PROTOCOL ADX-102-UV-005

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

PROTOCOL VERSION AND DATE: VERSION 4.0 20JUN2018
IND NUMBER: 122305

ALDEYRA THERAPEUTICS, INC.
131 HARTWELL AVENUE, SUITE 320
LEXINGTON, MA 02421

[redacted]

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

Investigator Statement

Protocol Number: ADX-102-UV-005

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

I understand that all information concerning ADX-102 in connection with this study and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Study Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this study without approval from the Institutional Review Board/Ethics Committee and I understand that any changes in the protocol must be approved in writing by Aldeyra Therapeutics, Inc., and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

I will use only the informed consent form approved by Aldeyra Therapeutics and by my Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number ADX-102-UV-005, and will conduct the trial in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

_____
Site Name

_____
Site Address

_____
Investigator's Printed Name

_____ _____
Investigator's Signature Date

1 Synopsis

<table>
<tr><td colspan="2">Name of Sponsor Company:
Aldeyra Therapeutics, Inc.</td><td>Drug Under Study:
ADX-102</td></tr>
<tr><td colspan="3">Title of Protocol: 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</td></tr>
<tr><td>Protocol Number:
ADX-102-UV-005</td><td>Phase: 3</td><td>Indication: Anterior Uveitis</td></tr>
<tr><td colspan="3">Primary Objective: To evaluate the efficacy of ADX-102 Ophthalmic Solution on anterior chamber cell count (ACC), in subjects with non-infectious anterior uveitis.

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.</td></tr>
<tr><td colspan="3">Study Endpoints
Signs and symptoms of anterior uveitis which include anterior chamber cell count, anterior chamber flare, limbal injection, hypopyon, peripheral anterior synechiae, keratic precipitates, posterior synechiae, ocular pain, lacrimation, photophobia, blurry vision and visual acuity
Incidence of adverse events (AEs), changes in clinical laboratory values and changes in intraocular pressure (IOP) values
Self-reported visual function with the National Eye Institute Visual Function Questionnaire (VFQ-25)</td></tr>
<tr><td colspan="3">Study Design:
This is a randomized, double-masked, vehicle-controlled Phase 3 clinical trial in which approximately 120 subjects with endogenous non-infectious anterior uveitis will be randomized (1:1) to receive either:

Group 1 ADX-102 Ophthalmic Solution (0.5%)

Group 2 Vehicle of ADX-102 Ophthalmic Solution

Randomization will be stratified based on baseline ACC score. The dosing schedule is summarized in Table 1.

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 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/EOT/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.

At the Screening/Randomization Visit, subjects will provide written informed consent and then study eligibility will be assessed. Eligible subjects will be randomized, dispensed study drug and instructed on dosing as well as on completing the subject dosing diary. Subjects will be randomly assigned treatment as described above.

Treatment Period: Subjects will be instructed to administer study drug and to return to the clinic for Weeks 1 through 4.

Rescue therapy will be available to all subjects that do not demonstrate a clinical response based on predefined rescue criteria. Rescued subjects will complete the Week 4 / End of Treatment/Early Termination (EOT/ET) visit.</td></tr>
</table>

Rescue Therapy

[redacted]

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.

Concomitant Medications

[redacted]

Subject Population: Subjects with endogenous non-infectious anterior uveitis

Number of Subjects: Approximately 120 subjects (male and female)	**Number of Centers:** Approximately 45 centers in the United States
Test Product and Doses: • ADX-102 Ophthalmic Solution (0.5%) • Vehicle of ADX-102 Ophthalmic Solution	**Route of Administration:** Topical ocular solution

Criteria for Inclusion:

All subjects entered into this trial must meet the following criteria:

1. Subject is willing and able to comply with the protocol requirements, has gone through the consent process and has signed an approved informed consent form.
2. Male or female subjects aged ≥ 18 years and ≤ 85 years.
3. Subjects with acute endogenous non-infectious anterior uveitis with onset of symptoms within the previous 2 weeks.* Subjects experiencing a bilateral episode of anterior uveitis may be eligible for study in both eyes. Evaluations for selective infectious etiologies, including but not limited to Syphilis, Tuberculosis (if indicated), Herpes Simplex, Herpes Zoster, CMV, Lyme Disease or other suspected infectious etiology, must be performed during the screening period or within 3 months of randomization.
4. Presence of 6-50 anterior chamber cells within one field of view as measured with a slit lamp microscope (Grade 1+ to Grade 3+, Appendix 1) in the study eye(s).
5. Subjects must have pachymetry corrected IOP <21 mmHg at baseline and non-glaucomatous cups in the opinion of the investigator with non-glaucomatous visual fields if available, and may only administer a maximum of 1 topical medication to control IOP in the study eye.
6. Best corrected visual acuity (BCVA) better than or equal to 35 letters in the study eye and 65 letters in the non-study eye using ETDRS testing. Note: this criteria is also applicable for a subject with bilateral uveitis.
7. Females of childbearing potential must be using or willing to use a medically acceptable method (as defined by the Investigator) of birth control. Women not of childbearing potential are defined as women who are either surgically sterile or postmenopausal. Postmenopausal women are defined as women with cessation of menstruation for 12 consecutive months prior to signing of the informed consent form.

**A history of prior flare-ups or subsequent flare-ups in the non-study eye should not affect eligibility, provided that the subject is deemed capable of administering separate treatments to each eye. For example, if an enrolled subject experiences a flare-up in the non-study eye, the subject should remain in the study, and the non-study eye should receive the standard of care treatment. Likewise, if a potential subject was already receiving standard of care treatment in the non-study eye prior to enrollment, the second eye is eligible for the study and the non-study eye will continue to receive the standard of care.*

Criteria for Exclusion:

Subjects will be excluded from this trial if they meet any of the following criteria:

