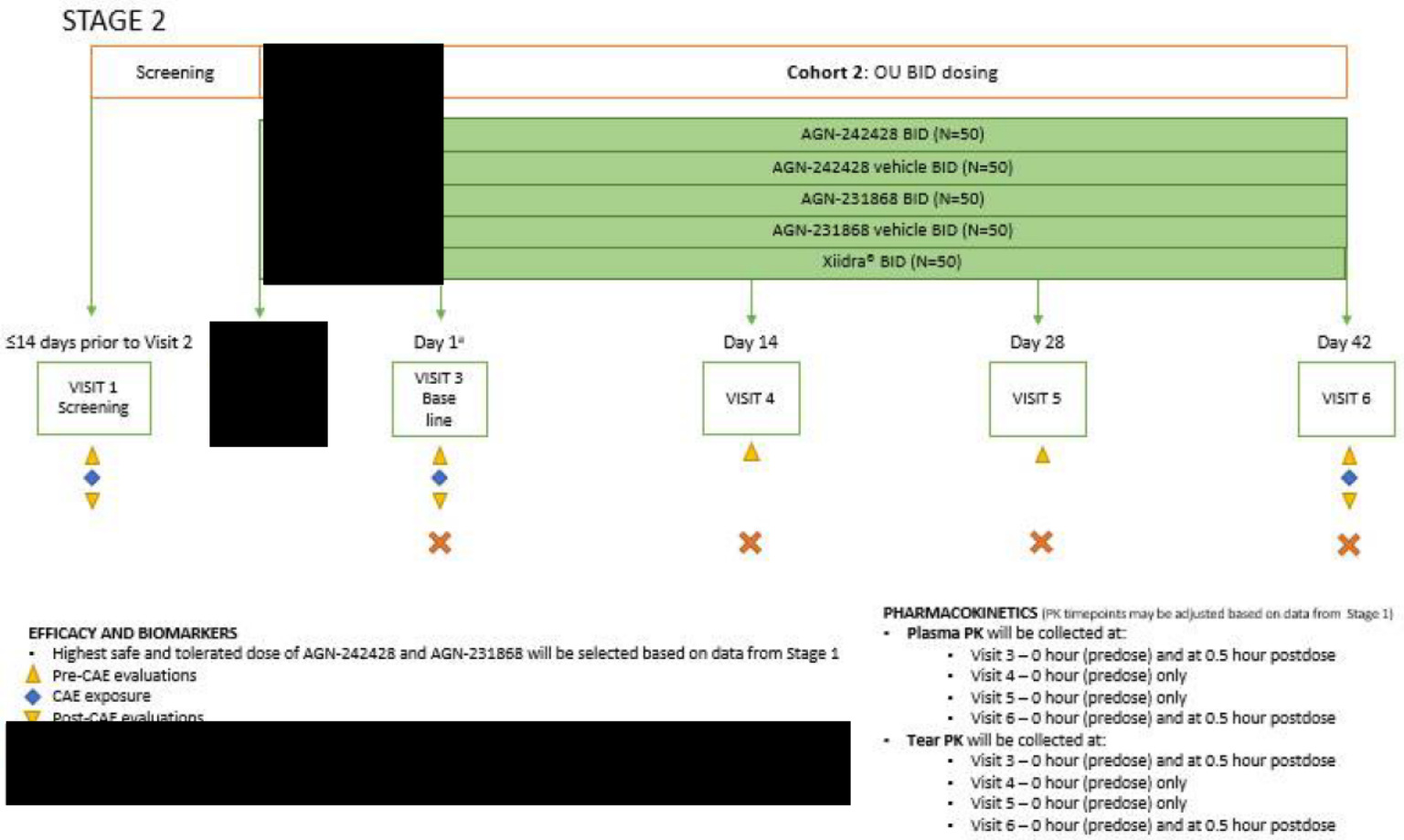


- DMC review
- QD dosing will be administered as a single drop on Day 1 (Baseline) to left eye only
- BID dosing will be administered to both eyes
- All participants will have dry eye disease
- **Plasma PK** will be collected at:
  - Visit 2 – 0 hour (predose) only
  - Visit 3 – 0 hour (predose) and at 0.5, 1, 2, 4, 8, and 12 hours postdose
  - Visit 4 – 0 hour (predose) and at 0.5 hours postdose
  - Visit 5 – 0 hour (predose) and at 0.5, 1, 2, 4, 8, and 12 hours postdose
- **Tear PK** will be collected from both eyes at:
  - Visit 3 – 0 hour (predose) and at 0.5, 2, 4, 8, and 12 hours postdose
  - Visit 4 – 0.5 hours postdose
  - Visit 5 – 0 hour (predose) and at 0.5, 2, 4, 8, and 12 hours postdose

[redacted]

BID = twice daily; DMC = data monitoring committee; PK = pharmacokinetics; QD = once daily

Figure 1-2 Study Flow Diagram – Stage 2



[a] On Day 1, participants will be randomized 1:1:1:1:1 to the 5 study intervention groups shown.

[b] The study eye will be defined as the eye with the highest [redacted]. If both eyes qualify and have the same [redacted] If both eyes still qualify, the right eye will be designated as the study eye.

BID = twice daily; CAE = controlled adverse environment; OU = both eyes; [redacted]; PK = pharmacokinetic(s)

1.3. Schedule of Activities (SoA)

Table 1-1 Schedule of Activities – Stage 1

Study Day (*Unless otherwise specified, all examinations/procedures for a timepoint must be performed in the order listed below*)	**Visit 1 Screening**	**Intervention Period**				**Notes**
		Visit 2 (Baseline)	**Visit 3**	**Visit 4**	**Visit 5 (Exit) or Early Termination**	
	Day -14 to Day -1	Day 1	Day 2	Day 8 (+1)	Day 15 (+2)	
Informed consent	X					
Inclusion and exclusion criteria	X	X				Recheck participant eligibility before randomization and/or first dose of study intervention.
Demographics	X					
Medical, ophthalmic, and surgical history (includes substance usage)	X	X				
Prior or concomitant medication review	←==========→					
AE review	←==========→					
Vital signs (RR, height, and weight)	X				X	Height measurement will not be performed at Visit 5 or the Early Termination visit.
Vital signs (blood pressure, pulse rate, and temperature)	X	X	X	X	X	
Physical examination	X				X	
12-lead ECG	X				X	At the Exit visit, ECG will be performed at 0 hour (predose) and 45 ± 15 minutes postdose.
Pregnancy test (WOCBP only)	X	X			X	Serum pregnancy test will be performed at Screening; at all other indicated visits, serum or urine pregnancy test will be performed.
Drugs of abuse screen	X	X				Breathalyzer may be used for alcohol.
Hematology, chemistry, and urinalysis	X				X	Participants will be instructed to fast (ie, water only) for at least 10 hours prior to blood collection for safety laboratory tests.
Serology	X					

Study Day (*Unless otherwise specified, all examinations/procedures for a timepoint must be performed in the order listed below*)	**Visit 1 Screening**	**Intervention Period**				**Notes**
		Visit 2 (Baseline)	**Visit 3**	**Visit 4**	**Visit 5 (Exit) or Early Termination**	
	Day -14 to Day -1	Day 1	Day 2	Day 8 (+1)	Day 15 (+2)	
[redacted]	X	X				
Manifest refraction	X	X	X	X	X	
Best-corrected visual acuity	X	X	X	X	X	
Slit lamp biomicroscopy	X	X	X	X	X	
[redacted]	X	X				
[redacted]	X	X				
Intraocular pressure	X	X	X	X	X	
Dilated fundus exam	X				X	
Randomization		X				
Blood sample collection for PK analysis		X	X	X	X	Blood samples for PK analysis will be collected at Visit 2 at 0 hour (predose) and at Visits 3 and 5 at 0 hour (predose) and 0.5, 1, 2, 4, 8, and 12 hours postdose. In addition, at Visit 4, a sample will be collected at 0 hour (predose) and at 0.5 hours postdose. At Early Termination visit, only a single sample will be collected. For the full blood sample collection schedule, refer to Table 8-12.
[redacted]						

Study Day (*Unless otherwise specified, all examinations/procedures for a timepoint must be performed in the order listed below*)	**Visit 1 Screening**	**Intervention Period**				**Notes**
		Visit 2 (Baseline)	**Visit 3**	**Visit 4**	**Visit 5 (Exit) or Early Termination**	
	Day -14 to Day -1	Day 1	Day 2	Day 8 (+1)	Day 15 (+2)	
Tear sample collection for PK analysis			X	X	X	Tear samples for PK analysis will be collected at Visits 3 and 5 at 0 hour (predose) and 0.5, 2, 4, 8, and 12 hours postdose. In addition, at Visit 4, a sample will be collected at 0.5 hours postdose. Tear samples will be collected from both eyes. For the full tear sample collection schedule, refer to Table 8-14. Tear collection will not be performed at the Early Termination visit.
Administration of study intervention		X	X	X	X	Study interventions will be administered as a single drop to the left eye on Day 1 and as a single drop to both eyes, twice daily (approximately 12 hours apart) for 13 days (Days 2-14), followed by a single dose administration to both eyes on Day 15. The morning dose will be administered by site staff on visit days. Dosing will not be performed at the Early Termination visit.
Drop Tolerability Questionnaire		X	X	X	X	Drop Tolerability Questionnaire must be administered within approximately 5 minutes following morning administration of study intervention. Drop Tolerability Questionnaire will not be administered at the Early Termination visit.
Dispensing of study intervention to participant			X	X		
Collection of used and unused study intervention				X	X	

AE = adverse event; ECG = electrocardiogram; [redacted]; PK = pharmacokinetic; RR = respiration rate; WOCBP = women of childbearing potential

Table 1-2 Schedule of Activities – Stage 2

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period**							**Early Termination**	**Notes**
			Visit 2 [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**			
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
Informed consent	X										
Inclusion and exclusion criteria	X	X		X	X						Recheck participant eligibility before randomization and/or first dose of study intervention
Demographics #	X										
Medical, ophthalmic, and surgical history (includes substance usage) #	X		X	X							
Prior or concomitant medication review #	X		X	X		X	X	X		X	Any use of prohibited concomitant medications (see Section 6.5.4), will be reviewed by the investigator and/or the sponsor, who will determine if the participant should be discontinued from the study.
AE review #	←═══→										
Vital signs (RR, height, and weight) #	X							X		X	Height measurement will not be performed at Visit 6 or Early Termination visit.
Vital signs (blood pressure, pulse rate, and temperature) #	X			X		X	X	X		X	
Physical examination #	X							X		X	

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period**							**Notes**
			Visit 2 [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**		**Early Termination**	
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
12-lead ECG #	X							X	X	X	ECGs will be performed in approximately 20% of all participants. ECGs will be conducted at selected sites only. For more information, see Section 8.1.7. At Visit 6, ECGs will be performed at 0 hour (predose) and at 45 ± 15 minutes postdose.
Pregnancy test (WOCBP only) #	X			X				X		X	Serum pregnancy test will be performed at Screening visit; at all other indicated visits serum or urine pregnancy test will be performed.
Drugs of abuse screen #	X			X							Breathalyzer may be used for alcohol.
Hematology, chemistry, and urinalysis #	X			X			X	X		X	
Serology #	X										
[redacted]											

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period**								**Notes**
			Visit 2 [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**		**Early Termination**	
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
[redacted]											
Manifest refraction	X							X		X	
Best-corrected visual acuity	X		X	X		X	X	X		X	
Slit lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X	
[redacted]											

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period**							**Notes**
			Visit 2 [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**		**Early Termination**	
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
Blood sample collection for PK analysis				X	X	X	X	X	X	X	Blood samples for PK analysis will be collected at time 0 hour (predose) and prior to CAE entry (where applicable) at Visits 3, 4, 5, and 6. In addition, samples will be collected at 0.5 hour postdose, after CAE exposure on Visits 3 and 6. At the Early Termination visit, only a single sample will be collected. For the full blood sampling schedule, refer to Table 8-13.
[redacted]											
Tear sample collection for PK analysis				X	X	X	X	X	X		Tear samples for PK analysis will be collected at time 0 hour (predose) prior to CAE entry (where applicable) on Visits 3, 4, 5, and 6. In addition, samples will be collected at 0.5 hour postdose, after CAE exposure on Visits 3 and 6. See Section 8.4.3. Not performed at the Early Termination visit if a participant is discontinued due to the use of prohibited medication.

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period**							**Notes**
			Visit 2 [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**		**Early Termination**	
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
[redacted]											
CAE exposure	X			X				X			Not performed at the Early Termination visit if a participant is discontinued due to the use of prohibited medication.
Randomization					X						

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period**							**Notes**
			Visit 2 [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**		**Early Termination**	
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
Administration of study intervention			X		X	X	X		X		Assigned study intervention will be administered as a single drop to both eyes, twice daily (approximately 12 hours apart) on Days -14 to 41, followed by a single dose administration to both eyes on Day 42. The morning dose will be administered by site staff on visit days. Not performed at the Early Termination visit if a participant is discontinued due to the use of prohibited medication.
Drop Tolerability Questionnaire					X	X	X		X		Drop Tolerability Questionnaire will commence 5 (± 1) minutes following morning administration of study intervention. Not administered at the Early Termination visit if a participant is discontinued due to the use of prohibited medication.

Study Day *Unless otherwise specified with a '#', all examinations/procedures for a timepoint will be performed in the order listed below**	**Visit 1 Screening**		**Intervention Period** **Visit 2** [redacted]	**Visit 3 (Baseline)**		**Visit 4**	**Visit 5**	**Visit 6 (Exit)**		**Early Termination**	**Notes**
	up to 14 days before Visit 2		Day -14 (± 2)	Day 1		Day 14 (± 2)	Day 28 (± 3)	Day 42 (± 5)		NA	
	Pre-CAE	Post-CAE	NA	Pre-CAE	Post-CAE	NA	NA	Pre-CAE	Post-CAE	NA	
Dispensing of the study intervention to participant			X		X	X	X				
Collection of used and unused study intervention					X	X	X		X	X	If necessary, to facilitate participant flow at the site on any given day, collection of used and unused study intervention can be done upon arrival of participants.
Intraocular pressure		X							X	X	
Dilated fundus exam		X							X	X	
Study exit									X	X	

AE = adverse events; CAE = controlled adverse environment; ECG = electrocardiogram; NA = not applicable; [redacted]; PK = pharmacokinetic; RR = respiration rate; [redacted] WOCBP = women of child bearing potential

* After completion of Informed Consent and Inclusion/Exclusion Criteria, for assessments listed with a '#' flexibility in procedure order is allowed, [redacted]

2. Introduction

This study is the first-in-human (FIH) evaluation of the safety, tolerability, pharmacokinetics (PK), and exploratory efficacy of 2 novel interventions, AGN-242428 and AGN-231868, applied through topical ocular instillation. Both compounds are being developed for the treatment of the signs and symptoms of dry eye disease (DED).

