PROTOCOL ADX-2191-PVR-001

THE GUARD TRIAL: A MULTICENTER, PROSPECTIVE, ADAPTIVE PHASE 3 CLINICAL TRIAL OF REPEATED INTRAVITREAL INJECTIONS OF ADX-2191 FOR THE PREVENTION OF PROLIFERATIVE VITREORETINOPATHY

PROTOCOL VERSION AND DATE: VERSION 5.0 / 5 MAY 2021
IND NUMBER: 133536

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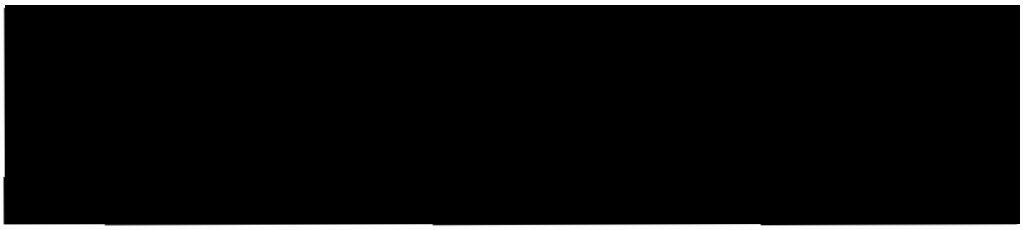
Sponsor Signature:



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

INVESTIGATOR STATEMENT

Protocol Number: ADX-2191-PVR-001

Protocol Title: A multicenter, prospective, adaptive Phase 3 clinical trial of repeated intravitreal injections of ADX-2191 for the prevention of proliferative vitreoretinopathy.

I understand that all information concerning ADX-2191 in connection with this clinical trial and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Trial Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this clinical trial without approval from the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC) 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, Inc. and by my IRB/REB/IEC and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/IEC responsible for this clinical trial.

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-2191-PVR-001, and will conduct the trial in accordance with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and applicable regulatory requirements.

_____
Site Name

_____
Site Address

_____
Investigator's Printed Name

_____ _____
Investigator's Signature Date

SYNOPSIS

Name of Sponsor Company: Aldeyra Therapeutics, Inc.		**Investigational Product:** ADX-2191
Title of Protocol: A multicenter, adaptive Phase 3 clinical trial of repeated intravitreal injections of ADX-2191 versus standard-of-care for the prevention of proliferative vitreoretinopathy		
Protocol Number: ADX-2191-PVR-001	**Phase:** 3	**Indication:** Prevention of Proliferative vitreoretinopathy
Subject Population: Adult subjects undergoing pars plana vitrectomy for the following indications: • Recurrent retinal detachment due to proliferative vitreoretinopathy (PVR) with documented starfolds in at least three cumulative clock hours on retinal imaging. • Retinal detachment associated with open globe injury (OGI).		
Number of Subjects: The trial will utilize an adaptive design with the number of subjects enrolled for Part 2 determined in Part 1. **Part 1:** Approximately 100-120 subjects will be enrolled to obtain approximately 100 evaluable eyes (50 subjects per treatment). **Part 2:** An additional 100-360 subjects will be enrolled to obtain approximately 100-300 evaluable eyes (50-150 subjects per treatment); to be statistically powered following completion of Part 1.		
Number of Centers: Approximately up to 30 sites in the United States		
Test Products / Dose / Mode of Administration: ADX-2191 (intravitreal methotrexate 0.8%) 400 mcg in 0.05 mL for 13 repeated intravitreal injections over 16 weeks		
Overall Design: In Part 1a of the GUARD Study (prior to activation of Protocol Version 5.0, dated May 5 2021), eligible subjects will be randomized 1:1 intraoperatively to either the Control or Intervention cohort. Subjects in the Control cohort will receive Standard Procedures only. In Part 1b of the GUARD Study (after activation of Protocol Version 5.0, dated May 5 2021), eligible subjects will no longer be randomized and all enrolled subjects will be placed in the Intervention Cohort. Subjects in the Intervention cohort will receive Standard Procedures and intravitreal ADX-2191 injections (Figure 1). In Part 1a, stratification will be used to balance treatment assignments within key subgroups. Subjects are to be stratified by clinical presentation (recurrent retinal detachment vs. OGI) and number of recurrent retinal detachments (>3 vs. ≤3). Subjects enrolled in Part 1 will not be eligible to participate in Part 2 nor will they be eligible to be randomized again during Part 1. Clinical trial procedures to be conducted in Part 1 and Part 2 are outlined in the Schedule of Assessments (Table 1).		

Primary Objective:

To evaluate the safety and efficacy of repeated intravitreal ADX-2191 injections as a pharmacologic approach to prevent PVR secondary to recurrent retinal detachment and OGI.

Secondary Objective (Part 1 only):

Part 1 will confirm the sample size to be utilized in Part 2.

Primary Endpoint:

The primary endpoint in Part 1 and Part 2 is the rate of recurrent retinal detachment requiring reoperation within 24 weeks from time of enrollment in drug-treated subjects compared to historical rates of retinal detachment for Grade C PVR. An evaluating investigator should determine whether the primary endpoint has been met. The primary endpoint requires verification by the Central Reading Center (CRC) before recurrent retinal detachment reoperation. In cases where CRC verification is not possible due to technical limitations with the Optical Coherence Tomography or fundus photograph, then the evaluating investigator will contact the trial medical monitor to confirm whether the primary endpoint has been met.

Recurrent retinal detachment is defined as either one, or, both of the following:

1. Spectral-Domain Optical Coherence Tomography (SD-OCT) demonstrating fovea-off retinal detachment (subfoveal fluid that is contiguous with a peripheral detachment);
2. Color fundus photographic documentation of a rhegmatogenous or tractional (or undetermined) retinal detachment that has progressed posterior to the Mandatory Reoperation Zone, as defined by a circle centered on the fovea, with a radius halfway between the arcades and the equator (Figure 2).

Stable, peripheral rhegmatogenous or tractional (or undetermined) detachments anterior to the mid-periphery may be observed or demarcated with laser at the Investigator's discretion and will not be counted as a failure.

Subjects who have retinal detachment within 1-week post-operatively will be deemed to have failed Day 0 (day of surgery) and will be removed from the efficacy analysis. Retinal detachment is defined as subjects who meet either of the recurrent retinal detachment imaging criteria as defined in the Primary Endpoint.

Secondary Endpoints:

- Comparison of retinal detachment rates across standard of care and drug-treated subjects.
- Best-corrected Visual Acuity (BCVA) change from Screening (Visit 1) level to Week 24 (as measured using an Early Treatment Diabetic Retinopathy Study [ETDRS] chart by masked technicians).

Exploratory Endpoints:

Exploratory endpoints in Part 1 and Part 2 include:

- Total number of vitrectomy surgeries performed by Week 24
- Total retinal attachment at Week 24
- Total macular attachment at Week 24
- Central macular subfield thickness (as measured by SD-OCT) at Week 24
- Macular epiretinal membrane (as visualized by SD-OCT) at Week 24
- Macular and extramacular epiretinal membrane visible on color fundus photographs at Week 24
- Percentage of eyes with intraocular pressure (IOP) < 5 mmHg at Week 24

Safety Evaluations:

Safety endpoints in Part 1 and Part 2 include:

- BCVA at distance utilizing an ETDRS chart
- IOP
- Slit-lamp examination
- Dilated ophthalmoscopy
- Adverse event (AE) query (reported, elicited, and observed)

Criteria for Inclusion:

Subjects meeting ALL of the following criteria will be considered eligible for clinical trial entry:

1. Subject is 18 years or older of any gender or any race.
2. Subjects are undergoing pars plana vitrectomy for the following indications:
   a. Recurrent retinal detachment due to proliferative vitreoretinopathy (PVR) with documented starfolds in at least three cumulative clock hours on retinal imaging.
   b. Retinal detachment associated with open globe injury (OGI).
3. Subjects must undergo silicone oil tamponade as part of the pars plana vitrectomy.
4. Investigators must agree to follow surgical principles as outlined in Section 6.9
5. At the conclusion of the retinal detachment surgical repair, the retina must be completely reattached, and, in the surgeon's best judgment, the subject should have a high likelihood of benefitting from enrollment in the clinical trial.
6. Subject is willing and able to provide written informed consent, comply with clinical trial procedures, and return for all clinical trial visits.
7. Subjects of childbearing potential, both male and female, must agree to use two forms of birth control for the duration of the clinical trial. Males should continue to use the two forms of birth control for a minimum of three months after last injection (30 days after completion of Visit 16/Week 24). Females of childbearing potential must use the two forms of birth control for a minimum of 30 days following their last injection.
8. For females of child-bearing potential, subjects must have a negative pregnancy test at Screening and not lactating.

Criteria for Exclusion:

Subjects meeting ANY of the following criteria in the study eye will be excluded from the clinical trial:

1. No Light Perception vision at screening exam.
2. Pre-phthisis eyes as per Investigator's assessment.
3. History of severe non-proliferative or proliferative diabetic retinopathy.
4. History of significant intraocular inflammatory disease requiring the use of systemic anti-inflammatory medication or an intraocular anti-inflammatory medication.
5. History of severe dry eye or other significant corneal disease.
6. History of incisional glaucoma surgery or ciliary body destructive procedures.

7. Other planned eye surgery during the course of the trial (including subjects with a diagnosis of bilateral detachments).
8. Participation in a clinical trial with an investigational medicinal product or investigational device within 90 days of subject enrollment.
9. Any clinically significant laboratory test abnormalities or a history of any other systemic or ophthalmic condition or circumstances which, in the opinion of the Investigator, could compromise the subject's ability to comply with the protocol or that could compromise the subject's safety or the interpretation of the clinical trial results.
10. History of more than 6 retinal detachments.
11. Hypersensitivity to Methotrexate medication.
12. Have previously received Methotrexate intravitreally at any time or plan to receive intravitreal methotrexate during the study period, or received systemic Methotrexate administration within 3 months of Screening visit.
13. Patients who might need to use Methotrexate for other medical conditions during the study period.