1. Have severe/serious ocular pathology in the study eye(s) which may preclude study completion, in the judgement of the Investigator.
2. Any medical condition or clinical laboratory test which in the judgment of the Investigator makes the subject unsuitable for the study.
3. Currently or within past 5 years, have a history of malignancy other than successfully treated squamous or basal cell carcinoma of the skin or successfully treated in situ cervical cancer.
4. Active intermediate or posterior uveitis in the study eye(s). Note: a subject with isolated macular edema without evidence of active intermediate or posterior uveitis is eligible for enrolment.
5. Known or observed mild to severe (1-4+) fibrinoid reaction.
6. Previous anterior uveitis episode in the study eye ≤ 4 weeks prior to **Visit 1**.
7. Cataract and intraocular lens (IOL) implantation surgery or corneal transplantation surgery in the study eye(s) within the past 3 months prior to Visit 1, or subjects who may require penetrating intraocular surgery in the study eye(s) during the study.
    - Subjects who are 3 months past uncomplicated cataract and IOL implantation surgery and have shown documented complete clearing of inflammation post-surgery in the study eye(s) are eligible.
    - Any other penetrating intraocular surgery in the study eye(s) within 3 months prior to Visit 1 are eligible, assuming documented complete clearing of inflammation post-surgery in the study eye(s).
8. Oral corticosteroid within the past 14 days prior to **Visit 1**.
9. Topical ocular corticosteroid treatment in the study eye within the past 14 days prior to **Visit 1** (Maximum of 3 doses of topical ocular steroid in the study eye in the 7 days prior to **Visit 1** is permitted).
10. Intravitreal corticosteroid treatment in the study eye within the past 4 months prior to **Visit 1**.
11. Sub-Tenon corticosteroid treatment in the study eye within the past 3 months prior to **Visit 1**.

[redacted]

14. Prescribed nonsteroidal anti-inflammatory agents or immunosuppressive agents, unless the dose has been stable for the last 6 weeks prior to Visit 1 and no change in dosing is anticipated for the duration of the study.
15. Systemic immunomodulatory agents (e.g. azathioprine, methotrexate, mycophenolate mofetil), unless the dose has been stable for the last 6 weeks prior to Visit 1 and no change in dosing is anticipated for the duration of the study.
16. Pregnant or lactating female, or female of childbearing potential and using inadequate birth control methods.
17. Have participated in another investigational device or drug study within 30 days prior to **Visit 1**.
18. Participation in a prior ADX-102 study.

Subjects with test results which do not meet the above inclusion/exclusion criteria may have the underlying test repeated once if it is thought to represent a laboratory error; a reversible, clinically insignificant intermittent condition; or is not consistent with the subject's historical values. If inclusion/exclusion criteria are not met after the repeat test, the subject should be considered a screen failure and should not be enrolled in the study.

Criteria for Evaluation:

Efficacy:

Anterior chamber cell count
Anterior chamber flare
Limbal injection
Hypopyon
Peripheral anterior synechiae
Keratic precipitates
Posterior synechiae
Ocular pain
Photophobia
Lacrimation
Blurry Vision
Visual acuity

Safety:

Adverse events
Changes in clinical laboratory values
Changes in corrected IOP

Statistical Analysis:

Efficacy

The primary efficacy analysis will be time to treatment success, where such time is defined as when a cell count of 0 is achieved and maintained to Week 4 without being rescued at any time prior to Week 4 will be analyzed using the method of Kaplan and Meier. Between group comparisons will be made using the log rank test.

Sample Size Rationale

[redacted]

Safety

Adverse events will be summarized, and event rates will be presented by treatment arm. Any other information collected (such as severity or relationship to study drug) will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

DSMB

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 (AEs). 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.

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

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]	✓	✓	✓	✓	✓	✓	
[redacted]	✓					✓	
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] [redacted]

[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
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). Appendix 2.

2 Table of Contents

List of Tables

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3 List of Abbreviations and Definition of Terms

The following abbreviations and specialist terms are used in this study protocol.

(w/v %)	Weight/volume Concentration
βHCG	Beta human chorionic gonadotropin
ACE	Angiotensin-converting enzyme
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Antineutrophil Cytoplasmic Antibodies
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BCVA	Best-corrected Visual Acuity
BID	Twice a day
BP	Blood pressure
bpm	Beats per minute
CBC	Complete blood count
CDROM	Compact disc read-only optical memory
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract research organization
CS	Clinically significant
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
EOS	End of study
EOT	End of treatment
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FTA-ABS	Fluorescent Treponemal Antibody-absorption
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
HLA-B27	Human leukocyte antigen subtypes B*2701-2759
HR	Heart rate
IB	Investigator's Brochure
IBD	Irritable bowel disease
ICH	International Conference on Harmonization

IOL	Intraocular Lens
IOP	Intraocular pressure
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHA-TP	Micro-hemagglutination assay
mL	milliliter
mmHg	millimeters of mercury
NCS	Not clinically significant
PI	Principal Investigator
PRN	As needed
QD	Once a day
qHS	At bedtime
QID	Four times a day
RPR	Rapid Plasma Reagin
RR	Respiratory rate
SAE	Serious adverse event
SBECD	Sulfobutylether-beta-cyclodextrin
SBP	Systolic blood pressure
SD	Standard deviation
STD	Sexually Transmitted Disease
TEAE	Treatment emergent adverse events
TID	Three times a day
TP-PA	T. pallidum particle agglutination assay
VAS	Visual Analog Scale
[redacted]	[redacted]
WBC	White blood cells
WOCBP	Women of child-bearing potential
EX	example abbreviation

4 Introduction

4.1 Non-infectious Anterior Uveitis

[redacted]

[redacted]

4.1.1 Current Treatments of Non-infectious Anterior Uveitis

[redacted]

4.2 Inflammation & Aldehyde Toxicity

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

4.3 Clinical Studies of ADX-102

[redacted]

[redacted]

[redacted]

4.3.2 Phase 2 Clinical Trial of ADX-102 in Allergic Conjunctivitis Patients

[redacted]

4.3.3 Phase 2 Clinical Trial of ADX-102 in Non-infectious Anterior Uveitis

[redacted]

4.4 Minimization of Risk

[redacted]

[redacted]

[redacted]

4.5 Potential Benefit

[redacted]

4.6 Dose Rationale

[redacted]

Figure 1. 0.5% ^{14}C-ADX-102 Distribution to the Anterior Eye Cup Following Topical Ocular Application of 40 µL in Cynomolgus Macaques

4.7 Conduct of the Study

This study will be conducted according to the protocol and in compliance with current principles of Good Clinical Practices (GCP) and International Conference on Harmonization (ICH). Further information on the ethical conduct of the study is provided in Section 13.

5 Trial Objectives and Purpose

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 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.

5.2 Study Endpoints

- Signs and symptoms of anterior uveitis which include anterior chamber cell count, anterior chamber flare, limbal injection, hypopyon, peripheral anterior synechiae, keratic precipitates, posterior synechiae, ocular pain, lacrimation, photophobia, blurry vision and visual acuity
- Incidence of AEs, changes in clinical laboratory values and changes in IOP values
- Self-reported visual function with the National Eye Institute VFQ-25

5.3 Overall Study Design and Plan: Description

This is a randomized, double-masked, vehicle-controlled Phase 3 clinical trial in which approximately 120 subjects with endogenous non-infectious anterior uveitis will be randomized (1:1) to receive either:

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

Randomization will be stratified based on baseline ACC score. The dosing schedule is summarized in Table 1.

