CLINICAL TRIAL PROTOCOL OTX-101-2016-002

An Open-Label Extension of a Randomized, Multicenter, Double-Masked, Vehicle-Controlled Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca

Study Phase:	Phase 3
Product Name:	OTX-101 Ophthalmic Solution
Indication:	Treatment of keratoconjunctivitis sicca
Sponsor:	Ocular Technologies SARL [redacted]
Medical Monitor:	Robert David, MD
Original Protocol:	6 July 2016
Amendment 1:	23 March 2017

Confidentiality Statement

SPONSOR SIGNATURE

Study Title:	An Open-Label Extension of a Randomized, Multicenter, Double-Masked, Vehicle-Controlled Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca
Study Number:	OTX-101-2016-002
Original Protocol:	6 July 2016
Amendment 1:	23 March 2017

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Ocular Technologies SARL:

INVESTIGATOR'S AGREEMENT

Study Title:	An Open-Label Extension of a Randomized, Multicenter, Double-Masked, Vehicle-Controlled Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca
Study Number:	OTX-101-2016-002
Original Protocol:	6 July 2016
Amendment 1:	23 March 2017

I have received and read the OTX-101-2016-002 protocol. The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with ICH guidelines, and all applicable United States federal regulations and local legal and regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Project manager	[redacted]	[redacted]
Medical monitor	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company: Ocular Technologies SARL	
Name of Investigational Product: OTX-101 0.09%	
Name of Active Ingredient: Cyclosporine	
Title of Study: An Open-Label Extension of a Randomized, Multicenter, Double-Masked, Vehicle-Controlled Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca	
Studied Period (Years): 1 Estimated date first patient enrolled: August 2016 Estimated date last patient completed: September 2017	**Phase of Development:** 3
Objective: The objective of this study is to evaluate the long-term safety of OTX-101 0.09% ophthalmic solution in the treatment of keratoconjunctivitis sicca (KCS).	

Methodology: This is an open-label extension of OTX-101-2016-001, a randomized, multicenter, double-masked, vehicle-controlled study in which subjects were randomized to 1 of 2 treatment arms and treated for 12 weeks as follows:

- OTX-101 0.09% (N = [redacted] subjects)
- Vehicle (N = [redacted] subjects)

Subjects successfully completing Study OTX-101-2016-001 may be eligible to enroll in this 40 to 52 week open label extension study in which all subjects will receive OTX-101 0.09% therapy. Subjects may also use unpreserved artificial tears, as needed. **Subjects assigned to OTX-101 0.09% in Study OTX-101-2016-001 will participate for 40 weeks. Subjects assigned to vehicle in Study OTX-101-2016-001 are eligible to participate for 52 weeks. Both subject sets will total 52 weeks of participation receiving OTX-101 0.09%.**

Subjects may enroll in Study OTX-101-2016-002 for up to 14 days following completion of Visit 5 of Study OTX-101-2016-001. At Visit 5a, sites will obtain signed informed consent and dispense study medication. If Visit 5a is not conducted on the same day as Visit 5 of Study OTX-101-2016-001, any female subject of childbearing potential must also have a negative urine pregnancy test. Study "Day" approximately reflects the cumulative number of days of exposure to study drug since the baseline visit of Protocol OTX-101-2016-001, regardless of actual calendar time elapsed.

Subjects will self-administer study medication topically to both eyes BID for 40 to 52 weeks depending on their treatment assignment in Study OTX-101-2016-001. Safety evaluations for all subjects will be conducted at study visits on Days 182, 273 and 364; the window for Visits 6 (Day 182) and Visit 7 (Day 273) will be ± 7 days; the window for Visit 8 (Day 364) will be +14 days for those subjects assigned to OTX-101 0.09% in Study OTX-101-2016-001. (± 14 days for subjects assigned to vehicle in Study OTX-101-2016-001, participating for 52 weeks in Study OTX-101-2016-002). Subjects assigned to vehicle in Study OTX-101-2016-001, participating for 52 weeks in Study OTX-101-2016-002, will also be evaluated at Visit 9 (Day 448), which will have a visit window of +14 days. Both eyes will be assessed at each visit. Adverse events and concomitant medications will be documented from signing of informed consent to the subject's final visit.

Number of Subjects (Planned): Approximately [redacted] subjects are to be enrolled in the Study OTX-101-2016-001 (approximately [redacted] treatment arm) at approximately 50 clinical sites. Approximately [redacted] subjects successfully completing that study may be eligible to enter into this extension study.

Diagnosis and Main Criteria For Inclusion:

Inclusion Criteria

1. Successful completion of participation in Protocol OTX-101-2016-001.
2. All subjects must provide signed written consent prior to participation in any study related procedures.
3. Female subjects of childbearing potential must have a negative urine pregnancy test at Visit 5 (Day 84) of Protocol OTX-101-2016-001 or at Visit 5a of Protocol OTX-101-2016-002, if conducted at a later date. Women of childbearing potential (i.e., women who are not either postmenopausal for one year or surgically sterile) and men who have partners of childbearing potential must use an acceptable form of contraception throughout the study.
4. Corrected Snellen visual acuity (VA) of better than 20/200 in both eyes at Visit 5 (Day 84) of Protocol OTX-101-2016-001