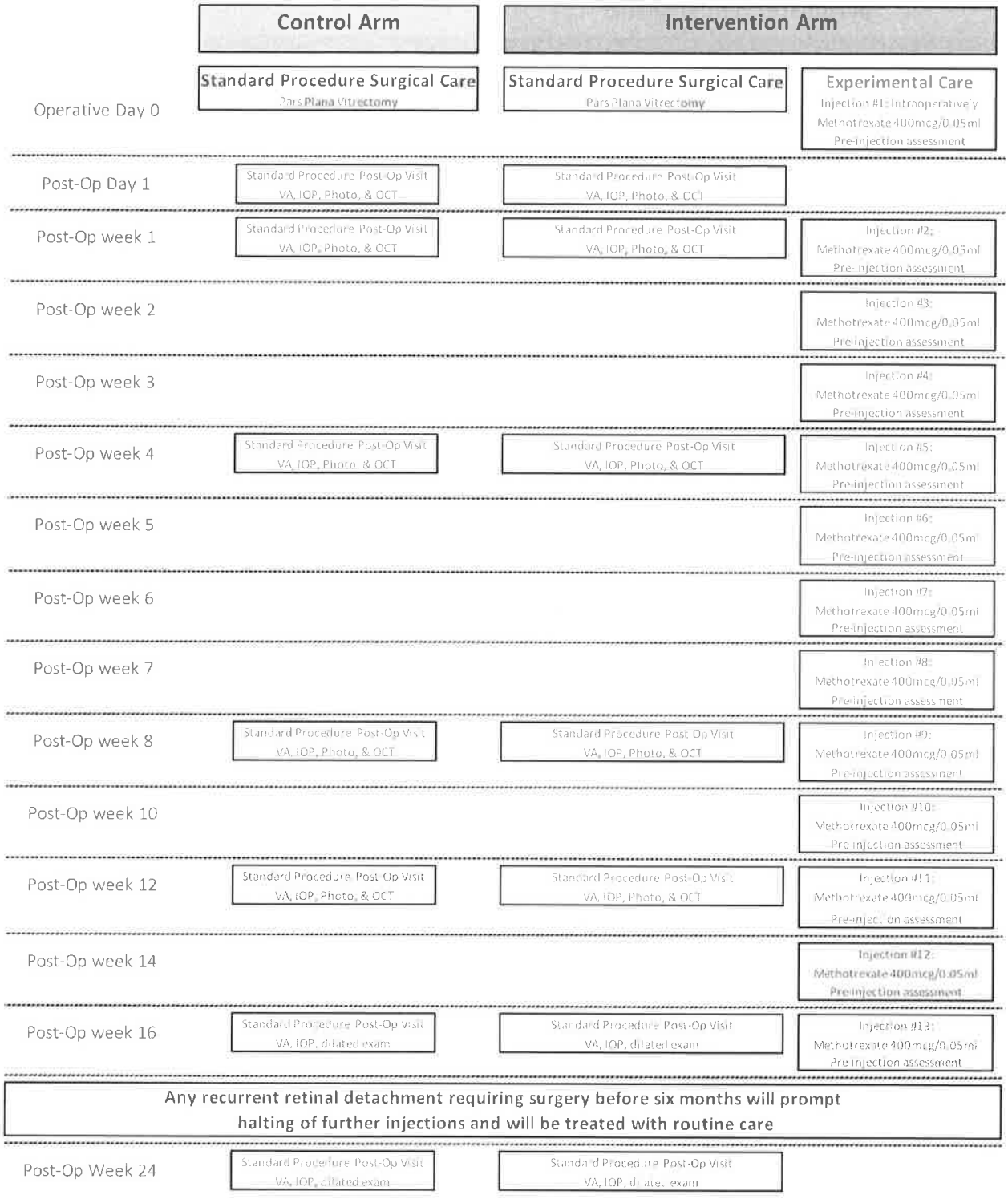
Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to the Investigator's Brochure

Data Safety Monitoring Board:

Masked safety data will be reviewed throughout the clinical trial by Aldeyra. An external Data Safety and Monitoring Board (DSMB) will review selected unmasked data for safety assessment. The review frequency, criteria, and the process for making recommendations will be defined in the DSMB charter.

Figure 1: Clinical Trial (Part 1 and Part 2) Flow Diagram



Note: The initial ADX-2191 intravitreal injection may be performed Day 0 (intra-operatively) or Day One (post-operatively). As of Protocol Version 5.0 (dated May 5 2021), eligible subjects will no longer be randomized and all enrolled subjects will be placed in the Intervention Cohort.

Table 1: Schedule of Events and Assessments for Part 1 and Part 2

NOTE: Event weeks are defined as post-operative Week One starts the calendar week following surgery (e.g., if Day One is Friday, Week One can start on Monday). Post-operative Week 24 must be at least 24 weeks from day of surgery ± 2 weeks. Subjects randomized (Part 1a only) to the Control cohort will attend the following study visits: Screening (Visit 1), Day 0 (Visit 2), Day 1 (Visit 3), Week 1 (Visit 4), Week 4 (Visit 7), Week 8 (Visit 11), Week 12 (Visit 13), Week 16 (Visit 15), and Week 24 (Visit 16). Subjects enrolled in the Intervention Cohort will attend all study visits.

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16 / EOS / ET
	Screening[9]	Day 0	Day 1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16	Week 24
Informed Consent	X															
Eligibility Review	X	X														
Demographics	X															
Medical and Social History	X															
Concomitant Medications	X	X	X	X			X				X		X		X	X
Adverse Events	X	X	X	X			X				X		X		X	X
Vital Signs	X															X
Physical Exam[1]	X															X
Clinical Laboratory Testing[2]	X															X
Urinalysis	X															X
Pregnancy Test[3]	X	X														X
Best Corrected Visual Acuity[4]	X		X	X			X				X		X		X	X
Intraocular Pressure	X		X	X			X				X		X		X	X
Fundus Photographs[5]	X		X	X			X				X		X		X	X
Macular Optical Coherence Tomography	X		X	X			X				X		X		X	X
Surgery: Pars Plana Vitrectomy		X														
Randomization (Part 1a only)[11]		X														
Clinical Ophthalmic Screening/ Follow-Up Examination By Treating Investigator	X		X	X			X				X		X		X	X
Endpoint Evaluation By Evaluating Investigator [10]				X			X				X		X		X	X

[redacted]

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16 / EOS / ET
	Screening[9]	Day 0	Day 1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16	Week 24
INTERVENTION TREATMENT GROUP ONLY[11]																
Pregnancy Test[3,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADX-2191 Injection By Treating Investigator		X[7]		X	X	X	X	X	X	X	X	X	X	X	X	
Pre-Injection Assessment By Treating Investigator[8]				X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Artificial Tears/Lubricating Ointment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Physical exam includes height and weight.
2. Clinical laboratory testing includes chemistry and hematology. Refer to Section 6.7 for more detail.
3. Pregnancy test for all women of childbearing potential. Post randomization (Part 1a) and all WOCBO Part 1b, pregnancy testing only required for intervention treatment group.
4. Best Corrected Visual Acuity and ocular exam will be performed in both eyes at Visit 1/Screening and Visit 16/Week 24/EOS/ET visits. During the clinical trial, best corrected visual acuity and ocular exams will be performed in study eye only.
5. Fundus photographs measured by ultra-wide field imaging. However, standard 4-field or 7-field photos if ultra-wide field imaging is not available. At Screening, fundus photographs not required for subjects with open globe injury and retinal detachment.
6. Post randomization pregnancy testing required for intervention treatment group.
7. The initial ADX-2191 intravitreal injection may be performed while in the operating room Day 0 or on post-operative Day One.
8. Pre-Injection Assessment by treating investigator to include visual acuity assessment, slit-lamp examination, intraocular pressure measurement, and dilated ophthalmoscopy. Refer to Section 6.13 for more detail.
9. The screening visit should optimally occur within 2 weeks of the Day of Surgery (Visit 2)
10. If a separate evaluating investigator is not available, the assessment may be made by the treating investigator and noted in the eCRF (section 6.8.4).
11. As of Protocol Version 5.0 (dated May 5 2021), eligible subjects will no longer be randomized and all enrolled subjects will be placed in the Intervention Cohort.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	Centigrade
°F	Fahrenheit
µg	micrograms
AE	Adverse Event/Adverse Experience
BCVA	Best Corrected Visual Acuity
eCRF	Electronic Case Report Form
CRC	Central Reading Center
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
CBC	Complete Blood Count
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ETDRS	Early Treatment Diabetic Retinopathy
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCPs	Good Clinical Practices
IEC	Independent Ethics Committee
ITT	Intent-to-Treat
ICH	International Council on Harmonisation
IND	Investigational New Drug Application
IP	Investigational Product
IOL	Intraocular lens
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
mL	Milliliters
mm	Millimeter
SD-OCT	Optical Coherence Tomography

OGI	Open globe injury
PPV	Pars Plana Vitrectomy
PVR	Proliferative vitreoretinopathy
QID	Four Times Daily
REB	Research Ethics Board
RD	Retinal detachment
RR	Relative Risk
SAE	Serious Adverse Event/Serious Adverse Experience
US	United States
VA	Visual Acuity
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1. Proliferative Vitreoretinopathy

Currently, proliferative vitreoretinopathy (PVR) is the leading cause of failure of rhegmatogenous retinal detachment surgery, resulting in recurrent retinal detachment in 5%–10% of all cases. (Pastor 2008) PVR is an abnormal wound healing response that involves the proliferation of ectopic cell sheets, in which cells grow uncontrollably within the vitreous cavity as well as beneath and/or on the surface of the retina resulting in periretinal membrane formation, retinal traction, and re-detachment. Despite tremendous advances in ophthalmic surgical instrumentation and techniques, anatomic success following recurrent detachment from PVR is reported to be only 45%–80%, depending on the severity of the cases (Banerjee, Bunce, & Charteris, 2013). Furthermore, functional success (visual acuity 5/200 or better) is achieved in only 40%–80% of subjects who achieve anatomic success.

The current standard-of-care for the treatment of PVR is vitreoretinal surgery in order to remove these tractional membranes. Currently, there are no specific therapeutic agents used for the prevention or treatment of PVR. Pharmacological agents have been tested for the treatment of PVR with different activities including anti-inflammatory, anti-proliferative, anti-neoplastics, and anti-growth factor agents; albeit without reproducible success. (Asaria et al., 2001; Banerjee et al., 2017; Sundaram, Barsam, & Virgili, 2010; Wiedemann, Hilgers, Bauer, & Heimann, 1998) Although some approaches have shown success in early animal models or limited human trials, larger human studies have failed to show a beneficial effect.