5.3.1 Treatment Arms

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.

5.4 Assessments by Study Visit

5.4.1 Screening Visit/Visit 1

The following procedures and assessments are to be performed during the Screening Visit / Visit 1:

- Explain the purpose of the study to prospective subject and obtain written informed consent.
- Review inclusion/exclusion criteria (See Sections 6.1 and 6.2).
- Obtain ocular scores on the Visual Analog Scale (VAS); ocular pain, blurry vision, photophobia, tearing scores (Section 9.1.6).
- [redacted]
- Document medical history and collect demographic information (See Sections 9.1.1 and 9.1.2).
- Complete uveitis questionnaire.
- Record concomitant medications (ocular and non-ocular) that the subject is taking in the 30 days prior to consent.
- Collect height, weight, and vital signs. (See Sections 9.1.3).
- Collect blood and urine samples for clinical laboratory tests (hematology and chemistry; see Section 9.1.4). The laboratory tests will include a urine βHCG for women of childbearing potential (WOCBP). Any woman with a positive pregnancy test will be ineligible for the study.

    - 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
        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.

- Complete visual acuity examination (Section 9.1.7).
- Assess IOP (Section 9.1.8).
- Perform slit lamp examination (Section 9.1.9).
- Perform fundus exam (Section 9.1.10).
- Perform corneal pachymetry (Section 9.1.11).
- Once deemed eligible by the investigator, randomize subject through Interactive Web Response System (IWRS). Note: A subject may be rescreened only once.
- Review study requirements and instructions on dosing and completing subject dosing diary.
- Dispense study drug as assigned.
- Dispense subject dosing diary.
- Confirm day and time of Visit 2 (Day 4).
- Assess for AEs

5.4.2 Visit 2/Day 4 (Day 4 +/- 1 Day)

The following procedures and assessments are to be performed during the Visit 2 / Day4:

- Assess for AEs and use of concomitant medications.
- Obtain ocular scores; ocular pain, blurry vision, photophobia, tearing scores (Section 9.1.6).
- Complete visual acuity examination (Section 9.1.7).
- Assess IOP (Section 9.1.8).
- Perform slit lamp examination (Section 9.1.9).
- Perform fundus exam (Section 9.1.10).
- Confirm day and time of Visit 3.

5.4.3 Visits 3 through 5

Visit 3 through 5, occur Week 1 (Day 8 +/- 1 day), Week 2 (Day 15+/- 2 days), and Week 3 (Day 22 +/- 2 days).

The following procedures and assessments are to be performed during the Visit 3 through 5:

- Collect subject dosing diary and review for dosing compliance. Remind subjects of requirements and instructions on dosing and completing subject dosing diary.
- Collect all used and unused study drug.
- Obtain ocular scores; ocular pain, blurry vision, photophobia, tearing scores (Section 9.1.6)
- Assess for AEs and use of concomitant medications.
- Complete visual acuity examination (Section 9.1.7).
- Assess IOP (Section 9.1.8).
- Perform slit lamp examination (Section 9.1.9).
- Perform fundus exam (Section 9.1.10).
- Dispense a new subject dosing diary.
- Dispense study drug as assigned.
- Confirm day and time of next visit.

5.4.4 Visit 6/End of Treatment (EOT) or Early Termination (ET) Visit

Visit 6/EOT is to occur at Week 4 (Day 29 +/- 3 days). Subjects that terminate the study early for any reason should undergo the Visit 6 assessments as an ET visit.

Once it is determined that rescue therapy is needed the subject should be considered an ET and the below assessments should be completed.

The following procedures and assessments are to be performed during the Visit 6/EOT/ET:

- Collect dosing diary and review for completion and dosing compliance.
- Collect all used and unused study drug.
- Obtain ocular scores; ocular pain, blurry vision, photophobia, tearing scores (Section 9.1.6).
- Have subject complete VFQ-25 (Section 9.1.5).
- Assess for AEs and use of concomitant medications.
- Collect Vital Signs (Section 9.1.3).
- Collect blood samples for clinical laboratory tests (hematology and chemistry; see Section 9.1.4).
- Complete visual acuity examination (Section 9.1.7).
- Assess IOP (Section 9.1.8).
- Perform slit lamp examination (Section 9.1.9).
- Perform fundus exam (Section 9.1.10).

- For WOCBP a urine pregnancy test will be performed.
- Confirm day and time for End of Study telephone call.

5.4.5 Visit 7/End of Study (EOS) Visit

Visit 7/EOS is to occur at Week 5 (Day 36 +/- 3 days).

The following will be collected via a follow up telephone call:

- Assess for AEs and use of concomitant medications.
- Remind subjects to report any new SAEs/AEs for up to 30 days after the last dose.

6 Selection and Withdrawal of Subjects

6.1 Inclusion Criteria

All subjects entered into this trial must meet the following criteria:

1. Subject is willing and able to comply with the protocol requirements, has gone through the consent process and has signed an approved informed consent form.
2. Male or female subjects aged ≥ 18 years and ≤ 85 years.
3. Subjects with acute endogenous non-infectious anterior uveitis with onset of symptoms within the previous 2 weeks.* Subjects experiencing a bilateral episode of anterior uveitis may be eligible for study in both eyes. Evaluations for selective infectious etiologies, including but not limited to Syphilis, Tuberculosis (if indicated), Herpes Simplex, Herpes Zoster, CMV, Lyme Disease or other suspected infectious etiology, must be performed during the screening period or within 3 months of randomization.
4. Presence of 6-50 anterior chamber cells within one field of view as measured with a slit lamp microscope (Grade 1+ to Grade 3+, Appendix 1) in the study eye(s).
5. Subjects must have pachymetry corrected IOP <21 mmHg at baseline and non-glaucomatous cups in the opinion of the investigator with non-glaucomatous visual fields if available, and may only administer a maximum of 1 topical medication to control IOP in the study eye.
6. Best corrected visual acuity (BCVA) better than or equal to 35 letters in the study eye and 65 letters in the non-study eye using ETDRS testing. Note: this criteria is also applicable for a subject with bilateral uveitis.
7. Females of childbearing potential must be using or willing to use a medically acceptable method (as defined by the Investigator) of birth control. Women not of childbearing potential are defined as women who are either surgically sterile or postmenopausal.