Exclusion Criteria

1. Subjects reporting an Adverse Event that has not resolved by Visit 5 of Protocol OTX-101-2016-001 may be excluded if, in the judgment of the Principal Investigator and Medical Monitor, it would not be in the subject's best interest to continue treatment with study drug.
2. Use of Restasis or any topical cyclosporine preparation following Visit 5 of Protocol OTX-101-2016-001.
3. Use of any prescription topical ophthalmic medications (including antiglaucoma medications) other than the assigned study medication during the study period. Unpreserved artificial tears are permitted.
4. Current active eye disease other than KCS (i.e., any disease for which topical or systemic ophthalmic medication is necessary).
5. History of herpes keratitis.
6. Unstable macular disease (e.g., age-related macular degeneration, diabetic maculopathy). Stable macular disease is defined as no reduction in central VA since the screening visit of Study OTX-101-2016-001.
7. Diagnosis of chronic uveitis.
8. Corneal transplant following Visit 5 of Protocol OTX-101-2016-001.
9. Corneal refractive surgery following Visit 5 of Protocol OTX-101-2016-001.
10. Non-laser glaucoma surgery following Visit 5 of Protocol OTX-101-2016-001.
11. Lagophthalmos or clinically significant eyelid margin irregularity of the study eye whether congenital or acquired.

Exclusion Criteria (continued):

12. Presence of conjunctivochalasis (i.e., mechanical blockage of the lower lid punctum by redundant conjunctiva).
13. Presence of pterygium in either eye.
14. Unwilling to discontinue use of contact lenses during the duration of the study.
15. Preplanned elective surgery or hospitalization during the study period.
16. HIV-positive.
17. Unable to reliably report symptoms and history.
18. Has a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment or follow-up.
19. Women who are pregnant or breastfeeding.

Investigational Product, Dosage, and Mode of Administration: OTX-101 0.09%, 1 drop in both eyes BID

Reference Therapy, Dosage, and Mode of Administration: N/A

Duration of Treatment: 40 - 52 weeks

Study Procedures: Ophthalmic examinations must be conducted in the order listed in the Schedule of Procedures.

Visit 5a
The site will obtain signed informed consent, inclusion/exclusion criteria, and dispense study medication. If Visit 5a is not conducted on the same day as Visit 5 of Protocol OTX-101-2016-001, the site will also update concomitant medications and conduct a urine pregnancy test for female subjects of childbearing potential.

Visits 6 and 7 (Days 182 and 273)
The site will update concomitant medications, conduct a urine pregnancy test for female subjects of childbearing potential, conduct ophthalmic examinations as specified, document any AEs, and dispense study medication.

Visit 8 (Day 364): Final Treatment Visit for Subjects assigned to OTX-101 0.09% in Study OTX-101-2016-001
The site will update concomitant medications, conduct a urine pregnancy test for female subjects of childbearing potential, conduct ophthalmic examinations as specified and document any AEs. Study medication will be dispensed to those subjects continuing in the study for an additional 12 weeks.

Visit 9 (Day 448): Final Treatment Visit for Subjects assigned to vehicle in Study OTX-101-2016-001
The site will update concomitant medications, conduct a urine pregnancy test for female subjects of childbearing potential, conduct ophthalmic examinations as specified and document any AEs.

Clinical site personnel will document all received and returned study medication at each visit. Study medication accountability will be conducted by the monitor at each applicable monitoring visit.

If a study subject is discontinued from study medication before Visit 8 or Visit 9, as appropriate, every effort should be made to perform all Visit 8 or Visit 9 procedures during the visit when the subject is discontinued.

Efficacy Assessments:

None

Safety Assessments:

Safety assessments will include corrected Snellen VA, slit lamp examination, IOP, dilated fundoscopy/ophthalmoscopy and collection of AEs and concomitant medications

Criteria for Evaluation:

- The safety of OTX-101 0.09% as determined by ocular and non ocular AEs

Statistical Methods:

Analysis Population:

- Safety: The safety population will include all patients who have received at least one dose of the study medication.

Statistical Analyses:

Descriptive statistics will be used to summarize continuous outcomes (number of subjects, mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point. All summary tables will be supported with individual subject data listings.

Table 2: Schedule of Procedures

Procedures	**Visit 5a**	**Visit 6**	**Phone Contact**	**Visit 7**	**Phone Contact**	**Visit 8**	**Phone Contact**	**Visit 9**	**Early**
Day of Study [a]	**84**	**182 ± 7**	**227 ± 7**	**273 ± 7**	**318 ± 7**	**364 + 14 [i]**	**409 ± 7**	**448 + 14**	**Discontinuation**
Days since Visit 5a	**-**	**98**	**143**	**189**	**234**	**280**	**325**	364	
Informed consent [j]	X								
Inclusion/exclusion criteria	X								
Concomitant medication history/review	X[b]	X	X	X	X	X	X	X	X
Urine pregnancy test [c]	X[b]	X		X		X		X	X
Corrected Snellen Visual Acuity		X		X		X		X	X
Slit lamp examination		X		X		X		X	X
Ophthalmoscopy/dilated fundoscopy						X[g]		X[g]	X
IOP [d]		X		X		X		X	X
Study medication distribution	X	X		X		X[h]			
Adverse event assessment [e]	X	X	X	X	X	X	X	X	X
Study medication accountability [f]		X		X		X		X	X

[a] "Day" approximately reflects the cumulative number of days in study (Protocol OTX-101-2016-001 and OTX-101-2016-002), regardless of actual calendar time elapsed. And 'Day of Study' is used along with Visit, throughout this protocol – e.g., Visit 6 (Day 182), etc.