DED, also known as keratoconjunctivitis sicca, is a multifactorial disease of the tears and ocular surface; symptoms include discomfort, visual disturbance, and eye dryness, with the potential for exposure of and damage to the ocular surface (Craig et al 2017). The condition is accompanied by increased osmolarity of tears and inflammation of the ocular surface. Symptoms can be caused by defects in the aqueous, lipid, and/or mucin layers of the tear film (Craig et al 2017). Many of the current therapies for DED are palliative, focusing on replacement of tears to reduce symptoms. With respect to pharmaceuticals, various strategies exist for targeting the underlying ocular inflammation associated with DED with 2 products (Restasis® [0.05% cyclosporine ophthalmic emulsion, Allergan, Irvine, California, USA] and Cequa™ [0.09% cyclosporine ophthalmic solution, Sun Pharma, Princeton, New Jersey, USA]) indicated for increased tear production in patients with DED and a third, Xiidra® (lifitegrast ophthalmic solution, Shire, Lexington, Massachusetts, USA), indicated for the treatment of the signs and symptoms of DED. The short-term application of topical ocular steroids is also used as induction therapy or for acute management of DED.

The etiologies of DED are varied. The disease has been linked to age-related decreases in systemic androgen support to the lacrimal gland, ocular surgeries, use of contact lens, and systemic autoimmune diseases such as Sjögren's syndrome (Gayton et al 2009). A growing body of research suggests that DED is the result of an underlying cytokine and receptor-mediated inflammatory process. It has also been shown that, at least in part, the inflammation is mediated by lymphocytes (Kunert et al 2000) and that the clinical manifestation of DED may be associated with T-cell activation and migration (Stern et al 2002).

Several types of T-cells have been associated with development and progression of DED. T-helper (Th)17 cells, next to Th1 cells that secrete interferon gamma, are thought to be the primary effector T-cells of DED (El Annan et al 2009; De Paiva et al 2009). Th17 cells are a subtype of T-cells that express interleukin (IL)-17, which is thought to play a crucial role in the disruption of the corneal epithelial barrier in DED (De Paiva et al 2009). Blockade of IL-17 in experimental models of DED reduced the progression and severity of the disease. In the clinic, tear levels of IL-17 were increased in DED patients when compared with healthy volunteers (Roy et al 2017). Retinoic acid receptor-related orphan receptor γt (RORγt) is a nuclear hormone receptor that is known to regulate differentiation of Th17 cells and production of IL-17 (Korn et al 2009). AGN-242428 is a RORγt inhibitor that is expected to reduce ocular inflammation associated with activation of Th17 cells and increased production of IL-17.

Another approach to target ocular inflammation is to reduce infiltration of immune cells to the surface of the eye. Chemokines are a group of peptides that play an important role in

orchestrating leukocyte recruitment and function, and therefore represent an important target for anti-inflammatory therapies (Wells et al, 2006). In fact, blockage of chemokine receptor 2 (CCR2) in a murine model of DED, significantly improved the signs of DED (Goyal et al 2009). Antigen-presenting cells and T-cell chemokines and chemokine receptors were also shown to be expressed in the tear film and on the ocular surface of DED patients (Choi et al 2012; Gulati et al 2006; Na et al 2012). However, the chemokine system is complex, with ~50 chemokines and 20 chemokine receptors identified in humans, often acting with redundancy, making selection of specific antagonists difficult (Gerard and Rollins 2001). Because multiple chemokines and chemokine receptors have been shown to correlate with antigen-presenting cell and T-cell mediated immunopathology in DED, the use of a broad-spectrum chemokine receptor antagonist, which inhibits the function of a wide range of chemokines, may be beneficial over selective/dual chemokine receptor antagonists. AGN-231868 is a multichemokine receptor antagonist that is expected to reduce ocular inflammation associated with lymphocyte infiltration and activation.

As noted above, Xiidra is the only therapeutic approved by the Food and Drug Administration (FDA) for the treatment of DED. Like AGN-242428 and AGN-231868, it also targets inflammation, through another mechanism of action. The active substance, lifitegrast, is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that is thought to reduce T-cell activation and migration. More information on Xiidra can be found in the Xiidra package insert (Xiidra US package insert 2016).

2.1. Study Rationale

This is the FIH study to evaluate the safety, tolerability, PK, [redacted] 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 DED. Data from this study will guide future development of either or both of these compounds for the treatment of DED.

2.2. Background

Inflammation plays a crucial role in the pathogenesis of DED. Therefore, an overarching approach to treating DED is to target the underlying inflammatory response that leads to epithelial damage and ocular symptoms such as dryness and discomfort. AGN-242428 and AGN-231868 are designed to reduce ocular inflammation associated with DED through 2 distinct mechanisms. Both interventions have favorable safety profiles and have been shown to be efficacious in nonclinical models. Xiidra was selected as the active comparator in Stage 2 because it is considered the current standard of care for the treatment of DED in the United States.

A detailed description of the chemistry, pharmacology, PK, efficacy, and safety of AGN-242428 and AGN-231868 is provided in the respective investigator's brochures. A detailed description of the chemistry, pharmacology, PK, efficacy, and safety of Xiidra can be found in the Xiidra package insert (Xiidra US package insert 2016).

2.2.1. AGN-242428

2.2.1.1. Pharmacology

RORγt is a nuclear hormone receptor that constitutively induces IL-17A gene expression. Inhibition of RORγt blocks the transcription of IL-23R, IL-17A, IL-17F, and IL-22, suppressing the IL-23 and IL-17 driven inflammation process. AGN-242428 is an inverse agonist (inhibitor) that binds in the ligand binding domain blocking the transcriptional activity of the receptor and suppressing cytokine production.

AGN-242428 is a potent and selective inhibitor of human RORγt. AGN-242428 inhibits the secretion of IL-17 from stimulated human peripheral blood mononuclear cells in serum-free media [redacted]. This activity reflects the potential to modulate Th17-mediated responses that contribute to corneal barrier disruption and sustained disease observed in chronic DED. In vivo studies have demonstrated that AGN-242428 can prevent disease in experimental models of ocular allergy and autoimmunity that represent the cellular responses observed in chronic DED.

2.2.1.2. Pharmacokinetics

The ocular and systemic PK of [redacted] AGN-242428 were characterized in rabbits. Following topical ocular administration of [redacted] AGN-242428 to rabbit eyes, AGN-242428 concentrations in ocular tissues, including cornea, conjunctiva, and tears, were sustained above the anticipated efficacious levels for at least 12 hours postdose. Systemic exposure after a single dose of [redacted] AGN-242428 in rabbits was minimal. Minimal (up to 2-fold) systemic accumulation of AGN-242428 was observed in the toxicokinetic studies after 42 days of dosing with [redacted] AGN-242428 up to twice daily in the left eye and 4 times daily in the right eye in rabbits and dogs.

2.2.1.3. Toxicology

The toxicology profile of AGN-242428 was established through systemic and ocular toxicology, safety pharmacology, and genetic toxicology studies.

In the pivotal Good Laboratory Practice (GLP) studies, rabbits and dogs were administered doses up to [redacted] 4 times daily for 6 weeks (up to 420 µg/eye/day), which is 24 times greater than the starting clinical dose of [redacted] with little or no ocular and systemic findings. The no observed adverse effect level (NOAEL) was considered the highest dose in each of these ocular studies.

AGN-242428 was not genotoxic and did not have any effects on central nervous system (CNS), cardiovascular, or respiratory parameters that could be expected at systemic exposures attained with ocular dosing.

Adequate margins of safety have been demonstrated with AGN-242428 in the toxicology species. Systemic exposures at the NOAEL in rats (60 mg/kg/day) and dogs (5 mg/kg/day) after oral administration were approximately [redacted] greater by AUC and [redacted] greater by C_{max}

compared with systemic exposures anticipated after ocular dosing in humans at [redacted] AGN-242428 (the highest anticipated clinical ocular dose).

2.2.1.4. Clinical Experience

AGN-242428 delivered orally in support of a systemic treatment for psoriasis has been evaluated in 4 clinical trials with administration as single ascending doses (SAD) to 40 healthy volunteers (VTP-43742-001); administration once daily for 10 consecutive days to 30 healthy volunteers (VTP-43742-002 Part 1); administration once daily for 28 consecutive days to 29 patients with moderate to severe plaque psoriasis (VTP-43742-002 Part 2); and administration once daily for up to 12 weeks to 17 patients with moderate to severe plaque psoriasis (1957-201-001). The fourth trial was a single dose study comparing the relative bioavailability of 2 oral formulations of AGN-242428 (VTP-43742-003). More details are available in the AGN-242428 investigator's brochure.

In past assessment of AGN-242428 administered orally to participants with psoriasis (Allergan Study 1957-201-001), 4 study participants met the stopping criteria for liver function test (LFT) elevations (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] were at or above 5 × upper limit of normal [ULN]). Elevated LFT was found for 1 participant receiving 225 mg, 1 participant receiving 350 mg, and 2 participants receiving 450 mg AGN-242428. The earliest finding of elevated LFT was observed following 4 weeks of daily treatment with 450 mg of AGN-242428. There were no cases with associated serious adverse events (SAEs), and there were no combination cases (transaminases $\geq 3 \times$ ULN + total bilirubin $\geq 2 \times$ ULN) as all participants with elevated transaminases had total bilirubin values that were within normal limits. All 4 participants were asymptomatic and lab abnormalities resolved upon treatment discontinuation.

Even though there is a liver safety concern with AGN-242428 administered orally at doses of 225 mg/day and higher, the maximum daily dose proposed for administration in this study is substantially lower than the doses administered orally. The total daily dose following twice daily administration of the highest dose strength of AGN-242428 topical ocular solution will be approximately 0.36 mg, which is 625 times lower than the lowest oral dose associated with elevated LFT (225 mg/day) in Study 1957-201-001. Even though the systemic exposure after administration of the highest proposed ocular dose of AGN-242428 is expected to be very low and not associated with LFT elevations, liver safety tests will be included in both stages of this study.

There is no clinical experience with AGN-242428 administered through ocular instillation.

2.2.2. AGN-231868

2.2.2.1. Pharmacology

Chemokine receptors are cell membrane G-protein coupled receptors that mediate several physiological and pathological processes via chemokine ligand binding. AGN-231868 inhibits the function of chemokine receptors CCR1, CCR2, CCR5, and CCR9, and has the potential to

block signaling of several chemokines including MIP-1a, MIP-1b, RANTES, MCP-3, and MCP-1. AGN-231868 is an allosteric inhibitor of these receptors and thus, does not compete with endogenous chemokine ligand binding.

AGN-231868 is a potent and selective inhibitor of human CCR1, CCR2, CCR5, and CCR9 chemokine receptors, with [redacted]. In vivo studies have demonstrated that AGN-231868 can prevent disease in an experimental autoimmune encephalomyelitis (EAE) model. EAE is a chronic relapsing-remitting inflammation mouse model, in which CCR1, CCR2, and CCR5 signaling contributes to immune-mediated pathology. The cellular mechanisms observed in DED are similar to the immune response observed in EAE mice. On the basis of these findings, it is demonstrated that AGN-231868 modulates immune mechanisms relevant to DED and this supports the initiation of studies in humans.

2.2.2.2. Pharmacokinetics

The ocular and systemic PK of [redacted] and [redacted] AGN-231868 were characterized in rabbits. Following a single bilateral topical ocular administration of AGN-231868 at [redacted] or [redacted] the concentrations in target tissues, such as cornea and conjunctiva, were sustained above the anticipated efficacious levels for at least 12 or 24 hours postdose, respectively. Systemic exposure after administration of either dose was minimal. Systemic accumulation, assessed in the toxicokinetic studies following 42 days of unilateral dosing of up to [redacted] AGN-231868 4 times daily in rabbits and monkeys, was minimal (up to 2-fold).

2.2.2.3. Toxicology

The toxicology profile of AGN-231868 was established through systemic and ocular toxicology, safety pharmacology, and genetic toxicology studies.

AGN-231868 was well tolerated in the eyes when administered topically to rabbits and monkeys at doses of [redacted] administered 4 times daily for up to 42 days. No tolerability concerns or ocular effects were observed in rabbits and monkeys at doses higher than those proposed to be administered clinically.

AGN-231868 did not display clinically significant effects on CNS, cardiovascular, or pulmonary parameters at systemic exposures higher than those attained with ocular dosing. AGN-231868 is not genotoxic.

Adequate margins of safety have been demonstrated with AGN-231868 in the toxicology species and by the intended route of exposure. Systemic exposures at the NOAEL in rats (100 mg/kg/day) and monkeys (500 mg/kg/day) after oral administration were approximately [redacted] by AUC and [redacted] greater by C_{max} compared with systemic exposures anticipated after ocular dosing in humans at [redacted] AGN-231868 (the highest anticipated clinical ocular dose).

2.2.2.4. Clinical Experience

There is no clinical experience with AGN-231868 administered through any route.

2.3. Benefit/Risk Assessment

Based on the pharmacology of the 2 proposed interventions (AGN-242428 and AGN-231868) and the nonclinical data, it is reasonable to expect that either molecule has the potential to reduce the signs and symptoms of DED.

Based on existing toxicology data, AGN-242428 and AGN-231868 are expected to be well tolerated after topical ophthalmic administration in humans.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AGN-242428 and AGN-231868 may be found in the respective investigator's brochures.

Risks and benefits of Xiidra can be found in Xiidra package insert (Xiidra US package insert 2016).

3. Objectives and Endpoints

3.1. Stage 1

Objectives	Assessments/Endpoints
Primary	
• To evaluate the safety and tolerability of AGN-242428 and AGN-231868 and their respective vehicles in participants with DED	• 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
• To characterize the plasma and tear PK of AGN-242428 and AGN-231868 in participants with DED following a single bilateral dose and 13 days of twice daily administration followed by a single dose administration to both eyes	• The PK parameters to be calculated 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 ($t_{1/2}$) • The PK parameters to be calculated 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 $t_{1/2}$

3.2. Stage 2

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 postdose ($C_{0\ 5h}$)
Tertiary/Exploratory	
[redacted]	

[a] The exact statistical comparisons will be described in detail in the statistical analysis plan and will include, but will not be limited to, assessments of changes from baseline and responder analyses.