A consistency in prior PVR trial design, however, has been that the agents in question were given at the time of surgery only, despite PVR being a disease that manifests 2-3 months later.

Dr. Dean Eliott, observed that intraocular/vitreoretinal lymphoma suspect patients who underwent diagnostic chorioretinal biopsy did not develop epiretinal membranes or PVR when intravitreal methotrexate therapy was used to treat the lymphoma.

A Phase 1b clinical study was previously carried out at Massachusetts Eye and Ear Infirmary under a sponsor-investigator Investigational New Drug application (IND 114127). The purpose of the study was to determine the safety and tolerability of administering repeated weekly intravitreal injections of methotrexate into eyes at high-risk for the development of PVR after retinal detachment repair. Ten subjects were enrolled into a prospective, non-comparative clinical trial. Eight of these subjects had recurrent retinal detachment due to PVR after multiple prior surgeries and two subjects had retinal detachment associated with traumatic open globe injury. A protocol was designed to administer ten intravitreal injections of 400 µg/0.1 mL preservative free methotrexate over a three-month period to each of these ten subjects who underwent retinal detachment repair with silicone oil tamponade (each patient received ten injections). With a mean follow-up duration of more than three years, there were no unexpected ocular and systemic adverse events related to the drug. Furthermore, the conspicuous lack of post-operative visible PVR in eyes that were exposed to multiple injections of methotrexate suggested potential benefit of methotrexate in the prevention of recurrent retinal detachment due to PVR. (Stryjewski & Eliott, 2018)

Aldeyra is currently proposing to conduct a clinical trial to administer repeated intravitreal injections of ADX-2191, at a dose of 400 µg/0.05 mL (13 injections over a four-month period), following surgical repair of retinal detachment in eyes at high-risk for the development of PVR.

1.2. Therapeutic Rationale for ADX-2191 in Prevention of Proliferative Vitreoretinopathy

No treatments to date have been found to be preventive against PVR. Once PVR develops, surgery is the only treatment.

The clinical pharmacology of ADX-2191 (intravitreal methotrexate) is based on inhibition of dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates before they can be utilized in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with deoxyribonucleic acid (DNA) synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal, intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

Intravitreal injection provides the clinician with a means to bypass the blood retinal barrier that will provide more therapeutic doses of the methotrexate to the affected tissues than could otherwise be achieved.

1.3. Potential Risks and Benefits

1.3.1. Potential Risks

General risks for intravitreal injection include infection, hemorrhage; precipitated angle closures; elevated intraocular pressure (IOP) with perfusion compromise; wound leak and hypotony; anaphylactic reaction to either the agent or periprocedural materials.

In addition, known risks associated with use of intravitreal methotrexate include:

- keratopathy. Therefore, all subjects will receive lubricating eye drops and/or ointment at a minimum of four times a day, up to hourly while awake, during the injection period.
- mild conjunctival hyperemia ("red eye") and slight pain at injection site. This hyperemia and/or slight pain is seen in almost all eyes receiving methotrexate and resolves within several hours. (Frenkel, Hendler, Siegal, Shalom, & Pe'er, 2008)

1.3.2. Potential Benefit

Taking part in the clinical trial may or may not improve the subject's surgical outcomes. However, information learned from the clinical trial will help doctors understand more about how to improve post-surgical treatments that may reduce the incidence of PVR.

2. CLINICAL TRIAL OBJECTIVE AND ENDPOINTS

2.1. Clinical Trial Objectives

2.1.1. Primary Objective

To evaluate the safety and efficacy of repeated intravitreal ADX-2191 injections as a pharmacologic approach to prevent recurrent retinal detachment due to PVR secondary to recurrent retinal detachment and open globe injury (OGI).

2.1.2. Secondary Objective

Part 1 will confirm the sample size to be utilized in Part 2.

2.2. Clinical Trial Endpoints

2.2.1. Primary Endpoints

The primary endpoint in Part 1 and Part 2 is recurrent retinal detachment requiring reoperation within 24 weeks from time of enrollment. An evaluating investigator should determine whether the primary endpoint has been met. The primary endpoint requires verification by the Central Reading Center (CRC) before recurrent retinal detachment reoperation. In cases where CRC verification is not possible due to technical limitations with the Optical Coherence Tomography or fundus photograph, then the evaluating investigator will contact the trial medical monitor to confirm whether the primary endpoint has been met. These verification processes provide an additional level of objectivity in end point evaluation.

Definition of recurrent retinal detachment (defined as either one OR both of the following):

1. Spectral-Domain Optical Coherence Tomography (SD-OCT) demonstrating fovea-off retinal detachment (subfoveal fluid that is contiguous with a peripheral detachment);
2. Color fundus photographic documentation of a rhegmatogenous or tractional (or undetermined) retinal detachment that has progressed posterior to the Mandatory Reoperation Zone, as defined as defined by a circle centered on the fovea, with a radius halfway between the arcades and the equator (Figure 2).

Stable, peripheral rhegmatogenous or tractional (or undetermined) detachments anterior to the mid-periphery may be observed or demarcated with laser at the investigator's discretion and will not be counted as failure.

Subjects who have retinal detachment within 1-week post-operatively will be deemed to have failed Day 0 (day of surgery) and will be removed from the efficacy analysis. These will be considered "dropped" subjects. Subjects receiving investigational product during this period will continue to be followed for safety. Retinal detachment is defined as subjects who meet either of the recurrent retinal detachment imaging criteria as defined in the Primary Endpoint.

2.2.2. Secondary Endpoints

The secondary endpoint in Part 1 and Part 2 is Best-corrected Visual Acuity (BCVA) change from Screening (Visit 1) level to Week 24 (as measured using an Early Treatment Diabetic Retinopathy Study [ETDRS] chart by masked technicians).

2.2.3. Exploratory Endpoints

Exploratory endpoints in Part 1 and Part 2 include:

1. Total number of vitrectomy surgeries performed by Week 24
2. Total retinal attachment at Week 24
3. Total macular attachment at Week 24
4. Central macular thickness (as measured by SD-OCT) at Week 24
5. Macular epiretinal membrane (as visualized by SD-OCT) at Week 24
6. Macular and extramacular epiretinal membrane visible on color fundus photographs at Week 24
7. Percentage of eyes with intraocular pressure (IOP) < 5 mmHg at Week 24

2.2.4. Safety Endpoints

Safety endpoints analyzed in Part 1 and Part 2 include:

- BCVA at distance utilizing an ETDRS chart
- IOP
- Slit-lamp evaluation
- Dilated ophthalmoscopy
- Adverse event (AE) query (reported, elicited, and observed)

3. INVESTIGATIONAL PLAN

3.1. Overall Clinical Trial Design and Plan

A Phase 3, multicenter, adaptive clinical trial comprised of approximately 100 evaluable eyes in Part 1 (Part 2 sample size will be determined after analysis of Part 1) at high-risk for recurrent retinal detachment due to PVR, or with OGI that may or may not have PVR.

- Subjects in the **Control cohort** (Part 1a only) will receive Standard Procedures only (defined in Section 7).
- Subjects in the **Intervention cohort** (Part 1a and 1b) will receive Standard Procedures and repeated intravitreal injections of ADX-2191 at a dose of 400 µg/0.05 mL for 16 weeks (Figure 1).

In Part 1a of the GUARD Study (prior to activation of Protocol Version 5.0, dated May 5 2021), eligible subjects will be randomized 1:1 intraoperatively to either the **Control** or **Intervention** cohort. Subjects in the **Control** cohort will receive Standard Procedures only. In Part 1b of this study (after activation of Protocol Version 5.0, dated May 5 2021), eligible subjects will no longer be randomized and all enrolled subjects will be placed in the **Intervention** Cohort. Subjects in the Intervention cohort will receive Standard Procedures and intravitreal ADX-2191 injections (Figure 1).

In Part 1a, stratification was used to balance treatment assignments within key subgroups. Subjects are to be stratified by clinical presentation (recurrent retinal detachment vs. OGI) and number of recurrent retinal detachments (>3 vs. ≤3).

Subjects enrolled in Part 1 will not be eligible to participate in Part 2 nor will they be eligible to be enrolled again during Part 1.

Clinical trial procedures to be conducted in Part 1 and Part 2 are outlined in the Schedule of Assessments (Table 1).

For Part 1, approximately 100 evaluable eyes must complete the 24-week clinical trial. Up to 50 additional subjects may be recruited to achieve the minimum number of evaluable subjects.

3.2. Assigning Subjects to Treatment Groups

3.2.1. Subject Numbering

Each subject screened for the clinical trial will be assigned a unique subject number that will be used to identify the subject throughout subject participation in the clinical trial. If a subject fails to be enrolled, the reason should be documented in the source documents and electronic case report form (eCRF). The subject will be considered a screen failure.

3.2.2. Randomization

Per screening evaluations, all subjects will require a confirmation from the CRC and Medical Monitor that they meet the retinal imaging inclusion criteria to be eligible. If urgent (<24 hours) CRC verification is required, the Medical Monitor may unilaterally review the images and authorize the planned enrollment. In the event there is a discrepancy between the CRC and Medical Monitor review, the Medical Monitor determination will be the study-accepted reading of accountability.In Part 1a, eligible subjects are randomized to either standard procedure or standard procedure with intervention. This randomization is a 1:1 ratio within the stratified cohort groups. In Part 1b, subjects must still meet all inclusion criteria prior to enrollment. This verification process provides an additional level of objectivity in assuring subject qualification for participation in the clinical trial. If the photographic image is too poor in quality to verify eligibility, then the subject will be noted as screen failures. As noted in Section 6.8.5, in cases where preoperative color photography is technically difficult for image acquisitions (i.e., dense lens opacity, constricted pupil, intraocular bleeding, etc.), then intraoperative imaging using the operative microscope is allowed.

In Part 1a, those subjects that meet enrollment criteria will enter the randomization process and will be allocated to the Control vs. Intervention cohorts. The assignment to cohort will be

revealed intraoperatively at the conclusion of the surgery to the investigator after retinopexy has been applied. Note: administratively, the randomization may occur prior to surgery if logistically required by the site. However, the investigator must remain blinded to randomization until the defined timepoint. When administrative randomization occurs prior to surgery, all measures must be taken to avoid indicating assigned treatment group prior to conclusion of surgery.

Randomization scheme will be managed by an Interactive Response Technology (IRT) system. Subjects will be randomized by indication (recurrent retinal detachment due to PVR or any RD associated with OGI).

