Statistical Analysis Plan

Sponsor: Aldeyra Therapeutics, Inc.

Protocol Number: ADX-102-UV-005

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Protocol Title: A Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial to Evaluate the Safety and Efficacy of ADX-102 Ophthalmic Solution in Subjects with Non-infectious Anterior Uveitis

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACC	Anterior Chamber Cell
ACE	Angiotensin-converting enzyme
ADaM	CDISC Analysis Dataset Model
ADaMIG	Analysis Data Model Implementation Guide
AEs	Adverse events
ALT (SGPT)	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Antineutrophil Cytoplasmic Antibodies
ANU	Non-infectious anterior uveitis
AST (SGOT)	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best-corrected visual acuity
BID	Twice a day
BP	Blood pressure
bpm	Beats/Breaths per minute
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CO2	Carbon dioxide
CPK	Creatinine phosphokinase
CRFs	Case report forms
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical study report
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board

eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
°F	Fahrenheit
FTA-ABS	Fluorescent Treponemal Antibody-absorption
HLA-B27	Human leukocyte antigen subtypes B*2701-2759
HR	Heart rate
IA	Immunoassay
LOCF	Last observation carried forward
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHA-TP	Micro-hemagglutination assay
mm	Millimeter
mmHg	Millimeter of mercury
MMRM	Mixed effect Model Repeat Measurement
NCS	Not clinically significant
NEI-VFQ	National Eye Institute Visual Function Questionnaire
PP	Per protocol
PRN	As needed
PT	Preferred term
QD	Once a day

QID	Four times a day
RBC	Red blood cell
RPR	Rapid Plasma Reagin
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SDTMIG	Submission Data Standards Study Data Tabulation Model Implementation Guide: Human Clinical Trials
SOC	System organ class
STD	Sexually Transmitted Disease
TEAE	Treatment emergent adverse event
TID	Three times a day
TP-PA	T. pallidum particle agglutination assay
um	Micrometer
VAS	Visual Analog Scale
VFQ-25	Visual Functioning Questionnaire - 25
WBC	White blood cells
WHODRUG	World Health Organization Drug Dictionary

2. INTRODUCTION

This document presents the statistical analysis plan (SAP) for Aldeyra Therapeutics, Inc. based on Protocol ADX-102-UV-005 (Version 4, June 20, 2018): A Phase 3 Randomized, Double-Masked, Vehicle-Controlled Trial to Evaluate the Safety and Efficacy of ADX-102 Ophthalmic Solution in Subjects with Non-infectious Anterior Uveitis (NAU). The analyses described in this document will be performed for the final clinical study report (CSR) after the database lock and unmasking. Any deviations from the statistical analysis plan will be described and a justification given in the final CSR.

All analyses will be conducted using SAS version 9.4 or higher.

2.1. Study Objectives

2.1.1. Primary Objective

To evaluate the efficacy of ADX-102 ophthalmic solution on anterior chamber cell count in subjects with non-infectious anterior uveitis.

2.1.2. Secondary Objectives

To evaluate the safety and efficacy of ADX-102 ophthalmic solution on the signs and symptoms of anterior uveitis in subjects with non-infectious anterior uveitis.

2.2. Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

- Time to Treatment Success

2.2.1.2. Secondary Efficacy Endpoints

- Time to Cell Grade Reduction
- Time to Flare Treatment Success
- Time to Flare Grade Reduction
- Time to Rescue
- Proportion of subjects with an Anterior Chamber Cell (ACC) Grade of 0

2.2.1.3. Other Study Efficacy Endpoints

- Change in signs and symptoms of anterior uveitis which include Anterior Chamber Cell Grade, Anterior Chamber Flare Grade, Limbal Injection, Hypopyon, Peripheral Anterior Synechiae, Posterior Synechiae and Keratic Precipitates by Slit Lamp Exam
- Change in Ocular Pain, Lacrimation, Photophobia and Blurry Vision by Visual Analogue Scale (VAS).
- Change in Best Corrected Visual Acuity (BCVA)
- Change in Visual Functioning Questionnaire – 25 (VFQ-25) Scores

2.2.2. Safety Endpoints

2.2.2.1. Primary Safety Endpoint

- Adverse Events (AEs) reported during the study

2.2.2.2. Ocular Safety Endpoints

- Intraocular Pressure (IOP) Measurements
- Dilated Fundus Exam
- Corneal Pachymetry

2.2.2.3. Other Safety Endpoints

- Safety Labs
- Vital Signs

2.3. Study Design

2.3.1. Study population

Approximately 120 subjects (male and female), aged ≥ 18 years and ≤ 85 years with non-infectious anterior uveitis will be enrolled in approximately 45 centers in the United States for the study.

The subjects must have a presence of 6-50 anterior chamber cells and have pachymetry corrected IOP <21 mmHg at baseline in the study eye, BCVA better than or equal to 35 letters in the study eye and 65 letters in the non-study eye using Early Treatment Diabetic Retinopathy Study (ETDRS) testing.

All inclusion and exclusion criteria can be found in the Protocol Section 6.1, and 6.2.

2.3.2. Treatment groups and dosing

Subjects will be randomized to one of 2 treatment arms to receive ADX-102 ophthalmic solution or vehicle of ADX-102 ophthalmic solution in a 1:1 ratio.

Group 1	ADX-102 ophthalmic solution (0.5%)
Group 2	Vehicle of ADX-102 ophthalmic solution

Randomization will be stratified based on baseline ACC grade in the study eye (SAP Section 3.2.7). The dosing schedule is summarized in Table 1.

Table 1. Dosing Schedule for Eye Drop Regimens

	Group 1	Group 2
Week	**ADX-102**	**Vehicle**
1	8x/Day	8x/Day
2	6x/Day	6x/Day
3	4x/Day	4x/Day
4	4x/Day	4x/Day
5	None	None

2.3.3. Study visits and assessments

Subjects will be followed for up to five (5) weeks and monitored for safety and efficacy at seven (7) scheduled visits. Efficacy will be assessed by standard ophthalmic examination procedures and response to treatment will be graded according to established uveitis scales.

Each subject's study participation will consist of the following scheduled visits: Screening/Randomization (Day 1; Visit 1), Day 4 +/- 1 day (Visit 2), Week 1 (Day 8 +/- 1 day; Visit 3), Week 2 (Day 15 +/- 2 days; Visit 4), Week 3 (Day 22 +/- 2 days; Visit 5), Week 4 (Day 29 +/- 3 days; Visit 6/ End of Treatment [EOT]/Early Termination [ET]) and Week 5 telephone follow-up (Day 36 +/- 3 days; Visit 7/End of Study [EOS]). The total time in the study is approximately 5 weeks.