4. Study Design

4.1. Overall Design

This will be 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 and Stage 2 will be conducted at up to approximately 8 sites in the United States.

Stage 1 will evaluate the safety, tolerability, and PK (plasma and tear) of a maximum of 3 dose levels of AGN-242428 ([redacted]) and AGN-231868 ([redacted]) in participants with DED. Participants in Cohort 1A will be randomized 3:3:1:1 to receive 1 drop of [redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles (4 dosing arms total) to the left eye on Day 1. In the absence of significant study intervention-related safety findings, starting on Day 2, participants will administer 1 drop of the same randomized study intervention twice daily (approximately every 12 hours) to both eyes for additional 13 days (through Day 14), followed by a single dose administration to both eyes on Day 15. The sponsor will decide whether to proceed to Cohort 1B after review of Cohort 1A data by the data monitoring committee (DMC). The DMC will be masked to the interventions but can request to be unmasked at any time. More details on the DMC are available in Section 10.1.11.

Participants in Cohort 1B will be randomized 3:3:1:1 to receive [redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles. The same dosing regimen used in Cohort 1A will be applied in Cohort 1B. If any significant safety findings are identified during dosing in Cohort 1B, the DMC can recommend proceeding to Cohort 1C. In Cohort 1C, participants will be randomized 3:3:1:1 to receive [redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles. The same dosing regimen used in the previous cohorts will be applied in Cohort 1C. If no significant safety or tolerability findings are identified in Cohort 1B (high dose), Cohort 1C (mid dose) will not be initiated. It is possible that only 1 of the 2 tested experimental interventions (AGN-242428 or AGN-231868) and corresponding vehicle will proceed to the next cohort following DMC review of safety data.

After the sponsor's determination of adequate safety and tolerability of study interventions in Stage 1, Stage 2 will begin. The AGN-242428 and AGN-231868 doses will be selected based on safety and tolerability assessed in Stage 1; ie, the highest safe and tolerated dose of each intervention will be selected for testing in Stage 2. It is possible that only 1 experimental intervention (AGN-242428 or AGN-231868) will have acceptable safety to proceed to 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 requalified participants will administer 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. Exploratory efficacy endpoints will be assessed on Day 42 with and without the use of the CAE. In addition, exploratory efficacy without the use of the CAE will be assessed on Days 14 and 28.

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

Assuming no early termination, 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)
- For participants in Stage 2: approximately 2.5 months (up to 14 days prior to Visit 2 on Day -14 through the last assessment on Day 42)

4.2. Scientific Rationale for Study Design

4.2.1. Duration of Treatment in Stage 1 and Stage 2

In Stage 1, on Day 1 participants will receive a single drop of the intervention to the left eye only. Starting on Day 2, the participants will administer a single drop to both eyes twice daily (approximately 12 hours apart) for additional 13 days (through Day 14), followed by a single dose administration to both eyes on Day 15. Two weeks of administration was estimated to be sufficient to evaluate safety and tolerability of each dose level.

In Stage 2, participants will administer a single drop of the assigned intervention to both eyes twice daily (approximately 12 hours apart) for 41 days, followed by a single dose administration to both eyes on Day 42. Based on the pharmacology of AGN-242428 and AGN-231868, 6 weeks of twice daily treatment is expected to provide sufficient time to improve the signs and/or symptoms of DED.

4.2.2. Cohorts in Stage 1

Up to 3 cohorts are planned in Stage 1. Cohort 1A will be the lowest dose cohort. Once Cohort 1A is completed, the DMC will review the data and provide recommendation if the study should proceed to Cohort 1B (high dose). Following completion of Cohort 1B, the DMC will review the data, and in the event that any concerning safety and/or tolerability findings are identified, the study may proceed to Cohort 1C (mid dose). If no safety concerns are identified in Cohort 1B, Cohort 1C will not be conducted and the study will proceed to Stage 2. This design

will allow for identification of the highest tolerated/feasible dose of each intervention to proceed to Stage 2.

It is possible that only 1 of the 2 tested experimental interventions (AGN-242428 or AGN-231868) and its vehicle will proceed to the next cohort based on the safety data review.

4.2.3. Dose Selection for Stage 2

AGN-242428 and AGN-231868 dose levels in Stage 2 will be selected by the sponsor based on the data from Stage 1. The highest tolerated dose of each intervention (established in Stage 1) will be selected for testing in Stage 2 to maximize the potential to achieve proof of concept. It is possible that only 1 experimental intervention (AGN-242428 or AGN-231868) will have acceptable safety to proceed to Stage 2.

4.2.4. Controlled Adverse Environment

The CAE challenge will be used to select participants in Stage 2 and to assess exploratory efficacy of the interventions in addition to efficacy assessments conducted in the environment (without the use of the CAE).

Accurate assessment of a DED therapy is particularly challenging because the participant's daily activities and environmental conditions can influence the severity of the signs and symptoms of DED. Factors such as humidity, air movement, and temperature can have an impact on the tear film and ocular discomfort (Ousler 2005). The use of CAE in Stage 2 of this study is intended to reduce the "background noise" associated with the daily environmental and behavioral differences between study participants. The CAE is an environmental chamber that provides standardized environmental conditions by regulating humidity, temperature, airflow, lighting conditions, and visual stimuli to challenge each participant in the same way. The CAE is commonly used in development of DED therapies (Semba 2012; Meerovitch 2013; Petrov 2016). In this study, the signs and symptoms of DED will be evaluated using both environmental conditions (no use of CAE, or pre-CAE assessments) and CAE conditions. This will maximize the potential to achieve proof of concept.

In Stage 2 of this study, participants will be selected based on several criteria (refer to Section 5.2 for the full list of inclusion and exclusion criteria), including response to the CAE.

[redacted]

[redacted]

4.3. Justification for Dose

4.3.1. AGN-242428

The starting dose of AGN-242428 selected for testing in this study is [redacted] and the highest anticipated clinical dose is [redacted]. The highest clinical dose was selected based on the feasibility and limitations of the ophthalmic formulation. The starting dose was selected based on nonclinical data and is predicted to deliver safe, pharmacologically active levels of AGN-242428 to target ocular tissues.

In an ocular PK study in rabbits, a single bilateral topical ocular administration of AGN-242428 at [redacted] resulted in AGN-242428 concentrations in target tissues, such as cornea, conjunctiva, and tears that were sustained above the anticipated efficacious levels [redacted] for at least 12 hours postdose. Assuming linear PK, the estimated AGN-242428 concentrations in ocular target tissues following administration of [redacted] dose will be sustained above the anticipated efficacious levels for at least 12 hours postdose.

No drug-related ocular effects were observed in rabbit and minimal ocular effects were observed in dog toxicity studies with topical ocular administration of AGN-242428 at doses up to [redacted] 4 times daily. [redacted] Cumulative data from ocular and systemic toxicity studies support the proposed dose range of [redacted] AGN-242428 dosed bilaterally up to twice daily for 42 days.

4.3.2. AGN-231868

The starting dose of AGN-231868 selected for testing in this study is [redacted] and the highest anticipated clinical dose is [redacted]. The highest clinical dose was selected based on the feasibility of the ophthalmic formulation. The starting dose was selected based on nonclinical data and is predicted to deliver safe, pharmacologically active levels of AGN-231868 to target ocular tissues.

In an ocular PK study in rabbits, a single bilateral topical ocular administration of AGN-231868 at [redacted] resulted in AGN-231868 concentrations in target tissues, such as cornea and conjunctiva, that were sustained above the anticipated efficacious levels (the estimated [redacted]

[redacted]

No tolerability concerns or ocular effects were observed in ocular toxicity studies with 4 times daily dosing of up to [redacted] AGN-231868 for 42 days. [redacted] Cumulative data from ocular and systemic toxicity studies support the proposed dose range of [redacted] AGN-231868 dosed bilaterally up to twice daily for 42 days.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study.

The Exit visit is defined as the last visit or the last scheduled procedure shown in the SoA for each stage of the study (Section 1.3). A participant is considered to have completed the study if he/she has completed all study visits including the Exit visit. If the participant is discontinued or withdraws from the study before the Exit visit, the last visit before the discontinuation or withdrawal will be considered an Early Termination visit.

5. Study Population

All participants will have DED. In addition, participants enrolled in Stage 2 of this study will have to respond to the CAE challenge with increased signs and symptoms of DED (see Sections 4.1 and 4.2.4 for more details).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Stage 1

5.1.1. Inclusion Criteria for Stage 1

Participants are eligible to be included in Stage 1 of the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be ≥ 18 years of age at the time of signing the informed consent
2.	**Type of Participant and Disease Characteristics**
2.01	Both of the following signs of DED in at least 1 eye at Screening and Baseline visits (the same eye does *not* need to qualify at both visits): • Total corneal fluorescein staining score ≥ 2 and ≤ 9 based on the NEI grading scale, with no score > 2 in any 1 region • Schirmer test with topical anesthesia score ≥ 1 and ≤ 10 mm/5 min
2.02	Symptoms of DED at both the Screening and Baseline visits as defined by an OSDI total score of ≥ 13 with ≤ 3 responses of "not applicable (NA)".
2.03	BCVA of 20/100 or better in both eyes at the Screening visit
2.04	Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history, physical examination, fasting blood chemistry and hematology, urinalysis, vital signs, and 12-lead ECG results at the Screening and Baseline visits, as applicable per the SoA (Section 1.3).
3.	**Sex**
3.01	Male or female

4.	**Contraceptives**
4.01	Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study • A male participant with a heterosexual partner who is a woman of childbearing potential (WOCBP) must agree to use contraception as detailed in Appendix 7 during the intervention period and refrain from donating sperm during this period
4.02	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study • A female participant is eligible to participate if she is either: o Not a WOCBP as defined in Appendix 7 (proper documentation must be provided to confirm non-WOCBP status) OR o A WOCBP who is not pregnant (ie, has a negative serum pregnancy test result at the Screening visit and has a negative serum or urine pregnancy test result at the Baseline visit), and agrees to follow the contraceptive guidance in Appendix 7 during the intervention period
5.	**Informed Consent**
5.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
5.02	Written informed consent from the participant has been obtained prior to any study-related procedures
6.	**Other**
6.01	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

5.1.2. Exclusion Criteria for Stage 1

Participants are excluded from Stage 1 of the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Current diagnosis of glaucoma or ocular hypertension; evidence of glaucoma or mean intraocular pressure > 21 mm Hg determined by Goldmann applanation tonometry, in either eye
1.02	History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, likely interfere with the interpretation of the study results or participant safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. (Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.)
1.03	Diagnosis of recurrent, ongoing, or active ocular infection including, but not limited to herpes simplex or zoster, vaccinia, varicella, tuberculosis of the eye, acanthamoeba, or fungal disease
1.04	History of ocular surgery within 12 months prior to Screening visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (eg, cataract surgery or any surgery involving limbal or corneal incision)
1.05	Have had a corneal transplant in either or both eyes
1.06	At the Screening visit, at the investigator's discretion, have active or uncontrolled, severe: • Systemic allergy • Chronic seasonal allergies at risk of being active during the study • Rhinitis or sinusitis
1.07	History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, coagulation, gastrointestinal, endocrine, immunologic, dermatologic, ophthalmologic, neurologic or psychiatric disease. Significant is defined as any disease that, in the assessment of the investigator, would put the safety of the participant at risk through participation, or which would prevent or confound protocol-specified assessments (eg, severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.)

2.	**Prior/Concomitant Therapy**
2.01	Use of artificial tears within 24 hours prior to the Screening visit or anticipated use during the study
2.02	Use of systemic immunomodulators (eg, hydroxychloroquine, methotrexate, cyclosporine) within 14 days prior to the Screening visit or anticipated use during the study
2.03	Use of corticosteroids administered through any route within 7 days of the Screening visit or anticipated use during the study
2.04	Use of any form of topical ophthalmic cyclosporine (eg, RESTASIS or other ophthalmic form) within 7 days prior to the Screening visit or anticipated use during the study
2.05	Use of topical ocular glaucoma medications or topical ocular allergy medications (over-the-counter [OTC], herbal, prescription, or nutritional supplements including all mast cell stabilizers and antihistamines) within 7 days prior to the Screening visit or anticipated use during the study
2.06	Use of Xiidra (lifitegrast ophthalmic solution, 5%) or TrueTear™ within 7 days prior to the Screening visit or anticipated use during the study
2.07	Use of medications associated with the treatment of severe DED and/or Meibomian gland disease such as oral antimuscarinics, cevimeline, oral macrolides, tetracyclines, tetracycline derivatives, and retinoids within 14 days prior to the Screening visit or anticipated use during the study
2.08	Use of contact lenses in either eye within 14 days prior to the Screening visit or planned use during the study
2.09	Punctal or intracanalicular plug present in either eyelid within 1 year of the Screening visit or anticipated plug insertion or occlusion at any time during the study
2.10	Use of lid-heating therapy (ie, LipiFlow, iLUX, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression in either eye within 3 months prior to the Screening visit or anticipated use during the study

2.11	The start date of any systemic medication (including OTC, herbal, prescription, or nutritional supplements), which may affect DED or vision is < 7 days prior to the Screening visit or a change in dosage is anticipated during the study. Systemic medications, which may affect DED or vision, include but are not limited to the following: antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants, and phenothiazines.
2.12	The start date of hormone replacement therapy program, oral or transdermal contraception, other estrogen or progesterone treatments, or other medications required for long-term treatment of chronic diseases is < 7 days prior to the Screening visit or a change in dosage is anticipated during the study
2.13	The start date of any androgen therapy is < 7 days prior to the Screening visit or a change in dosage is anticipated during the study
2.14	Use of inhalable or ingestible cannabis products, or transdermal patches containing THC within 30 days prior to the Screening visit or anticipated use during the study
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug, device, or any observational study or participation in such a study within 30 days prior to the Screening visit
3.02	Participation in a blood or plasma donation program within 60 or 30 days, respectively, prior to study intervention administration, or anticipated participation during the study
4.	**Other**
4.01	Known allergies or sensitivity to the study interventions or study diagnostic agents including sodium fluorescein, etc.
4.02	The participant has a condition or is in a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study
4.03	Positive test results for anti–HIV type 1 and 2, hepatitis B surface antigen, or anti-hepatitis C virus at the Screening visit
4.04	Positive test results for benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, alcohol, cannabinoids, opiates, or phencyclidine at the Screening or Baseline visits
4.05	Positive pregnancy test at Screening or Baseline visits

4.06	Currently breastfeeding or plans to breastfeed during the study
4.07	Has symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19

5.2. Stage 2

5.2.1. Inclusion Criteria for Stage 2

Participants are eligible to be included in Stage 2 of the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be ≥ 18 years of age at the time of signing the informed consent.
2.	**Type of Participant and Disease Characteristics**
2.01	Have used, and/or desired to use artificial tears for DED symptoms within 2 months prior to the Screening visit
2.02	**ALL** of the following in at least 1 eye at both the Screening and Baseline visits and the *same eye* must qualify at both Screening and Baseline visits: • [redacted]
2.03	Symptoms of DED at both the Screening and Baseline visits as defined by both: • [redacted]

2.04	Increase in the signs and symptoms of DED based on the CAE exposure at both Screening and Baseline visits, demonstrated by: [redacted]
2.05	BCVA of 20/100 or better in both eyes at the Screening visit
2.06	Normal lid/lash anatomy, blinking function, and closure as determined by the investigator
2.07	Good general and ocular health, as determined by the investigator using medical history, ophthalmic examination and history, physical examination, blood chemistry and hematology, urinalysis, vital signs, and 12-lead ECG (in participants who undergo ECG evaluations) results at the Screening and Baseline visits, as applicable per the SoA (Section 1.3).
3.	**Sex**
3.01	Male or female

4.	**Contraceptives**
4.01	Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study • A male participant with a heterosexual partner who is a WOCBP must agree to use contraception as detailed in Appendix 7 during the intervention period and refrain from donating sperm during this period.