Postmenopausal women are defined as women with cessation of menstruation for 12 consecutive months prior to signing of the informed consent form.

**A history of prior flare-ups or subsequent flare-ups in the non-study eye should not affect eligibility, provided that the subject is deemed capable of administering separate treatments to each eye. For example, if an enrolled subject experiences a flare-up in the non-study eye, the subject should remain in the study, and the non-study eye should receive the standard of care treatment. Likewise, if a potential subject was already receiving standard of care treatment in the non-study eye prior to enrollment, the second eye is eligible for the study and the non-study eye will continue to receive the standard of care.*

6.2 Exclusion Criteria

Subjects will be excluded from this trial if they meet any of the following criteria:

1. Have severe/serious ocular pathology in the study eye(s) which may preclude study completion, in the judgement of the Investigator.
2. Any medical condition or clinical laboratory test which in the judgment of the Investigator makes the subject unsuitable for the study.
3. Currently or within past 5 years, have a history of malignancy other than successfully treated squamous or basal cell carcinoma of the skin or successfully treated in situ cervical cancer.
4. Active intermediate or posterior uveitis in the study eye(s). Note: a subject with isolated macular edema without evidence of active intermediate or posterior uveitis is eligible for enrolment.
5. Known or observed mild to severe (1-4+) fibrinoid reaction.
6. Previous anterior uveitis episode in the study eye ≤ 4 weeks prior to **Visit 1**.
7. Cataract and intraocular lens (IOL) implantation surgery or corneal transplantation in the study eye(s) within the past 3 months prior to Visit 1, or subjects who may require penetrating intraocular surgery in the study eye(s) during the study.

    - Subjects who are 3 months past uncomplicated cataract and IOL implantation surgery and have shown documented complete clearing of inflammation post-surgery in the study eye(s) are eligible.
    - Any other penetrating intraocular surgery in the study eye(s) within 3 months prior to Visit 1 are eligible, assuming documented complete clearing of inflammation post-surgery in the study eye(s).

8. Oral corticosteroid within the past 14 days prior to **Visit 1**.

9. Topical ocular corticosteroid treatment in the study eye within the past 14 days prior to **Visit 1** (Maximum of 3 doses of topical ocular steroid in the study eye in the 7 days prior to **Visit 1** is permitted).
10. Intravitreal corticosteroid treatment in the study eye within the past 4 months prior to **Visit 1**.
11. Sub-Tenon corticosteroid treatment in the study eye within the past 3 months prior to **Visit 1**.

[redacted]

14. Prescribed nonsteroidal anti-inflammatory agents or immunosuppressive agents, unless the dose has been stable for the last 6 weeks prior to Visit 1 and no change in dosing is anticipated for the duration of the study.
15. Systemic immunomodulatory agents (e.g. azathioprine, methotrexate, mycophenolate mofetil), unless the dose has been stable for the last 6 weeks prior to Visit 1 and no change in dosing is anticipated for the duration of the study.
16. Pregnant or lactating female, or female of childbearing potential and using inadequate birth control methods.
17. Have participated in another investigational device or drug study within 30 days prior to **Visit 1**.
18. Participation in a prior ADX-102 study.

Subjects with test results which do not meet the above inclusion/exclusion criteria may have the underlying test repeated once if it is thought to represent a laboratory error; a reversible, clinically insignificant intermittent condition; or is not consistent with the subject's historical values. If inclusion/exclusion criteria are not met after the repeat test, the subject should be considered a screen failure and should not be enrolled in the study.

6.3 Protocol Exceptions and Deviations

Exceptions to the above eligibility criteria will not be granted. It is expected that subjects will meet all eligibility criteria. Departures from the protocol should be avoided, unless required for the safety of the subject. Protocol deviations will be documented by the study monitor and will be included in the final clinical study report. Protocol deviations should be submitted to the Institutional Review Board (IRB), in accordance with the site's IRB requirements.

6.4 Subject Withdrawal Criteria

Subjects may voluntarily withdraw from the study, or be removed from the study at the discretion of the Investigator or Sponsor, at any time. The Investigator may withdraw a subject

at any time if it is determined that continuing in the study would result in a significant safety risk to the subject.

If such withdrawal occurs, or if the subject fails to return for visits, the Investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study records.

Premature withdrawal may occur for any of the following reasons:

- Rescue therapy
- Non-compliance with the protocol requirements
- Death
- Adverse event (AE)
- Subject request
- Investigator request
- Sponsor request

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents all steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.
All subjects prematurely discontinuing from the trial (prior to **Visit 6**), regardless of cause, should be seen as soon as possible for **Visit 6/EOT/ET** assessments (Section 5.4.4).

Subjects who are withdrawn from the study for any reason will not be replaced.

7 Treatment of Subjects

7.1 Subject Numbering

Each subject will be assigned a unique subject number. If a subject fails to be randomized, the reason for not being randomized should be documented in the source documents and case report forms (CRFs). The subject will be considered a screen failure.

7.2 Description of Study Drug

For study purposes ADX-102 and vehicle of ADX-102 ophthalmic solution are both referred to as study drug.

7.3 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 CRFs.

[redacted]

7.3.1 Rescue Therapy

[redacted]

[redacted]

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.

7.4 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 part of exclusion criteria (See Section 6.2)

7.5 Treatment Compliance

Study drug will be taken by the subject at home throughout the study. Subjects will be dispensed study drug at Visit 1, Visit 3, Visit 4 and Visit 5. Information on the time and date of each dose will be recorded by the subject in the dosing diary. Subjects will be instructed to return all used and unused study drug and the dosing diary to the clinic at Visits 3 through 6.

7.6 Randomization and Masking

Subjects will be randomized through a central randomization process by IWRS during **Screening/Visit 1**. A randomization number will be assigned for dosing.
ADX-102 and/or vehicle of ADX-102 ophthalmic solution will be provided in subject packs masked to the subject, Investigator and study staff.

7.7 Unmasking Procedures

7.7.1 Emergency Unmasking of Treatment Assignment

Emergency unmasking should only be performed when necessary in order to treat the subject. There is no known antidote to ADX-102, so symptomatic and supportive management of any suspected and treatment related adverse event, if necessary, is clinically indicated.