Study assessments schedule is outlined in Table 2.

Table 2. Schedule of Visits and Assessments

	Visit 1 (Screening)	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6 (EOT/ET)**	**Visit 7 (EOS)**
Test/Procedure	**Day 1**	**Day 4** Day 4 (± 1 day)	**Week 1** Day 8 (± 1 day)	**Week 2** Day 15 (± 2 days)	**Week 3** Day 22 (± 2 days)	**Week 4** Day 29 (± 3 days)	**Week 5**[a] Day 36 (± 3 days)
Informed Consent	✓						
Eligibility Criteria	✓						
Medical History	✓						
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓
Demographics	✓						
Ocular scores; ocular pain, blurry vision, photophobia, tearing scores[b, c]	✓	✓	✓	✓	✓	✓	
VFQ-25[b]	✓					✓	
Uveitis Questionnaire	✓						
Height and weight	✓						
Vital Signs	✓					✓	
Uveitis-specific laboratory tests and Chest X-Ray[d]	✓						
Safety laboratory tests[e]	✓					✓	
Urine pregnancy test[f]	✓					✓	
Best Corrected Visual Acuity	✓	✓	✓	✓	✓	✓	
Intraocular pressure[g]	✓	✓	✓	✓	✓	✓	
Slit lamp exam	✓	✓	✓	✓	✓	✓	
Fundus exam	✓	✓	✓	✓	✓	✓	
Corneal pachymetry	✓						
Subject Dosing Diary Dispensing	✓		✓	✓	✓		
Adverse events	✓	✓	✓	✓	✓	✓	✓

EOT/ET = end of treatment/early termination; EOS = end of study; VFQ-25 = Visual Function Questionnaire

[a] The Week 5/EOS visit will consist of a follow up phone call to collect Adverse Events and Concomitant Medications.

[b] Ocular scores and VFQ-25 self-administered survey (version 2000) will be completed prior to any other study procedures at that visit. The only exception is for the VFQ-25 when a subject is being seen for a routine study visit that becomes an ET visit because the subject receives rescue therapy. In these cases, the VFQ-25 must still be administered but it may be after other examinations.

[c] Ocular pain, lacrimation, photophobia, and blurry vision will be measured by the subject completing a Visual Analog Scale (VAS).

[d] During Screening only, the following 3 uveitis-specific diagnostic tests will be obtained in all subjects experiencing their first episode of anterior uveitis, or in subjects experiencing a repeat episode where prior tests of this nature have not been previously performed:

1) HLA-B27 (Human leukocyte antigen subtypes B*2701-2759)
2) Chest X-ray
3) Treponemal antibody test(s) including one or more of the following:
    a. FTA-ABS (Fluorescent treponemal antibody absorption)
    b. TP-PA (T. pallidum particle agglutination assay)
    c. MHA-TP (Micro-hemagglutination assay)
    d. Laboratory specific automated Immunoassay (IA)

A non-treponemal antibody test such as RPR (Rapid Plasma Reagin) alone is not sufficient.

If the study subject was tested prior to the screening visit, there needs to be evidence that these tests were performed:

1) HLA-B27 at any time in the past
2) Chest X-ray within the previous 6 months unless new onset pulmonary symptoms are documented
3) Treponemal antibody test(s) within the previous 6 months unless intervening new onset symptoms of any STD, or STD exposure are documented

Additional testing such as for RPR, ACE, ANCA, quantiferon and ANA may be performed at the discretion of the investigator.

[e] Safety laboratory tests are hematology including: "hemoglobin, hematocrit, red blood cell (RBC) count, RBC morphology, white blood cell (WBC) count with differential, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and absolute platelet count" and chemistry including: "albumin, alkaline phosphatase, alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO2), chloride, creatinine, creatinine phosphokinase (CPK), glucose, phosphate, potassium, sodium, total protein, and uric acid."

[f] Required for women of child-bearing potential; must be negative for the subject to be randomized.

[g] Once a subject has enrolled in the study, the same tonometry method should be used for that subject throughout the duration of the study. IOP corrected for pachymetry (Ehlers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. *Acta Ophthalmol.* 1975;53:34-43). See Protocol Appendix 2.

2.3.4. Medications

2.3.4.1. Prior and Concomitant Medications

All medications that are taken by the subject in the 30 days prior to consent must be recorded during the Screening (Visit 1). Any changes in dosage or new medications added as a result of intercurrent illness must be recorded in the case report forms (CRFs).

Recommendations regarding concomitant medications taken during the study are outlined in the Protocol Section 7.3.

2.3.4.2. Prohibited Medications

Use of the following medications is prohibited for the duration of a subject's participation in the study from **Screening (Visit 1)** through **Week 4 (Visit 6/EOT/ET)**:

- Any investigational treatment other than ADX-102
- Any medication as part of exclusion criteria (Protocol Section 6.2)

2.3.4.3. Rescue Therapy

Rescue therapy will be administered after completion of the **Week 1** or **Week 2** assessments if any one of the below criteria are met:

- Worsening of visual acuity due, in the opinion of the Investigator, to non-infectious anterior uveitis by ≥ 2 lines or ≥ 10 letters using ETDRS testing from **Day 1** to **Week 1** or any time after **Week 1** (compared to Day 1)
- Subject demonstrates one unit or more increase in ACC grade from **Day 1** to **Week 1** or any time after **Week 1** (compared to Day 1)
- Subject fails to show improvement in ACC grade from **Day 1** to **Week 2**

The protocol recommended rescue therapy is Durezol® (difluprednate ophthalmic emulsion 0.05%) four times a day (QID) plus Cyclogyl (cyclopentolate hydrochloride ophthalmic solution, 1%) up to QID, as needed (PRN). Durezol® tapered to three times a day (TID), twice a day (BID), once a day (QD) each subsequent week if ocular exam and symptoms improve. Alternative rescue therapy may be given at the discretion of the Investigator.

Once it is determined that rescue therapy is needed, the subject should be considered an Early Termination and the Week 4 (Visit 6) assessments should be completed.

2.3.5. Randomization and Masking

Subjects meeting the study entry criteria will be centrally randomized via an interactive web response system (IWRS) during **Screening/Visit 1** in a 1:1 ratio to one of 2 groups and stratified on baseline ACC grade, 1+, 2+, 3+ in the study eye (SAP Section 3.2.7).