[b] Performed if Visit 5a is not conducted on the same calendar day as Visit 5 of Protocol OTX-101-2016-001.

[c] Women of childbearing potential only.

[d] Measure IOP using Goldmann applanation tonometry.

[e] Collection of AEs extends from signing of informed consent until the last study visit.

[f] Clinical site personnel will document all received and returned medication at Days 182, 273, 364 and 448. Study medication accountability will be performed by the monitor at each applicable monitoring visit.

[g] Examination is required only at the subject's final visit,

[h] Medication is dispensed if the subject is participating for an additional 12 weeks

[i] 364 ± 14 days if the subject is participating for an additional 12 weeks

[j] Updated ICF due to Amendment #1 to be signed by all participating subjects for Protocol OTX-101-2016-002 Amendment #1

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations

Abbreviation or Specialist Term	Explanation
AE	adverse event
BID	twice daily
DSEK	Descemet's stripping endothelial keratoplasty
FDA	Food and Drug Administration
eCRF	electronic case report form
EDC	electronic document capture
ERG	electroretinography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HLA-DR	human leukocyte antigen-DR
HPRT-1	hypoxanthine phosphoribosyltransferase 1
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
IFN-γ	interferon gamma
IL	interleukin
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
LASIK	laser-assisted in situ keratomileusis
LFU	lacrimal function unit
LOCF	last observation carried forward
LRI	limbal relaxing incision
KCS	keratoconjunctivitis sicca
MAR	missing at random
MMP	matrix metalloproteinase
NZW	New Zealand white (rabbit)
OTC	over-the-counter
PRK	photorefractive keratectomy

Abbreviation or Specialist Term	Explanation
QID	four times daily
SAE	serious adverse event
SOP	standard operating procedures
US	United States
VA	visual acuity

4. INTRODUCTION

4.1. Background

Keratoconjunctivitis sicca (KCS) is a common multifactorial ophthalmologic disorder of the tears and ocular surface characterized by symptoms of burning, stinging, itching, grittiness, scratchiness, foreign body sensation, dryness, stickiness, and tired eye sensation. The onset of symptoms is usually gradual, bilateral, and chronic. Symptoms typically become more bothersome later in the day and are intensified by various environmental factors.

The prevalence of KCS varies but it has been estimated to affect up to 35% of the population, although this number may be underreported and may be increasing especially in the older population (International Dry Eye Workshop, 2007).

Keratoconjunctivitis sicca is generally caused by a disturbance of the lacrimal function unit (LFU), an integrated system comprising the lacrimal glands, ocular surface and lids, and the sensory and motor nerves that connects them. The LFU controls and regulates the major components of the tear film and responds to the various intrinsic and extrinsic environmental factors that a person encounters.

The overall function of the LFU is to preserve the integrity of the tear film, the transparency of the cornea, and the quality of the image projected onto the retina. Damage to any component of the LFU can result in KCS, but the main mechanism for KCS is driven by tear hyperosmolarity, tear film instability, and inflammation.

Activation of innate and adaptive immune systems by tear hyperosmolarity and desiccation leads to increased production of inflammatory mediators that can disrupt corneal barrier function (interleukin [IL]-17, matrix metalloproteinase [MMP]-3 and MMP-9), sensitize corneal and ocular surface nerve endings (IL-1β and IL-6), cause epithelial cell death (apoptosis, interferon gamma [IFN-γ]) and loss of mucus producing goblet cells (IFN-γ), and cause infiltration of T cells in the conjunctival tissue that further destabilizes the tear film and leads to more severe ocular surface disease ([redacted]). Increased human leukocyte antigen-DR (HLA-DR) expression by the conjunctival epithelium has been observed as a universal feature of KCS. The effectiveness of cyclosporine in the treatment of KCS may be due to its effects on the pathogenesis of this disease.

In the United States, Restasis®, a 0.05% ophthalmic emulsion of cyclosporine, is the only approved prescription product for patients with KCS. Restasis is indicated for the increase in tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS (Restasis Prescribing Information, 2013). This product has been shown to be effective in a relatively small percentage (15%) of patients, and, as a consequence, there is an unmet medical need for alternative drug treatments for the treatment of KCS. To meet this unmet medical need, Ocular Technologies SARL is developing OTX-101, a new nanomicellar formulation of cyclosporine for the treatment of KCS.

4.2. Rationale for the Use of OTX-101 Ophthalmic Solution in the Treatment of KCS

OTX-101 is being investigated as a treatment for KCS. Cyclosporine has immunomodulatory and anti-inflammatory properties that are of presumed benefit for the treatment of KCS. Cyclosporine acts by binding calcineurin, an intracellular protein that ultimately controls transcription factors required for cytokine production and T-lymphocyte maturation, and also inhibits mitochondria-mediated apoptosis ([redacted]). By suppressing the immune-based inflammation of the ocular surface, treatment with cyclosporine allows the lacrimal glands to produce tears, potentiating the return of a more stable tear film and normal ocular surface.

Cyclosporine applied topically to the eye at concentrations of 0.05%, 0.1%, 0.2%, and 0.4% has previously been evaluated in various nonclinical and clinical studies for systemic and ocular effects. Additionally, Restasis® was approved in 2002 based on studies submitted to the Agency in support of New Drug Applications (NDAs) #050790 and #021023. Restasis studies showed significant improvement in Schirmer's test wetting [redacted] in [redacted] of patients in the treatment group compared with 5% of patients in the vehicle group ($P \leq 0.05$).