Unmasking will result in the subject being discontinued from the study, irrespective of whether the Investigator ultimately agrees with the event being related to study drug (ADX-102). Most

often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. The Investigator will have the ability to break the mask for any subject through the centralized randomization system (IWRS). However, the Investigator should make every effort to contact the Sponsor's medical monitor or their designee to discuss the subject's emergency situation and the need to unmask prior to unmasking any subject, but must contact the Sponsor or designee within one working day after the unmasking occurs. The mask may be broken in the case of a pregnancy should the subject desire this information. Any subject for whom the mask is broken is to be discontinued from future study treatment. The date, time and reason for breaking the mask are to be recorded in the subject's source documents.

7.7.2 Unmasking for Regulatory Authorities

In cases where unmasking is required for the purposes of reporting expedited safety events to country specific regulatory agencies or IRBs, the unmasking will be performed by an authorized member of the team. A masked version of any documents to be submitted to the authorities will be shared as appropriate with study staff and site personnel. Only the authorized person(s) within the Pharmacovigilance and Regulatory Affairs will have access to the unmasked version of any documents. The procedures for requesting and obtaining unmasked information and for maintaining the integrity of the data and clinical trial are outlined in safety management plan.

8 Study Drug Materials and Management

8.1 Study Drug

[redacted]

More information on ADX-102 can be found in the Investigator's Brochure.

8.2 Study Drug Packaging and Labeling

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

8.3 Study Drug Storage

[redacted]

8.4 Study Drug Preparation

No preparation will be required.

8.5 Administration

Study drug will be self-administered by the subject (or care giver). Subjects will begin with one drop in the study eye 8 times per day and then taper weekly and as described in Table 1.

8.6 Study Drug Accountability

Under supervision of the Investigator, the study pharmacist or designee will be responsible for drug accountability. The pharmacist or designee will keep an accurate inventory of test article(s) and dispensing using a drug dispensing log. The pharmacist or designee must keep study drug inventory available for inspection by the Sponsor, an agent for the Sponsor, and regulatory authorities.

Subjects will be required to return all used and unused study drug to the pharmacist or designee. If any unused material is remaining at the site at study completion, the pharmacy will be instructed how to dispose of or return the material to the Sponsor after the Sponsor's representative has performed accountability. The Sponsor's representative will complete authorization forms for disposal or return with the responsible pharmacist or designee. Copies of these forms should be included with the returned material. The original form should be maintained in the pharmacy within the site study files.

9 Treatment Assessments

9.1 Efficacy and Safety Parameters

Standardization of data capture is provided in detail in the remainder of this section. Assessments should be performed as indicated.

9.1.1 Medical History and Concomitant Medications

[redacted]

Concomitant medications used in the 30 days prior to consent to treat any medical conditions will be recorded on the CRF.

A standard uveitis questionnaire will be completed at **Screening (Visit 1)**.

9.1.2 Demographics

During **Screening (Visit 1)**, age, gender, race and ethnicity will be recorded on the CRF.

9.1.3 Height, Weight and Vital Signs

Height and weight will be measured at **Screening (Visit 1)**.

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 **Screening (Visit 1)** and **Week 4 (Visit 6-EOT/ET)**. All vital

sign measurements will be performed by appropriately qualified and authorized study personnel, using appropriate equipment.

Blood pressure (BP) will be measured after at least 5 minutes of rest by using an automated or manual sphygmomanometer. The same method should be used for an individual subject throughout the study. The results will be recorded in millimeters of mercury (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.

9.1.4 Clinical Laboratory

Samples of blood and urine will be collected for clinical laboratory tests. Tests will be conducted as designated below:

9.1.4.1 Clinical Laboratory Tests Conducted

Clinical laboratory evaluations will include:

At **Screening (Visit 1)** and **Week 4 (Visit 6-EOT/ET)** - 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.

At **Screening (Visit 1)** and **Week 4 (Visit 6-EOT/ET)** - 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.

At **Screening (Visit 1)** and **Week 4 (Visit 6-EOT/ET)** - For WOCBP a urine pregnancy test will be performed and must be negative for subjects to be enrolled.

9.1.4.2 Abnormal and Clinically Significant Results

The Investigator must categorize all abnormal hematology and chemistry laboratory values as either clinically significant (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in laboratory parameters, which has medical consequences that result in an alteration in the subject's medical care. In case of CS laboratory results, the Investigator will

continue to monitor the subject with additional laboratory assessments until (1) values have reached normal range and/or baseline levels, or (2) the Investigator has judged that the abnormal values are not related to the administration of study drug or other protocol-specific procedures.

9.1.5 [redacted]

[redacted]

[redacted]

[redacted]

9.1.6 Ocular Scores

Ocular pain, blurred vision, photophobia and tearing will each be measured using a visual analogue scale (VAS). The VAS is a continuous 100 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 on the scale. The subject's completed VAS will become the source document and the response, measured in mm from the left, will be transcribed into the CRF.

The VAS will be administered **at Screening, Day 4**, **Week 1**, **Week 2**, **Week 3** and **Week 4**.

9.1.7 Visual Acuity

Visual acuity will be measured with spectacle or pinhole correction at each visit. The subject will be asked to read a standardized eye chart (ETDRS). Detailed instructions on Visual Acuity Testing are provided in the Study Manual. Subjects should be encouraged to make an effort to read as many letters as possible on the chart. Distance visual acuity only will be measured. The right eye should be tested first. Visual acuity will be measured at **Screening, Day 4**, **Week 1**, **Week 2**, **Week 3** and **Week 4**.

9.1.8 IOP Measurements

IOP measurements will be taken using an accepted tonometry method, which includes pneumatic tonometry, Tono-Pen applanation tonometry or Goldmann applanation tomnometry – depending on the preferred method at each site. *Once a subject has enrolled in the study, the same tonometry method will be used for that subject throughout the duration of the study*. IOP will be measured at **Screening**, **Day 4**, **Week 1**, **Week 2**, **Week 3** and **Week 4**.

9.1.9 Slit Lamp Exam

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice. The clinician will examine and grade the eyelid and then examine the conjunctiva, cornea and anterior chamber of the eye with the aid of a slit lamp. Fluorescein dye will be instilled into the ocular cul-de-sac to facilitate this examination. The subject will be seated during the examination. See Appendix 1 for grading scales. ACC grade will be determined and for Grade 1+ and lower only, a numerical cell count will be obtained. Slit lamp examination will be completed at **Screening**, **Day 4**, **Week 1**, **Week 2**, **Week 3** and **Week 4**.