Group 1 ADX-102 ophthalmic solution (0.5%)
Group 2 Vehicle of ADX-102 ophthalmic solution

Subjects are eligible for enrolment with ACC Grade 1+ to 3+ disease. However, if ≥ 60 study subjects are noted to have Grade 1+ ACC severity further enrolment of ACC Grade 1+ severity will be halted as the study population is designed to represent a range of NAU subjects and not predominantly Grade 1+ disease.

A randomization code will be computer-generated by a contract research organization (CRO) Axio Research LLC. A randomization number will be assigned for dosing.

The randomization schedule will be generated by a statistician at Axio Research (who is not on the project team) or designee and maintained in a secure and limited-access location separate from the study investigator and members of the project team. The study subject, investigative staff, the Sponsor, and the Sponsor study team (includes contractors and vendors) will be masked to treatment assignments until completion of the study and database lock. The treatment assignments may be unmasked per the procedures detailed in the Protocol Section 7.7.

ADX-102 and/or vehicle of ADX-102 ophthalmic solution will be provided in subject packs masked to the subject, Investigator and study staff.

2.3.6. Sample Size and Power

Based on the Phase 2 clinical trial results, a true hazard rate of 0.2672 and 0.1098 is assumed for the time to treatment success in ADX-102 and vehicle group, respectively. With approximately 53% censoring rate, a sample size of 90 subjects (45 per group) yields 82% power to detect the superiority of ADX-102 over vehicle group with the use of a 2-sided log-rank test and a type I error of 0.05. Under the same assumption, a sample size of 120 subjects (60 per group) will provides 91% power.

3. GENERAL CONSIDERATION FOR DATA ANALYSES

3.1. Analysis Sets

3.1.1. Intent-To-Treat Analysis Set

The intent-to-treat analysis set (ITT) is the population of all subjects who are randomized into a treatment group and received at least one dose of study drug. Subjects in this population will be analyzed according to the treatment group to which they were randomized. This population will be used for analyses of efficacy and pre-study/baseline characteristics.

3.1.2. Per Protocol Analysis Set

The per protocol (PP) analysis set is the subset of ITT subjects who meet all inclusion and exclusion criteria, remain on study medication, comply with treatment instructions, and do not have any significant protocol deviations or violations. Rescued subjects will not be excluded from PP solely on the basis of having been rescued and withdrawal of study medication and withdrawal from the study. Subjects in this population will be analyzed according to the treatment they receive.

3.1.3. Safety Analysis Set

The safety analysis set consists of all randomized subjects who receive at least one dose of study drug, regardless of whether or not they undergo any study assessments. Subjects in this population will be analyzed according to the treatment which they received. All safety analyses will be based on this population.

3.2. Statistical Analysis Issues

3.2.1. Strata and Covariates

The randomization of the study is stratified based on baseline ACC grade: 1+, 2+, 3+ in the study eye (SAP Section 3.2.7). For time to efficacy endpoints, a stratified log-rank test to test treatment effect stratified by the baseline ACC grade used for randomization stratification will be performed. Stratified Cox proportional hazards regression model will also be performed.

3.2.2. Examination of Subject Subsets

Subgroup analysis for efficacy endpoints may be performed by stratification group if deemed necessary.

3.2.3. Multiple Comparisons

A single endpoint is selected for the purpose of statistical inference on the primary efficacy and no adjustment for multiple testing is planned.

3.2.4. Multi-center Studies

The study will be conducted in up to 45 centers in the United States. Randomization to the treatment groups will not be stratified by study center as the number of subjects available at some study centers may be small. Subjects from all centers will be pooled for analyses.

3.2.5. Missing Data and Outliers

Every attempt will be made to capture all study data. The method on how to handle the complete and/or partial missing date in the adverse events and medications will be addressed in these individual analysis sections of the SAP. Any other type of missing, unused, or spurious data will be noted in the CSR.

The primary analysis of anterior chamber cell count will be conducted on the ITT population with last observation carried forward (LOCF) for missing data. The within subject best and worst observation imputation will be used for sensitivity analysis.

The key secondary endpoints listed in Section 2.2.1.2 will be analyzed using the same data imputation approach as used for the primary endpoint.

3.2.6. Data Conventions and Transformations

Laboratory numeric data may be recorded with a '<' or '>' sign (e.g., < 0.1 or > 0.1) in the character result for the original and/or standard units. In order to summarize the data numerically in the standard units, the original value will be converted to 0.09 in the case of < 0.1 and to 0.11 in the case of > 0.1. The same principle will be used if the data has additional extended significant digits. The actual character values will be presented in the data listings.

3.2.7. Study Eye

A study eye will be determined at the Screening Visit as follows: If only one eye qualifies for treatment, that eye will be the study eye. If both eyes qualify for treatment, the eye with the higher anterior chamber cell score will be the study eye; or if both have the same score, the right eye will be the study eye. Although it is possible for the subjects who are experiencing a bilateral episode of anterior uveitis be treated in both eyes, the study eye will be used as the primary eye in the analyses.

3.2.8. Study Baseline and Study Day

For purposes of analysis the baseline value is defined as the last non-missing value obtained prior to initiation of study drug, nominally the Screening Visit. Measurements that are obtained after the first dose of study drug will be considered post-baseline values. If a measurement of a variable is not made on a given subject prior to the first dose of study drug, then that subject will be considered not to have a baseline value for that parameter. Change from baseline is defined as non-missing post-baseline assessment value minus baseline assessment value.

Study day for events on or after the date of the first dose will be defined as the number of days from the date of the first dose of study drug, plus 1 day, so that the date of the first dose will be defined as Day 1. For events before the date of the first dose, study day will be calculated as the difference in days between the date of the first dose and the date of interest. Thus, the day before the date of the first dose will be defined as Day -1.

3.2.9. Visit Windows

Unless otherwise noted, any analysis using study visit will be mapped using the analysis window and presented as follows. If assessments are collected multiple times within a given study visit window, the result closest to the scheduled visit day will be used for summary presentations. If two measurements have the same distance to the expected day, the earlier value will be used. If a subject has multiple non-missing scheduled values on the same day, then the last one is used, as determined by the time collected, if available. If a scheduled assessment and an unscheduled or early termination assessment are collected within a given visit window, the value from the scheduled visit will be chosen over the value from the unscheduled visit. Unscheduled and early termination visits will be assigned to an unplanned study visit and visit number using the analysis windows described in Table 3 in case the scheduled visit was not performed. All assessments will be presented with the original study visit in the listings.