4.02	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study
	• A female participant is eligible to participate if she is either:
	  • Not a WOCBP as defined in Appendix 7 (proper documentation must be provided to confirm non-WOCBP status)
	  OR
	  • A WOCBP who is not pregnant (ie, has a negative serum pregnancy test result at the Screening visit and has a negative serum or urine pregnancy test result at the Baseline visit), and agrees to follow the contraceptive guidance in Appendix 7 during the intervention period

5.	**Informed Consent**
5.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
5.02	Written informed consent from the participant has been obtained prior to any study-related procedures
6.	**Other**
6.01	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits

5.2.2. Exclusion Criteria for Stage 2

Participants are excluded from Stage 2 of the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Current diagnosis of glaucoma or ocular hypertension; evidence of glaucoma or mean (or median) intraocular pressure > 21 mm Hg determined by Goldmann applanation tonometry, in either eye at the Screening visit
1.02	History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, likely interfere with the interpretation of the study results or participant safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. (Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.)
1.03	Diagnosis of recurrent, ongoing, or active ocular infection including, but not limited to herpes simplex or zoster, vaccinia, varicella, tuberculosis of the eye, acanthamoeba, or fungal disease
1.04	History of ocular surgery within 12 months prior to the Screening visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (eg, cataract surgery or any surgery involving limbal or corneal incision)
1.05	Have had a corneal transplant in either or both eyes
1.06	At the Screening visit, at the investigator's discretion, have active or uncontrolled, severe: • Systemic allergy • Chronic seasonal allergies at risk of being active during the study • Rhinitis or sinusitis

1.07	History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, coagulation, gastrointestinal, endocrine, immunologic, dermatologic, ophthalmologic, neurologic or psychiatric disease. Significant is defined as any disease that, in the assessment of the investigator, would put safety of the participant at risk through participation, or which would prevent or confound protocol-specified assessments (eg, severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.)
2.	**Prior/Concomitant Therapy**
2.01	Use of artificial tears within 24 hours prior to the Screening visit or anticipated use during the study, with the exception of [redacted]
2.02	Use of systemic immunomodulators (eg, hydroxychloroquine, methotrexate, cyclosporine) within 3 months prior to the Screening visit or anticipated use during the study
2.03	Use of corticosteroids administered through any route within 3 months prior to the Screening visit or anticipated use during the study
2.04	Use of cyclosporine administered through any route within 3 months prior to the Screening visit or anticipated use during the study
2.05	Use of topical ocular glaucoma medications or topical ocular allergy medications (over-the-counter [OTC], herbal, prescription, or nutritional supplements including all mast cell stabilizers and antihistamines) within 30 days prior to the Screening visit or anticipated use during the study
2.06	Use of Xiidra (lifitegrast ophthalmic solution, 5%) within 3 months prior to the Screening visit; or anticipated use during the study, with the exception of those participants who are randomized to receive Xiidra during the study
2.07	Use of TrueTear within 14 days prior to the Screening visit or anticipated use during the study
2.08	Use of medications associated with the treatment of severe DED and/or Meibomian gland disease such as oral antimuscarinics, cevimeline, oral macrolides, tetracyclines, tetracycline derivatives, and retinoids within 3 months prior to the Screening visit or anticipated use during the study
2.09	Use of contact lenses in either eye within 14 days prior to the Screening visit or planned use during the study

2.10	Punctal or intracanalicular plug present in either eyelid within 1 year of the Screening visit or anticipated plug insertion or occlusion at any time during the study
2.11	Use of lid-heating therapy (ie, LipiFlow, iLUX, etc), Meibomian gland probing, or therapeutic Meibomian gland expression in either eye within 6 months prior to the Screening visit or anticipated use during the study
2.12	The start date of any systemic medication (including OTC, herbal, prescription, or nutritional supplements), which may affect DED or vision is < 3 months prior to the Screening visit or a change in dosage is anticipated during the study. Systemic medications, which may affect DED or vision, include but are not limited to the following: antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants and phenothiazines
2.13	The start date of hormone replacement therapy program, oral or transdermal contraception, other estrogen or progesterone treatments, or other medications required for long-term treatment of chronic diseases is < 3 months prior to the Screening visit or a change in dosage is anticipated during the study
2.14	The start date of any androgen therapy is < 3 months prior to the Screening visit or a change in dosage is anticipated during the study
2.15	Use of inhalable or ingestible cannabis products, or transdermal patches containing THC within 30 days prior to the Screening visit or anticipated use during the study
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug, device, or any observational study or participation in such a study within 30 days prior to the Screening visit
3.02	Participation in a blood or plasma donation program within 60 or 30 days, respectively, prior to study intervention administration, or anticipated participation during the study
4.	**Other**
4.01	Known allergies or sensitivity to the study interventions or study diagnostic agents [redacted].
4.02	The participant has a condition or is in a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study

4.03	Positive test results for anti–HIV type 1 and 2, hepatitis B surface antigen, or anti-hepatitis C virus at Screening visit
4.04	Positive test results for benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, alcohol, cannabinoids, opiates, or phencyclidine at the Screening or Baseline visits
4.05	Positive pregnancy test at Screening or Baseline visits
4.06	Currently breastfeeding or plans to breastfeed during the study
4.07	Has symptoms that, in the opinion of the investigator, may be associated with COVID-19 or in the last 14 days came into contact with someone diagnosed with COVID-19

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will be instructed to fast (ie, water only) for at least 10 hours prior to blood collection for safety laboratory tests. Fasting will not be required for the blood PK sample collections. In Stage 2, fasting will not be required.

In Stage 1, participants will be served meals at appropriate times at Visits 3 and 5.

5.3.2. Caffeine, Alcohol, Tobacco, and Cannabis

Participants must abstain from drinking alcohol for at least 3 days before each blood collection for safety laboratory tests (Stage 1: Visits 1 and 5 or Early Termination; Stage 2: Visits 1, 3, 5, 6, or Early Termination). This will not be required for the blood PK sample collections.

There are no restrictions on the consumption of caffeine or use of tobacco. However, the participant's current smoking status or use of nicotine-containing products will be assessed at the Screening visit and recorded on the eCRF.

Participants must abstain from using inhalable or ingestible cannabis products or transdermal patches containing THC for at least 30 days before the Screening Visit and throughout the duration of the study.

5.3.3. Activity

Participants must abstain from strenuous exercise for at least 12 hours before each blood collection for safety laboratory tests. This will not be required for the blood PK sample collections.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once. A participant who is rescreened will be screened again in the interactive web response system (IWRS) and given a new participant number.

6. Study Intervention

Study intervention is defined as any investigational intervention, or marketed product intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 6-1 Study Interventions

Study Intervention Name	AGN-242428	AGN-231868	Xiidra	AGN-242428 vehicle	AGN-231868 vehicle	[redacted]
Dosage Formulation	Ophthalmic solution	Ophthalmic solution	Ophthalmic solution	Ophthalmic solution	Ophthalmic solution	
Manufacturer	Allergan	Allergan	Shire	Allergan	Allergan	
Concentrations	[redacted]	[redacted]	5%	NA	NA	
Route of Administration	Topical eyedrop	Topical eyedrop	Topical eyedrop	Topical eyedrop	Topical eyedrop	
Dosing Instructions	Participants will be instructed to instill a single drop per eye, twice daily (approximately 12 hours apart) (with the exception of Day 1 in Stage 1 where only the left eye will be dosed once with a single drop and the last day of dosing in both stages where a single dose will be administered to both eyes). On visit days, the morning dose of the intervention will be administered by the site staff. More details on the dosing regimen can be found in Section 6.1.1.					

Packaging and Labeling

In Stage 1, AGN-242428, AGN-231868 and their vehicles will be provided in identical single-use bottles. In Stage 2, 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] All interventions will be supplied in identical cartons.

All study interventions, including vehicles and marketed products, will be labeled with the protocol number, kit number, warning language (Caution: New Drug—Limited by Federal Law to Investigational Use. Keep Out of Reach of Children), and instructions to take as directed.

Immediately before dispensing the study intervention, the investigator (or appropriately trained designee) will write the participant number, and the date dispensed on the label.

6.1.1. Dosing Regimen

6.1.1.1. Dosing Regimen in Stage 1

Stage 1 includes up to 3 consecutive cohorts, with 24 participants in each cohort. Participants from 1 cohort will not be allowed to enroll into the subsequent cohort(s). Participants in each cohort will be 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)

The morning dose of the assigned study intervention will be administered by the site staff at Visits 2, 3, 4, and 5 (except for Early Termination visit).

All participants will receive 1 drop of the assigned intervention to the left eye on Day 1 (Visit 2) (administered by the site staff). On Days 2 to 14, the participants will administer a single drop to both eyes, twice daily (approximately 12 hours apart). On Day 15 (Visit 5), the participants will be administered a single dose to both eyes.

6.1.1.2. Dosing Regimen in Stage 2

In Stage 2, [redacted] approximately 250 participants, who requalify at Baseline visit, will be randomized into 5 groups, in a 1:1:1:1:1 ratio within each site, as follows:

- AGN-242428 (N = 50)
- AGN-242428 vehicle (N = 50)
- AGN-231868 (N = 50)
- AGN-231868 vehicle (N = 50)
- Xiidra (N = 50)

The morning dose of the assigned study intervention will be administered by the unmasked site staff at Visits 2, 3, 4, 5, and 6. Any masked staff members should not be present in the room during dosing to prevent unmasking.

During the intervention period, participants will be instructed to administer 1 drop of assigned intervention twice daily (approximately 12 hours apart) to both eyes on Days 1 to 41. On Day 42, the participants will be administered a single dose to both eyes. The highest tolerated doses of AGN-242428 and AGN-231868 (established in Stage 1) will be selected for testing in Stage 2 to maximize the potential to achieve proof of concept.

[redacted]

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area with access limited to the investigator and authorized site staff.

The investigator, designee, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All used and unused study intervention must be returned to the sponsor at the end of the study. Reconciliation will be performed when the study intervention is returned, and all study intervention must be accounted for.

Further guidance and information for the final disposition of unused study interventions are provided in the Study Procedure Manual.

6.3. Measures to Minimize Bias: Randomization and Masking

6.3.1. Method of Intervention Assignment

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Stage 1: There will be up to 3 cohorts in Stage 1. For Cohort 1A, at the time of randomization (Day 1 [Visit 2]), 24 qualified participants will be randomized to 1 of 4 intervention groups in a 3:3:1:1 ratio to receive [redacted] AGN-242428, [redacted] AGN-231868, AGN-242428 vehicle, or AGN-231868 vehicle. Separate randomization lists will be created for Cohorts 1B and 1C. For Cohort 1B, at the time of randomization (Day 1 [Visit 2]), 24 qualified participants will be randomized to 1 of 4 intervention groups in a 3:3:1:1 ratio to receive [redacted] AGN-242428, [redacted] AGN-231868, AGN-242428 vehicle, or AGN-231868 vehicle. For Cohort 1C, at the time of randomization (Day 1 [Visit 2]), 24 qualified participants will be randomized to 1 of 4 intervention groups in a 3:3:1:1 ratio to receive [redacted] AGN-242428, [redacted] AGN-231868, AGN-242428 vehicle, or AGN-231868 vehicle.

Stage 2: [redacted]

[redacted] 250 participants, who requalify at the Baseline visit (Day 1 [Visit 3]), will be randomized 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.

The IWRS system will provide the site with the specific kit numbers for each randomized participant at the time of randomization. Sites will dispense the study intervention according to the IWRS instructions and the SoA (Section 1.3). Returned study intervention must not be redispensed to the participants. All IWRS notifications are to be maintained with the study source documents.

The IWRS will be programmed with mask-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unmasking of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unmasking is warranted, the investigator should make every effort to contact the sponsor prior to unmasking a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unmasked, the sponsor must be notified within 24 hours after breaking the mask. The date and reason that the mask was broken must be recorded in the source documentation and case report form, as applicable.

6.3.2. Masking

In Stage 1, the investigator, site staff (with the exception of unmasked pharmacy staff), and participants will be fully masked to study intervention and all interventions will be provided in identical single-use bottles and cartons.

In Stage 2, [redacted] During the intervention period, 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]. Participants in Stage 2 will be instructed not to communicate with each other about the look of the vials or the features of the interventions. All the interventions in Stage 2 will be supplied in identical cartons.