9.1.10 Fundus Exam

A dilated funduscopic exam will be performed to evaluate the vitreous, retina, choroid and optic nerve. Fundus findings will be noted, described and graded as normal or abnormal. Qualitative descriptions will be provided for any abnormal findings. A fundus examination will be completed at **Screening**, **Day 4**, **Week 1**, **Week 2**, **Week 3** and **Week 4**.

9.1.11 Corneal Pachymetry

Central corneal thickness will be measured by applanation ultrasound pachymetry. For each measurement the highest and lowest of five consecutive readings will be discarded, and the average of the remaining three will be recorded. In cases where a pachymeter is used that

calculates an average central corneal thickness from five or more measurements with a single touch to the eye, this average measurement may be used for the purposes of calculating the pachymetry corrected IOP. Corneal pachymetry will be completed at **Screening**.

9.1.12 Dosing Instructions

All subjects will receive written dosing instructions about how to properly administer their eye drops along with a printed dosing diary in which to document each dose. At Visit 1, the staff will review these materials with the subject and confirm that the subject understands the instructions on how to dose and how to complete the diary. Subjects will be instructed to bring the dosing diary with them to Visit 3 through Visit 6 to be reviewed by the site staff. The site staff will ensure compliance and review/ remind the subject on instructions as needed.

Missed Doses: If subjects forget to take a dose at the scheduled time, they should take that dose as soon as they remember and record the time of dosing in the dosing diary.

Exceptions: Subjects should not take a "make-up" dose within one hour of another scheduled dose. Instead they should take the next scheduled dose and note the missed dose on the dosing diary.

9.2 Adverse Events and Serious Adverse Events

9.2.1 Adverse Events

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a study drug, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to the study drug. AEs will be collected from the time the subject signs the informed consent form through 30 days after the last study drug administration.

Abnormal laboratory and other abnormal investigational findings (i.e., physical exam) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the screening period that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are not to be considered AEs.

All AEs must be recorded in the site's study records and the AE CRF with the following information:

1. Relationship to Study Drug: The Investigator must assess whether they consider an AE to be drug-related. In assessing this relationship, the Investigator must use information about the drug as outlined in the Investigator's Brochure (IB), the subject's pre-existent medical conditions/concurrent medication, and chronology of the event relative to drug administration.

   The following definitions will be used:

   - **Definitely or possibly related** applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered by the Investigator (or other qualified physician) to have at least a possible relationship to study drug.

   - **Unlikely or not related** applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered by the Investigator (or other qualified physician) to have no relationship, or an unlikely possibility of a relationship, to study drug.

2. Event Severity: The Investigator will be asked to use their medical judgment to assess the severity of the AE.

The following are guidelines to be used by the Investigator to judge the event severity of an AE:

[redacted]

- Life Threatening

3. Duration: Start and end dates and times, or if continuing.
4. Frequency: whether the event is a single episode, recurrent or continuous.
5. Action taken.
6. Whether it constitutes a SAE, per definition below.
7. Outcome: resolved, resolved/ with sequelae, continuing, death, or unknown (only for subjects that are lost to follow-up).

The Investigator (or designee) should attempt to establish a diagnosis of the AE based on signs, symptoms and/or other clinical information. In such cases, the diagnosis, and not the individual signs/symptoms or laboratory abnormalities, should be documented in the subject's source documentation and the CRF unless the etiology of the event is unknown. An assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to study drug, the interventions required to treat it and the outcome.

9.2.2 Treatment Emergent Adverse Events (TEAE)

A TEAE will be an AE that occurred during the study after the first dose of study drug or that was present prior to dosing and exacerbates after the first dose of study drug.

9.2.3 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death: This includes death unrelated to the study drug (e.g. car accident). If a subject dies during the study and an autopsy is performed, autopsy results will become part of the subject's study chart and a copy should be sent to the Sponsor.
- Life-threatening experience. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Required or prolonged inpatient hospitalization: Exceptions will be hospitalizations for a) elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug or b) treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission
- Persistent or significant disability/incapacity
- Congenital anomaly
- Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered a SAE when, based upon medical judgment,

they may jeopardize the patient and may require intervention to prevent one of the outcomes listed above.

9.2.4 Unexpected Adverse Event

An unexpected adverse event is defined as an AE, the nature or severity of which is not consistent with the information in the Investigator's Brochure for ADX-102.

9.3 Reporting Serious Adverse Events

The Investigator is responsible for reporting all SAEs, **regardless of causality**, to the Sponsor or their designated representative by phone or fax (or email) within 24 hours of learning of the occurrence. The reporting timeframe starts when the subject signs the informed consent form through 30 days after the last study drug administration. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. These preliminary reports will be followed by detailed descriptions that will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

Complications or progression of an initial SAE must be reported as a follow-up SAE Report to the original SAE, regardless of when the follow-up information is received by the Investigator. A follow-up SAE Report must be submitted within 24 hours of the Investigator receiving the follow up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new SAE.

In the event of a SAE, the investigator must immediately notify the **appropriate contact in the Study Manual**.

The procedures for reporting SAEs are as follows:

- Complete the "Serious Adverse Event Report Form". The Investigator may contact Pharmacovigilance via the telephone hotline for assistance with SAE reporting.
- Fax or email the SAE Form to the attention of Pharmacovigilance within 24 hours of the Investigator's knowledge of the event.

The original copy of the SAE Report Form and the fax confirmation sheet (or email) must be kept with the source documentation at the study site.

Follow-up information should be communicated the same way, using a new SAE Report Form stating that it is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE was not previously documented in the Investigator's Brochure and is thought to be related to study drug, the Sponsor or their designee may urgently require further information from the Investigator for regulatory authority reporting. The Sponsor may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported.

The Investigator and study personnel should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include clinical laboratory tests not specified in the protocol, histopathologic examinations, or consultations with specialists. The Sponsor or their designee may also request the Investigator to conduct supplemental assessments.

The Investigator should notify Pharmacovigilance of any SAE occurring after a subject has withdrawn from the study when such a SAE occurs within 30 days of the last dose of study drug and may reasonably be related to the study drug.

9.4 Follow-up of Adverse Events

All AEs will be followed until clinical database lock (or stabilization/resolution if it occurs before database lock). All SAEs will undergo active follow-up until resolved or the event becomes chronic or stable. Follow up data for SAEs obtained after clinical database lock will be incorporated into the safety database.

9.5 Reporting Safety Information to the IRB

The Investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to the IRB.