Table 3: Analysis Windows

Visit	Target Day [1]	Window [1]
Day 4	4	Day 2 - Day 5
Week 1	8	Day 6 - Day 11
Week 2	15	Day 12 - Day 18
Week 3	22	Day 19 - Day 25
Week 4	29	Day 25+

[1] Days are determined based on the first dose of study drug.

3.3. Clinical Data Interchange Standards Consortium (CDISC) Implementations

The submission data for this study will be CDISC compliant. The following standards will be implemented.

Exchange Standards	SDTM 1.4 / SDTM IG v3.2 ADaM 2.1 / ADaM IG v1.0 Define.xml v2.0
Terminology Standards	CDISC SDTM 2017-12-22 CDISC ADaM 2017-09-29 MedDRA v19.0 WHODRUG B3 ENHANCED (SEPTEMBER 2017)

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

An independent data safety monitoring board (DSMB) will be established. They will review all available safety data after approximately 25 subjects have completed the study visit 7. The assessment of safety will be determined from ophthalmologic endpoints including slit lamp examinations, ocular scores, visual acuity and IOP, vital sign measurements, physical examinations, hematology and chemistry laboratory testing, use of concomitant medications, and review of adverse events. Based on the safety data provided, the DSMB will determine if it is acceptable to continue the study or modify the study design as appropriate. Additional DSMB reviews will occur throughout the trial approximately every 6 months or as deemed necessary by the DSMB or Sponsor to ensure subject safety and well-being. Study enrollment and dosing will continue while the DSMB evaluates data. A DSMB charter will be prepared. The charter will contain the required information for the formation, activities and conduct of the DSMB.

There is no other type of interim analysis planned for this study.

5. GENERAL ANALYSIS METHODS

Continuous variables will be summarized using descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, 25% percentile, 75% percentile, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Percentages will be calculated using the total number of subjects in each treatment group for each applicable population and/or subpopulation, unless otherwise noted.

Number of subjects, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, standard deviations, standard errors and quartiles will be calculated to one more decimal place than the source data. Percentages will be calculated to the nearest one decimal place. Zero count cells will be displayed as "0" with percentage of (0%).

Unless otherwise noted, summaries will be performed by the treatment group [in the order of ADX-102 (0.5%) and Placebo (vehicle)] with randomization stratum combined. The term "Placebo" will be used instead of "Vehicle" in the analysis and from this point forward.

If statistical tests are performed, the tests will be done at the two-sided, 5% significance level to compare ADX-102 vs. Placebo, unless otherwise specified. The point estimate and 95% confidence interval (CI) for the treatment differences may be displayed along with the p-value for the treatment comparison. P-values will be presented to three decimal places. P-values < 0.0005 will be presented as < 0.001. P-values greater than 0.999 will be presented as > 0.999.

Unless otherwise noted, the study eye will be used as the primary eye in the analyses.

Key listings per the ICH CSR guidelines will be programmed from the ADaM dataset. All other listings will be programmed using SDTM data. Subjects who were screen failures, subjects who were never randomized, and subjects who were randomized and never treated will be accounted for in the data listings if the data are available.

5.1. Terminology

The term "Placebo" will be used instead of "Vehicle" in the analysis and from this point forward. The term "Study Drug" refers to both ADX-102 and Placebo in the analysis.

6. SUBJECT DISPOSITION

6.1. Enrollment and Disposition of Subjects

Subjects' enrollment and disposition during the study will be summarized by treatment group. The summary will be based on the ITT analysis set and will include the following:

- Number and percentage of subjects randomized and treated (ADX-102 or Placebo)
- Number and percentage of subjects randomized and treated with both eyes
- Number and percentage of subjects randomized and treated who completed the treatment at Week 4
- Number and percentage of subjects randomized and treated who discontinued from the treatment
- The reasons for treatment discontinuation

- Number and percentage of subjects randomized and treated who completed the study Follow-Up visit
- Number and percentage of subjects randomized and treated who discontinued the study Follow-Up visit
- The reasons for Follow-Up visit discontinuation
- Number and percentage of randomized and treated subjects included in the Safety and PP analysis set
- Number and percentage of subjects excluded from the PP and the reasons for the exclusion.

The reasons for discontinuation will be listed in the order as they appear on the eCRF. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set.

6.2. Extent of Exposure

6.2.1. Duration of Exposure to Study Drug

Study drug exposure for the study eye from the daily dosing diary during the treatment period will be summarized on the ITT analysis set by treatment group for subjects who have received at least one dose of study drug in the study eye. Total number of doses of study drug taken and total duration of exposure to study drug (days) will be summarized by descriptive statistics. No inferential statistics will be calculated.

The total number of doses of study drug taken will be calculated as the sum of the doses each day (indicated by date) that subject recorded in the daily dosing diary eCRF.

The total duration of exposure of study drug will be calculated as the total number of days from the first dose date to the last dose date in the daily dosing diary eCRF plus 1 regardless of temporary dose interruptions. If the data are collected on the unscheduled/early termination visits, it will be included in the calculation.

The number and percentage of subjects in the total duration of exposure categories of: '<1 week', '1 week to <2 weeks', '2 weeks to <3 weeks', '3 weeks to <4 weeks', and '≥4 weeks' will also be summarized. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set.

6.2.2. Study Drug Compliance

Subjects will be asked to record each administration of study drug on the diary card provided. The overall treatment compliance will be assessed by the data from the daily dosing diary eCRF and will be summarized by treatment group on the ITT analysis set.

The overall treatment compliance (%) will be calculated as (total number of doses have been taken / total number of doses that should have been taken)*100. The total number of doses have been taken is defined in the Section 6.2.1 above. The total number of doses that should have been taken is defined as the protocol required total number of doses to be administered from the first dose date to the last dose date (i.e. Week 1: 8x/Day, Week 2: 6x/Day, Weeks 3 and 4: 4x/Day). Compliance will be adjusted for the early withdrawals.

The overall compliance will be summarized descriptively as well as the number and percentage of subjects in the following study drug overall compliance categories: '≤80%', '>80% to <120%' and '≥120%' will be summarized by treatment group. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set.

Overall compliance ≤80% or ≥120% is a protocol deviation.

6.3. Protocol Deviations

Deviations from the protocol will be documented on an ongoing basis on the protocol deviations eCRF throughout the study. The number and percentage of subjects with any deviation and within each deviation category will be summarized by treatment group on the ITT analysis set. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set. The deviations will be listed in the order as they appear on the eCRF.