In addition, further steps will be taken in Stage 2 to reduce the concern that exists in dry eye clinical trials, in which the active study intervention elicits a significant participant response (for example, ocular irritation, dysgeusia, and reduced visual acuity are reported in 5% to 25% of patients administered Xiidra [Xiidra US package insert 2016]), and where the documentation and subsequent follow-up of these reports may imply that the affected participants are on the active study intervention and create bias in the completion of the trial's efficacy assessments. To reduce the potential for bias in participant-reported symptoms and investigator-graded signs, certain parties will not be made aware of changes in a participant's medical status, concomitant

medications, or AEs until their role in completing the efficacy-related assessments conducted on any given day is complete. The parties subject to this restriction include any individual who will participate in an assessment related to trial efficacy (eg, an investigator grading staining, technicians explaining and recording questionnaires, or a technician facilitating CAE exposure). The unmasked staff members who administer the intervention in the morning of visit days will also not be allowed to participate in any efficacy or safety-related assessments conducted on any given day, considering that Xiidra vials will look different than vials with AGN-242428, AGN-231868, and their vehicles, which can imply that the participant is on the active study intervention. This information restriction is to be suspended when deemed medically necessary by the investigator, in the event of a medical emergency, or in order to protect the rights and welfare of a participant.

Participant-Reported Information: For each day on which there is a participant visit, an appropriately trained and delegated technician will be designated as the "Non-Efficacy Technician". Multiple technicians may receive this designation, as needed, and it will not affect their participation in the clinical trial beyond the day on which the assignment is made. This technician is primarily responsible for conducting medical status updates with the participant at the beginning of the visit. As part of the update, the technician will query any changes to the participant's health and concomitant medications, record new participant-reported AEs, and follow-up on any existing AEs or other problems. The technician will request that the participant avoid discussing their medical status, AEs, and experience with the investigational product with other technicians, participants, or the investigator unless specifically told otherwise by clinical trial staff or in the event of a medical emergency. The designated Non-Efficacy Technician may assist with or perform other tasks that have no bearing on trial efficacy and for which they are appropriately trained and delegated (eg, pregnancy tests, participant check-in, participant check-out, etc.).

Investigator-Graded Signs: The investigator grading participant signs will not be made aware of a participant's new AEs, updates to existing AEs or problems, or changes in medical status and concomitant medications until after all efficacy assessments in which they will participate are complete at any given visit. For visits at which the participant will enter the CAE, the investigator's role in the efficacy assessments will not be complete until after the post-CAE evaluation at a minimum. When the investigator is no longer involved with the completion of a participant's efficacy assessments for a given visit, they are to evaluate and grade AEs and address other issues as needed with the participant.

6.4. Study Intervention Compliance

During both stages, on visit days, the morning dose of the assigned study intervention will be administered by designated site personnel; all other doses will be administered by the participant.

On visit days, study intervention compliance will be assumed to be 100% when dosing has been recorded in the eCRF.

In-between office visits, study intervention compliance will be closely monitored by counting the number of used and unused vials/bottles dispensed and returned.

The study center will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

Any medication or vaccine (including OTC, prescription medicines, vitamins, herbal supplements, and/or cannabis or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

From Screening to the end of the study, site staff will question each participant specifically on the use of concomitant medications. Site staff must notify the sponsor immediately if a participant consumes or applies any concomitant medications that are not permitted by the protocol.

Any use of prohibited concomitant medications (see Section 6.5.4), including [redacted] will be reviewed by the investigator and/or the sponsor, who will determine if the participant should be discontinued from the study.

6.5.1. Prohibited Interventions and Washout Before the Study

Participants must discontinue the use of any of the medications or interventions listed in Table 6-2 or Table 6-3 in both eyes for the specified period prior to the Screening visit.

Table 6-2 Stage 1: Required Washout Intervals for Prohibited Medications or Interventions Prior to the Screening Visit

Drug Class/Treatment	Washout Required Prior to the Screening Visit
Artificial tears	24 hours
Systemic immunomodulators (eg, hydroxychloroquine, methotrexate, cyclosporine)	14 days
Corticosteroids administered through any route	7 days
Topical ophthalmic cyclosporine	7 days
Lifitegrast ophthalmic solution (Xiidra)	7 days
TrueTear	7 days
Topical ocular glaucoma medications or topical ocular allergy medications (OTC, herbal, prescription, or nutritional supplements including all mast cell stabilizers and antihistamines)	7 days
Medications associated with the treatment of severe DED and/or Meibomian gland disease such as oral antimuscarinics, cevimeline, oral macrolides, tetracyclines, tetracycline derivatives, and retinoids	14 days
Contact lenses	14 days
Punctal or intracanalicular plugs	1 year
Lid-heating therapy, Meibomian gland probing, or therapeutic Meibomian gland expression	3 months
Systemic medication (including OTC, herbal, prescription, or nutritional supplements) which may affect DED or vision, including but not limited to: antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants and phenothiazines	7 days if the medication was stopped or dosage changed[a]
Hormone replacement therapy program, oral or transdermal contraception, other estrogen, or progesterone treatments, or other medications required for long-term treatment of chronic diseases	7 days if the medication was stopped or dosage changed[a]
Any androgen therapy	7 days if the medication was stopped or dosage changed[a]
Inhalable or ingestible cannabis products or transdermal patches containing THC	30 days

[a] The use of these medications is allowed during Stage 1 of the study provided that the dosing regimen is stable for at least 7 days prior to the Screening visit and does not change at any time during the study.

Table 6-3 Stage 2: Required Washout Intervals for Prohibited Medications or Interventions Prior to the Screening Visit

Drug Class/Treatment	Washout Required Prior to the Screening Visit
Artificial tears	24 hours
Systemic immunomodulators (eg, hydroxychloroquine, methotrexate, cyclosporine)	3 months
Corticosteroids administered through any route	3 months
Cyclosporine administered through any route	3 months
Lifitegrast ophthalmic solution (Xiidra)	3 months
TrueTear	14 days
Topical ocular glaucoma medications or topical ocular allergy medications (OTC, herbal, prescription, or nutritional supplements including all mast cell stabilizers and antihistamines)	30 days
Medications associated with the treatment of severe DED and/or Meibomian gland disease such as oral antimuscarinics, cevimeline, oral macrolides, tetracyclines, tetracycline derivatives, and retinoids	3 months
Contact lenses	14 days
Punctal or intracanalicular plugs	1 year
Lid-heating therapy, Meibomian gland probing, or therapeutic Meibomian gland expression	6 months
Systemic medication (including OTC, herbal, prescription, or nutritional supplements) which may affect DED or vision, including but not limited to: antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants and phenothiazines	3 months if the medication was stopped or dosage changed[a]
Hormone replacement therapy program, oral or transdermal contraception, other estrogen, or progesterone treatments, or other medications required for long-term treatment of chronic diseases	3 months if the medication was stopped or dosage changed[a]
Any androgen therapy	3 months if the medication was stopped or dosage changed[a]
Inhalable or ingestible cannabis products or transdermal patches containing THC	30 days

[a] The use of these medications is allowed during Stage 2 of the study provided that the dosing regimen is stable for at least 3 months prior to the Screening visit and does not change at any time during the study.

6.5.2. Permitted Interventions

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor.

The sponsor or designee must be contacted if there are any questions regarding concomitant or prior therapy.

Use of the following systemic medications and vitamins is permitted during the study:

Stage 1:

- Systemic medications (including OTC, herbal, prescription, or nutritional supplements), which may affect DED or vision, including but not limited to the following: antihistamines, cholinergic agents, anticholinergics, antimuscarinics, beta blocking agents, tricyclic antidepressants, and phenothiazines (provided that the dosing regimen is stable for at least 7 days and does not change at any time during the study)
- Hormone replacement therapy program, oral or transdermal contraception, other estrogen or progesterone treatments, androgen therapy or other medications required for long-term treatment of chronic diseases other than those listed in Section 6.5.4 (provided that the dosing regimen is stable for at least 7 days and does not change at any time during the study)
- Androgen therapy (provided that the dosing regimen is stable for at least 7 days and does not change at any time during the study)

Stage 2:

- Systemic medications (including OTC, herbal, prescription, or nutritional supplements), which may affect DED or vision, including but not limited to the following: antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants and phenothiazines (provided that the dosing regimen is stable for at least 3 months and does not change at any time during the study)
- Hormone replacement therapy program, oral or transdermal contraception, other estrogen or progesterone treatments, or other medications required for long-term treatment of chronic diseases other than those listed in Section 6.5.4 (provided that the dosing regimen is stable for at least 3 months and does not change at any time during the study)
- Androgen therapy (provided that the dosing regimen is stable for at least 3 months and does not change at any time during the study)

Any medication taken during the study between the date of the first dose of study intervention and the date of the Exit visit or Early Termination visit will be recorded in the eCRF as a concomitant medication; any medication started after the Exit visit or Early Termination visit will not be considered a concomitant medication and must not be captured in the eCRF.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

6.5.4. Prohibited Interventions During the Study

The decision to administer a prohibited intervention is done with the safety of the study participant as the primary consideration. When possible, Allergan must be notified before the prohibited intervention is administered. Use of the following interventions is prohibited during the study:

Stage 1:

- Use of ophthalmic prescription or OTC eye medications (eye drops, gels, or ointments) or artificial tear products as outlined in the exclusion criteria
- Corticosteroids administered through any route
- Systemic immunomodulators (eg, hydroxychloroquine, methotrexate, cyclosporine)
- Cyclosporine administered through any route
- Medications associated with the treatment of severe DED and/or Meibomian gland disease (eg, oral antimuscarinics, cevimeline, oral macrolides, tetracyclines, tetracycline derivatives, and retinoids)
- Xiidra (lifitegrast ophthalmic solution, 5%)
- TrueTear
- Contact lens wear in either eye
- Punctal or intracanalicular plugs
- Lid-heating therapy (ie, LipiFlow, iLUX, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression
- Systemic medications, which may affect DED or vision (antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants and phenothiazines) unless the start date is > 7 days prior to the Screening visit and the dosing regimen is not changed during the study
- Hormone replacement therapy, oral or transdermal contraception, estrogen, progesterone, or other medications required for long-term treatment unless the start date is > 7 days prior to the Screening visit and the dosing regimen is not changed during the study
- Androgen therapy unless the start date is > 7 days prior to the Screening visit and the dosing regimen is not changed during the study
- Inhalable or ingestible cannabis products or transdermal patches containing THC

Stage 2:

- [redacted]
- Systemic immunomodulators (eg, hydroxychloroquine, methotrexate, cyclosporine)
- Cyclosporine administered through any route
- Corticosteroids administered through any route
- Medications associated with the treatment of severe DED and/or Meibomian gland disease (eg, oral antimuscarinics, cevimeline, oral macrolides, tetracyclines, tetracycline derivatives, and retinoids)
- Xiidra (lifitegrast ophthalmic solution, 5%), with the exception of those participants who are randomized to the Xiidra intervention arm
- TrueTear
- Contact lens wear in either eye
- Punctal or intracanalicular plugs
- Lid-heating therapy (ie, LipiFlow, iLUX, etc.), Meibomian gland probing, or therapeutic Meibomian gland expression
- Systemic medications, which may affect DED or vision (eg, antihistamines, cholinergic agents, anticholinergics, beta blocking agents, tricyclic antidepressants and phenothiazines) unless the start date is > 3 months prior to the Screening visit and the dosing regimen is not changed during the study
- Hormone replacement therapy, oral or transdermal contraception, estrogen, progesterone, or other medications required for long-term treatment unless the start date is > 3 months prior to the Screening visit and the dosing regimen is not changed during the study
- Androgen therapy unless the start date is > 3 months prior to the Screening visit and the dosing regimen is not changed during the study
- Inhalable or ingestible cannabis products or transdermal patches containing THC

6.6. Dose Modification

No dose modifications will be allowed in this study.

In Stage 1, the decision to proceed from one cohort to the next will be made by the sponsor after review of data by the DMC, as described in Section 10.1.11.

In Stage 2, the highest tolerated dose of AGN-242428 and AGN-231868 (established in Stage 1) will be selected by the sponsor for testing to maximize the potential to achieve proof of concept.

6.7. Intervention after the End of the Study

No interventions after the end of the study are planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made available to the sponsor and will be clearly documented on the appropriate eCRF.

Reasons for discontinuation from the study intervention and/or the study may include the following:

- AE
- Death
- Disease relapse
- Failure to meet randomization criteria
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by subject
- Other

7.1. Discontinuation of Study Intervention

Participants who discontinue the study intervention early will be encouraged to return for the Early Termination visit assessments. See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up, and for any further evaluations that need to be completed.

Discontinuation of study intervention for abnormal liver function must be considered by the investigator when a participant meets the potential Hy's Law criteria outlined in the adverse events of special interest (AESI) section (Appendix 3) or if the investigator believes that it is in best interest of the participant.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Participants may be discontinued at the discretion of the investigator and/or the sponsor if they use any prohibited treatments described in Section 6.5.4.
- For participants who discontinue from the study early, every effort must be made to have these participants return to the clinical center for completion of the Early Termination visit. AEs leading to participant early discontinuation must be followed-up as appropriate.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- See the SoA (Section 1.3) for data to be collected at the time of study discontinuation (Early Termination). If the Early Termination visit falls on the same day as another scheduled visit, only Early Termination visit assessments will be conducted.
- Study termination

The dosing of study intervention may be paused due to safety concerns at any time by the site investigator. The sponsor and DMC must be notified immediately if the dosing was paused.

The sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoAs for Stage 1 (Table 1-1) and Stage 2 (Table 1-2). The overall study design is illustrated in Figure 1-1 (Stage 1) and Figure 1-2 (Stage 2). The visit schedule for Stage 1 includes 5 visits: Screening, Baseline (Day 1), Day 2, Day 8, and Day 15 (Exit). The visit schedule for Stage 2 includes 6 visits: Screening, [redacted], Baseline (Day 1), Days 14, 28, and 42 (Exit). Unless otherwise specified, procedures must be performed in the order listed in the SoAs.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant must continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The study will be discussed with the participant and a participant wishing to participate must give informed consent prior to any study-related procedures. The participants must also give authorization in accordance with the relevant local privacy requirements (where applicable) prior to any study-related procedures.
- Each participant who provides informed consent will be assigned a participant number that will be used on participant documentation throughout the study.
- All screening laboratory tests must be evaluated and determined to be acceptable to the investigator prior to participant randomization into the study. Screening safety laboratory tests may be repeated once at the discretion of the investigator or the sponsor.
- Female participants of childbearing potential must have a negative pregnancy test result prior to entry into the study.
- A participant is considered to have entered the study at the time of randomization to intervention at Baseline (Day 1) for Stage 1; for Stage 2, a participant is considered to have entered the study at the time of randomization to intervention at Baseline (Day 1; post-CAE). See Section 6.3.1 for the method for assignment to intervention groups/randomization.
- For Stage 2, [redacted]. If both eyes qualify and have the same [redacted], then study eye will be defined as the eye with the [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.