OTX-101, an aqueous nanomicellar solution of cyclosporine, is being developed in the expectation that it will be efficacious and well tolerated in the treatment of KCS.

4.3. Description of the Investigational Product: OTX-101 Ophthalmic Solution

The investigational drug product in this study, OTX-101, is an aqueous nanomicellar formulation of cyclosporine for topical ophthalmic use.

The nonclinical toxicology program for OTX-101 currently includes 5 studies. The ocular tolerability of OTX-101 administered 4 times daily (QID) was evaluated in 5 repeat-dose studies conducted in NZW rabbits: (1) a pilot 5-day ocular tolerability and tissue distribution study with OTX-101 0.1% , (2) a pilot 6-day ocular tolerability study with OTX-101 0.05%, (3) a pilot 7-day ocular toxicity and toxicokinetic study with OTX-101 0.05% and 0.1% compared to Restasis, (4) a GLP 28-day ocular toxicity and toxicokinetic study with a 14-day recovery period evaluating OTX-101 at 0.01%, 0.05%, or 0.1% concentrations and (5) a GLP 13-week ocular toxicity and toxicokinetic study with a 28-day recovery period evaluating OTX-101 at 0.01%, 0.05%, or 0.1% concentrations. Results demonstrated that OTX-101 dosed QID at concentrations as high as 0.1% for up to 13 weeks was safe and well tolerated, producing no clinical observations, no changes in intraocular pressure and retinal function, and no histopathology findings.

Following single-dose or repeat-dose administration of OTX-101 there was significant cyclosporine ocular tissue exposure but minimal systemic exposure. The highest exposure to cyclosporine was in the tears and eyelid, followed by the cornea and conjunctiva. Ocular cyclosporine exposure was higher with OTX-101 at either 0.1% or 0.05% concentrations than it was with Restasis. Following repeat dosing, the 0.05% OTX-101 nanomicellar formulation of cyclosporine produces approximately 1.3 to 2.5 times the tissue levels of Restasis (0.05% cyclosporine) in the cornea, conjunctiva, sclera, aqueous humor, and iris/ciliary body. The 0.1%

nanomicellar formulation of cyclosporine appears to produce approximately 1.8 to 4.5 times the tissue levels of Restasis.

With respect to systemic exposure, maximum concentration (C_{max}) for whole blood concentrations of cyclosporine was estimated to be 1.4 ng/mL following a single dose of the OTX-101 nanomicellar 0.1% formulation and 6.2 ng/mL following the final dose for QID dosing of OTX-101 0.1% at 2-hour intervals for 7 days.

For further background, including further information regarding the nonclinical studies related to OTX-101, and clinical and nonclinical studies related to cyclosporine, please consult the Investigator's Brochure (IB).

4.4. Clinical Studies

One clinical trial of OTX-101 has been completed. Study OTX-101-2014-001 was a Phase 2b dose-ranging, parallel-group, vehicle-controlled, double-masked trial of 12 weeks conducted in 455 subjects with KCS. The efficacy and safety of 2 concentrations of OTX-101 ([redacted] and [redacted]%) were compared with vehicle in subjects aged 22 to 91 years with dry eye disease as confirmed by study evaluations of signs and symptoms. Following a 2-week run-in period during which all subjects received vehicle BID, qualified subjects were randomized to OTX-101 [redacted]%, OTX-101 [redacted]%, or vehicle in a [redacted] ratio and treated BID for 12 weeks.

Both concentrations of OTX-101 demonstrated large, statistically significant differences from vehicle in mean change from baseline at 12 weeks for the first co-primary endpoint, lissamine green conjunctival staining, as well as for total corneal fluorescein staining, central corneal staining, and Schirmer's tear test (categorized) (Sponsor, data on file). Of note, a dose response trend was observed in central corneal staining, with OTX-101 [redacted] achieving a statistically significant difference from vehicle ($P < .01$). Neither active dose demonstrated a difference from vehicle in the second co-primary endpoint, global symptom score (Symptom Assessment iN Dry Eye [SANDE]).

In addition to an analysis of mean change from baseline, the Schirmer's tear test data were also analyzed with respect to the proportions of subjects demonstrating an increase from baseline at 12 weeks of [redacted] A dose response trend across some variables was observed, with rates of [redacted] for OTX-101[redacted], respectively. The [redacted] difference in rates between OTX-101 [redacted] and vehicle was statistically significant ($P < .01$). Similar results were obtained when a *post hoc* analysis was performed on the subset of subjects with baseline Schirmer's scores in the range of [redacted] comprising [redacted] of the study population (n[redacted]). Rates of [redacted] were observed for OTX-101 [redacted], respectively. The [redacted] difference in rates between OTX-101 [redacted] and [redacted] was also statistically significant ($P < .05$).

The most common ocular AEs (≥ 3 subjects) were instillation site pain (15.1%), eye irritation, and increased lacrimation (2.0% each) in the OTX-101 0.09% group; instillation site pain (13.2%), eye pruritus, and vitreous detachment (2.0% each) in the OTX-101 0.05% group; and instillation site pain (3.3%), eye pruritus, and blurred vision (2.6% each) in the vehicle group. Ocular AEs in all 3 treatment groups were predominantly mild to moderate and resolved without treatment (no action necessary regarding study drug). The most common non-ocular AEs (≥ 3 subjects) were upper respiratory tract infection in the OTX-101 0.09% group (2.0%),

bronchitis and sinusitis in the OTX-101 0.05% group (2.0% each), and nasopharyngitis in the vehicle group (2.6%).