Inclusion and exclusion criteria data will be listed for all subjects.

7. BASELINE DATA

7.1. Demographic and Baseline Characteristics

Demographic (age [years], gender, race, ethnicity, height [cm], weight [kg]), subjects with bilateral uveitis, study eye(s) identified at randomization, baseline ACC grade [randomization stratification] and baseline characteristics (IOP measurement [mmHg], BCVA letter score) will be summarized descriptively by treatment group on the ITT, PP and Safety analysis sets. For categorical parameters, the percentages will be calculated based on the number of subjects in each treatment group of the ITT, PP and Safety analysis sets. The baseline characteristic

parameters will be summarized for both the Study Eye (see SAP Section 3.2.7 for definition) and the Non-Study Eye if the assessments are done on each eye separately.

Age at Screening (Visit 1) will be calculated as (the informed consent date-birth date)/365.25.

7.2. Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0).

The number and percentage of subjects with any medical and/or surgical history will be summarized by treatment group on the ITT analysis set. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency. Subjects will be counted only once for each SOC and PT. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set.

The medical and surgical history in this study includes both the ocular and the general (non-ocular) history. Ocular Medical History, Ocular Surgical History, General (non-ocular) Medical History and General (non-ocular) Surgical History will be summarized separately.

8. MEDICATION AND THERAPY

8.1. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG) for anatomical therapeutic chemical classification (ATC) and preferred drug name. The September 2017 version of the dictionary will be used for the coding.

The number and percentage of subjects with coded medications will be summarized by treatment group on the ITT analysis set. A subject who used multiple medications will be counted only once for each ATC and preferred drug name. ATC will be sorted alphabetically and preferred drug name within each ATC will be sorted by overall descending order of frequency. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set.

Prior and concomitant medications will be summarized separately. In addition to the overall summary, ocular and non-ocular medications will also be summarized.

Prior medications are defined as any medications that started and stopped prior to the date of first dose of study drug. Concomitant medications are defined as any medications that (1) started

prior to the date of first dose of study drug and were either stopped or were ongoing at or after the date of first dose of study drug; (2) started at or after the date of first dose of study drug. Where a medication recorded with a partially or fully missing start/stop date or time, and it is unclear as to whether the medication is concomitant, it will assume concomitant.

8.2. Rescue Therapies

The number and percentage of subjects administered rescue therapy and the reasons for administering the rescue therapy will be summarized by treatment group on the ITT analysis sets. A subject who has more than one reason for prompting the rescue therapy will be counted under each reason. Protocol recommended and non-protocol recommended rescue therapies given will also be summarized. The percentages will be calculated based on the number of subjects in each treatment group of the ITT analysis set.

9. EFFICACY ANALYSES

All of the efficacy analyses will be performed on the ITT analysis set. The PP analysis set will be used as supportive analyses for the primary and secondary efficacy endpoints. Unless otherwise noted, unscheduled and early termination visits will be assigned to an unplanned study visit using the analysis windows described in SAP Section 3.2.9 (Table 3) in case the scheduled visit was not performed.

Although it is possible for the subjects who are experiencing a bilateral episode of anterior uveitis be treated in both eyes, the study eye will be used as the primary eye in the efficacy analyses. The definition of the study eye is described in SAP Section 3.2.7. Summary of descriptive statistics will be presented for all study visits at which efficacy data were collected. In addition, descriptive statistics summary will be performed separately on the study eye and on the non-study eye where it is applicable.

For the time to event data, Kaplan-Meier method and Cox proportional hazards regression model will be used for the analysis. Descriptive summary [n (%) subjects with event, n (%) subjects censored without event, median, 25^{th} and 75^{th} percentiles] by treatment group. Stratified and unstratified log-rank test will be used for the treatment group comparison. The stratified analysis based on the baseline ACC grade used for randomization stratification will be the primary method.

For the categorical data, stratified Cochran-Mantel-Haenszel (CMH) test and/or Fisher's exact test will be used for the treatment group comparison. If both stratified CMH and Fisher's tests are used, the stratified CMH test will be the primary method.

Non-primary or secondary efficacy endpoints will be summarized for descriptive statistics only. No statistical treatment group comparison will be performed.

9.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the time to treatment success, where such time (in days) is defined as from initiation of study drug to when a cell count of 0 is achieved and maintained (without cell count increase to > 0) to Week 4 without being rescued (or discontinued due to the requirement for rescue therapy) at any time prior to Week 4. All rescued subjects and subjects who did not achieve treatment success will be right censored. Subjects who discontinue from the study for reasons other than rescue will be real-time censored. Event and censoring definitions are described in Table 4 below.

The primary analysis to test superiority of ADX-102 over vehicle is the stratified log-rank test, stratified for the baseline ACC grade, with missing data imputed using the last observation carried forward (LOCF) approach. The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the time to treatment success curve. The Cox proportional hazards model with treatment group as a factor, stratified by the baseline ACC grade, will be used to estimate the hazard ratio and corresponding 95% confidence interval.

Table 4: Event and Censoring for Time to Treatment Success Analysis

Situation	Event / Censored	Date of Event / Censoring
Treatment success	Event	Date when the first cell count of 0 is achieved prior to or at Week 4 and maintained (without cell count increase to > 0) to Week 4 without being rescued any time prior to Week 4
Cell count greater than 0 at Week 4	Censored	Date of Week 4
Rescued	Censored	Date of Week 4
Early discontinuation from study for reasons other than rescue	Censored	Date of study discontinuation or Week 4, whichever is the earlier

Sensitivity Analyses

The following sensitivity analyses will be conducted to evaluate the robustness of the result from the primary analysis:

1) *Unstratified Analysis:* An unstratified log-rank test on the ITT population with missing data imputed by the LOCF approach. The unadjusted hazard ratio and 95% CI will be estimated from Cox model.
2) *Best Within-Subject Observation:* A stratified log-rank test on the ITT population with missing data imputed by the within-subject best observation from Day 1 to Week 4 or Early Termination. The hazard ratio and 95% CI will be estimated from Cox model stratified for the baseline ACC grade.
3) *Worst Within-Subject Observation:* A stratified log-rank test on the ITT population with missing data imputed by the within-subject worst observation from Day 1 to Week 4 or Early Termination. The hazard ratio and 95% CI will be estimated from Cox model stratified for the baseline ACC grade
4) *Subjects with Unscheduled Visits:* A stratified log-rank test on the ITT population with missing data imputed by the LOCF approach. Values from scheduled and unscheduled visits will be pooled before imputation. The hazard ratio and 95% CI will be estimated from Cox model, stratified for the baseline ACC grade

Throughout this Statistical Analysis Plan, rescue will be defined as disease worsening or lack of disease improvement that, at the discretion of the investigator, requires rescue therapy. Prior to database lock, discontinued subjects will be adjudicated as to whether the discontinuation was primarily due to the requirement of rescue therapy.