Eligible subjects will be randomized 1:1 intraoperatively to either group:

Control: Standard Procedures

Intervention: Standard Procedures with the addition of repeated intravitreal injections of ADX-2191 until post-operative Week 16.

In Part 1b of the GUARD study with activation of Protocol Version 5.0 (dated May 5 2021), eligible subjects will no longer be randomized and all enrolled subjects will be placed in the Intervention Cohort.

3.3. Safety Oversight

During the clinical trial, subject safety will be monitored on a continuous basis by the Sponsor Medical Monitor until the last subject completes the last scheduled clinical trial assessment.

3.4. Data Safety Monitoring Board

Masked safety data will be reviewed throughout the clinical trial by Aldeyra.

An external Data Safety and Monitoring Board (DSMB) will review selected unmasked data for safety assessment. The review frequency, criteria, and the process for making recommendations will be defined in the charter.

3.5. Clinical Trial Duration for Individual Subjects

The clinical trial consists of 16 clinic visits over a period of approximately 24 weeks.

3.6. Clinical Trial Population Selection

The intended population will be adult subjects undergoing pars plana vitrectomy for the following indications:

1. Recurrent retinal detachment due to PVR with documented starfolds in at least three cumulative clock hours on retinal imaging. (Imaging modality methods defined in Section 6.8.5).
2. Retinal detachment associated with open globe injury (the open globe retinal detachments may or may not have PVR at the time of enrollment).

3.6.1. Inclusion Criteria

Subjects meeting **ALL** of the following criteria will be considered eligible for clinical trial entry:

1. Subject is 18 years or older of any gender or any race
2. Subjects are undergoing pars plana vitrectomy for the following indications:
   a. Recurrent retinal detachment due to proliferative vitreoretinopathy (PVR) with documented starfolds in at least three cumulative clock hours on retinal imaging
   b. Retinal detachment associated with open globe injury (OGI)
3. Subjects must undergo silicone oil tamponade as part of the pars plana vitrectomy
4. Investigators must agree to follow surgical principles as outlined in Section 6.9
5. At the conclusion of the retinal detachment surgical repair, the retina must be completely reattached, and in the surgeon's best judgment, the subject should have a high likelihood of benefitting from enrollment in the clinical trial
6. Subject is willing and able to provide written informed consent, comply with clinical trial procedures, and return for all clinical trial visits
7. Subjects of childbearing potential, both male and female, must agree to use two forms of birth control for the duration of the clinical trial. Males should continue to use the two forms of birth control for a minimum of three months after last injection (30 days after completion of Visit 16/Week 24). Females of childbearing potential must use the two forms of birth control for a minimum of 30 days following their last injection.
8. For females of child-bearing potential, subjects must have a negative pregnancy test at Screening and not lactating

3.6.2. Exclusion Criteria

Subjects meeting **ANY** of the following criteria will be excluded from the clinical trial:

1. No Light Perception vision at screening exam in study eye.
2. Pre-phthisis eyes as per Investigator's assessment in study eye.
3. History of severe non-proliferative or proliferative diabetic retinopathy
4. History of significant intraocular inflammatory disease requiring the use of systemic anti-inflammatory medication or an intraocular anti-inflammatory medication
5. History of severe dry eye or other significant corneal disease
6. History of incisional glaucoma surgery or ciliary body destructive procedures
7. Other planned eye surgery during the course of the trial (including subjects with a diagnosis of bilateral detachments)
8. Participation in a clinical trial with an investigational medicinal product or investigational device within 90 days of subject enrollment
9. Any clinically significant laboratory test abnormalities or a history of any other systemic or ophthalmic condition, or circumstances which, in the opinion of the Investigator, could

compromise the subject's ability to comply with the protocol or that could compromise the subject's safety or the interpretation of the clinical trial results

10. History of more than 6 retinal detachments
11. Hypersensitivity to Methotrexate medication
12. Have previously received Methotrexate intravitreally at any time or plan to receive intravitreal methotrexate during the study period, or received, or systemic Methotrexate administration within 3 months of Screening visit.
13. Patients who might need to use Methotrexate for other medical conditions during the study period.

3.7. Strategies for Recruitment and Retention

Subjects will be recruited directly from the investigative sites' patient population or will be referred for treatment by other physicians. Once enrolled, subjects will be provided with the visit schedule and reminders from the clinical trial staff in advance of their visits to assist with compliance to the schedule of events for the clinical trial.

Subjects who discontinue early from investigational product treatment will complete the end-of-study visit (Week 24) at time of discontinuation. The Sponsor and Investigator will make all efforts to retain all subjects in the clinical trial until the end-of-study visit (Week 24) and to follow-up with early discontinued subjects for safety purposes.

4. SUBJECT DISPOSITION

4.1. Completed Subjects

A completed subject is one who has not been discontinued from the clinical trial.

4.2. Discontinued Subjects

Subjects may be discontinued prior to their completion of the clinical trial due to:

- Subject request/withdrawal
- AEs
- Positive pregnancy results
- Protocol violations
- Administrative reasons (e.g., inability to continue, lost to follow-up)
- Sponsor termination of the clinical trial
- Any sound medical reason, as determined by the investigator
- Others

Notification of a subject discontinuation and the reason for discontinuation will be made to the Sponsor or designee and will be clearly documented on the eCRF. Subjects who are discontinued from the clinical trial will not be replaced.

4.3. Subject Withdrawal

If intraoperative complete retinal reattachment is not achieved, subjects will not complete enrollment. These subjects will be dropped from enrollment and will be noted as screen failures.

Subjects who have retinal detachment within 1-week post-operatively will be deemed to have failed Day 0 (day of surgery) and will be removed from the efficacy analysis. These will be considered "dropped" subjects. Subjects receiving investigational product during this period will continue to be followed for safety.

Subjects will be removed from the clinical trial if they develop infectious endophthalmitis and/or no light perception vision.

Subjects may also be removed at the discretion of the principal investigator or at the wishes of the subject himself/herself.

4.4. Handling of Subject Withdrawals or Subject Discontinuation of Clinical Trial Intervention

Subjects that are dropped from the clinical trial prior to administration of the interventional investigational product or whom fail to achieve intraoperative complete retinal reattachment will be considered screen failures and will not be enrolled or included in analysis.

Subjects who have retinal detachment within 1-week post-operatively will be deemed to have failed Day 0 (day of surgery) and will be removed from the efficacy analysis. These will be considered "dropped" subjects.

Any subject receiving the investigational product will be followed for safety throughout the scheduled course of the clinical trial, or until the subject has reached a status of un-reachable.

It is anticipated that there will be a potential drop-out rate of up to 20%. To assure the clinical trial meets the required approximate 100 evaluable eyes for analysis, additional subjects may need to be enrolled to meet this goal.

4.5. Premature Termination or Suspension of Clinical Trial

In the event of premature termination or suspension of clinical trial, the subject will continue to follow with his/her surgeon as part of their standard of care management.

5. INVESTIGATIONAL TREATMENT

Product Name: ADX-2191 (methotrexate 0.8%) for intravitreal injection.

5.1. Description of Investigational Product

Methotrexate is an antimetabolite and antifolate drug that has been used for cancer treatment since the 1950s. The drug was originally approved in 1959 and is now available generically. It

has exceptionally well-understood biological and clinical effects. Methotrexate is currently FDA-approved for oral administration and for intravenous, intramuscular, intrathecal, or intra-arterial injection. Approved indications include psoriasis, rheumatoid arthritis, and certain neoplastic diseases. Other mechanisms of action involve direct effects on inflammatory pathways, in particular neutralization of the effects of TNF- α and IL-1β, though the molecular mechanisms underlying these effects remain largely uncharacterized.

Several case series have been published using intravitreal injections of methotrexate, most commonly for intraocular lymphoma. (Frenkel et al., 2008; Hardwig, Pulido, & Bakri, 2008; Hardwig, Pulido, Erie, Baratz, & Buettner, 2006; Samson, Waheed, Baltatzis, & Foster, 2001)

5.2. Packaging and Labeling

ADX-2191 drug product is formulated as a sterile and aqueous solution for intravitreal delivery. The drug product will be supplied in single-dose, 2 mL glass vials with a 0.5 mL fill volume.

[redacted]

The quantitative composition of the ADX-2191 drug product are presented in Table 2.

[redacted]

5.3. Investigational Product Storage

[redacted]

The Investigational Product (IP) must be stored in a secure area accessible only to the investigator and his/her designees. The IP will be administered only to subjects entered into the clinical trial, in accordance with the conditions specified herein.

The subject kit label will include, but not limited to, the following information:

- trial protocol number
- contents
- subject number and initials (manually recorded)
- storage conditions

- Investigational New Drug statement
- Sponsor's name, address, and phone number

The vial label will be included, but not limited to, the following information:

- trial protocol number
- contents
- storage conditions
- Investigational New Drug statement
- manufacturer name and address
- Sponsor name, address, and phone number

5.4. Investigational Product Dosage, Preparation, and Administration

Proposed dosage of ADX-2191: 400 μg in 0.05 mL intravitreal injection

ADX-2191 will be provided as the investigational product to clinical trial sites that have obtained IRB approval. The IP will be supplied in single-use vials. ADX-2191 should be withdrawn from the vial into an appropriate syringe allowing excess volume to accommodate needle fill if the needle will be exchanged. Used vials/syringes should be disposed of appropriately in accordance with local policy which may include use of yellow "chemo waste" bags.

It is preferred that the ADX-2191 be drawn into the syringe at time of administration, however, if local policy requires the IP to be drawn up in the pharmacy, this is acceptable as long as all sterility guidelines are met. Appropriate destruction and documentation of any IP must be completed.

Administration of ADX-2191 is described in Section 6.11. Refer to the Pharmacy Manual for additional details.

5.5. Investigational Product Accountability

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s) and is only to be used in accordance with this protocol. The IP must be distributed only to subjects properly qualified under the conditions specified herein.

The investigator or designated qualified site staff is responsible for monitoring the inventory of IP and for the accountability of all used and unused IP received from the supplier. This includes the amount of IP dispensed to subjects, and the amount returned or disposed upon the completion of the trial. Inventories must be carefully and accurately documented according to applicable state, federal, and local regulations, current Good Clinical Practices (GCPs), including the International Council for Harmonisation (ICH) guidelines, and clinical trial procedures. IP accountability will be available for Sponsor's review and will be verified by the clinical trial monitor during site visits and at the completion of the trial.