- For Stage 2, after completion of Informed Consent and Inclusion/Exclusion Criteria, for assessments listed with a '#' in Table 1-2 of SoA flexibility in procedure order is allowed, [redacted]

8.1. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.1.1. Best-corrected Visual Acuity

Testing of BCVA should precede any examination requiring contact with the eye. BCVA will be quantified using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol. BCVA must be preceded by manifest refraction at Visits 1, 2, 3, 4, 5 and/or Early Termination visit in Stage 1 and at Visits 1, 6, and/or Early Termination visit in Stage 2. Certification and procedures for performing the normal luminance BCVA measurements will be included in the Study Procedure Manual.

8.1.2. Slit lamp Biomicroscopy

Findings other than those listed below must be recorded under "other" for the appropriate location of the finding.

8.1.2.1. Eyelid/Eyelid Margins/Lashes

The grading scales for slit lamp biomicroscopy (eyelid/eyelid margins/lashes) are shown in Table 8-1 and Table 8-2, respectively.

Table 8-1 Erythema Grading Scale (Eyelid/Eyelid Margins/Lashes)

0	None	No erythema
+0.5	Trace	Localized, minimal (trace) flush reddish color
+1	Mild	Localized, mild, flush reddish color
+2	Moderate	Diffuse reddish color encompassing the entire lid margin
+3	Severe	Deep diffuse reddish color of lid margins and superior and/or inferior eyelid

Table 8-2 Edema Grading Scale (Eyelids)

0	None	No edema
+0.5	Trace	Localized, minimal (trace) swelling
+1	Mild	Localized, mild swelling
+2	Moderate	Diffuse, moderate swelling
+3	Severe	Diffuse, severe swelling

8.1.2.2. Conjunctiva

Hyperemia

Bulbar and palpebral hyperemia will be graded separately. Grading will be based on comparison to the appearance of standard photographs (Allergan Bulbar Hyperemia Grading Guide), illustrating none, trace, mild, moderate, and severe hyperemia as described in Table 8-3. No lid retraction is to be performed when examining the conjunctiva.

Table 8-3 Allergan Bulbar Hyperemia Grading Guide Photo Descriptions (Conjunctiva)

Grade	Grade Equivalent	Description
0	None	Normal. Vessels of bulbar conjunctiva easily observed
+ 0.5	Trace	Trace flush, reddish pink
+ 1	Mild	Mild flush, reddish color
+ 2	Moderate	Bright red color
+ 3	Severe	Deep, bright diffuse redness

Following grading of hyperemia, the presence and severity of edema and subconjunctival hemorrhage in either the bulbar or palpebral conjunctiva are to be assessed using the scales in Table 8-4 and Table 8-5, respectively.

Table 8-4 Grading Scale for the Presence and Severity of Edema (Conjunctiva)

0	None	No edema
+0.5	Trace	Localized, minimal (trace) swelling
+1	Mild	Localized, mild swelling
+2	Moderate	Diffuse, moderate swelling
+3	Severe	Diffuse, severe swelling

Table 8-5 Grading Scale for the Presence and Severity of Subconjunctival Hemorrhage (Conjunctiva)

0	None	No hemorrhage
+0.5	Trace	Flat hemorrhage ≤ 1 quadrant
+1	Mild	Elevated hemorrhage ≤ 1 quadrant, or flat and > 1 quadrant
+2	Moderate	Elevated hemorrhage > 1 but ≤ 2 quadrants
+3	Severe	Elevated hemorrhage > 2 quadrants

8.1.2.3. Cornea

The grading scales for corneal edema and superficial punctate keratopathy are shown in Table 8-6 and Table 8-7, respectively.

Table 8-6 Edema Grading Scale (Cornea)

0	None	No edema
+0.5	Trace	Localized, minimal (trace) epithelial haze
+1	Mild	Dull glass appearance of epithelium that may include fine localized microcystic changes
+2	Moderate	Dull glass appearance of epithelium with large number of cystic changes with or without stromal edema
+3	Severe	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Table 8-7 Grading Scale for Superficial Punctate Keratopathy (Cornea)

0	=	No superficial punctate keratopathy
+0.5	=	Trace
+1	=	Mild
+2	=	Moderate
+3	=	Severe

8.1.2.4. Anterior Chamber

For the measurements of cells and flare based on standardized uveitis nomenclature (SUN Working Group, 2005), the settings in Table 8-8 must be used. The scales for the measurement of anterior chamber cells and flare are shown in Table 8-9 and Table 8-10, respectively.

Table 8-8 Settings for Measurements of Cells and Flare in the Anterior Chamber

• 1 x 1 mm slit	• High magnification
• Highest slit lamp voltage	• Low ambient lighting
• Illumination angle of 45 degrees	• Same grader and slit lamp whenever possible

Table 8-9 Grading Scale for Cells in the Anterior Chamber

0	=	0 cells
+0.5	=	1 to 5 cells (trace)
+1	=	6 to 15 cells
+2	=	16 to 25 cells
+3	=	26 to 50 cells
+4	=	> 50 cells

Table 8-10 Grading Scale for Flare in the Anterior Chamber

0	=	None: no flare seen
+1	=	Faint: faint flare seen
+2	=	Moderate: iris and lens details clear
+3	=	Marked: iris and lens details hazy
+4	=	Intense: fibrin or plastic aqueous

8.1.2.5. Iris/Pupil

The iris/pupil will be evaluated for pathology. If pathology is present, it will be described.

8.1.3. Intraocular Pressure

The IOP must be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. At least 2 measurements will be taken by qualified study site personnel using a Goldmann applanation tonometer affixed to a slit lamp with the participant seated. 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 median of the 3 measures will be used to determine participant eligibility as per the exclusion criteria.

8.1.4. Dilated Fundus Exam

Biomicroscopic examination, indirect lenses, direct/indirect ophthalmoscopy, etc. are to be used as appropriate to visualize. Dilating drops should not be administered until slit lamp biomicroscopy and IOP measurements are completed.

8.1.4.1. Lens

Lens Status

Lens status will be assessed as phakic, pseudophakic, or aphakic. The lens (including the posterior capsule for participants who have undergone lens extraction) will also be evaluated for pathology. If pathology is present, it will be described.

Cataract Assessment (phakic eyes only)

Under dilated examination, the presence and severity of nuclear, cortical and posterior subcapsular cataract lens opacities will be evaluated. At the first dilated examination, each type of cataract, if present, will be graded using the scale below. At the last follow-up dilated examination, each type of cataract will be assessed for change from baseline and if changed, the current severity will be graded using the scale in Table 8-11.

Table 8-11 Grading Scale for Cataract Assessment

0	=	None
+1	=	Mild
+2	=	Moderate
+3	=	Severe

8.1.4.2. Vitreous

The vitreous will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

8.1.4.3. Fundus

The fundus (posterior pole; periphery, when dilated) will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

8.1.4.4. Optic Nerve

The optic nerve will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

The cup/disc ratio will be reported using a 0.0 to 1.0 scale. The Armaly chart, supplied by the sponsor, provides a pictorial scale of cup/disc ratio of 0.0 to 0.8. Note if the condition is not evaluable.

8.1.5. Physical Examinations

The physical examination will consist of a routine evaluation of organ systems including: head/EENT (eye, ear, nose, and throat), neck, cardiovascular, pulmonary, abdomen, skin/extremities, neurological, lymph nodes, and musculoskeletal. At the Exit visit, the physical exam will also include a query of the participant to determine whether changes in physical condition have occurred since the Screening examination.

8.1.6. Vital Signs

Systolic and diastolic blood pressure will be measured using an appropriate sphygmomanometer after participants have been at rest (seated) for at least 5 minutes. Blood pressure will be recorded in mm Hg.

Pulse rate will be measured in beats per minute (bpm) after the participant has been in a resting state (seated) for at least 5 minutes.

Respiration rate will be measured after the participant has been in a resting state (seated) for at least 5 minutes and will be assessed over a 60 second interval.

8.1.7. Electrocardiograms

The ECGs will be conducted for all participants in Stage 1 and for approximately 20% of participants (no fewer than 10 participants per study intervention arm) in Stage 2. During Stage 2, ECGs will only be conducted at selected sites. A standard 12-lead ECG will be performed in the supine position at the nominal times (relative to dosing) as outlined in the SoAs (Section 1.3). Assessments performed outside this window will be noted as protocol deviations, and the reason for deviation must be documented in the source documents. In Stage 1, predose ECGs at Visit 5 must be performed within 120 minutes prior to dosing. In Stage 2, predose ECGs at Visit 6 must be performed within 240 minutes prior to dosing. The ECG equipment will be provided to the sites by a central reading center for use during this study. Sites will receive training on the use of ECG equipment. Sites will transmit ECG data to the central reader after interpretation of the results is performed by a qualified physician or designee at the site.

8.1.8. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- At Screening, the investigator or subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- Any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF.
- All laboratory tests with values considered clinically significant during participation in the study are to be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical safety physician (MSP).
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology must be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted at the central laboratory in accordance with the SoA.
    - Nonprotocol-specified laboratory assessments may be performed by the central laboratory or a local laboratory. If the local laboratory is used, and the test results lead to a change in participant management, or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then these results must be recorded in the eCRF as an SAE/AE. If these results are related to liver function, they must be reported to the sponsor's medical monitor.
- Prior to utilizing a local laboratory, the study center must ensure that the laboratory is listed on the Form FDA 1572 and that copies of the laboratory certificates and reference ranges are provided to the sponsor.

8.1.9. Pregnancy Test (WOCBP Only)

All WOCBP will have serum pregnancy tests performed at the Screening visit. At all other visits where a pregnancy test is required, either serum or urine test may be used based on site preference.

The definitions of WOCBP and female participants not considered WOCBP, along with the required documentation needed to waive the need for pregnancy testing, are provided in Appendix 7.

8.1.10. Other Assessments

Drop Tolerability Questionnaire

Participants will be asked to rate the acute overall tolerability attributes of study interventions on an 8-question visual analog scale (VAS) Drop Tolerability Questionnaire. Rating will commence 5 (± 1) minutes after the in-office eye drop administration. Participants will be instructed to mark a vertical line on the anchored VAS that best captures their experience with the study eye drops. This is an overall evaluation, not per eye. The questionnaire will include the following questions:

- How comfortable are the study eye drops in your eyes?
- How soothing are the study eye drops in your eyes?
- How moistening/lubricating are the study eye drops in your eyes?
- How clear is your vision with the study eye drops in your eyes?
- How much stickiness do you have with the study eye drops in your eyes?
- How much blur do you have with the study eye drops in your eyes?
- How much burning/stinging do you have with the study eye drops in your eyes?
- How much discomfort do you have with the study eye drops in your eyes?

Each question will be accompanied by the VAS scale. The assessment line length of the scale will be 100 mm and will be similar to the following depiction (Figure 8-1).

Figure 8-1 Drop Tolerability Questionnaire: Visual Analog Scale Assessment

How comfortable are the study eye drops in your eyes?

0 **100**

(Not at all comfortable) (Very comfortable)

8.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study (see Section 7).

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs from the signing of the ICF until the Exit visit or Early Termination visit will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (AESI, as defined in Appendix 3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or

designee to elucidate the nature and/or causality of the AE, SAE, or AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.2.5. Pregnancy

- If a pregnancy is confirmed after the participant has received the study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the Exit visit or Early Termination visit.
- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform Allergan within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.2.6. AEs of Special Interest

The AESI that warrant ongoing monitoring and rapid communication by the investigator to the sponsor are outlined in Appendix 3.

8.2.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study intervention
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration, including wrong site of administration (eg, wrong eye)
- Wrong participant (ie, not administered to the intended participant)

8.3. Treatment of Overdose

Treatment of overdose is not applicable to this ophthalmology study.

8.4. Pharmacokinetics

As indicated in the SoA (Section 1.3), at each timepoint, the blood sample will be collected first, followed by collection of the tear samples for biomarker analysis (if applicable) and PK analysis.

8.4.1. Pharmacokinetic Blood Draw Schedule

Blood samples for PK analysis will be collected according to the schedules presented in Table 8-12 and Table 8-13. A single blood sample will also be collected at Early Termination visit in both stages, when applicable.

Table 8-12 Blood Sampling Schedule for Pharmacokinetics – Stage 1

Blood Sampling Time	Visit 2 (Day 1)	Visit 3 (Day 2)	Visit 4 (Day 8)	Visit 5 (Day 15)
Prior to the morning dose: 0 hour (predose)	X	X	X	X
Following the morning dose: 0.5 h ± 5 min			X	
Following the morning dose: 0.5 h ± 5 min, 1 h ± 5 min, 2 h ± 15 min, 4 h ± 15 min, 8 h ± 30 min, 12 h ± 30 min		X		X

Table 8-13 Blood Sampling Schedule for Pharmacokinetics – Stage 2

Blood Sampling Time	Visit 3 (Day 1)	Visit 4 (Day 14)	Visit 5 (Day 28)	Visit 6 (Day 42)
Prior to the morning dose (prior to CAE exposure)	X	X	X	X
Following the morning dose: at 0.5 h ± 5 min	X			X

CAE = controlled adverse environment

Blood samples to determine plasma AGN-242428 and AGN-231868 concentrations should be drawn at the nominal times specified in Table 8-12 for Stage 1 and Table 8-13 for Stage 2, relative to dosing, and the actual time of the blood draw must be recorded in the source documents and eCRFs. Samples taken outside of the specified time window in Table 8-12 and Table 8-13 will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs. Predose samples will be drawn approximately at the time of predose tear sample collection and tear sample collection for biomarker analysis (see SoA in Section 1.3).

Study center staff will record the times of all blood draws for each participant and will label Vacutainer and polypropylene tubes with a coded label that corresponds to the participant number and blood draw time.

Drug concentration information that may unmask the study will not be reported to investigative sites or masked personnel until the study has been unmasked.

Bioanalytical representatives will be unmasked for PK sample bioanalysis during the conduct of the study. The unmasking of bioanalytical representatives is to be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unmasked. Only blood samples collected from participants who received AGN-242428 or AGN-231868 are to be analyzed.