The Investigator must promptly report to his or her IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all serious adverse events reasonably or possibly associated with the use of study drug. It is recommended that all SAEs occurring at a site, regardless of causality, be reported to the site's IRB in accordance with the IRB requirements.

ADX-102 has been filed under an IND application with the US FDA. An SAE may require safety reports to be filed to regulatory agencies if the SAE is related to the study drug and is unexpected based upon the current Investigator's Brochure. In this case, the Investigator will receive a copy of the safety report as submitted to the regulatory agencies. The Investigator is responsible for submitting the safety report (initial and follow up) or other safety information (e.g., revised Investigator's Brochure) to the IRB in accordance with the IRB requirements and maintain a copy in their files.

9.6 Pregnancies

To ensure subject safety, each pregnancy in a subject on study drug must be reported to Pharmacovigilance within 24 hours of learning of its occurrence. Subjects who become pregnant will be withdrawn from the study. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a subject's source documents and a Pregnancy Notification and Outcome Form and reported by the Investigator to Pharmacovigilance using the same procedure for reporting SAEs detailed in Section 9.3. A pregnancy, by itself, is not a SAE. Pregnancy follow-up should also be recorded and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any pregnancy-related SAE (e.g. spontaneous abortion) or any other SAE experienced during pregnancy must be recorded on a separate SAE Report Form and reported per SAE reporting procedures in Section 9.3.

10 Statistics

10.1 Sample Size

[redacted]

10.2 Randomization

This is a multicenter, randomized, double masked, parallel group study.

[redacted]

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.

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

10.3 Data Safety Monitoring Board (DSMB)

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 (AEs). 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.

10.4 Analysis

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.

10.5 Analysis Populations

The statistical analysis will be based on the analysis populations as defined below

Safety population The safety population 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

ITT population The intent-to-treat population (ITT) is the population of all subjects who are randomized into a treatment group. 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.

PP population The per protocol (PP) population 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. Significant protocol violations prior to being rescued may exclude a rescued subject from the PP. Subjects in this population will be analyzed according to the treatment they receive.

10.6 Accountability and Background Characteristics

10.6.1 Enrollment and Disposition

The number of subjects enrolled will be presented by treatment group. The primary reasons for discontinuation will be summarized by treatment and based on the ITT population. The number and percentage of subjects with protocol deviations leading to exclusion from the PP population will be presented by reason for exclusion, stratified by treatment. All deviations and rescued subjects will be listed.

10.6.2 Subject Characteristics

Subject characteristics will be obtained at the **Screening/Visit 1** prior to randomization and will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous measures (sample size, mean, standard deviation, median, minimum, maximum) and for categorical measures (sample size, frequency and percentages).

Subject characteristics will be summarized on all study populations.

10.6.3 Treatment Compliance

Treatment compliance will be assessed in terms of the actual dose. Treatment compliance will be used to characterize the subjects and determine clinical evaluability for some analyses. Treatment compliance will be summarized within each treatment group by means of descriptive statistics (n, mean, SD, median, minimum and maximum).

10.7 Efficacy Analyses

All of the efficacy analyses will be performed on the ITT population. The PP population will be used as supportive analyses.

[redacted]

10.8 Safety Analyses

Values for all safety variables will be listed by subject and time point.

Where appropriate, safety variables will be summarized by using descriptive statistics, separated by treatment arm, and time of assessment. Descriptive statistics for quantitative variables will

include: n, mean, median, minimum, maximum, and standard deviation. Descriptive statistics for qualitative variables will include frequency counts and percentages.

10.8.1 Adverse Events

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, and all summary tables for AEs will be organized by these categories. Frequency counts and percentages will be presented for subjects with AEs within each system organ class and preferred term, separated by treatment arm. Both subjects ever experiencing an event as well as total events will be presented. Descriptive statistics will also be presented for AE relationship and AE severity. If multiple intensities are reported for a given AE for a subject, the most severe intensity will be counted.

SAEs and TEAEs that resulted in termination of the study drug and withdrawal from the study will be presented.

11 Direct Access to Source Data/Documents

11.1 Study Monitoring

The investigator will allow the Sponsor or a designee to:

- Inspect the site, the facilities, and the material used for the study;
- Meet all members of the team involved in the study;
- Consult all the documents relevant to the study;
- Check that the CRFs have been correctly completed;
- Have direct access to source documents for comparison of data therein with the data in the CRFs;
- Check that AEs have been documented; and
- Verify that the study is carried out in compliance with the protocol.

This study will be monitored at regular intervals, by agreement of the Investigator.
All information dealt with during these visits will be treated as strictly confidential.

The Investigator will provide the sponsor with the following:

- Progress reports at regular intervals
- Adequately completed CRFs

11.2 Data Collection

For each subject, CRF and corresponding source records will be maintained at each clinical site. Case report forms should be completed in a timely manner, and every effort should be made to have forms completed and current in anticipation of a visit by the Sponsor's monitor. Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 14.

11.3 Audits and Inspections

The Investigator may be informed that an audit will be carried out, at the request of the Sponsor, before, during, or after the study.

The Investigator will be informed that the Regulatory Agencies may also carry out an inspection. In this case, the Investigator must inform the sponsor as soon as he receives the notification of inspection.

The Investigator must allow the representatives of the Regulatory Agencies and persons responsible for the audit to:

- Inspect the site, facilities, and material used for the study;
- Meet all members of his team involved in the study;
- Have direct access to study data and source documents; and
- Consult all the documents relevant to the study.

12 Quality Control and Quality Assurance

The Investigator or the appointed persons agree to complete the subject's CRF. Only the Investigator or appointed persons in his/her team may fill out or correct the CRFs.

The Sponsor or their designee will review the CRFs entered by investigational site staff for completeness and accuracy and instruct the investigational site staff to make any required corrections or additions. Queries will be sent to the investigational site and designated investigational site staff will be required to respond to the query and edit data as necessary.

All corrections and alterations of data on the CRFs must be made by the Investigator or by the appointed persons as instructed in the CRF guidelines. If corrections or alterations are required of paper source documents, corrections may be made in the following manner: strike through the datum to be corrected using a single line so that the original remains legible; correction fluid

must never be used. The correction should be written to the side or above the original entry and must be initialed and dated by the Investigator or designee.

It is the responsibility of the monitor to make certain that all data are completed on the CRFs. At the end of each study period, the Investigator must sign and date the CRF to attest to the:

- Authenticity of the data collected in the CRF, and
- Coherence between the data in the CRF and those in the source documents.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and study drug dispensation will be tracked using a centralized randomization process. The system will be supplied by a vendor managing the database.