At the conclusion of the trial, IP reconciliation will be performed, and all remaining IP not returned to the sponsor, will be destructed and disposed of according to clinical site's SOP. Sponsor will be provided with a final accounting of IP for approval prior to destruction.

The investigator or designated qualified site staff will maintain accurate records of receipt and condition of IP, including dates of receipt, and temperature log of storage conditions. In addition, accurate records will be kept of the date of IP administration and the subject to whom IP was administered. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded.

5.6. Investigational Product Retention

IP must be retained until completion or termination of the clinical trial, and written authorization from the Sponsor has been received. All unused and used IP drug should be destroyed at the site or returned to the distributor, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused IP may be disposed until fully accounted for by the clinical trial monitor.

5.7. Subject Compliance with Investigational Product Administration

Compliance or product administration will be assessed through accurate medication administration records maintained at the clinical sites. The investigator/or appropriately licensed designee will administer the investigational product as defined in the protocol administration schedule. IP compliance will be assessed through review of the subject's medical record.

5.8. Subject Compliance with Clinical Trial Intervention

Protocol compliance will be assessed at each clinical trial visit. Compliance information will be collected from the medical/research record and reported via an eCRF. This information will be reviewed by the clinical trial monitor in accordance with the Monitoring Plan.

5.9. Assessment of Clinician and/or Subject Compliance with Clinical Trial Procedural Intervention

Clinician/subject compliance will be assessed at each clinical trial visit. Compliance information will be collected from the medical/research record and reported via a case report form. This information will be reviewed by the clinical trial monitor in accordance with the Monitoring Plan.

5.10. Concomitant Therapy and Procedures

The use of any concomitant medication, prescription or over the counter, taken within 30 days prior to signing consent, is to be recorded on the source document and corresponding electronic eCRF along with the reason the medication was taken.

Concurrent enrollment (within 90 days of enrollment) in another investigational drug or medical device clinical trial is not permitted.

5.11. Prohibited Concurrent Therapies and Procedures

Prohibited medications, treatments, and procedures during the clinical trial are outlined in the Exclusion Criteria (Section 3.6.2).

6. CLINICAL TRIAL PROCEDURES

Clinical trial assessments and evaluations should be performed by the investigator and/or qualified site staff according to Schedule of Events and Assessments (Table 1). Refer to the Clinical Trial Activities Schedule (Section 7).

6.1. Informed Consent

Informed consent forms must be approved for use by the reviewing Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC). Informed consent must be obtained for all subjects participating in the clinical trial prior to performing any procedures. The informed consent process must be adequately documented in the source records.

6.2. Eligibility Review

The investigator or qualified site staff will confirm that all inclusion and exclusion criteria have been met. Per screening evaluations, all subjects will require a confirmation from the CRC and Medical Monitor that they meet the retinal imaging inclusion criteria to be eligible. If urgent (<24 hours) CRC verification is required, the Medical Monitor may unilaterally review the images and authorize the planned enrollment. In the event there is a discrepancy between the CRC and Medical Monitor review, the Medical Monitor determination will be the study accepted reading of accountability.

6.3. Demographics, Medical History, and Social History

Demographic information to be captured include subject initials (where locally permitted), date of birth (alternatively year of birth, if full date of birth is not allowed to be collected for legal reasons), age, sex, race, and ethnicity will be obtained from the subject and recorded in the eCRF.

Medical and social history will be recorded in the eCRF. Current underlying conditions, including conditions diagnosed within the last 30 days of consent, which may have resolved before screening, must be recorded.

6.4. Physical Examination

A physical examination will be performed including, but may not be limited to, an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems at Screening. Additional examinations may be obtained on Principal Investigator's discretion. The physical examination may be performed by any medically qualified physician or certified PA, whether part of the study team or not, as long as documentation of the required examination is available. The ophthalmic examinations must be performed by a member of the study team.

6.5. Concomitant Medications

Concomitant medications used 30 days prior to consent to treat any medical conditions will be recorded in the eCRF. Any changes in dosage or new medications added must be recorded in the

subject eCRF. The Sponsor and investigator or qualified site staff will review and evaluate concomitant medication usage on an ongoing basis.

6.6. Adverse Events

Any serious, unexpected adverse events (AE) believed to be due to the intervention rather than the natural disease process will prompt a filing of an adverse event form with the local IRB office and the FDA.

AEs will be collected from the time the subject signs the informed consent form through 30 days after the last dose of IP. AEs must be recorded in the eCRF. The Sponsor and investigator or qualified site staff will review and evaluate AEs on an ongoing basis. See Section 8 for further detail on AE reporting.

6.7. Safety Testing

Samples of blood and urine will be collected for clinical laboratory tests which includes general safety parameters (hematology, serum chemistry, and urinalysis) and pregnancy. All subjects will provide blood samples for clinical laboratory testing for chemistry and hematology, as well as urine for a urinalysis at Screening Visit (Visit 1) and Final Visit (Visit 16 / Week 24; or at subjects last visit when subject is terminated and follow up is not available through Week 24, if possible).

Chemistry profile includes blood urea nitrogen (BUN), calcium, chloride, creatinine, creatinine to BUN ratio, carbon dioxide (CO_2), potassium, sodium, albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), Aspartate aminotransferase (AST), total bilirubin, and total protein.

Hematology profile includes hematocrit, hemoglobin, platelets, red blood cells, and white blood cells (without differentials).

For women of childbearing potential (WOCBP) enrolled in the Intervention cohort, a pregnancy test will be collected at the Screening Visit (Visit 1), and prior to each injection of ADX-2191, through Visit 16 / Week 24. Results must be available and confirmed to be negative before the subject may be enrolled in the clinical trial. IP must be discontinued for any subject with a positive pregnancy test result.

6.8. Ophthalmic Examinations

6.8.1. Best-Corrected Visual Acuity

BCVA will be collected at Screening (V1), Day 1 (V3), Weeks 1 (V4), 4 (V7), 8 (V11), 12 (V13), 16 (V15), and 24 (V16). The BCVA will be measured using ETDRS chart by masked technicians at a standard photopic light level of at least 85 cd/m^2. These assessments are to be conducted in both eyes at Visit 1(screening) and Visit 16 (end of study/early termination). The study eye only may be examined at other time points.

6.8.2. Intraocular Pressure

IOP will be collected at Screening (V1), Day 1 (V3), Weeks 1 (V4), 4 (V7), 8 (V11), 12 (V13), 16 (V15), and 24 (V16).

6.8.3. Clinical Ophthalmic Examination

Routine full ophthalmic, dilated follow-up exams will be performed on Screening (V1), Day 1 (V3), Weeks 1 (V4), 4 (V7), 8 (V11), 12 (V13), 16 (V15), and 24 (V16) by the Treating Investigator. This exam is inclusive of a slit lamp exam. Additional follow-up exams may be scheduled by the Treating Investigator at his or her discretion.

6.8.4. Endpoint Evaluation

It is preferred that an evaluating investigator assess whether the primary endpoint has been met at the pre-specified evaluation timepoints Weeks 1 (V4), 4 (V7), 8 (V11), 12 (V13), 16 (V15), and 24 (V16). If an evaluating investigator is not available, the Treating Investigator may determine whether the primary endpoint has been met. The primary endpoint requires verification by the CRC before recurrent retinal detachment reoperation. In cases where CRC verification is not possible due to technical limitations with the Optical Coherence Tomography or fundus photograph, then the evaluating investigator will contact the trial medical monitor to confirm whether the primary endpoint has been met. Regardless, SD-OCT and wide-field imaging will be collected and verified by the CRC when the endpoint has been met, or at conclusion of the clinical trial, whichever is sooner.

6.8.5. Color Fundus Photographs

All subjects will undergo pre-operative color widefield, 4-field or standard 7-field retina photos. Photos will be interpreted as per reading center protocol with masked readers. Pre-operative anterior segment photos are also preferred, if possible. In cases where preoperative color photography is technically difficult for image acquisitions (i.e. dense lens opacity, constricted pupil, intraocular bleeding, etc.), then intraoperative imaging using the operative microscope is allowed.

The CRC and Medical Monitor will review the pre/intraoperative photos and approve all subjects prior to their planned enrollment. If urgent (<24 hours) CRC verification is required, the Medical Monitor may unilaterally review the images and authorize the planned enrollment. Fundus Photographs will be collected at Screening, (V1; with the exception of subjects with OGIs and retinal detachment; or subjects who require intraoperative photos as stated above), Day 1 (V3), Weeks 1 (V4), 4 (V7), 8 (V11), 12 (V13), 16 (V15), and 24 (V16). The CRC will certify all imaging technicians.

6.8.6. Macular Spectral-Domain Optical Coherence Tomography (SD-OCT)

Macular SD-OCT imaging may be done using Heidelberg Spectralis or Zeiss Cirrus (Spectralis imaging is preferred if available). SD-OCTs will be interpreted as per CRC protocol with masked readers. Note that subjects should be imaged consistently with the same SD-OCT machine if multiple machines are available in the same facility.

SD-OCT will be collected at Screening (V1), Day 1 (V3), Weeks 1 (V4), 4 (V7), 8 (V11), 12 (V13), 16 (V15), and 24 (V16).

6.9. Pars Plana Vitrectomy

All subjects will receive Pars Plana Vitrectomy (PPV) in the usual manner on Day 0 (V2). The PPV will be performed under local or general anesthesia using a small gauge system (23, 25, or 27 gauge) at the discretion of the investigators.

Investigators will agree to observe the following principles:

1. Lens status:

   If Phakic:

   1. If phakic with a clear lens, the lens may be preserved
   2. If lensectomy is performed, a complete capsulectomy is required
   3. Cataract extraction with implantation of a posterior intraocular lens is permitted

   If Pseudophakic:

   1. May keep intraocular lens (IOL), or may remove IOL and capsular bag at surgeon discretion

   If Aphakic:

   1. May not insert secondary IOL at time of re-detachment surgery
2. Epiretinal, subretinal, and epiciliary membranes will be removed at the discretion of the investigator, including anterior vitreous base dissection when indicated.
3. Use of intravitreal triamcinolone, chemical dyes including indocyanine green and brilliant blue, relaxing retinectomy, scleral buckle, and perfluorocarbon liquid will be used as needed at the discretion of the investigator.
4. Intraoperative triamcinolone to identify tissue planes/vitreous is acceptable, but an additional injection in or around the eye at the end of surgery is not permitted.
5. If retinectomy is performed, removal of the anterior retina is strongly encouraged.
6. Moderate to intense white laser retinopexy burns will be used to seal any retinal breaks. 2-3 laser rows as per the investigator's usual routine but an additional row of laser burns is recommended. No cryopexy may be used.
7. Silicone oil 1000 or 5000 centistokes will be used as the preferred tamponade.
8. The injection is given into the oil bubble as the last step of the procedure before suturing the sclerotomies. Subjects that will receive the alternative option of ADX-2191 on Day 1 (Visit 3) will be given injection into the oil bubble following the required safety assessment.
9. No subconjunctival, peribulbar, intravenous, oral, or sustained-release intraocular steroids will be used. Topical ophthalmic steroid eye drops, or ointment may be used per surgeon's usual routine. If patient is already on oral steroids for a different condition, this may be continued at the same dose or less.