The exact postdose sample collection time in Stage 2 may be adjusted based on PK data (T_{max}) from Stage 1. The sponsor's clinical pharmacology representative will remain masked for the analysis of Stage 1 data to provide the recommendation for blood sampling timepoint selection for Stage 2. The selected timepoints will remain the same for all intervention groups to retain masking. Any changes in the timing or addition of timepoints for any planned study assessments will ensure masking in Stage 2 and must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

8.4.2. Pharmacokinetic Blood Sampling Procedure

Required blood collection tubes, processing instructions, and storage instructions will be provided in the Study Procedure Manual.

8.4.3. Pharmacokinetic Tear Sampling Schedule

Tear samples for PK analysis will be collected according to the following schedules:

Table 8-14 Tear Sampling Schedule for Pharmacokinetics – Stage 1

Tear Sampling Time	Visit 2 (Day 1)	Visit 3 (Day 2)	Visit 4 (Day 8)	Visit 5 (Day 15)
Prior to the morning dose: 0 hour (predose)		X		X
Following the morning dose: 0.5 h ± 10 min			X	
Following the morning dose: 0.5 h ± 10 min, 2 h ± 15 min, 4 h ± 15 min, 8 h ± 30 min, and 12 h ± 30 min		X		X

Table 8-15 Tear Sampling Schedule for Pharmacokinetics – Stage 2

Tear Sampling Time	Visit 3 (Day 1)	Visit 4 (Day 14)	Visit 5 (Day 28)	Visit 6 (Day 42)
Prior to CAE exposure:	X	X	X	X
Following CAE exposure and following the morning dose: 0.5 h ± 10 min	X			X

CAE = controlled adverse environment

All tear samples for PK analysis will be collected from the nonstudy eye. The study eye will be defined as the eye with the [redacted] then study eye will be defined as the eye with the [redacted]. If both eyes still qualify, the right eye will be designated as the study eye.

Tear samples to determine AGN-242428 and AGN-231868 concentrations will be collected at the nominal times specified in Table 8-14 for Stage 1. Tear samples to determine AGN-242428, AGN-231868, and lifitegrast concentrations will be collected at the nominal times specified in Table 8-15 for Stage 2. In Stage 1, tear samples for PK analysis will be collected from both eyes. In Stage 2, tear samples collected from the nonstudy eye will be used for PK analysis. On Visit 3, at time 0 (predose), since study eye and nonstudy eye determination is not made prior to tear collection, tears will be collected from both eyes, one followed by the other and indicated as 'right' and 'left'. Once study eye determination is made, the appropriate sample will be assigned to PK analysis.

Samples will be collected at the nominal times relative to dosing, and the actual time of the sample collection and the sampled eye (right or left) must be recorded in the source documents and eCRFs. Samples taken outside of time window specified in Table 8-14 and Table 8-15 will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs.

Study center staff will record the times of all tear sample collections for each participant.

Drug concentration information that may unmask the study will not be reported to investigative sites or masked personnel until the study has been unmasked.

Bioanalytical representatives will be unmasked for PK sample bioanalysis during the conduct of the study. The unmasking of bioanalytical representatives is to be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unmasked. Only tear samples collected from participants who received AGN-242428 or AGN-231868 in Stage 1, and participants who received AGN-242428, AGN-231868, or Xiidra in Stage 2, are to be analyzed.

The exact sample collection times in Stage 2 may be adjusted based on PK data from Stage 1. The sponsor's clinical pharmacology representative will remain masked for the analysis of Stage 1 data to provide the recommendation for tear sampling timepoint selection for Stage 2. The selected timepoints will remain the same for all intervention groups to retain masking. Any changes in the timing or addition of timepoints for any planned study assessments will ensure masking in Stage 2 and must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

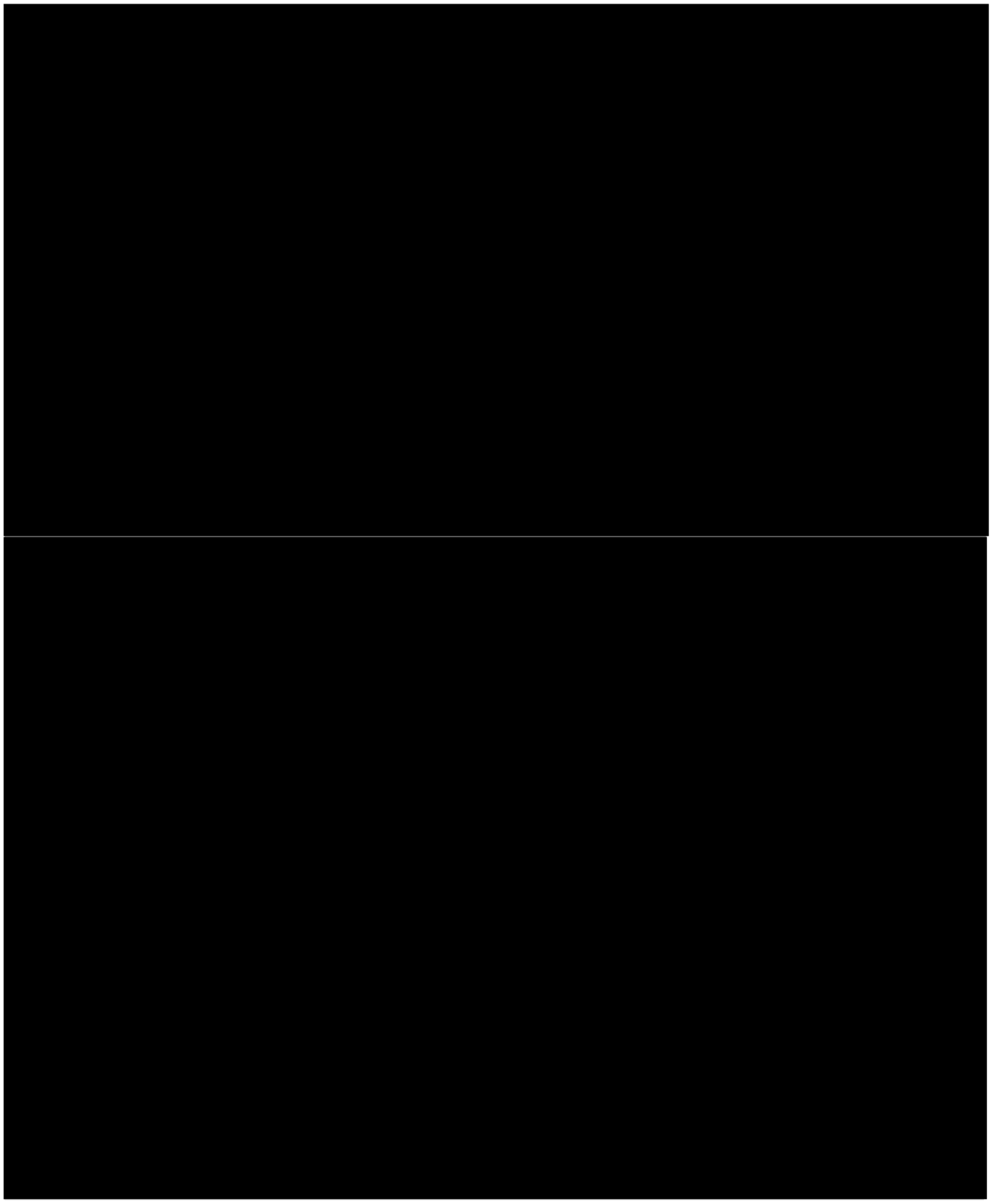
8.4.4. Pharmacokinetic Tear Sampling Procedure

Information related to required tear collection methods, supplies, processing instructions, and storage instructions will be provided in the Study Procedure Manual.

8.4.5. Pharmacokinetic Sample Bioanalysis

Plasma concentrations of AGN-242428 and AGN-231868 will be determined using validated liquid chromatography-tandem mass spectrometry methods. Tear AGN-242428, AGN-231868, and lifitegrast concentrations will be determined using qualified liquid chromatography-tandem mass spectrometry methods.

[redacted]

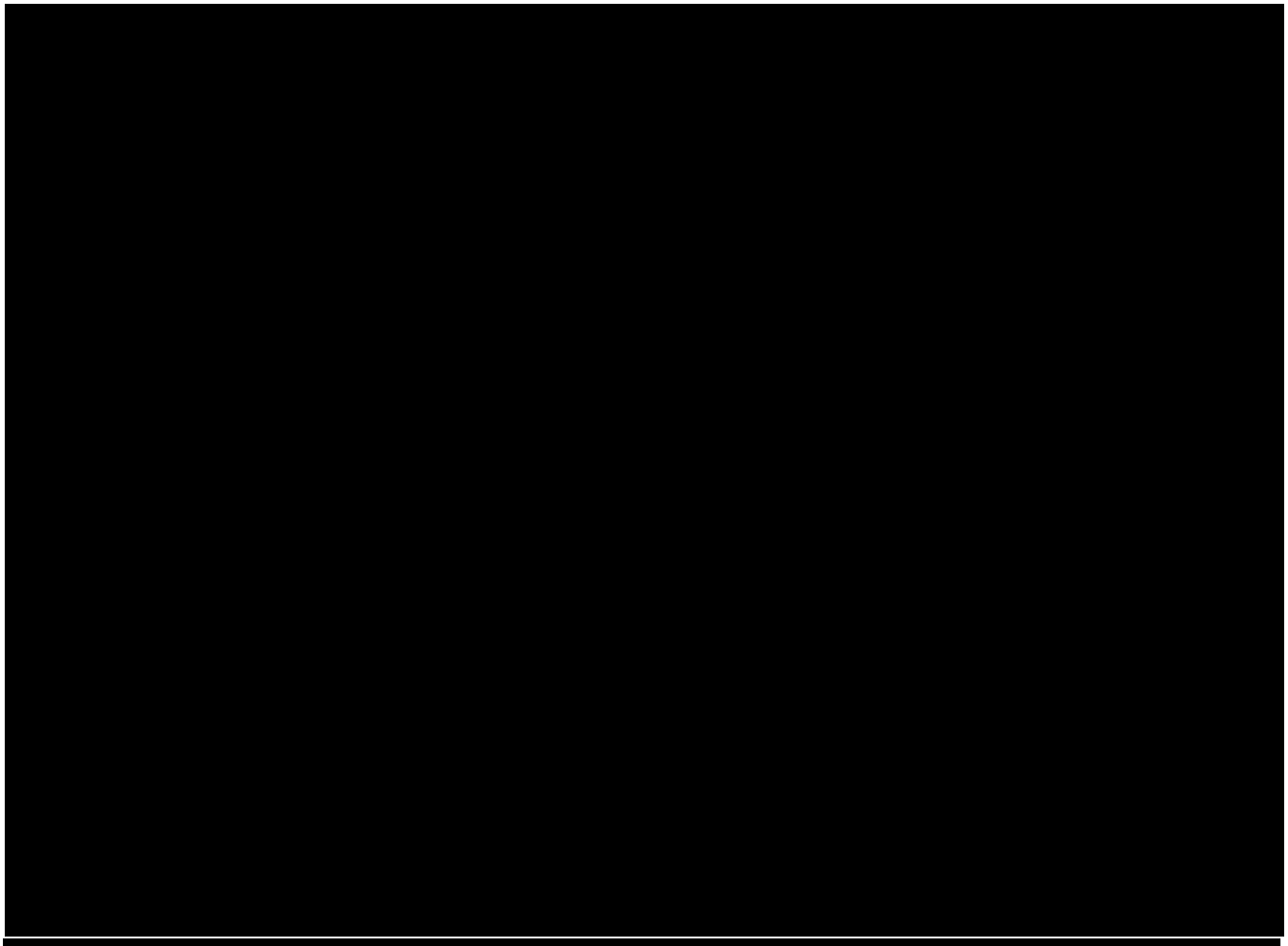


[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

[redacted]

[redacted]

8.8.1.1. Tear Sampling Procedure

Information on required tear collection methods, supplies, processing instructions, and storage instructions will be provided in the Study Procedure Manual.

[redacted]

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study. Any medications (including those prohibited or allowed) that the participant is receiving at the time of enrollment or receives during the study will be recorded, as described in Section 6.5.

9. Statistical Considerations

There will be an interim database lock at the end of Stage 1 and a final database lock after completion of Stage 2. Separate statistical analysis plans (SAPs) for each stage will be developed and finalized before the interim database lock for Stage 1 and before the final database lock for Stage 2 and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses for this study.

Separate PK analysis plans will be developed for each stage and finalized before the interim database lock for Stage 1 and before the final database lock for Stage 2.

9.1. Statistical Hypotheses

No hypothesis testing will be performed.

9.2. Sample Size Determination

For Stages 1 and 2, the sample size is not based on statistical considerations and is determined empirically.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined in Table 9-1.

Table 9-1 Analysis Populations

Population	Definition
Intent-to-Treat (ITT) (Stage 2)	All randomized participants in Stage 2. Participants will be summarized according to the randomized study intervention.
Pharmacokinetic (Stage 1)	All participants who have evaluable PK parameters in Stage 1
Pharmacokinetic (Stage 2)	All participants with available plasma or tear concentrations in Stage 2
Safety (Stages 1 and 2)	All participants who received ≥ 1 administration of study intervention for the stage
Biomarker (Stages 1 and 2)	All participants who have evaluable tear biomarker samples for the stage

Exploratory efficacy analyses will be performed on ITT population. PK analyses will be performed on PK population. Safety analyses will be performed on safety population. [redacted]

9.4. Statistical Analyses

[redacted]

[redacted]

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The following safety parameters will be summarized as appropriate (eg, categorical or continuous descriptive variables):

- AEs
- Clinical laboratory assessments
- Vital signs
- ECGs
- BCVA
- IOP
- Slit lamp biomicroscopy
- Dilated fundus examination

For Stage 1 data, no statistical testing will be performed. For Stage 2 data, the main between-group comparisons are between AGN-242428 versus its vehicle and between AGN-231868 versus its vehicle. These comparisons will be performed using a chi-square or Fisher's exact test or Wilcoxon rank-sum test as appropriate. Data will be summarized for each group, which will be used to evaluate AGN-242428, AGN-231868, and Xiidra.

9.4.2.1. Adverse Events

For each stage, the Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs.

An AE will be considered a treatment-emergent AE (TEAE) if either of the following apply:

- The AE began on or after the first dose of study intervention.
- The AE was present before the date of the first dose of study intervention but increased in intensity or became serious on or after the date of the first dose of study intervention.