The majority of AEs were mild to moderate in intensity. Severe ocular events were reported for 2 subjects in the OTX-101 0.09% group (instillation site pain), for 3 subjects in the OTX-101 0.05% group (instillation site pain [n=2], eye irritation [n=1]) and 1 subject in the vehicle group (eye pain). All of these events resolved, and none led to discontinuation of study drug.

Events considered to be related to study drug were observed in the OTX-101 0.09% group in 19.7% of subjects, in the OTX-101 0.05% group in 15.9% of subjects, and in the vehicle group in 7.9% of subjects. Related events were predominantly ocular, mild to moderate in intensity, and resolved without treatment. Study drug-related AEs led to discontinuation of study drug for 8 subjects, 3 in the OTX-101 0.09% group (hypersensitivity, instillation site pain, and eye irritation), 4 in the OTX-101 0.05% group (eye pruritus, conjunctival hyperemia, and instillation site pain [n=2]), and 1 in the vehicle group (reduced visual acuity and instillation site reaction reported for the same subject).

4.5. Justification of Route, Dose, Regimen, and Treatment Period

Cyclosporine ophthalmic emulsion 0.05% (Restasis®) instilled topically twice daily (BID) is approved by the United States (US) Food and Drug Administration (FDA) to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS.

Although both concentrations of OTX-101 demonstrated efficacy for multiple signs of KCS in Study OTX-101-2014-001, only OTX-101 0.09% BID will be compared to vehicle in the OTX-101-2016-001 Phase 3 study due to the dose-responses observed for several efficacy parameters. Given the absence of dose-limiting safety and tolerability issues observed in that study, it was judged unnecessary to include a lower concentration.

This 40 week extension study will enroll subjects successfully completing Study OTX-101-2016-001. Study OTX-101-2016-002 is intended to obtain long-term patient safety data.

4.6. Good Clinical Practice Statement

This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Conference of Harmonisation (ICH) guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

4.7. Population to Be Studied

Study subjects will be male or female, 18 years of age and older, with a patient-reported history of KCS for a period of at least 6 months and a clinical diagnosis of bilateral KCS supported by OTX-101-2016-001 study assessments.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety of OTX-101 0.09% in subjects with KCS.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This will be an extension of OTX-101-2016-001, a randomized, multicenter, double-masked, vehicle-controlled study that enrolled male and female subjects, 18 years of age and older, with a patient-reported history of KCS for a period of at least 6 months, a clinical diagnosis of bilateral KCS supported by OTX-101-2016-001 study assessments, and corrected Snellen VA of better than 20/200 in both eyes at Screening and at Baseline.

Subjects who complete Visit 5 (Day 84) of Study OTX-101-2016-001 may be eligible to enroll in protocol OTX-101-2016-002 within 14 days at the discretion of the Principal Investigator and Sponsor. Subjects who provide written informed consent at Visit 5a and meet the inclusion/exclusion criteria requirements will be enrolled in the study and receive study medication (OTX-101 0.09%). All subjects will participate for at least 40 weeks. Subjects who were randomized to the vehicle arm in Study OTX-101-2016-001 may have the opportunity to participate for additional 12 weeks, total of 52 weeks.

Subjects will self-administer study medication topically to both eyes BID from Visit 5a to Visit 8 (Day 364) or Visit 9 (Day 448). Safety evaluations will be conducted at all study visits. The window for Visits 6 and 7 will be ± 7 days. The window for Visit 8 will be +14 days for those subjects assigned to OTX-101 0.09% in Study OTX-101-2016-001 (± 14 days for subjects assigned to vehicle in Study OTX-101-2016-001, participating for 52 weeks in Study OTX-101-2016-002), and Visit 9 will be +14 days. Both eyes will be assessed at each visit. Adverse events and concomitant medications will be documented from signing of informed consent at each study visit.

6.2. Number of Subjects

A total of approximately [redacted] subjects will be enrolled in Protocol OTX-101-2016-001 (approximately [redacted] at approximately 50 clinical sites. Subjects who successfully complete that study may be eligible to participate at the discretion of the Principal Investigator and the Sponsor with the goal of enrolling approximately [redacted] subjects in Protocol OTX-101-2016-002.

6.3. Treatment Assignment

The treatment assignments will be:

- OTX-101 0.09%

6.4. Criteria for Study Termination

The study may be terminated at any time by the Sponsor following appropriate notification.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

The subject will be included if he/she meets the following inclusion criteria:

1. Successful completion of participation in Protocol OTX-101-2016-001.
2. All subjects must provide signed written consent prior to participation in any study related procedures.
3. Female subjects of childbearing potential must have a negative urine pregnancy test at Visit 5 (Day 84) of Protocol OTX-101-2016-001 or at Visit 5a of Protocol OTX-101-2016-002, if conducted at a later date. Women of childbearing potential (i.e., women who are not either postmenopausal for one year or surgically sterile) and men who have partners of childbearing potential must use an acceptable form of contraception throughout the study.
4. Corrected Snellen visual acuity (VA) of better than 20/200 in both eyes at Visit 5 (Day 84) of Protocol OTX-101-2016-001.

7.2. Subject Exclusion Criteria

The subject will be included in the study if they meet the inclusion criteria listed in Section 7.1 and do not meet the exclusion criteria listed below.