10. All subjects receiving the investigational product will be required to aggressively use lubricating drops and/or ointment at least four times daily.
11. Silicone oil removal is required after Week 24.

Investigators will have discretion regarding the need for re-operation. Indications for re-operation may include endophthalmitis and recurrent retinal detachment, as defined in Section 3.6 . Silicone oil cannot be removed within the 24-week trial period, unless for the above indications.

Recurrence of retinal detachment requiring a return to the operating room will prompt cessation of any further intravitreal injections and only Routine Surgical Care will be provided. Subjects will be followed through the Week 24 assessment visit.

6.10. Randomization

As of Protocol Version 5.0 (dated May 5 2021), eligible subjects will no longer be randomized and all enrolled subjects will be placed in the Intervention Cohort.

Prior to Version 5.0, each subject was assigned to a cohort at the conclusion of the surgery prior to suturing the sclerotomies on Day 0. To complete a subject's enrollment in the clinical trial, the surgeon confirmed intraoperatively that the retina has been completely reattached and in the surgeon's best judgment, the subject should had a high likelihood of benefitting from randomization and possible enrollment in the clinical trial. If the surgeon proceeded to enrollment, then the surgeon would be notified by the clinical trial coordinator of subject randomization as described in Section 3.2.2.

Note: administratively, the randomization could occur prior to surgery if logistically required by the site. However, the investigator would remain blinded to randomization until the defined timepoint. When administrative randomization occured prior to surgery, all measures were taken to avoid indicating assigned treatment group prior to conclusion of surgery.

6.11. Investigational Product Intravitreal Injection

Upon completion of the PPV, subjects who are enrolled in the Interventional cohort will receive ADX-2191 400 µg/0.05 mL intravitreal injection, in accordance with the schedule of events (Table 1). The first injection will be administered intraoperatively on Day 0 (V2) or on post-operative Day 1 (V3) and subsequently will be injected on at post-operative Weeks 1 (V4), 2 (V5), 3 (V6) 4 (V7), 5 (V8), 6 (V9), 7 (V10), 8 (V11), 10 (V12), 12 (V13), 14 (V14), and 16 (V15).

Intravitreal ADX-2191 injections will be performed aseptically after the topical application or subconjunctival injection of an anesthetic agent and 5% povidone iodine to the conjunctiva. Each patient will receive an intravitreal injection of 400 µg/0.05 mL ADX 2191, 3.0 mm posterior to the limbus with a 30-gauge needle. It is required that subjects lie on their back/or in a reclined sitting position, with face up, for approximately 20 minutes after the injection to promote optimal IP positioning.

6.12. Dispense Artificial Tears and Lubricating Ointment

All subjects receiving the investigational product will receive artificial tears and/or lubricating ointment at a minimum of four times daily (QID) throughout the injection phase of the clinical trial. Artificial Tears will be dispensed at Day 0 (V2), post-operative Day 1 (V3), Weeks 1 (V4), 2 (V5), 3 (V6) 4 (V7), 5 (V8), 6 (V9), 7 (V10), 8 (V11), 10 (V12), 12 (V13), 14 (V14), and 16 (V15).

6.13. Pre-Injection Assessment

Beginning with Week one (V4), subjects must have a Visual Acuity Assessment, slit-lamp cornea examination, IOP measurement, and dilated ophthalmoscopy performed prior to injection of ADX-2191 to assure the safety and viability of proceeding with the investigational treatment.

7. CLINICAL TRIAL ACTIVITIES

Clinical trial activities are summarized in the Schedule of Events and Assessments (Table 1).

NOTE: Event weeks are defined as follows: post-operative Week One starts the calendar week following surgery (e.g., if Day One is Friday, Week One can start on Monday). Post-operative Week 24 must be at least 24 weeks from day of surgery ± 2 weeks.

7.1. Screening Visit (Visit 1)

- Review eligibility criteria (Section 6.2)
- Obtain written informed consent (Section 6.1)
- Collect demographic information and document medical and social history (Section 6.3)
- Collect vital signs
- Perform physical examination (Section 6.4)
- Perform Routine clinical ophthalmic examination (Section 6.8.3)
- Collect concomitant medications (Section 6.5)
- Collect samples for safety labs, urinalysis, and pregnancy test, if applicable (Section 6.7)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5; not required for subjects with OGIs and retinal detachment)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Submit images to CRC for review. All subjects will require a confirmation from the CRC and Medical Monitor that they meet the recurrent retinal detachment retinal imaging inclusion criteria to be eligible for enrollment. If urgent (<24 hours) CRC

verification is required, the Medical Monitor may unilaterally review the images and authorize the planned enrollment. If the photographic image is too poor in quality to verify eligibility, then the subject is not eligible for enrollment.

7.2. Day 0/Operative Day/Enrollment (Visit 2)

- Review eligibility criteria (Section 6.2)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Perform Pars Plana Vitrectomy (Section 6.9)
- Confirmation of enrollment prior to suturing the sclerotomies (Section 6.10)
  - To complete a subject's enrollment in the clinical trial, the surgeon must confirm intraoperatively that the retina has been completely reattached and that in the surgeon's best judgment, the subject has a high likelihood of benefitting from enrollment in the clinical trial.

Additional Procedures for the Intervention Group Only (Day 0 Intraoperative)

- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)

7.3. Day 1 (Visit 3)

- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)

Additional Procedures for the Intervention Group Only (Day 1 Post-Operative)

- If applicable, perform pregnancy test (Section 6.7; if subject receives initial Investigational Product Intravitreal Injection on Day 1)
- Investigational Product Intravitreal Injection (Section 6.11; if not administered on Day 0)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)

7.4. Week 1 (Visit 4)

- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)
- Endpoint evaluation by Evaluating Investigator (Section 6.8.4)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)

Additional Procedures for the Intervention Group Only [Week 1 (Visit 4)]

- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.5. Week 2 (Visit 5) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.6. Week 3 (Visit 6) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.7. Week 4 (Visit 7)

- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)

- Endpoint evaluation by Evaluating Investigator (Section 6.8.4)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)

Additional Procedures for the Intervention Group Only [Week 4 (Visit 7)]

- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.8. Week 5 (Visit 8) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.9. Week 6 (Visit 9) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.10. Week 7 (Visit 10) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)

- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.11. Week 8 (Visit 11)

- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)
- Endpoint evaluation by Evaluating Investigator (Section 6.8.4)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)

Additional Procedures for the Intervention Group Only [Week 8 (Visit 11)]

- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.12. Week 10 (Visit 12) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.13. Week 12 (Visit 13)

- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)
- Endpoint evaluation by Evaluating Investigator (Section 6.8.4)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)

- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)

Additional Procedures for the Intervention Group Only [Week 12 (Visit 13)]

- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.14. Week 14 Visit (14) Intervention Group Only

- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.15. Week 16 (Visit 15)

- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)
- Endpoint evaluation by Evaluating Investigator (Section 6.8.4)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)

Additional Procedures for the Intervention Group Only [Week 16 (Visit 15)]

- If applicable, perform pregnancy test (Section 6.7)
- Investigational Product Intravitreal Injection (Section 6.11)
- Dispense artificial tears and/or lubricating ointment (Section 6.12)
- Perform Pre-Injection Assessment (Section 6.13)

7.16. Week 24 (Visit 16)

- Collect vital signs
- Perform physical examination (Section 6.4)
- Collect adverse events (Sections 6.6 and 8)
- Collect concomitant medications (Section 6.5)
- Collect samples for safety labs, urinalysis, and pregnancy test, if applicable (Section 6.7)
- Perform Routine Clinical Ophthalmic Follow-up examination (Section 6.8.3)
- Endpoint evaluation by Evaluating Investigator (Section 6.8.4)
- Perform BCVA (Section 6.8.1)
- Perform IOP (Section 6.8.2)
- Collect Fundus Photographs (Section 6.8.5)
- Collect Macular Optical Coherence Tomography (Section 6.8.6)

8. ADVERSE EVENT REPORTING

AEs will be collected from the time the subject signs the informed consent form through 30 days after the last IP administration.

8.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered an IP, which does not necessarily have a causal relationship with the IP treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IP, whether or not it is considered related to the IP.

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.

8.2. Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the Screening Visit (Visit 1) that do not worsen in severity or frequency during the clinical trial are defined as baseline medical conditions and are not to be considered AEs.

Pregnancies are not considered AEs but must be reported, see Section 8.7.

Recurrent retinal detachments (and subsequent treatments) are a clinical endpoint of the clinical trial. They will not be captured as AEs/SAEs.

8.3. Recording Adverse Events

Safety assessments will include but not limited to evaluation of AEs using National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 2017, or higher, clinical laboratory results, pregnancy testing, and vital sign measurements. If a CTCAE grading is not listed for a specific event then the AE will be graded as mild, moderate or severe, per Section 8.4.

AEs will be recorded from the time of signing of informed consent up to the final clinical trial visit.

All AEs must be recorded in the site's clinical trial records and the AE eCRF. Investigators should use correct medical terminology when recording events and avoid abbreviations.

The investigator should attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. The diagnosis, and not the individual signs/symptoms, or laboratory abnormalities, should be documented in the subject's source documents and the eCRF unless the etiology of the event is unknown. If signs/symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE. If a diagnosis is subsequently established, it should be reported as follow-up information.

An assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to IP, the interventions required to treat it, and the outcome.