9.2. Analysis of Secondary Efficacy Endpoints

9.2.1. Time to Cell Grade Reduction

The time to cell grade reduction is defined as the time (in days) from initiation of study drug to the date that improvement (decrease) from baseline in ACC grade of at least 1 grade was achieved without being rescued (or discontinued due to the requirement for rescue therapy) at any time prior to Week 4. All rescued subjects and subjects who did not achieve treatment success will be right censored. Subjects who discontinue from the study for reasons other than rescue will be real-time censored. Event and censoring definitions are described in Table 5 below.

Missing ACC grade will be imputed using the LOCF approach. A log-rank test stratified by the baseline ACC grade will be performed for between-group comparison. The Kaplan-Meier plot will be generated. The Cox proportional hazards model, with treatment group as a factor and

stratified by the baseline ACC grade, will be used to estimate the hazard ratio and corresponding 95% confidence interval.

Table 5: Event and Censoring for Time to Cell Grade Reduction Analysis

Situation	Event / Censored	Date of Event / Censoring
Cell grade reduction	Event	Date when the first ACC grade with at least 1 grade decrease from baseline was achieved without being rescued at any time prior to Week 4
Cell grade reduction does not meet 1 grade reduction from baseline prior to or at Week 4	Censored	Date of Week 4
Rescued	Censored	Date of Week 4
Early discontinuation from study for reasons other than rescue	Censored	Date of study discontinuation or Week 4, whichever is the earlier

9.2.2. Time to Flare Treatment Success

The time to flare treatment success is defined as the time (in days) from initiation of study drug to the date that the anterior chamber flare grade reached 0 and maintained (without flare grade increase to > 0) to Week 4 without being rescued (or discontinued due to the requirement for rescue therapy) at any time prior to Week 4. All rescued subjects and subjects who did not achieve treatment success will be right censored. Subjects who discontinue from the study for reasons other than rescue will be real-time censored. Event and censoring definitions are described in Table 6 below.

Missing anterior chamber flare grade will be imputed using the LOCF approach. A log-rank test will be performed for between group comparison. The Kaplan-Meier plot will be generated. The Cox proportional hazards model with treatment group as a factor will be used to estimate the hazard ratio and corresponding 95% confidence interval.

Table 6: Event and Censoring for Time to Flare Treatment Success Analysis

Situation	Event / Censored	Date of Event / Censoring
Flare treatment success	Event	Date when the first anterior chamber flare grade of 0 is achieved prior to or at Week 4 and maintained (without flare grade increase to > 0) to Week 4 without being rescued any time prior to Week 4
Anterior chamber flare grade greater than 0 at Week 4	Censored	Date of Week 4
Rescued	Censored	Date of Week 4
Early discontinuation from study for reasons other than rescue	Censored	Date of study discontinuation or Week 4, whichever is the earlier

9.2.3. Time to Flare Grade Reduction

The time to flare grade reduction is the time (in days) from initiation of study drug to the date that improvement (decrease) in anterior chamber flare grade of at least 1 unit was reached without being rescued (or discontinued due to the requirement for rescue therapy) at any time prior to Week 4. All rescued subjects and subjects who did not achieve treatment success will be right censored. Subjects who discontinue from the study for reasons other than rescue will be real-time censored. Event and censoring definitions are described in Table 7 below.

Missing anterior chamber flare grade will be imputed using the LOCF approach. A log-rank test will be performed for between group comparison. The Kaplan-Meier plot will be generated. Cox proportional hazards model with treatment group as a factor will be used to estimate the hazard ratio and corresponding 95% confidence interval.

Table 7: Event and Censoring for Time to Flare Grade Reduction Analysis

Situation	Event / Censored	Date of Event / Censoring
Flare grade reduction	Event	Date when the first AC flare grade with at least 1 grade decrease was achieved prior to Week 4 without being rescued at any time prior to Week 4
Flare grade reduction does not meet 1 grade reduction from baseline prior to or at Week 4	Censored	Date of Week 4
Rescued	Censored	Date of Week 4
Early discontinuation from study for reasons other than rescue	Censored	Date of study discontinuation or Week 4, whichever is the earlier

9.2.4. Time to Rescue

The time to rescue is the number of days from initiation of study drug to the date of the first rescue therapy at any time prior to Week 4. All subjects who achieved treatment success will be right censored. Subjects who discontinue from the study for reasons other than rescue or who completed the study without rescue will be real-time censored. Event and censoring definitions are described in Table 8 below.

A log-rank test stratified by the baseline ACC grade will be performed for between group comparison. The Kaplan-Meier plot will be generated. The Cox proportional hazards model with treatment group as a factor, stratified by the baseline ACC grade, will be used to estimate the hazard ratio and corresponding 95% confidence interval.

Table 8: Event and Censoring for Time to Rescue Analysis

Circumstance	Event / Censored	Date of Event / Censoring
Rescued	Event	Date when the first rescue therapy or discontinuation due to requirement for rescue therapy was initiated
Study completion or study success	Censored	Date of Week 4
Early discontinuation for reasons other than rescue	Censored	Date of study discontinuation or Week 4, whichever is the earlier

9.2.5. Responder Analysis for Subjects with ACC Grade 0

A subject will be classified as a responder if an anterior chamber cell grade of 0 is achieved without rescue.

Unscheduled and early termination visits will not be assigned to an unplanned study visit using the analysis windows described in SAP Section 3.2.9 (Table 3) in case the scheduled visit was not performed.

The percentages of responders will be summarized by treatment. CMH stratified by baseline ACC grade and Fisher's exact tests will be used for the between treatment group comparisons.

9.3. Other Efficacy Endpoints

Other efficacy endpoints (Non-primary or secondary endpoints) will be summarized on the ITT analysis set by visit for descriptive statistics only. No statistical treatment group comparison will be performed, unless otherwise specified.