An AE will be considered a treatment-emergent SAE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

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

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by:

1) System Organ Class and Preferred Term
2) System Organ Class, Preferred Term, and severity

The number and percentage of participants reporting TEAEs and TESAEs will be tabulated separately by study intervention.

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 intensity and by relationship to study intervention.

Summary tables will be provided for participants with SAEs regardless of causality and participants with AEs leading to discontinuation.

The definitions of an AE and SAE can be found in Appendix 3.

9.4.2.2. Clinical Laboratory Assessments

For each stage, descriptive statistics for clinical laboratory values (in SI units) at baseline, Exit visit, and changes from baseline at the Exit visit or Early Termination visit will be presented by study intervention for each clinical laboratory assessment.

The criteria for potentially clinically significant (PCS) laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention for Exit visit or 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.

9.4.2.3. Vital Signs

For each stage, descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline, and changes from baseline at each postbaseline visit will be presented by study intervention.

Vital sign values will be considered as PCS values if they meet both the observed value criteria and the change from baseline value criteria that will be detailed in the SAP. 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 signs 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.

9.4.2.4. Electrocardiograms

For each stage, descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTc) at baseline, Exit visit or Early Termination visit, and changes from baseline at the Exit visit will be presented by study intervention.

The criteria for PCS ECG values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline ECG values will be tabulated by study intervention for Exit visit or 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.

9.4.2.5. Best-corrected Visual Acuity

For each stage, descriptive statistics for BCVA and changes from baseline at each postbaseline visit will be presented by study intervention for each eye. Change from baseline will also be summarized by study intervention for each eye at each visit in a categorical tabulation as severe ($\geq$ 30 letters decrease from baseline), moderate ($\geq$ 15 and $<$ 30 letters decrease from baseline) and no loss or mild ($<$ 15 letters decrease from baseline).

9.4.2.6. Intraocular Pressure

For each stage, descriptive statistics for IOP and changes from baseline at each postbaseline visit will be presented by study intervention for each eye.

9.4.2.7. Biomicroscopy

For each stage, cup/disc ratio will be reported using 0.0 to 1.0 scale according to an Armaly chart provided by the sponsor. All data will be listed. No summary statistics will be provided.

For each stage, the number of participants with ophthalmoscopy findings of at least 2-grade severity increase from baseline will be generated for each MedDRA preferred terms at each postbaseline 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.

9.4.3. Pharmacokinetics Analyses

9.4.3.1. Plasma Pharmacokinetic Parameters

Analyses of plasma PK will be performed in AGN-242428- and AGN-231868-treated participants only.

For Stage 1, if the plasma concentrations of AGN-242428 or AGN-231868 are measurable, PK parameters following morning dosing on Visit 3 and Visit 5 will be calculated separately for each visit. The PK parameters, including C_{max}, T_{max}, $AUC_{0\text{-tlast}}$, and $t_{1/2}$ will be calculated, whenever possible, using data collected at Visit 3. The PK parameters, including C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $C_{min,ss}$, $t_{1/2}$, and AI (for AUC and C_{max}) will be calculated, whenever possible, using data

collected at Visit 5. The PK parameters will be calculated from individual participant concentration versus time profiles using standard model independent techniques. Descriptive statistics (mean, standard deviation, etc), if applicable, will be computed for all PK parameters calculated.

The AUCs will be calculated by using the linear-log trapezoidal rule.

Estimates of $t_{1/2}$ will be calculated based on the terminal elimination rate constant (λ_z). The λ_z will be determined by performing a regression analysis on the terminal linear phase of semilogarithmic plots of individual AGN-242428 or AGN-231868 concentration-time data using a minimum of 3 concentration-time points in the elimination phase excluding C_{max}. The λ_z will be considered to be valid if $r^2 > 0.8$.

For Stage 2, if the plasma concentrations of AGN-242428 or AGN-231868 are measurable, trough plasma concentrations and concentrations postdose will be represented using descriptive statistics (mean, standard deviation, etc.) for each intervention.

Additional parameters may be calculated at the discretion of the clinical pharmacologist.

9.4.3.2. Tear Pharmacokinetic Parameters

Tear PK analyses will be performed only on samples obtained from participants treated with AGN-242428, AGN-231868, and Xiidra.

For Stage 1, PK parameters for AGN-242428 and AGN-231868 following morning dosing on Visit 3 and Visit 5 will be calculated separately for each visit. The PK parameters, including C_{max}, T_{max}, $AUC_{0\text{-tlast}}$, and $t_{1/2}$ will be calculated, whenever possible, using data collected at Visit 3. The PK parameters, including C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $C_{min,ss}$, $t_{1/2}$, and AI (for AUC and C_{max}) will be calculated, whenever possible, using data collected at Visit 5. The PK parameters will be calculated from individual participant concentration versus time profiles using standard model independent techniques. Descriptive statistics (mean, standard deviation, etc), if applicable, will be computed for all PK parameters calculated.

The AUCs will be calculated by using the linear-log trapezoidal rule.

Estimates of $t_{1/2}$ will be calculated based on λ_z. The λ_z will be determined by performing a regression analysis on the terminal linear phase of semilogarithmic plots of individual AGN-242428 or AGN-231868 concentration-time data using a minimum of 3 concentration-time points in the elimination phase excluding C_{max}. λ_z will be considered to be valid if $r^2 > 0.8$.

For Stage 2, trough tear AGN-242428, AGN-231868, and lifitegrast concentrations and concentrations postdose will be represented using descriptive statistics (mean, standard deviation, etc.) for each intervention.

Additional parameters may be calculated at the discretion of clinical pharmacologist.

9.4.3.3. Statistical Analyses of Pharmacokinetic Data

Details of the statistical analyses of PK data (concentrations and parameters) will be described in 2 separate PK data analysis plans that will be finalized, respectively, before the interim database lock for Stage 1 and before the final database lock for Stage 2.

Descriptive statistics will be provided for all PK parameters for participants in the PK population.

9.4.4. Other Analyses

[redacted]

9.4.4.1. Subgroup Analyses

Subgroup analyses, if applicable, will be described in the SAP.

9.5. Interim Analyses

An interim database lock will occur after completion of Stage 1. At this time, the data for Stage 1 will be unmasked and data analyses will be performed. This will not affect masking of Stage 2 and the results of the interim data analyses will not be necessary to proceed to Stage 2 (see Sections 4.1 and 4.2.2 for more information on how the decision to proceed to Stage 2 will be made). At the end of study, the final database lock will occur.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/International Organization for Standardization GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the United States National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, GCP: Consolidated Guidance and records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If a study is prematurely terminated or suspended due to safety issues, the sponsor shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB is also to be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study, except as agreed with Allergan.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB according to the IRB's reporting requirements.

10.1.11. 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.

In Stage 2, the DMC can convene if significant safety findings are observed. If the dosing of study intervention is paused due to safety concerns, the unmasked DMC members will review the safety data to provide recommendations to continue, modify the design, suspend, or terminate the study or study arm. Based on a comprehensive review of the safety data, the committee may recommend modifications to the protocol, including stopping dosing of 1 or more study interventions.

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.

10.2. Appendix 2: Clinical Laboratory Tests

- The protocol-required tests detailed in Table 10-1 will be performed by the central laboratory.
- Nonprotocol-specified laboratory tests may be performed by the central laboratory or a local laboratory. The results from any local laboratory tests must be entered in the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-required 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[e]) 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)		
Drugs of Abuse[b]	Benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, alcohol[c], cannabinoids, opiates, or phencyclidine at the Screening visit or Baseline		
Serology[d]	Hepatitis B surface antigen, anti-hepatitis C virus, and anti-human immunodeficiency virus type 1 and type 2		
Pregnancy test[b] (WOCBP only)	Serum β-hCG pregnancy test at Screening; serum or urine test on all other visits		

[a] In Stage 1, blood samples will be collected following 10-hour fasting period. In Stage 2, fasting will not be required.

[b] Urine dipstick kits may be used to conduct drugs of abuse and pregnancy tests; however, serum pregnancy test will be required at Screening

[c] Breathalyzer may be used for alcohol

[d] For screening purposes only

[e] Fasting requirement is for Stage 1 only

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **AE of Special Interest** An adverse event of special interest (AESI) (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESIs have been identified for the study intervention(s) in this protocol: • 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 (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia > 5%) For any participant who meets 1 of the above liver criteria resulting in discontinuation of study intervention, the following must be performed: 1) The laboratory abnormality must be captured as an AESI. 2) Nonserious AESIs should be reported to the sponsor within 72 hours and serious AESIs should be reported to the sponsor within 24 hours. 3) The AESI form, which is the Adverse Event of Interest Abnormal Liver Function Reporting Form, should be completed and used for reporting the AESI even if a serious outcome may not apply. 4) Every effort to determine the cause of the liver enzyme abnormalities must be made (in conjunction with the MSP and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

In addition, a potential Hy's Law case is also an AESI. Criteria for potential Hy's Law cases are as follows:

- ALT and/or AST ≥ 3 × ULN AND
- TBL ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must report every participant who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until the Exit visit or Early Termination visit.

A laboratory alert for potential Hy's Law cases will be in place and must notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's Law case must be reported as a SAE by completing an Adverse Event of Interest Abnormal Liver Function Reporting Form and sent to IR-Clinical-SAE@allergan.com (or faxed to the SAE fax number) as soon as possible (within 24 hours of learning of the potential Hy's Law case). The eCRF for potential Hy's Law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the MSP and in accordance with the *FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
  - The test result is considered to be an AE by the investigator or sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/ self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• See Section 8.2.3.

Reporting of SAEs

SAE Reporting within 24 hours
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
λ_z	terminal elimination rate constant
AE	adverse event
AESI	adverse event of special interest
AI	accumulation index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-tlast}}$	area under the plasma or tear concentration versus time curve from time 0 to time of the last measurable concentration
$AUC_{0\text{-}\tau}$	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
BUN	blood urea nitrogen
CAE	controlled adverse environment
CCR	C-C motif chemokine receptor
C_{max}	maximum plasma or tear drug concentration
$C_{min,ss}$	minimum plasma or tear drug concentration at steady state
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
DED	dry eye disease
DMC	data monitoring committee
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiogram
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HRT	hormonal replacement therapy
IC_{50}	50% inhibitory concentration
ICF	informed consent form

Abbreviation	Definition
ICH	International Council on Harmonisation
IND	investigational new drug
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LFT	liver function test
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MSP	medical safety physician
NA	not applicable
[redacted]	[redacted]
NOAEL	no observed adverse effect level
OD	right eye
[redacted]	[redacted]
OS	left eye
[redacted]	[redacted]
OTC	over-the-counter
PCS	potentially clinically significant
PK	pharmacokinetic
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
$t_{1/2}$	terminal elimination half-life
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
THC	tetrahydrocannabinol
T_{max}	time of maximum plasma drug concentration
ULN	upper limit of normal
[redacted]	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Noncompliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial 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
	Clinical Study Sponsor	Allergan Sales LLC
	Trial Phase Classification	Phase 1/2a trial
	Trial Indication	Dry eye disease
	Trial Indication Type	Treatment
	Trial Type	Exploratory Efficacy Safety Tolerability Pharmacokinetics
	Trial Length	The approximate duration of participation for each participant in the study: Stage 1: 1 month Stage 2: 2.5 months
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	Stage 1: 72 Stage 2: 250
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	Dry eye disease
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18 years
	Planned Maximum Age of Subjects	Not applicable
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not applicable

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	AGN-242428 AGN-231868
	Intervention Type	Drug
	Pharmacological Class of Investigational Therapy	AGN-242428: inverse agonist (inhibitor) of retinoic acid receptor-related orphan receptor γ (RORγt) AGN-231868: inhibitor of human chemokine receptors CCR1, CCR2, CCR5, and CCR9
	Dose per Administration	Stage 1: AGN-242428 ([redacted]); AGN-231868 ([redacted]) Stage 2: AGN-242428 and AGN-231868 doses will be selected based on safety and tolerability assessed in Stage 1; ie, the highest safe and tolerated dose of each intervention will be selected for testing in Stage 2.
	Dose Units	1 drop
	Dosing Frequency	Stage 1: 1 drop of assigned study intervention in the left eye on Day 1 and 1 drop in each eye twice daily (approximately 12 hours apart) from Day 2 to Day 14, followed by a single bilateral dose administration on Day 15. Stage 2: [redacted] 1 drop of assigned study intervention in each eye twice daily (approximately 12 hours apart) for 41 days, followed by a single dose administration to both eyes on Day 42
	Route of Administration	Topical ocular instillation
	Current Therapy or Treatment	Artificial tears, Restasis, Xiidra, Cequa, topical ophthalmic steroids
	Added on to Existing Treatments	No
	Control Type	Vehicle
	Comparative Treatment Name	Xiidra
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	Stage 1: 2 cohorts + 1 optional cohort (4 treatment arms in each cohort) Stage 2: 1 cohort (5 treatment arms)
	Trial Is Randomized	Yes

Parameter Group	Parameter	Value
	Randomization Quotient	Stage 1: Cohort 1a – 3:3:1:1 ([redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles) Stage 1: Cohort 1b – 3:3:1:1 ([redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles) Stage 1: Cohort 1c – 3:3:1:1 ([redacted] AGN-242428, [redacted] AGN-231868, or their respective vehicles) Stage 2: Participants will be randomized 1:1:1:1:1 within each site (AGN-242428, AGN-242428 vehicle, AGN-231868, AGN-231868 vehicle, or Xiidra)
	Trial Blinding Schema	Double masked
	Stratification Factor	No
	Adaptive Design	No
	Study Stop Rules	Study intervention dosing may be paused due to safety concerns at any time by the site investigator. The sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:

   Documented hysterectomy

   Documented bilateral salpingectomy

   Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Contraception Guidance:

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they have been sterilized for at least 1 year (with supporting documentation of absence of sperm in the ejaculate post vasectomy) prior to the Screening visit OR agree to one of the following for the duration of the study:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom with spermicide plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant

In addition, nonvasectomized male participants must refrain from donating sperm for the duration of the study.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- In both stages of the study, WOCBP must only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and also a negative serum or urine test at the Baseline visit (Day 1).
- Additional pregnancy testing will be performed as specified in the SoA.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.2.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.8. Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments

Adverse events related to liver safety are AESIs in this study. The definitions of these AESIs, along with their reporting requirements are detailed in Appendix 3.

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