8.4. Assessment of Causality and Severity

For each AE recorded, the investigator will make an assessment of causality and severity as follows:

1. Relationship to IP: 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, 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 Related
    - Probably Related
    - Possibly Related
    - Unlikely to be related
    - Not Related

    For regulatory authority reporting, only "related," or "not related" classification will be used. AEs identified as definitely, probably, or possibly, will be classified as "related." Those AEs identified as unlikely, or not related, will be classified as "not related."

2. Event Severity: The investigator will be asked to use their medical judgment to assess the severity of the AE.
3. The following are guidelines to be used by the investigator to judge the event severity of an AE:
    - Mild - awareness of sign or symptom, but easily tolerated
    - Moderate - discomfort enough to cause interference with usual activity
    - Severe - incapacitating with inability to work or perform usual activity
4. Expectedness: The expectedness of an AE should be determined based on upon existing safety information about the IP using the following explanations:
    - *Unexpected*: an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.
    - *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.
    - *Not applicable:* an AE unrelated to the IP.
    - AE events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product but are not specifically mentioned as occurring with the particular product under investigation, are to be considered unexpected.
    - The investigator should initially classify the expectedness of an AE, but the final classification is subject to the determination of the Sponsor's Medical Monitor.
5. Duration: Start and end dates and times, or if continuing.
6. Frequency: whether the event is a single episode, recurrent or continuous.
7. Action taken.
8. Whether it constitutes a SAE, per definition below.
9. Outcome: resolved, resolved with sequelae, continuing, death, or unknown (only for subjects that are lost to follow-up).

8.5. Treatment-Emergent Adverse Events

A TEAE is defined as an AE that occurred during the clinical trial after the first dose of IP or was present prior to dosing and exacerbates after the first dose of IP.

8.6. Serious Adverse Events

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

- death;
- a life-threatening AE;
- Note: An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor/designee, the subject is at immediate risk of death as a result of the AE.

"Life-threatening" does not include an AE that, had it occurred in a more severe form, might have caused death.

- inpatient hospitalization or prolongation of existing hospitalization;
  - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term subjects, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include emergency room visits; outpatient/same-day/ambulatory procedures; or admission to observation/short-stay units, rehabilitation facilities, hospice facilities, nursing homes, or clinical research/Phase 1 units.
  - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission, as determined by the investigator or treating physician.
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).
- a congenital anomaly/birth defect; and,
- other serious (Important Medical Events) events that do not fit other outcomes, where the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the SAE definition, based upon appropriate medical judgment.

8.6.1. 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.

8.6.2. Reporting Serious Adverse Events

The investigator is responsible for reporting all SAEs, regardless of causality, to the Sponsor designee within 24 hours of learning of the occurrence. SAEs should be captured in the eCRF. If the SAE paper form is used, it should be sent to NorthAmerica_Medical@parexel.com or faxed (1-781-434-5957). An SAE "hot-line" is available to site personnel: 1-781-434-5010 (during Eastern US business hours, Monday –Friday, 8:30 AM until 5:00 PM). Local toll-free numbers will be provided on the SAE report form cover sheet.

The reporting timeframe starts when the subject signs the informed consent or assent form through 30 days after the last IP 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.

A follow-up SAE Report must be submitted within 24 hours of the investigator receiving the follow-up information (such as information regarding complications, progression or resolution).

An SAE that is considered completely unrelated to a previously reported event should be reported separately as a new SAE.

The procedures for reporting SAEs are as follows:

- Complete the SAE eCRF or "Serious Adverse Event Report Form". The investigator may contact Pharmacovigilance via the telephone hotline for assistance with SAE reporting.
- If the "Serious Adverse Event Report Form" is utilized, 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 clinical trial 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 clinical trial participation.

The investigator and qualified site staff 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.

If the SAE was not previously documented in the Investigator's Brochure and is thought to be related to IP, 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 clinical trial with the same drug that this SAE has been reported.

The investigator should notify Pharmacovigilance of any death or SAE occurring after a subject has withdrawn from the clinical trial when such a death occurs within 30 days of the last dose of IP and may reasonably be related to the IP.

8.6.3. Follow-up of Adverse Events

All AEs will be followed until stabilization/resolution or until clinical database lock. AE's are to be reported to the IRB in accordance with IRB policy.

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.

8.6.4. Reporting Serious Adverse Events to Regulatory Health Authorities/ Institutional Review Boards/Research Ethics Boards/Independent Ethics Committees

The investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to their local IRB/REB/IEC.

The investigator must promptly report to his or her local IRB/REB/IEC 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 IP.

The Sponsor or their designee is responsible for appropriate reporting of relevant AEs, suspected unexpected serious adverse reactions (SUSARs) involving IP, to all regulatory authorities.

In addition, the Sponsor or designee will be responsible for the submission of safety letters (e.g., SUSARs) to the central IRB/REB/IEC and to participating investigators of all SUSARs involving IP according to applicable regulations.

After termination of the clinical trial (determined as last subject, last visit), any unexpected safety issue that changes the risk-benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority (ies) concerned together with proposed actions.

8.7. Reporting Pregnancies

Pregnancies for women will be reported from the time the subject signs the informed consent form through final clinical trial visit or 30 days after the last IP administration, whichever is later. Males will report pregnancy of their partners through 90 days after the last IP administration.

To ensure subject safety, each pregnancy in a subject on IP must be reported to Pharmacovigilance within 24 hours of learning of its occurrence. Subjects who become pregnant will be withdrawn from the clinical trial. 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 8.6.2. A pregnancy, by itself, is not an SAE. Pregnancy follow-up should also be recorded and should include an assessment of the possible relationship to the IP of any pregnancy outcome. Any pregnancy-related SAE (e.g., spontaneous abortion, birth defect) or any other SAE experienced during pregnancy must be recorded on a separate SAE Report Form and reported per SAE reporting procedures in Section 8.6.2.

9. STATISTICS HYPOTHESES AND METHODS OF ANALYSES

9.1. Clinical Trial Populations

9.1.1. Intent-to-Treat (ITT)

The Intent-to-Treat (ITT) population consists of all subjects who were randomized. All data will be included, and no subjects will be excluded because of protocol violations. All data will be included, and no subjects will be excluded because of protocol violations; subjects who have retinal detachment within 1-week post-operatively who will be deemed to have failed Day 0 (surgery) and will be removed from the efficacy analysis as per protocol per Section 2.2.1.

9.1.2. Per-Protocol Population

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the trial with no major protocol violations.

9.1.3. Safety Population

The safety population includes all subjects who received the test article. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

9.2. Statistical Hypothesis

The following hypotheses will be tested comparing the detachment rate of ADX-2191 (intravitreal methotrexate 0.8%) to that of a weighted historical control over 24 weeks.

- H0: There is no difference in rate of recurrent retinal detachment due to PVR between ADX-2191 (intravitreal methotrexate 0.8%) and historical control.
- H1: There is a difference in rate of recurrent retinal detachment due to PVR between ADX-2191 (intravitreal methotrexate 0.8%) and historical control.

9.3. Sample Size

9.3.1. Sample Size Part 1

The initial design of the GUARD Study was based on an recurrent retinal detachment rates of 0.2 and 0.5 for ADX-2191 and standard-of-care group, respectively. With a sample size of 90 subjects (45 per group) and 2-sided significant level at 0.05, the clinical trial would have approximately 80% power to detect the superiority of ADX-2191 over the standard-of-care.

The protocol was updated to an open-label, single arm study in Version 5.0.

Approximately 100 evaluable eyes will be recruited to complete the 24-week treatment period.

9.3.2. Sample Size Part 2

The estimated rate of recurrent retinal detachment from Part 1 will be used to determinate sample sizes and power in Part 2, which is expected to require approximately 100-300 evaluable eyes (50-150 per treatment).

9.4. Statistical Analysis

9.4.1. General Considerations

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) detailing all planned analyses. Any analyses conducted in addition to those specified in the SAP will be clearly documented as post hoc. A summary of the currently planned analyses for the primary and secondary outcome variables is found below.

Quantitative variables will be summarized descriptively using number of subjects (n), mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

All summaries will be presented by treatment group. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

All analyses will be two-sided at a significance level of 0.05. The 95% confidence intervals will be provided where appropriate.

The primary endpoint analysis will compare retinal detachment rates of drug-treated subjects to a historical control rate, which will be a weighted average of the retinal re-detachment rates from two prior Grade C PVR prospective clinical trials with similar inclusion criteria (Banerjee, 2017; Schiff, 2007).

The SAP will serve as the final determinant of the statistical procedures, notwithstanding language herein.

9.4.2. General Imputation Methods

Every attempt will be made to capture all clinical trial 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. No imputation method will be applied on recurrent retinal detachment data.

9.4.3. Multiplicity Consideration

Only one hypothesis will be tested. No multiplicity adjustment will be done in this clinical trial.

9.4.4. Demographic and Baseline Medical History

The demographic and baseline medical history data, obtained at screening, will be summarized descriptively. For quantitative variables, the summaries will include the number of observations, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

9.4.5. Primary Efficacy Analyses

The primary efficacy variable of recurrent of retinal detachments (defined in Section 3.6) due to PVR requiring re-operation within six months from enrollment will be measured as binary variable (indicating recurrent of detachment or not). Briefly, a 95% confidence interval around the proportion of retinal detachment in drug-treated subjects will be generated, and the primary endpoint will have been deemed to have been met if the upper bound of the confidence interval is lower than the weighted average historical control detachment rate. The primary efficacy analyses will be conducted on the ITT population with observed data only. Subjects who discontinue investigational treatment early will be encouraged to stay for any remaining safety assessments until the conclusion of the clinical trial. Subjects who have retinal detachment within 1-week post-operatively will be deemed to have failed Day 0 (day of surgery), and will be removed from the efficacy analysis.

9.4.6. Secondary Efficacy Analyses

The logistic regression model will be used to assess the superiority of ADX-2191 over standard-of-care in reducing the rate of recurrent retinal detachment. The covariate-adjusted difference in rate of recurrent retinal detachment and associated 95% CI will be summarized (Ge et al., 2011). The model will include a binary response variable (indicating recurrence of detachment or not), a treatment effect and stratification factor adjustment.

The secondary endpoint of the Best Correct Visual Acuity (BCVA) of change from level at Screening (Visit 1) to the level at Week 24 will be analyzed using an MMRM model. The MMRM model will be fit with Screening BCVA value, treatment, visit, and the interaction of treatment and visit. Change from Screening level of BCVA will be the dependent variable.