1. Subjects reporting an Adverse Event that has not resolved by Visit 5 of Protocol OTX-101-2016-001 may be excluded if, in the judgment of the Principal Investigator and Medical Monitor, it would not be in the subject's best interest to continue treatment with study drug.
2. Use of Restasis or any topical cyclosporine preparation following Visit 5 of Protocol OTX-101-2016-001.
3. Use of any prescription topical ophthalmic medications (including antiglaucoma medications) other than the assigned study medication during the study period. Unpreserved artificial tears are permitted.
4. Current active eye disease other than KCS (i.e., any disease for which topical or systemic ophthalmic medication is necessary).
5. History of herpes keratitis.
6. Unstable macular disease (e.g., age-related macular degeneration, diabetic maculopathy). Stable macular disease is defined as no reduction in central VA since the screening visit of Study OTX-101-2016-001.
7. Diagnosis of chronic uveitis.
8. Corneal transplant following Visit 5 of Study OTX-101-2016-001.

9. Corneal refractive surgery following Visit 5 of Study OTX-101-2016-001.
10. Non-laser glaucoma surgery following Visit 5 of Study OTX-101-2016-001.
11. Lagophthalmos or clinically significant eyelid margin irregularity of the study eye whether congenital or acquired.
12. Presence of conjunctivochalasis (i.e., mechanical blockage of the lower lid punctum by redundant conjunctiva).
13. Presence of pterygium in either eye.
14. Unwilling to discontinue use of contact lenses during the duration of the study.
15. Preplanned elective surgery or hospitalization during the study period.
16. HIV-positive.
17. Unable to reliably report symptoms and history.
18. Has a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment or follow-up.
19. Women who are pregnant or breastfeeding.

7.3. Subject Withdrawal Criteria

The following are the criteria for considering withdrawal from the study:

- Withdrawal of patient consent.
- Subject lost to follow-up.
- The subject has a clinically significant adverse event (AE) or serious adverse event (SAE) that would not be consistent with continuation in the study, as determined by the Investigator in discussion with the Medical Monitor.
- Pregnancy.

If a subject withdraws or is withdrawn from the study, the principal reason for withdrawal will be recorded on the electronic case report form (eCRF). If a study subject is discontinued from study medication before the final scheduled visit, all procedures scheduled for that visit should be conducted at the time the subject is discontinued.

8. STUDY TREATMENTS

8.1. Description of Study Medications

8.1.1. Investigational Product

OTX-101 is an aqueous nanomicellar formulation of cyclosporine for topical ophthalmic use. It is supplied in unit dose vials. The subject will self-administer one full drop to both eyes BID. If a full drop is not instilled into the eye, the subject will wait approximately 10-15 seconds and administer a second drop.

8.1.2. Reference Therapy

Not applicable

8.1.3. Rescue Therapy

Subjects are permitted the *ad libitum* use of unpreserved artificial tears

8.2. Randomization and Masking

All subjects will receive OTX-101 0.09%. A supply of study medication from the assigned kit will be dispensed to the subject at the end of the Visit 5a, at Visit 6 (Day 182) and at Visit 7 (Day 273). An additional box of medication will be dispensed at Visit 8 (Day 364) to those subjects who are scheduled to remain in the study until Visit 9 (Day 448).

8.2.1. Unmasking During the Study Period

Not applicable.

8.3. Concomitant Medications

8.3.1. Permitted Medications and Treatments

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator and in consultation with the Medical Monitor. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor.

Oral omega-3 fatty acids are permitted if the dosage has been stable for 3 months and the subject stays on the same dose until the end of the study. The subject should not begin oral omega-3 fatty acids during the study. Whenever possible, medications should be administered in dosages that remain constant throughout the study duration. All concomitant medications will be recorded in the eCRF.

Preservative-free artificial tears may be used *ad libitum*.

8.3.2. Prohibited Medications and Treatments

The Medical Monitor should be notified before prohibited medication or therapy is administered, unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration.

Prohibited ocular medications and therapies during the study include any prescription or over-the-counter topical ophthalmic medications other than the assigned study medication (unpreserved artificial tears are permitted) and ocular surgery/ocular laser treatment of any kind.

8.4. Treatment Compliance

Treatment compliance will be monitored by study medication accountability. Throughout the treatment phase, the amount of opened and unopened medication returned at each post-baseline visit will be documented by study site personnel.

8.5. Study Medication Materials and Management

8.5.1. Packaging and Labeling

Study medication will be packaged and labeled at a central packaging facility. Each subject kit will consist of a single Main Box which is to remain at the clinical site.

Each Main Box will contain 3 smaller boxes, each of which contains 210 unit dose vials (105 days supply). The smaller boxes will be sealed and labeled to include the kit number and the visit number at which it is to be dispensed directly to the subjects. Other label information will include patient instructions and safety information.

Clinical sites are to dispense study medication from the kit assigned to the subject at Visit 5a, Visit 6 (Day 182) and Visit 7 (Day 273).

An additional box of medication will be dispensed at Visit 8 (Day 364) to those subjects scheduled to continue treatment until Visit 9 (Day 448). Each box contains 210 unit dose vials (105 days supply).

8.5.2. Storage, Administration, and Dispensing

8.5.2.1. Storage

Study medication must be stored as indicated on the package label: “Store at [redacted] ([redacted])” in a secured area. A temperature log will be maintained at each clinical site. Subjects should be instructed to store study medication at home at room temperature. After opening a pouch, the remaining vials should be stored in the pouch until used. Subjects will retain all opened and unopened study medication materials (unit dose vials, foil pouches, boxes) to return to the site.