9.3.1. Slit Lamp External Eye Exam and Biomicroscopy

The examination of anterior uveitis is performed on both eyes (study and non-study eye) by external examination and biomicroscopy using a slit lamp. Slit lamp examination will be completed at Day 1 (Screening), Day 4, Week 1, Week 2, Week 3 and Week 4.

Changes from baseline in signs and symptoms of anterior uveitis which include Anterior Chamber Cell Grade, Anterior Chamber Flare Grade, Limbal Injection, Hypopyon, Peripheral Anterior Synechiae, Posterior Synechiae, Keratic Precipitates and Eyelid are the interest of treatment efficacy.

Descriptive summaries of the observed exam results at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes (study and non-study eye), without imputation. The numerical value of the exam result categories will be used in the summaries. The higher score representing more severe symptoms.

Number and percentage of subjects with Eyelid categories of Normal or Abnormal as well as the categorical shift from baseline at each post-baseline visit will also be summarized. The percentages will be calculated based on the number of subjects at each visit in each treatment group of the ITT analysis set. The percentages on the shift will be calculated based on the number of subjects with both baseline and post-baseline values.

In addition to the descriptive summary, the change from baseline in anterior chamber cell grade and flare grade will be analyzed using Mixed effect Model Repeat Measurement (MMRM) method. The MMRM model will include the fixed categorical effects of treatment, random effect visit, and treatment-by-visit interaction, as well as continuous fixed covariates of baseline score. An unstructured covariance structure of random effect will be used for modeling the within-subject errors. If the unstructured covariance structure matrix results in a lack of convergence, the model will be fit using covariance matrices of the following order until convergence is met:

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

9.3.2. Ocular VAS Scores

Ocular pain, blurred vision, photophobia and tearing will each be measured using a visual analogue scale. The VAS is a continuous 100 millimeter (mm) line and subjects will be asked to indicate their level of agreement to a statement (0 = no symptoms, 100 = worst possible symptoms) by placing a single vertical line on the scale. The VAS will be administered at Day 1 (Screening), Day 4, Week 1, Week 2, Week 3 and Week 4.

Descriptive summaries of the observed VAS scores at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented without imputation. The higher score representing more severe symptoms.

9.3.3. Best Corrected Visual Acuity

The BCVA is measured on both eyes (study and non-study eye) at Day 1 (Screening), Day 4, Week 1, Week 2, Week 3 and Week 4.

Descriptive summaries of the observed BCVA number of letters read at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes (study and non-study eye), without imputation. The higher number of letters read representing a better vision.

The number and percentage subjects with ≥5 letters change, ≥10 letters change, no change, or worsened from baseline will also be summarized. The percentages will be calculated based on the number of subjects with both baseline and post-baseline values in each treatment group of the ITT analysis set.

9.3.4. Visual Functioning Questionnaire – 25 (VFQ-25)

The VFQ-25 is a reliable and valid 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). The VFQ-25 will be self-administered at the beginning of the designated study visits, prior to any examinations (see Protocol Section 9.1.5 for exception). The VFQ-25 will be administered at Day 1 (Screening) and Week 4.

Scoring VFQ-25 with or without optional items is a two-step process:

First, original numeric values from the survey are re-coded following the scoring rules outlined in the "Version 2000, The National Eye Institute 25-Item, Visual Function Questionnaire" document (will refer it to as the Scoring Manual forward) Scoring Manual **Table 2**. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores. The 12 sub-scales are: General Health, General Vision, Ocular Pain, Near Activities, Distance Activities, Vision Specific Social Functioning, Vision Specific Mental Health, Vision Specific Role Difficulties, Vision Specific Dependency, Driving, Color Vision and Peripheral Vision. Scoring Manual **Table 3** indicates the items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

Sub-scale Scoring Formula:
Mean = Sum of (Score for each item with a non-missing answer) / Total number of items with non-missing answers

Note: 100 = Best, 0 = Worst possible score.

Composite Score Calculation:
To calculate an overall composite score for the VFQ-25, simply average the vision-targeted subscale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each sub-scale, whereas averaging the items would give more weight to scales with more items.

Descriptive summaries of the observed VFQ-25 scores at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented without imputation. The higher score representing better functioning. Both individual sub-scale score and the overall composite score of VFQ-25 will be summarized. Unscheduled and early termination visits will not be assigned to an unplanned study visit using the analysis windows described in SAP Section 3.2.9 (Table 3). Early termination visit will be summarized separately from the Week 4 summary. Unscheduled visit will not be summarized but will be listed.

In addition to the descriptive summary, the change from baseline at Week 4 in the overall composite score will be analyzed using the two-sample t-test with two-sided type 1 errors of 0.05.

10. SAFETY ANALYSES

The Safety Analysis Set will be used for all safety analyses. All data will be summarized as observed and no data imputation will be performed. No statistical treatment group comparison will be performed, unless otherwise specified.

10.1. Adverse Events

Adverse events will be coded using MedDRA version 19.0. If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest investigator assessment of relationship to study drug will be reported for the applicable summaries.

Treatment-emergent adverse events (TEAE) are defined as events for which the date/time of onset is on or after the date of first dose of study drug. Where an AE with a partially or fully missing start date or time, and it is unclear as to whether the AE is treatment emergent, it will assume treatment emergent unless the CRF question "Did AE onset occur before the first dose of study drug (Yes/No)?" indicates otherwise.

The number and percentage of subjects with adverse events will be summarized by treatment group. System organ class will be sorted alphabetically and preferred term within each SOC will be sorted by overall descending order of frequency. Subjects will be counted only once for each SOC and PT. The percentages will be calculated based on the number of subjects in each treatment group of the Safety analysis set.

Ocular and non-ocular adverse events will also be summarized.

All adverse events (treatment-emergent and non-treatment-emergent) will be listed.

10.1.1. Overall Adverse Events

The number and percentage of subjects with at least one adverse event will be summarized by treatment group for the following:

- Subjects with and without any adverse event
- Total number of adverse event
- Subjects with and without any treatment-emergent adverse event
- Total number of treatment-emergent adverse event
- Subjects with severe treatment-emergent adverse event
- Subjects with any study drug related treatment-emergent adverse event
- Any treatment-emergent adverse event leading to study drug discontinuation / study termination
- Subjects with any treatment-emergent serious adverse event (SAE)
- Subjects with any study drug related treatment-emergent serious adverse event
- Subjects with outcome of death

10.1.2. Incidence of Adverse Events

Subjects with at least one treatment-emergent adverse event will be summarized by SOC, PT, and by treatment group. Treatment-emergent adverse event that treated by rescue medications will also be summarized by SOC, PT, and by treatment group.