Subgroup analysis for BCVA will be conducted based on the following factors, if deemed necessary:

1. Lens status (phakia vs. aphakia vs. pseudophakia)
2. Prior recurrent retinal detachments (>3 vs. $\leq$3)
3. Longstanding retinal detachment (>1 month) (yes vs. no)
4. Pre-operative macular scar or macular hole (yes vs. no)

Exploratory efficacy endpoints will be summarized by visit for descriptive statistics only. No statistical between-group comparison will be performed, unless otherwise specified.

9.4.7. Safety Analysis

Safety endpoints analyzed in Part 1 and Part 2 include:

- BCVA at distance utilizing an ETDRS chart
- IOP
- Slit-lamp evaluation
- Dilated ophthalmoscopy
- Adverse event (AE) query (reported, elicited, and observed)

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages will be provided per treatment group of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation. An adverse event is treatment-emergent if it occurs or worsens after the first dose of investigational treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship.

All evaluations of safety will be described in the SAP.

9.4.8. Planned Interim Analyses (if applicable)

No interim analyses are planned for this clinical trial.

An interim analysis might be performed to support planning of further clinical development. To maintain the integrity of the ongoing clinical trial, individuals who are directly involved in clinical trial conduct and data management (e.g., personnel at investigational sites, Aldeyra Medical Safety Physician, Clinical Operations, and Data Management) would remain masked to treatment assignment of individual subjects until clinical trial completion.

9.4.9. Statistical Analyses Plan

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses. Any analyses conducted in addition to those specified in the SAP will be clearly documented as post hoc. The SAP will serve as the final determinant of the statistical procedures, notwithstanding language herein.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management will implement a system of quality assurance that includes all elements described in this protocol. Within this system, standard operating procedures (SOPs) from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and GCP. Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

11. CLINICAL TRIAL ADMINISTRATION

11.1. Institutional Review Board / Research Ethics Board / Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the investigator and approved in writing by the applicable IRB/REB/IEC in accordance with GCP prior to implementation. In addition, the IRB/REB/IEC must approve the written informed consent and assent forms, any consent or assent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects prior to implementation.

The investigator must provide an annual report to the IRB/REB/IEC on the progress of the clinical trial including number of subjects enrolled, discontinued, and SAEs, unless otherwise specified by the IRB/REB/IEC. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The investigator must provide notification to the IRB/REB/IEC of the completion, termination, or discontinuation of the clinical trial.

The investigator must supply the Sponsor with copies of all written correspondence with the IRB/REB/IEC.

The investigator will make all attempts to ensure that the IRB is constituted and operates in accordance with regulatory requirements, ICH GCP and any local requirements.

11.2. Ethical Conduct of the Clinical Trial

The clinical trial will be carried out in keeping with national and local legal requirements, including in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) Code of Federal Regulations (CFR) Title 21 [Part 50, Part 54, Part 56, Part 312 and Part 11] as well as the ICH GCP E6 Guidelines. This clinical trial 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 CFR Title 21], and with the ethical principles laid down in the Declaration of Helsinki.

11.3. Subject Informed Consent

The Sponsor will provide sample Informed Consent Forms for use in the clinical trial. Any changes to the proposed consent and assent forms suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/REB/EC. The investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the clinical trial.

Before each subject is enrolled in the clinical trial, written informed consent will be obtained according to the regulatory and legal requirements of the participating site.

The subjects should sign the current final IRB/REC/EC approved consent form. The process of obtaining informed consent and assent should be documented in the subject source documents. Each investigator must retain the original signed and dated informed consent and assent forms. A copy of the signed and dated informed consent and assent forms will be given to the subject. No subject can enter the clinical trial, or have clinical trial-specific assessments performed before his/her informed consent has been obtained.

The Informed Consent Forms should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the patient to participate. Revisions to the consent forms required during the clinical trial must be approved by the Sponsor, and a copy of the revised consent forms provided to the Sponsor. For any updated or revised forms, the subjects must be re-consented for continued participation in the clinical trial.

11.4. Confidentiality

All clinical trial findings and documents will be regarded as confidential. The investigator and qualified site staff must not disclose such information without prior written approval from the Sponsor. The investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

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 eCRFs and other documents submitted to the Sponsor by their initials (if locally permissible) and/or assigned subject number; not by name. Documents that identify the subject (e.g., the signed informed consent form) must be maintained in confidence by the investigator. All clinical trial documents are provided by the Sponsor in confidence to the investigator and qualified site staff. None of this material may be disclosed to any party not directly involved in the clinical trial without Sponsor's written permission. The investigator must assure that subjects' anonymity will be maintained. The investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from the Sponsor.

11.5. Protection of Subject Data

The collection and processing of personal data from subjects enrolled in the clinical trial will be limited to those data that are necessary to investigate the safety, quality, and utility of the IP) used in the clinical trial and to support the development and interpretation of the trial's clinical outcomes assessments.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the collection and processing of personal data and for the investigator to allow direct access to his or her original medical records for clinical trial-related monitoring, audit(s), IRB/REB/EC review, and regulatory inspection. The consent also addresses the transfer of the data to other entities and to other countries.

11.6. Clinical Trial Monitoring

Prior to initiation of the clinical trial at a site, the Clinical Trial Monitor, who is an authorized individual designated by the Sponsor, will visit the site to verify the qualifications of the investigator and designated site staff, inspect the adequacy of the facilities, and inform the clinical trial team of responsibilities and the procedures to ensure proper conduct of the clinical trial. During the conduct of the clinical trial, the Clinical Trial Monitor will visit the sites to verify adherence to the protocol, assess drug accountability, data integrity, and subject safety. The monitors will conduct 100% source document verification of subject data by comparing the eCRFs with the source documents to ensure accuracy and consistency.

All aspects of the clinical trial will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Clinical Trial Monitor will have access to all records necessary to ensure integrity of the data and safety of the subject, and will periodically review the progress of the clinical trial with the investigator.

Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the clinical trial is monitored adequately.

11.7. Procedures for Training of Clinicians on Procedural Intervention

All procedures required for the control and interventional cohorts are standard practice for the investigators of the clinical trial. To assure that procedures are consistent with the protocol, the investigator's will be trained on the required methods and procedures at site initiation or training Webex.

11.8. Procedures for Training Interventionists and Monitoring Intervention Fidelity

Prior to a site's enrollment of subjects, the investigator and applicable clinical trial team members will be trained on the protocol and associated documentation.

11.9. Case Report Forms and Source Documents

An electronic data capture (EDC) system will serve as the data management system for the clinical trial.

The investigator will be responsible for the accuracy of the data entered in the EDC system and ensure that the data collected are accurate and complete. Data will be monitored within the EDC system by the clinical trial monitor who has only reading rights. Any changes required following monitoring will be made by the investigator or qualified site staff and will be documented with a full audit trail within the EDC system. The responsible clinical trial monitor will check data at the monitoring visits to the clinical site.

The investigator or qualified site staff will prepare and maintain adequate and accurate clinical trial documents (e.g., medical records, AE and concomitant medication reporting, source data collection forms, etc.) designed to record all observations and other pertinent data for each subject. It is recommended that the author of an entry in the source documents be identifiable.

Source data may be directly captured from devices, transferred from third parties (e.g., laboratory data), or entered manually into the EDC system in use at the clinical center. In such case, many of the source data will only be available electronically. The remainder of the data, captured initially on paper, may be entered retrospectively into the EDC system.

For each subject, eCRF and corresponding source records will be maintained at each clinical site. eCRFs 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 or designee. Upon clinical trial completion, the monitor will arrange for a final review of the clinical trial files, after which the file should be secured by storage for the appropriate period as specified in Section 12.

The investigator will allow the Sponsor or designee(s), contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the clinical trial.

11.10. Access to Source Documents and Audits

Regulatory agencies may request access to all clinical trial records, including source documents, for inspection and copying, in keeping with country regulations. The investigator should immediately notify the Sponsor of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the clinical trial. The investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the EDC system.

11.11. Protocol Deviations and Violations

Exceptions to the 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. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the investigator should contact the Sponsor to discuss the appropriate course of action.

The investigator should document all protocol deviations/violations in the subject's eCRF and source documents or the investigator Site File, if appropriate. Protocol deviations will be documented by the clinical trial monitor and will be included in the final clinical trial report. Protocol deviations should be submitted to IRB/REB/IEC, in accordance with the site's IRB/REB/IEC requirements.

11.12. Amendments to the Protocol

To alter the protocol, amendments must be written by the Sponsor and approvals must be received from all parties that approved the original protocol (IRB/REB/IEC, and if applicable, the local regulatory authorities) before implementation. 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 the clinical trial, even if this action represents a deviation from the protocol.

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

11.13. Discontinuation of the Clinical Trial

The Sponsor reserves the right to discontinue the clinical trial under the conditions specified in the clinical trial agreement.

11.14. Investigator Responsibilities

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the IEC/REB/IRB, and/or the regulatory authority(ies).

The investigator is responsible for ensuring that the clinical trial is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and local requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical trial data are credible.

11.15. Financial Disclosure

The investigator is required to disclose any financial arrangement during the clinical trial and for one year after, whereby the outcome of the clinical trial could be influenced by the value of the compensation for conducting the clinical trial, or other payments the investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54(2)(b) (1998).

11.16. Registration of Clinical Studies and Disclosure of Results

The Sponsor or designee will register and/or disclose the existence of and the results of clinical trials as required by law.

11.17. Publication and Disclosure Policy

As is customary for multicenter trials, publication by individual clinical sites or investigator/institution will not be allowed without the explicit written permission of the Sponsor. The Sponsor will determine authorship of the principal clinical trial 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 clinical trial.

12. RETENTION OF RECORDS

The investigator agrees to adhere to the document retention procedures by signing the protocol. 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 clinical trial-related records are no longer required.

Essential documents include but are not limited to:

- IRB/REB/IEC approvals for the clinical trial protocol and all amendments
- All source documents and laboratory records
- eCRF copies
- Subjects' informed consent / assent forms (with clinical trial number and title of trial)
- Form FDA 1572
- Any other pertinent clinical trial documents

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, IP dispensing/disposition records) that support data in the eCRFs of each subject must be retained in the files of the responsible investigator.

According to ICH guidelines for GCP, essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period (25 years) if required by relevant regulatory or legal authorities.

If the responsible investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the clinical trial records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

No records should be disposed of without written approval of the Sponsor.

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