8.5.2.2. Administration

Subjects will self-administer study medication topically to both eyes BID for 40 or 52 weeks. The subject should be in a seated position and should tilt his or her head backward for

administration of the study medication. The vial of study medication should be held at an almost vertical position above the eye while the lower eyelid is pulled down gently, and one full drop is placed into the conjunctival cul-de-sac of each eye from the same vial. (Note: if a full drop is not instilled into the eye, the subject should wait approximately 10-15 seconds and administer a second drop.) The tip of the vial should not touch the eye. After instilling a drop in each eye, the remaining contents of the vial should be emptied and the vial should be stored in the foil pouch and placed back in the box.

Twice each day, approximately 12 hours apart, the subject will open a new unit dose vial and administer 1 full drop to each eye, store the used vial in the foil pouch, and place it back in the box for return to the clinical site. At each post-baseline visit, the box, complete with used vials/pouches and any unopened study medication will be returned to the clinical site where the used and unopened medication will be documented and the next designated box will be dispensed to the subject.

8.5.2.3. Dispensing

At Visit 5a, the kit labeled with that visit will be removed from the Main Box at the site and dispensed to the subject with instructions to return the box along with used and unused study medication at Visit 6. The two remaining kits will remain in the Main Box at the site.

At Visit 6 (Day 182), the kit returned by the subject will be taken by the site, sealed, and placed back into the Main Box and the site will dispense the kit labeled Visit 6 to the subject with instructions to return the box along used and unused study medication at Visit 7.

At Visit 7 (Day 273), the kit returned by the subject will be taken by the site, sealed, and placed back into the Main Box and the site will dispense the kit labeled Visit 7 to the patient with instructions to return the box along with used and unused study medication at Visit 8.

At Visit 8 (Day 364), the kit returned by the subject will be taken by the site, sealed, and placed back into the Main Box ready for the CRA to perform drug accountability and reconciliation. An additional box of drug will be dispensed to those subjects scheduled to continue treatment until Visit 9 (Day 448).

At Visit 9 (Day 448), the box returned by the subject will be taken by the site, sealed and retained for the CRA to perform drug accountability and reconciliation.

After site close out, the site or CRA will ship all materials back to the supplier.

8.5.3. Study Medication Accountability

The Investigator or designee (e.g., study coordinator or pharmacist) will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study medication using the inventories supplied by the Sponsor. Clinical site personnel will document all received and returned study medication at each post-baseline visit. Study drug accountability will be conducted by the monitor at each applicable monitoring visit.

As described in Section [redacted] the subject will return all opened vials/pouches as well as any unopened study medication at each post-baseline visit. The monitor will review dispensing and

drug accountability records during site visits and at the completion of the study and note any discrepancies.

All investigational study medication must be stored in a secure facility, with access limited to the Investigator and authorized staff.

9. STUDY ASSESSMENTS

Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign, and date the current Institutional Review Board (IRB)-approved version of the informed consent form. A full discussion of informed consent is presented in Section 13.3.

9.1. Background Characteristics

9.1.1. Medical/Ocular History

If Visit 5a does not occur on the date of Visit 5, the subject should be queried regarding relevant events that may have occurred in the interim.

9.1.2. Concomitant Medications

If Visit 5a does not occur on the date of Visit 5, the subject's concomitant medication list should be updated, if necessary.

9.2. Urine Pregnancy Test

A urine pregnancy test will be performed at each visit for women of childbearing potential only.

9.3. Efficacy Assessments

Efficacy assessments will not be performed in this safety study as the absence of a comparator group and the subject selection process would obviate the possibility of obtaining interpretable efficacy data. Investigators should nevertheless perform any assessments consistent with the standard of care in their practice.

9.4. Safety Assessments

Safety will be assessed at each visit by corrected Snellen VA, slit lamp examination, IOP, AE documentation, and concomitant medication review. Ophthalmoscopy/dilated fundus examination will be performed at the subject's last visit; i.e., Visit 8 (Day 364) or Visit 9 (Day 448).

9.4.1. Corrected Snellen Visual Acuity

Corrected Snellen VA measurement will be performed at each study visit with the Snellen eye chart using the subject's current corrective lens prescription. Subjects must read ≥ 50% of the letters on a single line to accept that VA line. The refraction used at the screening visit of Protocol OTX-101-2016-001 should be used for all subsequent VA assessments for the duration of the study. The subject must wear the same glasses, if applicable, at each visit. If the glasses are not available, the eyeglass prescription should be placed in a trial frame and used in place of the unavailable glasses.

9.4.2. Slit Lamp Examination

A routine slit lamp examination will be performed to evaluate the anterior segment of the eye, including lids, cornea, conjunctiva, anterior chamber, iris, and lens. Abnormalities will be documented.

9.4.3. Intraocular Pressure

Intraocular pressure will be measured via Goldmann applanation tonometry using the clinical site's standard procedures. Intraocular pressure in a given subject should be recorded using the same tonometer and the same observer each time, if possible. The IOP values will be recorded in the eCRF.

9.4.4. Ophthalmoscopy/Dilated Fundus Examination

Direct ophthalmoscopy with dilation will include assessment of the optic nerve head for pallor and cupping. A dilated fundus examination consisting of the vitreous, optic nerve, macula, and peripheral retina will be conducted. Abnormalities will be documented.

9.5. Adverse and Serious Adverse Events

9.5.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study subject administered a study medication (pharmaceutical/biological product) that does not necessarily have a causal relationship to this medication. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given during any phase of the study.