After the above actions have been completed and the database has been declared to be complete and accurate, it will be locked for data analysis. Any changes to the database after that time can only be made with the approval of Aldeyra Therapeutics, Inc.

The Investigator will enter all subjects screened for study participation and the reason why individual subjects did not enter the study into the CRF. The Investigator must submit to the Sponsor or its representatives a completed CRF for each subject who receives any study drug.

If computerized medical files are used, and if the computer system allows, no change made in the medical files by the Investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information. The Investigator will save data at regular intervals.

The Investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

13 Ethics

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local

regulations (US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.1 Ethics Review

13.1.1 IRB Opinion

Before initiation of the study, the Investigator must obtain approval or favorable opinion of the study, informed consent, privacy authorization, and any advertisement for subject recruitment from a properly constituted IRB before study start. A signed and dated statement that the protocol and informed consent and advertisement (as applicable) have been approved by the IRB must be given to Aldeyra Therapeutics, Inc. or its designated representative(s) before study initiation. Prior to study start, the Investigator is required to sign the Investigator statement page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol.

The Investigator is responsible for obtaining continued review of the study at intervals not exceeding one year or otherwise specified by the IRB. The Investigator must supply Aldeyra or its designated representative(s) with written documentation of continued review of the clinical study.

The Investigator must promptly inform their IRB of all SAEs or other safety information reported from Sponsor or its designated representatives.

13.2 Written Informed Consent

Subjects will be informed of the nature of the study, its aim, its possible risks and restrictions, its duration and the fee, if any, they will receive. The protocol will be explained during a meeting prior to the study and each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time. At this meeting, the informed consent form will be given to each subject. The subject should read the form and obtain answers to any questions prior to signing and dating the informed consent form. The process of obtaining informed consent should be documented in the subject source documents. Each Investigator must retain the original signed and dated informed consent form. A copy of the signed and dated informed consent form will be given to the subject. No subject can enter the study, or have study specific assessments performed before his/her informed consent has been obtained.

Aldeyra Therapeutics, Inc. or its designated representative(s) will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline

and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Aldeyra or its designated representative(s) before submission to the IRB, and a copy of the approved version must be provided to Aldeyra or its designated representative(s) after IRB approval.

13.3 Amendments to the Protocol

To alter the protocol, amendments must be written by Aldeyra Therapeutics, Inc., and approvals must be received from all parties that approved the original protocol (IRB, and if applicable, the local regulatory authorities) before implementation. However, in cases where an amendment is required for subject safety, an amendment may be implemented prior to IRB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol.

Aldeyra may make administrative changes (i.e., changes that do not significantly affect subject safety, the study's scope or scientific quality) without a formal protocol amendment.

13.4 Discontinuation of the Study

Aldeyra Therapeutics, Inc. reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

13.5 Study Drug Supply, Storage and Tracking

[redacted]

The pharmacist or designee will keep an accurate accounting of all study drug dispensed, destroyed or returned. Monitoring of drug accountability will be performed by the monitor during site visits and at the completion of the trial.

13.6 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from Aldeyra Therapeutics, Inc. Subject confidentiality will be strictly maintained to the extent possible under the law. Subject names must not be disclosed. Subjects will be identified on the CRFs and other documents submitted to Aldeyra, or its designated representative, by their initials and/or assigned subject number. Documents that identify the subject (e.g., the signed informed consent form) should not be submitted to Aldeyra or its designated representative, and must be maintained in confidence by the Investigator.

13.7 Publication Policy

As is customary for multicenter trials, publication by individual study sites or Investigator/Institution will not be allowed without the explicit written permission of the Sponsor. The Sponsor will determine authorship of the principal study manuscript(s) in conjunction with the Investigators, in abiding with current guidelines and requirements of medical journals. For such manuscript(s), masthead roles for Investigators will be determined based on subject enrollment and scientific contributions to the Study.

14 Retention of Records

Essential documents, as listed below, must be retained by the Investigator for as long as required by national and international regulations. The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required. The Investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include:

- IRB approvals for the study protocol and all amendments
- All source documents and laboratory records
- CRF copies (electronic copies on a CDROM)
- Subjects' informed consent forms (with study number and title of trial)
- FDA form 1572
- Any other pertinent study document

15 References

Balci M, Sahin S, Mutlu FM, et al. Investigation of oxidative stress in pterygium tissue. Mol Vis. 2011 Feb 9; 17: 443-7.

Boyer N, Higbee D, Currin M, Blakeley L, Chen C, Ablonczy Z, Crouch R, and Koutalos Y. Lipofuscin and N-Retinylidene-N -Retinylethanolamine (A2E) accumulate in retinal pigment epithelium in absence of light exposure: Their origin is 11-cis-retinal. J. Biol. Chem. 2012: 287:22276-22286.

Cejková J, Ardan T, Jirsová K, et al. The role of conjunctival epithelial cell xanthine oxidoreductase/xanthine oxidase in oxidative reactions on the ocular surface of dry eye patients with Sjögren's syndrome. Histol Histopathol. 2007 Sep; 22(9):997-1003.

Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic Biol Med. 1991: 11(1):81-128.

Maeda A, Golczak M, Chen Y et al. Primary amines protect against retinal degeneration in mouse models of retinopathies. Nat Chem Biol. 2011 Dec 25; 8(2): 170-8.

Natkunarajah M, S Kaptoge S, and Edelsten C. Risks of relapse in patients with acute anterior uveitis. Br J Ophthalmol. 2007: 91(3): 330-334.

O'Brien PJ, Siraki AG, Shangari N. Aldehyde sources, metabolism, molecular toxicity mechanisms, and possible effects on human health. Crit Rev Toxicol. 2005: 35(7):609-62.

Sandikci R, Türkmen S, Güvenen, et al. Lipid peroxidation and antioxidant defence system in patients with active or inactive Behçet's disease. Acta Derm Venereol. 2003; 83(5): 342-6.

Turk A, Aykut M, Akyol N, et al. Serum anti-carbonic anhydrase antibodies and oxidant–antioxidant balance in patients with acute anterior uveitis. Ocul Immunol Inflamm. 2014; 22(2):127-32.

Yadav U and Ramana K. Regulation of NF-_B-Induced Inflammatory Signaling by Lipid Peroxidation-Derived Aldehydes. Oxidative Medicine and Cellular Longevity. 2013: Volume 2013, Article ID 690545.

Appendix 2. Correction Table for Adjusting IOP Based on Central Corneal Thickness