Treatment-emergent adverse event summary by PT with descending order of frequency in the Total group will also be presented by treatment group. For PT with $\geq$ 10% occurrence in any treatment group, Fisher's exact test will be used for the treatment group comparison.

10.1.3. Relationship of Adverse Event to Study Drug

Treatment-emergent adverse events with closest relationship to study drug according to the categories specified in the protocol (Not Related, Unlikely Related, Possibly Related, Related and Definitely Related) will be summarized for related and non-related events by SOC, PT, and treatment group.

A study drug related AE is defined as any AE that is assessed by the investigator with the relationships of "Possibly Related", "Related" and "Definitely Related". Study drug non-related AE is defined as any AE that assessed by investigator with the relationships of "Not Related" and "Unlikely Related".

Any treatment-emergent AEs that have a missing relationship will be presented as "Related" in the summary table but will be presented with a missing relationship in the data listing.

10.1.4. Severity of Adverse Event

Treatment-emergent adverse events with maximum investigator-reported severity (mild, moderate, severe) will be summarized by SOC, PT, and treatment group.

Any treatment-emergent AEs that have a missing severity will be presented with the worst severity in the summary table but will be presented with a missing severity in the data listing.

10.1.5. Serious Adverse Events

All treatment-emergent SAEs will be summarized by SOC, PT, and by treatment group.

A summary of study drug related treatment-emergent SAEs by SOC, PT, and treatment group will also be presented.

10.1.6. Adverse Events Leading to Study Drug Discontinuation / Study Termination

All treatment-emergent adverse events that lead to study drug discontinuation or study termination will be summarized by SOC, PT, and by treatment group.

10.2. Ocular Safety Assessments

Specific ocular safety assessments include intraocular ocular pressure, dilated ophthalmoscopy and corneal pachymetry. Specific ocular safety assessments will be summarized on the Safety analysis set by visit for descriptive statistics only. The descriptive statistics summary will be performed separately on the study eye and on the non-study eye where it is applicable. No statistical treatment group comparison will be performed. Unless otherwise noted, unscheduled and early termination visits will be assigned to an unplanned study visit using the analysis windows described in SAP Section 3.2.9 (Table 3) in case the scheduled visit was not performed.

10.2.1. Intraocular Pressure Measurement

The IOP is measured on both eyes (study and non-study eye) in millimeter of mercury (mm Hg) at Day 1 (Screening), Day 4, Week 1, Week 2, Week 3 and Week 4.

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes, without imputation.

10.2.2. Dilated Ophthalmoscopy (Fundus Exam)

The dilated fundus exam is performed on both eyes (study and non-study eye) at Day 1 (Screening), Day 4, Week 1, Week 2, Week 3 and Week 4.

Number and percentage of subjects with observed values of Normal or Abnormal as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes. The percentages will be calculated based on the number of subjects at each visit in each treatment group of the Safety analysis set. The percentages on the shift will be calculated based on the number of subjects with both baseline and post-baseline values.

Descriptive summaries of the observed cup-to-disc ratio at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes, without imputation.

10.2.3. Corneal Pachymetry

Central corneal thickness will be measured by applanation ultrasound pachymetry on both eyes (study and non-study eye) in micrometer (um). For each measurement, the highest and lowest of five consecutive readings will be discarded, and the average of the remaining three will be recorded. Corneal pachymetry will be completed at Day 1 (Screening) only. The average value of the three measurements will be summarized by descriptive statistics for both eyes.

10.3. Laboratory Test and Other Safety Assessments

Laboratory test and other safety assessments will be summarized on the Safety analysis set by visit for descriptive statistics only. No statistical treatment group comparison will be performed. Unscheduled and early termination visits will not be assigned to an unplanned study visit using the analysis windows described in SAP Section 3.2.9 (Table 3). Early termination visit will be summarized separately from the Week 4 summary. Unscheduled visit will not be summarized but will be listed.

10.3.1. Clinical Laboratory Test

Blood samples for the clinical laboratory evaluations will be collected at Day 1 (Screening) and Week 4, and will include:

Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, RBC morphology, white blood cell (WBC) count with differential, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and absolute platelet count.

Serum Chemistry Profile: albumin, alkaline phosphatase, alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO2), chloride, creatinine, creatinine phosphokinase (CPK), glucose, phosphate, potassium, sodium, total protein, and uric acid.

Descriptive summaries of the observed test results at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented without imputation. Number and percentage of subjects with normal range of Low, Normal, High categories as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit. The percentages will be calculated based on the number of subjects at each visit in each treatment group of the Safety analysis set. The percentages on the shift will be calculated based on the number of subjects with both baseline and post-baseline values.

10.3.2. Specific Uveitis Diagnostic Test

During Screening only, the HLA-B27 (Human leukocyte antigen subtypes B*2701-2759) uveitis-specific diagnostic test will be obtained in all subjects experiencing their first episode of anterior uveitis, or in subjects experiencing a repeat episode where prior tests of this nature have not been previously performed. The test results will be listed only.

10.3.3. Urine Pregnancy Test

For women of childbearing potential, a urine pregnancy test will be performed at Day 1 (Screening) and Week 4. The test results will be listed only.

10.3.4. Vital Signs

Vital signs, measured after at least 5 minutes of rest, will include seated systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), and body temperature and will be obtained at Day 1 (Screening) and Week 4.

Blood pressure (BP) results will be recorded in mmHg. HR will be measured in the radial artery in the dominant arm for 30 seconds and will be recorded as beats per minute (bpm). RR will be measured and recorded in breaths per minute. Body temperature (oral measurement) will be measured using a digital thermometer in Fahrenheit (°F).

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented without imputation.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

These following changes are made in the SAP from Protocol Version 4 (June 20, 2018).

Protocol Section 10.5 Analysis Populations defines the ITT population as "The intent-to-treat population (ITT) is the population of all subjects who are randomized into a treatment group." The decision was made by the sponsor that SAP Section 3.1.1 modifies the ITT definition to "the population of all subjects who are randomized into a treatment group and received at least one dose of study drug." All efficacy analyses will use the new ITT definition from the SAP instead of the definition stated in the Protocol.

Protocol Section 10.5 Analysis Populations PP population definition includes a clarification of "Significant protocol violations prior to being rescued may exclude a rescued subject from the PP." It was determined by the sponsor that this clarification to be removed from SAP Section 3.1.2.

12. REFERENCES

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc.* 1958;53:457-481.

APPROVALS: