An Exploratory, Single-Center, Double-Masked, Crossover Clinical Trial to Assess Safety and Tolerability of 0.25% Reproxalap Ophthalmic Solution Compared to Xiidra® in Subjects with Dry Eye Disease in a Dry Eye Chamber

Study Sponsor (Principal Investigator)	[redacted]
Study Number(s)	C1D01056
Study Product(s)	Product A: 0.25% Reproxalap Ophthalmic Solution (reproxalap) (Manufactured by Aldeyra Therapeutics, Inc.) Product B: Xiidra® (5% lifitegrast ophthalmic solution) ([redacted])
Clinical Research Organization	[redacted]
Indication	Dry Eye Disease (DED)
Clinical Trial Phase	Phase 2
Regulatory Agency	Health Canada
Protocol Version	Final 1.0
Protocol Date	29 Jun 2021

PROTOCOL VERSION CONTROL

Version Number	Notes/Summary of Changes	Date
Final 1.0	Protocol Created	29 Jun 2021

STUDY SPONSOR (PRINCIPAL INVESTIGATOR) APPROVAL SIGNATURE PAGE

Study Title: An Exploratory, Single-Center, Double-Masked, Crossover Clinical Trial to Assess Safety and Tolerability of 0.25% Reproxalap Ophthalmic Solution Compared to Xiidra® in Subjects with Dry Eye Disease in a Dry Eye Chamber

I agree to conduct this clinical trial as outlined in the approved protocol and accordance with all applicable federal government codes, acts and regulations, the ethical principles that have their origins in the Declaration of Helsinki and all amendments, Good Clinical Practice (GCP) requirements, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance E6 (R2), and Tri-Council Policy Statement (Canada) and to allow applicable regulatory agencies the opportunity to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality.

[redacted]

Signature [redacted] Date [redacted]

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Principal Investigator

[redacted]

Signature _____ Date _____

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1. LIST OF ABBREVIATIONS

TERM	DEFINITION
AE	Adverse Event
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DEC	Dry eye Chamber
DED	Dry Eye Disease
DMP	Data Management Plan
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IUD	Intrauterine device
LASIK	Laser-assisted in situ keratomileusis
MedDRA	Medical Dictionary for Regulatory Activities
ºC	Degrees Celsius
PI	Principal Investigator
QA	Quality Assurance
RASP	Reactive Aldehyde Species
REB	Research Ethics Board
SAE	Serious Adverse Event
SLE	Slit-lamp examination
SOP	Standard Operating Procedures
SUSAR	Suspected Unsuspected Serious Adverse Reaction
SVA	Snellen Visual Acuity
USA	United States of America
WOCBP	Women of Childbearing Potential

2. SPONSOR REPRESENTATIVE (PRINCIPAL INVESTIGATOR)

[redacted]

3. STUDY ADMINISTRATIVE STRUCTURE

3.1 Clinical Research Organization

[redacted]

3.2 Clinical Facilities

[redacted]

[redacted]

3.3 Central Institutional Review Board (IRB)

[redacted]

3.4 Safety Management

[redacted]

4. STUDY SUMMARY

Study Title	An Exploratory, Single-Center, Double-Masked, Crossover Clinical Trial to Assess Safety and Tolerability of 0.25% Reproxalap Ophthalmic Solution Compared to Xiidra® in Subjects with Dry Eye Disease in a Dry Eye Chamber
Protocol Number	C1D01056
Study Phase	Phase 2
Study Objectives	To explore the safety and tolerability of reproxalap compared to Xiidra® in a dry eye chamber.
Study Endpoints	Exploratory Endpoints: • Change in ocular discomfort score (0-10) from baseline over 45 minutes in the dry eye chamber • Change in ocular itching score (0-10) from baseline over 45 minutes in the dry eye chamber Safety Endpoints: • Snellen visual acuity (SVA) • Slit-lamp examination (SLE) • Adverse event (AE) query
Study Design	C1D01056 is an exploratory, single-center, double-masked, crossover design trial to assess the safety and tolerability of reproxalap compared to Xiidra® in subjects with Dry Eye Disease (DED). The clinical trial will consist of 3 visits to the clinic over a period of approximately 34 days. This study will be an investigator-initiated trial.
Study Products and Treatment	Treatment Products Product A: 0.25% Reproxalap Ophthalmic Solution (reproxalap) (Manufactured by Aldeyra Therapeutics, Inc.) Product B: Xiidra® (5% lifitegrast ophthalmic solution) [redacted] Treatment products (reproxalap or Xiidra®) will be dosed topically in both eyes and administered once (1 drop in each eye) approximately 5 minutes prior to dry eye chamber (DEC) entry.
Route of Administration	Ophthalmic (topical ocular administration of eye drops)
Study Population	Approximately 50 subjects with DED, ages 18 to 70 years, are expected to be enrolled in the trial. The study will consist of 1 treatment group.
Study Conduct	The clinical trial will consist of 3 visits. At each visit, staff will update the subjects' concomitant medication and collect AEs. A urine pregnancy test will be administered to all female subjects. Coronavirus Disease 2019 (COVID-19) screening questionnaire, oral temperature and COVID-19 rapid test will be performed at Visits 1, 2 and 3. Eligibility

	criteria will be reviewed. There will be at least 7 days of washout period following Visits 1 and 2. **I. Medical Screening- Visit 1 (Day -21 to -8)** All subjects will undergo a medical screening visit (Visit 1), including written informed consent, demographics, medical/medication and ocular history. Intraocular Pressure (IOP) will be performed prior to DEC entry. SVA and SLE will be performed prior to DEC entry. Symptom questionnaires (Ocular Discomfort Score, Ocular Itching Score) will be performed approximately 15 minutes pre-saline dose and approximately every 5 (+2) minutes while in the DEC. Saline will be administered in the clinic approximately 5 minutes prior to DEC entry. Following DEC exit (approximately 45 minutes), SVA (EDTRS), and SLE will be performed following chamber exit. Dilated fundoscopy will be performed post-DEC after SVA and SLE. After at least 7 days of washout, subjects will return for Visit 2. **II. Treatment- Visit 2 (Day 1 + 2) and Visit 3 (Day 8 + 2)** A fixed treatment sequence is allotted for Visit 2 and 3. SVA and SLE will be performed prior to symptom questionnaires, and eligibility criteria will be reviewed. Symptom questionnaires (Ocular Discomfort Score and Ocular Itching Score) will be performed approximately 15 minutes pre-dose and approximately every 5 (+2) minutes while in the DEC. Test product will be administered in the clinic approximately 5 minutes prior to chamber entry. Subjects will be exposed to a DEC (approximately 45 minutes) with Ocular Discomfort Score and Ocular Itching Score assessments every 5 (+2) minutes. SVA (EDTRS) and SLE will also be performed following DEC exit. There will be at least 7 days of washout after Visits 1 and 2. Dilated fundoscopy will be performed post-DEC after SVA and SLE at Visit 3.
Inclusion Criteria	1. Eighteen (18) to 70 years of age at the time of screening (either gender and any race). 2. Ability to provide written informed consent. 3. Reported history of dry eye for at least 6 months prior to Visit 1. 4. Reported history of the use of eye drops within 6 months but not within 2 weeks of Visit 1. 5. [redacted]
Exclusion Criteria	1. Clinically significant slit-lamp, IOP, dilated fundoscopy and SVA findings at Visit 1 that may include active blepharitis, severe meibomian gland dysfunction, lid margin inflammation, glaucoma and any other retinol disorders or active ocular allergies that require treatment, or in the opinion of the Investigator may interfere with study parameters including inactive viral infections or history of inflammatory disease (except Dry Eye Disease). 2. Diagnosis of an ongoing ocular infection (bacterial, viral, or fungal) or active ocular inflammation at Visit 1. 3. Contact lens use within 7 days of Visit 1 or anticipate using contact lenses during the trial.

	4. Previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within 12 months of Visit 1 and/or planned ocular and/or lid surgeries over the study period or any other ocular surgery within 6 months of Visit 1. 5. Systemic corticosteroid or other immunomodulatory therapy (not including inhaled corticosteroids) within 60 days of Visit 1 or any planned immunomodulatory therapy throughout the study period. 6. Temporary punctal plugs during the study that have not been stable within 30 days of Visit 1. 7. Eye drop use within 2 weeks of Visit 1 and/or an unwillingness to discontinue any topical ophthalmic prescription or over-the-counter solutions, artificial tears, gels, or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial). 8. Corrected SVA greater than or equal to 20/50 measured binocularly at Visit 1 before DEC. 9. Women of childbearing potential (WOCBP) who are pregnant, nursing, or not using an effective means of contraception. All female subjects must have a negative pregnancy test at Screening and Visits 2 and 3. 10. If of childbearing potential (female or male), unwillingness to use an acceptable means of birth control. (Acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or a condom; intrauterine device [IUD]; or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the trial.) 11. Known allergy and/or sensitivity to the test article or its components. 12. A condition that the investigator feels may put the subject at significant risk may confound the study results or may interfere significantly with the subject's participation in the trial. 13. Current enrollment in an investigational drug or device study or has used an investigational drug or device within 30 days of Visit 1. 14. Xiidra® (lifitegrast ophthalmic solution) use within 1 year of Visit 1. 15. Reproxalap ophthalmic solution study participation within 1 year of Visit 1. 16. Current use of any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1. 17. Inability or unwillingness to follow instructions, including participation in all study assessments/procedures and visits. 18. Antihistamine use within 1 week prior to Visit 1. 19. COVID-19 vaccine administration within 3 days prior to Visit 1. 20. Positive COVID-19 test within 4 weeks prior to Visit 1.
Statistical Analysis	Due to the exploratory nature of the study statistical analysis will be performed as required.

Safety Analysis	Safety analysis will include descriptive analysis and listings according to received treatment. Safety analysis will be performed on all subjects receiving at least one dose of study medication. Subject's safety data will be presented according to the treatment they actually received. The Safety population will be used for all analyses of safety endpoints as well as demographics and baseline characteristics.

5. STUDY SCHEMATIC

Table 5.1-1: Schedule of Assessments

Procedure	Visit 1 Day –21 to -8 Screening/Baseline	Visit 2 Day 1 + 2 Randomization/ Dry Eye Chamber	Visit 3 Day 8 + 2 Dry Eye Chamber
COVID-19 screening questionnaire, oral temperature and COVID-19 rapid test	X	X	X
Informed Consent	X		
Demographics	X		
Medical/Medication & Ocular History	X		
Medical/Medication Update		X	X
Urine Pregnancy Test (for all female subjects)	X	X	X
Dry Eye Chamber[1]	X	X	X
Symptom Questionnaires (Ocular Discomfort Score/Ocular Itching Score)[2]	X	X	X
Inclusion/Exclusion Criteria Review	X	X	X
Snellen Visual Acuity[3]	X	X	X
Slit-lamp Examination[3]	X	X	X
Saline Instillation	X		
Intraocular Pressure (IOP)	X[4]		
Dilated Fundoscopy	X[5]		X[5]
Randomization		X	
Test Article Instillation		X	X
Adverse Event /Concomitant Medication Query	X	X	X
Study Exit			X

[1]Dry eye chamber exposure (approximately 45 minutes).
[2]Will be performed within approximately 15 minutes prior to the entry and every 5+2 minutes while in the chamber.
[3]Will be performed pre-chamber (prior to symptom questionnaires) and post-dry eye chamber.
[4]Will be performed prior to dry eye chamber entry. These tests will be performed prior to symptom questionnaires.

[5]Will be performed post-DEC after SVA and SLE

Note:
1. A washout period of at least 7 days following visits 1 and 2 is given in this study.
2. [redacted] training will be provided to the study participants at Visit 1, 2 and 3.

Table 5.1-2: Schedule of Subject Assessed Ocular Discomfort/Ocular Itching

Time points in minutes	0	5	10	15	20	25	30	35	40	45
Window (minutes)	-15	+2								
Visit 1, 2 and 3	X	X	X	X	X	X	X	X	X	X

5.1 Endpoints

5.1.1 Exploratory Endpoints

- Change in ocular discomfort score (0-10) from baseline over 45 minutes in the dry eye chamber
- Change in ocular itching score (0-10) from baseline over 45 minutes in the dry eye chamber

5.1.2 Safety Endpoints

The safety endpoints are as follows:

- Snellen visual acuity (SVA)
- Slit-lamp examination (SLE)
- Adverse event (AE) query

6. INTRODUCTION

6.1 Background and Study Rationale

Dry eye disease (DED) is a common, multifactorial tear film and ocular surface disorder that causes eye pain and vision impairment. DED, also called keratoconjunctivitis sicca, is characterized by several symptoms of ocular discomfort, including but not limited to dry eye sensation, foreign body sensation, irritation, burning, tearing, ocular pain, and itching. Patients with DED may experience significant ocular discomfort and reduced visual function, resulting in a decreased quality of life or work productivity.[1] DED is a globally prevalent disease that disproportionately affects older individuals (>50 years) and women. According to the Dry Eye Workshop II report, DED prevalence ranges from 5-50% worldwide, while several studies estimate prevalence in the 20–30% range, notably among individuals over 50 years old. The Dry Eye Workshop II meta-analysis corroborated prior findings that prevalence rises with age and is more prevalent in women than males. Dry eye symptoms were reported by 28.7% of surveyed patients in optometric clinics in the 1997 Canada Dry Eye Epidemiology Study (CANDEES). According to a recent survey, 21.3 percent of Canadians aged 18 and up have DED. [2,3]

For short-term treatment of DED, doctors typically give artificial tear eye drops and topical corticosteroids. Antibiotics (tetracyclines and macrolides), nonsteroidal anti-inflammatory drugs, autologous serum drops, omega fatty acids, mucin secretagogues, and anti-inflammatory drugs are used to treat DED symptoms. In addition, individuals with chronic DED are increasingly being prescribed prosthetic scleral lenses (i.e. PROSE) that also function as additional tear reservoirs to improve ocular surface hydration. Meibomian gland dysfunction, a major cause of evaporative dry eye illness, is frequently treated with hot eyelid compresses. Punctual plugs can be used to stop tear outflow in advanced cases of DED. To minimize tear evaporation in extreme cases of dry eye, tarsorrhaphy surgery, tear duct cauterization, or amniotic membrane transplantation may be required.[4, 5]

[redacted]

[redacted] Given the severity, frequency, and complexity of DED, as well as the restricted modes of action by which these two compounds treat dry eyes, there is a medical need for more dry eye therapies, particularly those with multiple modes of action that target a larger dry eye population and are effective and safe for long-term daily usage.[6,7]

Reproxalap is a novel, first-in-class aldehyde sequestering agent that binds rapidly and irreversibly to pro-inflammatory reactive aldehyde species (RASP). Topical ocular reproxalap has demonstrated clinical activity in Phase 2 and Phase 3 clinical trials in non-infectious anterior uveitis,[8] allergic conjunctivitis,[9] and DED.[10, 11] Reproxalap has been administered to more than 1200 subjects with no clinically significant safety concerns.

Reproxalap topical ophthalmic solution is formulated as a sterile, preservative-free, aqueous solution for topical ocular delivery. Subjects are expected to self-administer 1 drop of 0.25% Reproxalap Ophthalmic Solution (reproxalap) or Xiidra® (5% lifitegrast ophthalmic solution). Direct instillation is the most efficient method for delivery to the ocular surface and is an accepted and widely used method for topical application to the eye. This exploratory study will examine tolerability and activity of 0.25% Reproxalap Ophthalmic Solution versus Xiidra® dosed once prior to entering dry eye chamber (DEC) in subjects with DED.[12]

6.2 Nonclinical Data

Inhibition of RASP by reproxalap has been studied under various *in vitro* conditions in which reproxalap has been shown to rapidly and irreversibly bind several common pro-inflammatory and cytotoxic RASP. The data suggest that RASP preferentially form covalent adducts with reproxalap under conditions that may mimic the physiologic milieu.

Reproxalap has been well-tolerated in multiple non-clinical single-dose and repeat-dose pharmacology and toxicology studies in mice, rats, rabbits, dogs, and non-human primates, via topical ocular, intravitreal, topical dermal, oral, intraperitoneal, subcutaneous, and intravenous routes of administration. In a standard battery of genotoxicity tests, reproxalap was non-mutagenic and non-clastogenic. Furthermore, no adverse effects of reproxalap were evident in *in vivo* central nervous system, respiratory, and cardiovascular safety pharmacology studies.

Non-clinical pharmacokinetic studies have shown that topical ocular administered reproxalap is absorbed rapidly into ocular tissue and delivers potentially therapeutically relevant concentrations of reproxalap to the eye's anterior chamber while resulting in minimal systemic exposure.

Overall, the non-clinical data suggest that reproxalap administered as a topical ophthalmic solution will continue to be safe, well-tolerated, and effective in clinical testing.[12]

6.3 Effects in Humans

Reproxalap topical ophthalmic solution has been investigated in one healthy normal volunteer clinical trial (NS2-001) and thirteen clinical trials across three ocular indications. Six clinical trials were conducted in subjects diagnosed with allergic conjunctivitis, ranging from Phase 1/2 to Phase 3 (ALD NS2-203-D1, ADX-102- AC-004, ADX-102-AC-008, ADX-102-AC-010, and ADX-102-AC-011, ADX-102-AC-017). One Phase 1 tolerability trial (ADX-102-DED-018), three Phase

2 trials (ADX-102-DES-007, ADX-102-DED-009, and ADX-102-DED-013), and one Phase 3 trial (ADX-102-DED-012) were conducted in subjects with DED. A Phase 2 clinical trial (NS2-02) and a Phase 3 trial (ADX-102-UV-005) were conducted in subjects with non-infectious anterior uveitis.

In Phase 1 clinical trials, reproxalap was safe and well-tolerated. In all Phase 2 and 3 clinical trials, reproxalap was safe and well-tolerated, and consistently demonstrated statistically significant improvement from baseline or statistically significant improvement over the vehicle.[12]

6.4 Benefit/Risk Assessment

No clinically significant safety signals have been observed in more than 1200 subjects treated with topical ocular reproxalap. Generally, mild and transient instillation site discomfort is the most commonly reported adverse event. The acute tolerability of topical ocular reproxalap administration was characterized in two clinical trials where drop comfort was assessed and symptoms recorded within minutes of dosing. [redacted]

Similarly, ADX-102-AC-011 and ADX-102-AC-017 compared 0.25% reproxalap to the vehicle during peak symptomatology in an allergen chamber and indicated that reproxalap was statistically superior to the vehicle as soon as five to ten minutes after administration. [redacted]

6.5 Rationale for Dose Selection

Ophthalmic dosing is the optimal route of administration for ocular allergy treatments. The dosage and dosage regimen was selected based on previous data from non-clinical and clinical studies. 0.25% reproxalap is the intended commercial formulation for allergic conjunctivitis and DED, and is now in Phase 3 clinical testing for DED.

7. OBJECTIVES AND ENDPOINTS

7.1 Objectives

To explore the safety and tolerability of reproxalap compared to Xiidra® in a dry eye chamber.

8. STUDY DESIGN

8.1 Overall Study Design

C1D01056 is an exploratory, single-center, double-masked, crossover design trial to assess the safety and tolerability of 0.25% Reproxalap Ophthalmic Solution (reproxalap) compared to Xiidra® (5% lifitegrast ophthalmic solution) in subjects with DED.

[redacted] The DEC can exacerbate the signs and symptoms of dry eye in

subjects with dry eye. The controlled environment, over time, allows evaluation of subject responses at any time point throughout the chamber session.

Subjects will be administered with the following:

Product A: 0.25% Reproxalap Ophthalmic Solution (reproxalap) administered 1 drop in each eye approximately 5 minutes prior to DEC entry.

Product B: Xiidra® (5% lifitegrast ophthalmic solution) administered 1 drop in each eye approximately 5 minutes prior to DEC entry.

This study will include 3 clinic visits over a period of approximately 34 days.

At Visit 1 Screening (Days -21 to -8), subjects who meet screening inclusion/exclusion criteria will be treated with 1 drop of saline in each eye. At Visit 2, (Day 1), subjects who continue to meet inclusion/exclusion criteria will be eligible to receive test products as described above.

At Visits 1, 2 and 3, assessments of ophthalmic evaluations will be collected [redacted]. In the event of an [redacted] failure, paper diary cards will be used as a backup to collect symptom scores. Ocular Discomfort Score (0 – 10) and Ocular Itching Score (0 to 10) will be employed for subject-reported symptoms of ocular discomfort and ocular itching, respectively. For each scale, 0 is no symptomatology and 10 is maximum symptomatology.

Ocular activity will be assessed by symptom questionnaires (Ocular Discomfort Score/Ocular Itching Score). Safety will be assessed before and after chamber exposure by SVA testing and SLE.

9. SUBJECT SELECTION

9.1 Number of Subjects

The total sample size will be 50 subjects. Sufficient numbers of volunteers will be screened to enroll 50 subjects.

9.2 Inclusion Criteria for Study Volunteers

Each subject must meet the following criteria to be eligible:

1. Eighteen (18) to 70 years of age at the time of screening (either gender and any race).
2. Ability to provide written informed consent.
3. Reported history of dry eye for at least 6 months prior to Visit 1.
4. Reported history of the use of eye drops within 6 months but not within 2 weeks of Visit 1.
5. [redacted]

9.3 Exclusion and Restriction Criteria for Study Volunteers

9.3.1 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

1. Clinically significant slit-lamp, IOP, dilated fundoscopy and SVA findings at Visit 1 that may include active blepharitis, severe meibomian gland dysfunction, lid margin inflammation, glaucoma and any other retinol disorders or active ocular allergies that require treatment, or in the opinion of the Investigator may interfere with study parameters including inactive viral infections or history of inflammatory disease (except Dry Eye Disease).
2. Diagnosis of an ongoing ocular infection (bacterial, viral, or fungal) or active ocular inflammation at Visit 1.
3. Contact lens use within 7 days of Visit 1 or anticipate using contact lenses during the trial.
4. Previously had laser-assisted in situ keratomileusis (LASIK) surgery within 12 months of Visit 1 and planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1.
5. Systemic corticosteroid or other immunomodulatory therapy (not including inhaled corticosteroids) within 60 days of Visit 1 or any planned immunomodulatory therapy throughout the study period.
6. Temporary punctal plugs during the study that have not been stable within 30 days of Visit 1.
7. Eye drop use within 2 weeks of Visit 1 and unwillingness to discontinue any topical ophthalmic prescription or over-the-counter solutions, artificial tears, gels, or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial).
8. Corrected SVA greater than or equal to 20/50 measured binocularly at Visit 1 before DEC.
9. Women of childbearing potential (WOCBP) who are pregnant, nursing, or not using an effective means of contraception. All female subjects must have a negative pregnancy test at Screening and Visits 2 and 3.
10. If of childbearing potential (female or male), unwillingness to use an acceptable means of birth control. (Acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or a condom; intrauterine device [IUD]; or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the trial).
11. Known allergy and/or sensitivity to the test article or its components (reproxalap or lifitegrast).
12. A condition that the investigator feels may put the subject at significant risk may confound the study results or may interfere significantly with the subject's participation in the trial.
13. Current enrollment in an investigational drug or device study or has used an investigational drug or device within 30 days of Visit 1.
14. Xiidra® (lifitegrast ophthalmic solution) use within 1 year of Visit 1.
15. Reproxalap ophthalmic solution study within 1 year of Visit 1.

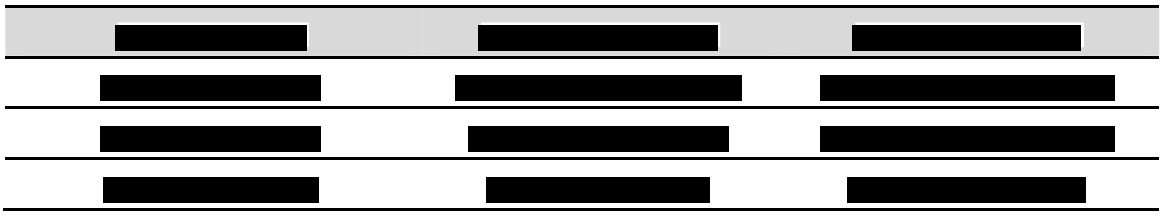
16. Current use of any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1.
17. Inability or unwillingness to follow instructions, including participation in all study assessments/procedures and visits.
18. Antihistamines use within 1 week prior to Visit 1.
19. COVID-19 vaccine administration within 3 days prior to Visit 1.
20. Positive COVID-19 test within last 4 weeks prior to Visit 1.

9.3.2 Restrictions and Concomitant Medications

Once the study has begun, the subjects will be instructed to take only the study medication(s) described in this protocol. If the subject takes any other medication during the study, the Investigator will record the necessary information.

Table 9.3.2-1: Restrictions and Concomitant Medications

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



Subjects who violate any of the above restrictions may be excluded or dropped from the study at the discretion of the Investigator. Individual exceptions to the above restrictions may be approved by the Investigator.

9.3.3 Female Subjects of Childbearing Potential

A female subject is considered of childbearing potential (WOCBP) if she is not post-menopausal, not congenitally sterile; not diagnosed as infertile (and not undergoing treatment to reverse infertility); or has not undergone successful surgical sterilization (such as tubal ligation, bilateral oophorectomy, or hysterectomy) completed at least 3 months prior to Screening. A woman is considered of non-childbearing potential if she is post-menopausal (if she is either amenorrheal for greater than 2 consecutive years, or naturally post-menopausal [no mense] for at least 1 year), surgically sterile (tubal ligation, bilateral oophorectomy, or hysterectomy), congenital sterility, or diagnosed as infertile and not undergoing treatment to reverse infertility.

WOCBP must use effective methods of birth control starting at least 4 weeks prior to the Screening Visit 1 and until the last study procedure, such as total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected or implanted non- or hormonal contraceptive. A sterile sexual partner is not considered an adequate form of birth control. Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least one month before the Screening Visit 1 and continue throughout the duration of the study.

WOCBP will be instructed to contact the Investigator immediately if they suspect they might be pregnant.

9.3.4 Male Subjects

Male subjects must commit to not father a child or donate sperm from the first dose until 3 months post-last dose.

Male subjects (with female partners of childbearing potential) must commit to the consistent and correct use of at least two effective methods of birth control (as listed below) or total abstinence from the Medical Screening Visit until 30 days after the last administration of the investigational product.

- Condom and diaphragm with spermicide (foam, cream, gel, sponge)
- Condom and cervical cap with spermicide (foam, cream, gel, sponge)
- Non-hormonal intrauterine device (IUD)

Female partner(s) of male volunteers also have the option to use the following highly effective hormonal method of contraception: implants, injectables, combined oral contraceptives, and IUDs.

10. STUDY PRODUCT AND TREATMENT SEQUENCE

10.1 Study Product and Treatment

The following products will be used in the study:

Product A: 0.25% Reproxalap Ophthalmic Solution (reproxalap) (Manufactured by Aldeyra Therapeutics, Inc.) administered 1 drop in each eye approximately 5 minutes prior to DEC entry.

Product B: Xiidra® (5% lifitegrast ophthalmic solution) (Manufactured by Novartis Pharmaceuticals Canada, Inc.) administered 1 drop in each eye approximately 5 minutes prior to DEC entry.

10.2 Treatment Sequence

At Visit 1, eligible subjects will be enrolled and scheduled for Visits 2 and 3. Subjects will be dosed as per a fixed sequence at Visits 2 and 3.

10.3 Masking and Unmasking

10.3.1 Masking

This is a double-masked clinical trial. The Sponsor (PI), Investigators, qualified site personnel (except delegated unmasked pharmacy staff), and subjects will be masked to the investigational product administered until database lock. Only the delegated unmasked pharmacy staff and Scientific Affairs staff involved with preparing the assignment of Treatment A and B to the fixed sequence will have access to the treatment under evaluation.

10.3.2 Emergency Unmasking

Emergency unmasking should only be performed when necessary to treat the subject. Most often, knowledge of the possible treatment assignments is sufficient to treat a clinical trial subject who presents with an emergency condition.

The investigator should make every effort to contact the Medical Monitor to discuss the subject's emergency and the need to unmask prior to unmasking any subject.

In situations in which the investigator has tried but is unable to reach the Medical Monitor, best judgement on the part of the investigator should be used, based on the nature and urgency of the clinical situation, and may proceed with unmasking without having successfully reached and discussed the situation with the Medical Monitor. Once a subject's treatment assignment has been unmasked, the Medical Monitor should be notified within 24 hours of the unmasking of the treatment, without revealing the treatment.

As this is a fixed sequence clinical trial, every attempt will be made to maintain the masking for the other subjects in the event of an unmasking must occur, an unmasking procedure will be developed.

The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and the Case Report Form (CRF) that the mask was broken and provide the date, time, and reason for breaking the mask.

Any AE or Serious Adverse Event (SAE) associated with breaking the mask must be recorded and reported as specified in the protocol. The investigator has the responsibility to contact the

Sponsor (PI) in the event of a drug-related, serious, unexpected AE, the ProPharma Group or designee will be provided with the treatment assignment for the subject for regulatory reporting.

If treatment assignment is unmasked, the treatment will be discontinued immediately, and the subject will be discontinued from the clinical trial.

The mask may be broken in the case of pregnancy should the subject desire this information.

11. STUDY VISITS

11.1 COVID-19 Screening

The following procedures will be performed as part of COVID-19 screening:

- Subjects will be pre-screened based upon a COVID-19 questionnaire at each clinic visit.
- Body temperature will be measured at each visit.
- A nasal swab will be collected for COVID-19 testing on the day of Visits 1, 2 and 3.

Subject's further participation in the study will be based on the COVID-19 test results and procedures.

11.2 Visit 1: Screening (Day -21 to -8)

The following activities will be completed at Visit 1:

- Subjects will be asked to sign and date the Informed Consent Form.
- Demographic data, including date of birth, age, race and ethnicity, will be recorded.
- Medical/Medication and Ocular history will be completed for each subject.
- A urine pregnancy test will be performed (for all female subjects). Subjects with a positive result will be excluded.
- The subjects will be evaluated for study inclusion, exclusion and restriction criteria.
- Symptom Questionnaires (Ocular Discomfort Score, Ocular Itching Score) will be performed within 15 minutes prior to DED entry and every 5 +2 minutes up to 45 minutes while in the chamber.
- An SVA and SLE will be performed pre and post-DEC.
- IOP will be performed prior to DEC entry and dilated fundoscopy will be performed post-DEC.
- Saline will be administered in the clinic approximately 5 minutes prior to the DEC entry.
- DEC session (approximately 45 minutes).
- Adverse events and concomitants medications will be recorded before the subject leaves the site.
- After 7 ± 1 day of washout period, eligible subjects will come to Visit 2

11.3 Visits 2 (Day 1 + 2) and 3 (Day 8 + 2): Treatment/Dry Eye Chamber

Eligible subjects will return for 2 treatment visits. The treatment visits will occur following at least 7 days after visits 1 and 2. At Visit 2 the subjects will be randomized to receive one of the 2 treatment sequences as mentioned in Section 10.2. At Visits 2 and 3, the following activities will be performed:

- Medical/medication and ocular history will be updated for each subject.
- A urine pregnancy test will be performed (for all female subjects). Subjects with a positive result will be excluded.
- The subjects will be evaluated for study inclusion, exclusion and restriction criteria.
- An SVA and SLE will be performed pre and post-DEC.
- Symptom questionnaires (Ocular Discomfort Score, Ocular Itching Score) will be performed within 15 minutes prior to study treatment administration and approximately every 5 minutes while in the chamber.
- Test product will be administered in the clinic approximately 5 minutes prior to the DEC entry.
- DEC session (approximately 45 minutes).
- Dilated fundoscopy will be performed post-DEC after SVA and SLE at Visit 3.
- Adverse events and concomitants medications will be recorded before the subject leaves the site.
- Study exit (Visit 3).

11.4 Phone call follow-up

For any subjects who withdraw prior to study exit, there will be a phone call within 7(+3) days to follow up on the subject's health.

12. STUDY ASSESSMENTS AND PROCEDURES

12.1 Efficacy Assessments

12.1.1 Ocular Discomfort Score and Ocular Itching Score

Ocular discomfort score and ocular itching score will be measured within 15 minutes before chamber entry and over 45 minutes (every 5 minutes) in the DEC. The ocular discomfort score is a participant-reported symptom index (0 to 10 scale; 0 represents no discomfort, 10 represents maximum discomfort). Ocular itching score is a participant-reported symptom index (0 to 10 scale; 0 represents no itching, 10 represents maximum itching). The assessments of ophthalmic signs and symptoms will be self-administered by subjects using an electronic P[redacted].

12.2 Safety Assessments

For details regarding the timing of procedures, refer to Table 5.1-1.

12.2.1 Snellen Visual Acuity (SVA)

SVA is a widely used metric for assessing the visual function that is sensitive to ophthalmic, retinal, and brain diseases. SVA chart contains lines, and each line contains five Sloan letters; the lines are all of the identical complexity, and the letter sizes increase geometrically from line to line. Each line on the chart has a similar assignment, with the font size being the only difference. Right and left eyes are tested using charts with distinct letter sequences. SVA will be measured at Visits 1, 2, and 3 as per the site's Standard Operating Procedure (SOP).

12.2.2 Slit-lamp Exam (SLE)

The slit-lamp will be placed in front of the subject's eyes and a narrow beam of bright light from the slit-lamp is directed into the eye. SLE observations will be graded as "normal" or "abnormal." Abnormal findings will be categorized as clinically significant or not. The cornea, conjunctiva, anterior chamber, lens, and eyelid will be examined. Slit-lamp Exam will be conducted at Visits 1, 2, and 3 as per the site's Standard Operating Procedure.

12.2.3 Intraocular Pressure (IOP)

The fluid pressure inside the eye is commonly known as IOP. IOP will be measured using non-contact tonometry at Visits 1as per the site's Standard Operating Procedure.

12.2.4 Dilated Fundoscopy

Examining the fundus is an effective strategy to acquire a sense of the subject total vasculature. The investigator or qualified staff will perform a dilated fundoscopy to evaluate clinically significant fundus abnormalities and vitreous pathology. Dilated fundoscopy will be performed at Visit 1 and 3 as per the site's Standard Operating Procedure.

Safety measurements may be obtained at the discretion of the Investigator in addition to the safety assessments described in this section.

12.2.5 COVID-19 Test (SARS-CoV-2)

At Visits 1, 2, and 3, a nasal swab will be collected at the clinical site for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Subjects with a positive test result will be excluded/withdrawn from the study.

12.2.6 Demographics and Medical/Medication and Ocular History

The demographic data and a complete medical/medication and ocular history will be recorded at the Screening Visit. The following demographic information will be recorded: date of birth, gender, race, ethnicity, height, and weight.

12.2.7 Adverse Event Query/Concomitant Medication Query

The staff will record all adverse events observed, queried, or spontaneously volunteered by the subjects. An adverse event query will be performed as scheduled as per Investigator's direction throughout the post-dose confinement period, prior to being released from confinement, and at each return visit for the study (if applicable). Subjects will be asked non-leading questions such

as “How do you feel now?”, “How have you felt since last asked?” or “Have you taken any medication since last asked?” If the presence of any symptom(s), adverse event(s), and/or concomitant medication is recorded, the clinical staff may advise the subjects to remain at the clinic site for safety reasons until the Investigator decides it is safe for the subjects to leave. If the subject decides to leave despite the Investigator's advice, he/she will be asked to sign a waiver.

13. ANALYSES AND REPORTS

13.1 Final Integrated Report

A final integrated report will be issued to the Sponsor (PI) by Cliantha Research, which will be reviewed and released by Cliantha Quality Assurance (QA). It will contain a narrative description of the clinical and statistical procedures used during the conduct of the study. Appropriate tables and graphs will be created to summarize the data.

The regulatory agency for submission will be Health Canada. The final integrated report may also be included in submissions to other international regulatory agencies.

14. STATISTICAL CONSIDERATIONS

14.1 Statistical Analyses

Due to the exploratory nature of the study, statistical analysis will be performed as required.

14.2 Safety Analysis

Safety analysis will include descriptive analysis and listings according to received treatment. Safety analysis will be performed on all subjects receiving at least one dose of study medication. Subject’s safety data will be presented according to the treatment they actually received. The Safety population will be used for all analyses of safety endpoints as well as demographics and baseline characteristics.

Adverse events and SAE will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 23.1 and presented by the treatment group. Summary tables listing the type, date of onset, date and time of resolution, incidence, severity, outcome, action taken, and Investigator’s opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization.

Concomitant medication used during the study will be listed by treatment and subject.

14.3 Interim Analyses No interim analysis is planned at this point.

14.4 Sub-group Analyses

No sub-group analysis is planned at this point.

15. ADMINISTRATIVE STUDY RECORDS

15.1 Subject Enrollment and Identification

Participants will be enrolled in the study prior to any screening procedures being performed. All participants will be assigned a unique subject identification number. This number will be used to identify their records until they are randomized into a fixed treatment sequence. Participants who

are randomized into the study will be assigned a unique randomization number which will be used to identify their records post-randomization.

15.2 Study Charts/Records and Source Documents

A study chart/record will be maintained on-site for each subject to file records such as general observations, medical and medication use history, physical examination, clinical laboratory data source documents and related documentation. The original record will be considered the data 'source document'. The source documents will be available for inspection (direct/remote) by the study monitors and/or representatives before, during, or upon completion of the study. Good documentation practices will be followed for source documentation. All corrections will be dated and initialled. The Investigator will retain the originals.

All clinical study data not available via electronic source will be collected by the Investigator and staff and recorded on source documents. The Investigator will assume responsibility for ensuring the completeness and accuracy of all clinical documents.

This clinical trial will be conducted, and the data will be generated, documented (recorded), and reported in compliance with the protocol, GCP standards, ICH and other applicable local laws and regulations.

All Cliantha Research staff will be appropriately trained to ensure the collection of accurate, consistent, complete, and reliable data are entered onto an electronic case report form (eCRF) unique for each subject.

All data collected in the study will be captured and maintained in a secure and validated electronic data capture (EDC) system. Cliantha Research staff will enter the data for each subject into an eCRF with the exception of the data collected in an electronic or paper source (e.g., lab data, diary data, etc.). Data source will be described in the Data Management Plan (DMP).

The eCRF and/or diaries will contain edit checks and/or controls to ensure the quality, integrity, accuracy and completeness of the data entered. The Medical Monitor (medical representative) may examine eCRF and diary data for preliminary medical review (direct/remote).

The eCRF data will be maintained in a validated study database with an audit trail of all changes that are made to the database, including the reason for the data change. AEs will be coded using a standard dictionary, Medical Dictionary for Regulatory Activities [redacted], while concomitant medications will be categorized using the World Health Organization Drug Dictionary (the most updated version of the dictionary) at the start of the study.

Creation and validation of the EDC system and management of the data will be conducted in accordance with Title 21 of the Code of Federal Regulations (CFR) Part 11 and the FDA Guidance for Industry on Computerized Systems Used in Clinical Investigations. Methods used to ensure the quality and integrity of the data will be documented in the DMP, which will be approved by the Data Management provider and the Sponsor (PI).

15.3 Retention and Availability of Investigational Records

All drug accountability records, CRFs, source data and related regulatory documents must be retained for at least 25 years following completion of the clinical trial.

16. DRUG ACCOUNTABILITY

All study product receipt, inventory, dispensing, dosing, and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study subjects according to established procedures.

16.1 Product Shipment

The drug supplies for this study will be shipped to:

[redacted]

16.2 Product Receipt

Upon receipt of drug supplies, the Investigator or designee will conduct an inventory and record the date received and the amount of drug received. If multiple containers of the test and/or reference products are received, the products will be randomized to dispensing inventory.

16.3 Product Storage

[redacted] The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. At the end of the study, all partially used and unused study products will be stored or disposed of as determined and agreed upon by the Sponsor (PI) and [redacted].

16.4 Drug Dose Package Labeling

The study medication will be dispensed in individual subject's kits and labeled with study-specific labels. Labels will reflect the use for the investigational purpose only, plus a unique number that will be used to assign the medication to the subject according to their randomized treatment assignment.

17. SUBJECT SAFETY MONITORING AND ADVERSE EVENTS

17.1 Subject Safety Monitoring

Study staff will monitor the subjects throughout the study. Between the time interval of the study periods, staff will be available for subject queries. An Investigator will be on-site for dosing and on-call throughout the duration of the study.

The Sponsor (PI) will designate qualified individuals to maintain a close liaison with the Investigator and study staff to ensure the clinical investigation follows the approved protocol and the research intent of GCP. Internal SOP for compliance with applicable government regulations will also be applied. This liaison will be documented by personal and/or telephone visits prior to study initiation and during the study to enable periodic reviews as well as clarify any questions, which may arise during the study. During on-site visits, Sponsor (PI) study monitors will be provided access to all study source documents to ensure the integrity of the data. Direct/remote access to such data during the inspection or audits/monitoring of the study will be provided to IRB, Sponsor (PI)/ his representatives and regulatory authorities, but they must agree to respect the confidentiality of the data.

17.1.1 Pregnancy

Any female with a confirmed positive pregnancy result during study participation (from the time of signing the informed consent form until the end of the study) will be excluded from the study or immediately withdrawn from the study. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the subject safety, the subject will be followed until the end of the pregnancy (including spontaneous or voluntary termination).

If a subject becomes pregnant or suspects that they became pregnant during the study or within 30 days after the study is complete, they must notify the clinical site.

The pregnancy will be recorded on a Pregnancy form (provided by the clinical site) and reported to ProPharma Group and IRB. In the absence of a pregnancy form, an adverse event form can be used.

Attempts to contact the subject to inquire about the status and progression of the pregnancy will be made at intervals deemed appropriate (e.g., at least every three months) until an outcome of the pregnancy is known. This contact will be documented.

17.2 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. AEs may include any changes in physical examination or laboratory parameters that are, in the Investigator's opinion, clinically significant changes.

An SAE is defined as any AE that, in the view of either the Investigator or Sponsor (PI), results in any of the following outcomes:

- Death
- A life-threatening AE
- In-patient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death be life-threatening or require hospitalization may be considered an SAE when based upon appropriate medical judgment. They may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening AE: Any AE that places the subject, in the view of either the Investigator or Sponsor (PI), at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Unexpected AE: Any AE not listed in the applicable product information (e.g., drug product label or Investigator's brochure) or that is not listed at the specificity or severity that has been observed.

"Unexpected," as used in this definition, also refers to AEs that are mentioned in the applicable product information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. If such an unexpected AE is suspected to be related to the drug, then it is known as "Suspected Unexpected Serious Adverse Reactions (SUSARs)".

17.2.1 Recording Adverse Events

The staff will record all AEs observed, queried, or spontaneously volunteered by the subjects (regardless of seriousness or relationship to study treatment) in the appropriate section of the subject's case report form or source documents. Subjects experiencing AEs (including those withdrawn from the study due to an AE) will be followed until recovery to a satisfactory state, or stabilization, or appropriate outcome is established as judged by the Investigator. Exacerbation of conditions related to the signs and symptoms of Dry Eye will not be reported as an AE.

The following details will be recorded for AEs:

- Description of event/symptom
- Onset date and time of event
- End date and time of event
- Maximum severity/intensity rated as follows:

  Mild: Causing no limitation of usual activities, the subject may experience slight discomfort.

  Moderate: Causing some limitation of usual activities, the subject may experience annoying discomfort

  Severe: Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain

- Action taken with study treatment noted as follows:
  - Dose not changed

- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

- Any other action taken (such as concomitant medication, non-drug therapy, hospitalization or none)
- Outcome of AE noted as follows:
  - Fatal
  - Not recovered/not resolved
  - Recovered/resolved
  - Recovered/Resolved with sequelae
  - Unknown
- Causality noted as follows:

Related:	A causal relationship between the study treatment and the AE is a reasonable possibility.
Not Related:	A causal relationship between the study treatment and the AE is not a reasonable possibility.

17.2.2 Reporting Serious Adverse Events

AEs and medical history will be coded and classified according to the MedDRA, and AEs will be reported with respect to severity, duration, relationship to study drug(s) and action taken. Concomitant medications will be categorized using the World Health Organization Drug Dictionary (the most updated version of the dictionary) at the start of the study.

All serious adverse experiences, whether deemed drug-related or not, will be reported to ProPharma Group preferably by email (or by telephone if email is not possible) immediately after the awareness by Investigator and in no case later than 24 hours, followed by a written report within 2 working days. The investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to their local IRB/Research Ethics Board (REB)/Independent Ethics Committee (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 the investigational product.

The Sponsor (PI) or their designee is responsible for appropriate reporting of relevant AEs, suspected unexpected serious adverse reactions (SUSARs) involving investigational product, to all regulatory authorities as per the below timeline:

- When neither fatal nor life-threatening, within 15 days after becoming aware of the information
- When fatal or life-threatening, immediately when possible and, in any event, within seven (7) days after becoming aware of the information
- Within eight (8) days after having informed Health Canada of the adverse drug reaction, submit a report that includes an assessment of the importance and implication of any findings

In addition, the Sponsor (PI) or designee will be responsible for the submission of safety letters (e.g., SUSARs) to the central IRB/REB/IEC and 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 (PI) as soon as possible to the competent authority (ies) concerned together with proposed actions.

The following Sponsor representative is to be contacted immediately following the occurrence of an SAE:

[redacted]
Phone: [redacted]
Email: [redacted]

17.2.3 Removal of Subjects from Study

Subjects will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator may withdraw a subject from the study to protect the health of that subject. A subject may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

All subjects who receive at least one dose of either of the study products will be included in the safety analysis. If a subject terminates from the study early, all efforts will be made to complete all applicable safety procedures. In case of early termination, the Investigator will fully document the reason for early termination. Reasons for the early termination may include the following:

- Voluntary withdrawal by subject.
- Significant AE that led the Investigator or subject to withdraw for safety reasons.

- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Pregnancy
- Participant enrolls in another clinical trial or is found to have previously enrolled in this clinical trial.
- Positive COVID-19 test result.

17.2.4 Termination of Study Due to Adverse Events

If, in the opinion of the Sponsor (PI), Regulatory authorities or the IRB, the incidence and severity of AE(s) outweighs the benefit of continuing the study, the study may be terminated.

18. ETHICS OF CONDUCT

This study will be conducted in compliance with the protocol and accordance with the appropriate guidelines and all applicable federal government codes, acts and regulations, the ethical principles that have their origins in the Declaration of Helsinki and all amendments, Good Clinical Practice (GCP) requirements, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance E6 (R2), and Tri-Council Policy Statement (Canada). Protocol and Informed Consent approval by the Ethics Board will be sought prior to the commencement of the study, and a copy of the Ethics attestation will be sent to the Sponsor (PI).

19. QUALITY CONTROL AND QUALITY ASSURANCE

Cliantha Research will implement and maintain quality control procedures to ensure that the study is conducted and that the data are generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents.

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor (PI) or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct/remote access to source data documents.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol, written SOPs, study-

specific plans and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Separate risk management plan will be developed prior to the start of the study in accordance with ICH E6 (R2).

19.1 Pandemic COVID-19 Response Plan

Regulatory authorities have recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of the clinical study. COVID-19 pandemic has created a lot of uncertainty in the current situation and has put the subject's safety, protocol compliance and data validity at high risk.

Due to the COVID-19 pandemic, challenges may arise for clinical study conduct, for example, quarantines of site personnel/study participants, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administration or use of the investigational product, housing duration or adhering to protocol specified visits and laboratory/diagnostic testing.

To accommodate these challenges and mitigate safety risks associated with COVID-19, changes may be required from approved protocol which includes (but not limited to) conducting the study in multiple groups, change in study procedures timing, change in subject's housing duration; ambulatory visits, additional test or parameter may be performed to standard inclusion or exclusion criteria at the discretion of Investigator/designee, etc. The changes made to the procedure will prioritize the subject's safety and data validity and integrity. For any significant change, as per regulatory guidelines, a planned protocol deviation will be filled and notified to IRB and/or local regulatory (as applicable).

All participants will be pre-screened prior to enrolment into the study and evaluated for risk factors and symptoms of COVID-19 according to the most recent regional Public Health guidelines[13] available at the time of pre-screening. The screening is conducted through telephone at the time of appointment confirmation and again when the subject arrives at the clinic for any visit.

Additional health checks, including body temperature or other vital sign monitoring, etc., may be performed during the study at the discretion of the Investigator/designee, even if not specified in the protocol. A subject who is tested positive to COVID-19 during the study will be withdrawn from the study. This subject and other subjects in close contact will be handled as per applicable local Public Health Guidelines.

As the science and regulations are continuously being adapted to the evolving information around the pandemic, additional measures apart from the ones mentioned here may be undertaken to ensure subject safety and appropriate study conduct. The IRB would be informed for their review and approval as applicable.

Risk Mitigation plan/Risk Evaluation and Mitigation strategy will be made to minimize the risk for COVID-19 exposure and to handle possible situations during the COVID-19 pandemic.

20. REGULATORY

20.1 Institutional Review Board/ Health Canada

The Investigator agrees to provide the IRB with all appropriate material, including a copy of the protocol, consent document, and advertising text (if study-specific advertising is used). The study will not be initiated without written IRB approval of the research plan and consent document. The Investigator will provide appropriate reports on the progress of this study to the IRB in accordance with applicable government and/or Institute regulations. The IRB will be informed of any modifications of the protocol or consent document. Approval in writing will be obtained from the IRB prior to implementation of any changes which may increase subject risk or which may alter the validity or objectives of the data collected. A copy of the IRB approval letter covering such alterations will be maintained by the Sponsor (PI). For modifications to the protocol which are administrative in nature or do not affect subject risk, the IRB will be notified in writing by the Sponsor (PI).

The Investigator must promptly report to the IRB all unanticipated problems involving risks to subjects. This includes AEs and other types of problems (i.e., AEs are a subset of unanticipated problems) that the Investigator is required to report to IRB.

Sponsor should submit a notification to Health Canada indicating that the trial is complete.

20.2 Consent Document

A properly executed, written consent in compliance with current federal codes, GCP, acts and regulations and in accordance with ICH Guidance E6 on GCP shall be obtained from each subject prior to entering the trial or prior to performing any unusual or non-routine procedure involving risk to the subject. The consent document(s) to be used will be reviewed and approved by the Sponsor (PI). It will be submitted by the Sponsor (PI) to the IRB for review and written approval prior to the start of the study. The Investigator shall provide a copy of the consent to the subject and a signed copy shall also be maintained in the study records. Attention is directed to the basic elements required in the consent document under current federal regulations for Protection of Human Subjects:

1. A statement verifying the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any experimental procedures.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility the applicable regulatory agencies and the study Sponsor may inspect the records.

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of consent, if appropriate, must be provided to the subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the study.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

When seeking informed consent for applicable clinical trials, a statement may be provided to the subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank, if applicable.

20.3 Confidentiality

All information disclosed to the Investigator by the Sponsor or Sponsor designees shall be treated by the Investigators as strictly confidential. The Investigator will only use this information for the purpose of conducting the clinical trial described within this protocol. The Investigator must agree not to disclose any information contained within this protocol to any third party, except to those involved in the conduct of this clinical study and who are bound by the obligations of confidentiality.

Information concerning the study treatment, patent applications, processes, unpublished scientific data, and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to those involved in the approval or conduct of the study. It is understood that the Investigator will use the information obtained during the clinical study in connection with the development of the treatment and therefore may disclose it as required to

regulatory agencies. The Investigator understands that he has an obligation to provide the Sponsor with all data obtained during the study.

20.4 Investigator's Statement

The Investigator agrees to conduct the trial as outlined in the approved protocol and in accordance with the [redacted] guidelines and all applicable federal government codes, acts and regulations, GCP requirements and ICH guidance E6 (R2) on Good Clinical Practice. These GCP guidelines include, but are not limited to:

1. Permission to allow the [redacted] or applicable regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality. If this study is to be inspected by a regulatory agency, Cliantha will be notified as soon as possible.
2. Submission of the proposed clinical investigation, including the protocol, consent document, and advertising text (if study-specific advertising is used) to a duly constituted IRB for approval and acquisition of written approval for each, prior to study initiation.
3. Use of a written consent document obtained prior to entry into the study or prior to the performance of any non-routine procedures that involve subject risk. The consent document(s) must contain all the elements specified in the federal regulations and have been previously approved by [redacted] and the IRB.
4. Submission of any proposed change in or deviation from the protocol to the IRB, using a signed formal amendment document prepared by [redacted] and/or Investigator. If the change or deviation increases the risk to the study population or adversely affects the validity of the clinical investigation or the subject's rights, IRB approval must be obtained prior to implementation. IRB will be notified regarding changes that do not involve risk or affect the validity of the investigation or the subject's rights.
5. Documentation and explanation of protocol deviations will be made on the appropriate case report form page, source document or by written documentation to Cliantha.
6. The Investigator shall promptly report to the [redacted] any severe adverse event that may reasonably be regarded as caused by, or probably caused by, the study treatments.
7. The Investigator shall submit timely progress reports to the IRB and Cliantha at appropriate intervals, but not to exceed one year. The final report will be submitted to the IRB within 4 months after study completion, termination, or discontinuation.
8. The Investigator and study staff shall maintain accurate source documents from which case report form data or source documents are based and accountability records that show the receipt and disposition of all test article(s) shipped to the Investigator.
9. When new information is relevant to participants' welfare, Investigator must promptly inform all participants to whom the information applies that requires to be reported to Health Canada as well.

The Investigator agrees that all information provided by the [redacted] (including pre-clinical data) protocols, case reports from data or source documents, and verbal and written information will

be kept strictly confidential and confined to the personnel involved in conducting the trial. It is recognized this information may be given in confidence to the IRB.

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