Medical conditions/diseases present before signing the informed consent form are only considered AEs if they worsen after the informed consent form is signed. Abnormal test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require additional therapy or a change in therapy.

At each study visit the subject will be asked how he/she has been feeling. All AEs whether observed by the Investigator or spontaneously reported by the subject will be documented in the subject's chart and the AE eCRF.

Adverse events also may be detected when they are volunteered by the subject between visits or through study assessments.

9.5.1.1. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Results in persistent or significant disability/incapacity (excluding progression/outcome of the disease under study),
- Is a congenital anomaly/birth defect,
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Is medically significant; i.e., defined as an event that jeopardizes the health of the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Treatment on an outpatient emergency basis that does not result in hospital admission with an overnight stay is not considered an SAE.

All SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until stabilization or resolution of the event.

9.6. Relationship to Study Medication

The relationship of AEs to the study medication should be assessed by the Investigator using the definitions below.

Not suspected: The temporal relationship of the event to the study medication makes a causal relationship unlikely, or, other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the event to the study medication makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered “suspected.”

If the relationship between the AE/SAE and the study medication is determined by the Sponsor to be “suspected,” the event will be considered to be related to the study medication for the purposes of expedited regulatory reporting.

9.7. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open-ended question from the study personnel or revealed by observation, regardless of severity or potential association with the study medication or study procedures, will be recorded in the eCRF. All AEs that occur after a subject has signed the informed consent form until the final study visit should be collected and recorded on the AE eCRF page. Adverse events will be followed until the event is resolved or stabilized, and SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until resolution.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Onset (date);
- Resolution (date);
- Severity grade (mild, moderate, severe);
- Relationship to study medication (not suspected, suspected);
- Action taken (none, study medication temporarily interrupted, study medication permanently discontinued, concomitant medication taken, hospitalization/prolonged hospitalization, other);
- Serious outcome (yes/no).

The severity grade should be determined by the Investigator using the definitions below:

- **Mild**: Discomfort noticed but no disruption of normal daily activity
- **Moderate**: Discomfort sufficient to cause interference with normal daily activity
- **Severe**: Incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as defined directly above) whereas seriousness is defined by the criteria under Section 9.5.1.1. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form, as well as in the eCRF. The Sponsor or its designee must also be notified. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

9.8. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the time the subject has signed the informed consent until the final study visit, following the end of treatment exposure. Any SAEs "suspected" to be related to the study medication and discovered by the Investigator at any time after the study should be reported.

Any SAE that occurs must be reported to the Medical Monitor within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to the Medical Monitor as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the clinical site with a copy emailed or faxed to the Sponsor or its designee. The Investigator must assess the SAE relationship and complete the SAE form. The Sponsor or its designee may

request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy will be faxed or emailed to the Sponsor or its designee.

In addition, all SAEs should be recorded on the Adverse Event eCRF page with the serious question marked "Yes."

It is the Investigator's responsibility to notify the approving IRB of any SAEs in accordance with IRB and regulatory requirements.

All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

All SAEs will be reported to the US FDA on the appropriate schedule depending if the event is drug related or not drug related, expected or unexpected (based on the available information in the IB).

Any death occurring during the study period should be reported as an SAE and the SAE form must be forwarded to the Medical Monitor within 24 hours of learning of its occurrence. A death that occurs after completion of the study does not require completion of the SAE form.

The Medical Monitor will review and evaluate accumulating safety data from the entire clinical trial database to identify new safety signals or increased frequency of events. This will include a complete review of all SAEs and all follow-up documentation whether relationship to treatment is considered "not suspected" or "suspected".

10. STUDY ACTIVITIES

Error! Reference source not found. provides a tabular summary of all scheduled visits and procedures to be performed during the clinical study.

NOTE: Ophthalmic assessments must be conducted in the order listed in the Schedule of Procedures.

10.1. Visit 5a

Subjects will provide written informed consent and then will be evaluated with respect to the inclusion/exclusion criteria. Assessments conducted at Visit 5 of Study OTX-101-2016-001 are not repeated.

If Visit 5a is not conducted on the same day as Visit 5 of Study OTX-101-2016-001, the following procedures will be conducted.

- AE assessment
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)

Subjects who meet all inclusion/exclusion criteria will be assigned a kit of study medication and are again instructed in topical ocular drop administration procedures.

- Dispense study medication

10.2. Treatment Visits

10.2.1. Visit 6 (Day 182), Visit 7 (Day 273) and Visit 8 (Day 364)*

Procedures performed on Days 128 (± 7 days), 273 (± 7 days) and 364* (± 14 days) will include the following:

- AE assessment
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- Corrected Snellen VA
- Slit lamp examination
- IOP
- Collect and document used and unopened study medication materials
- Dispense study medication

* If not the final visit

10.3. Final Study Visit: Visit 8 (Day 364) or Visit 9 (Day 448)

Procedures performed at the subject's final visit; i.e., Day 364 (+14 days) or Day 448 (+14 days), depending on their treatment assignment in Study OTX-101-2016-001, will include the following:

- Collect and document used and unopened study medication materials
- AE assessment
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- Corrected Snellen VA
- Slit lamp examination
- IOP
- Ophthalmoscopy/dilated fundus examination

10.4. Telephone Contact

The subject will be contacted by telephone approximately midway between scheduled visits (i.e., Days 227, 318 and 409) to assess the following:

- AE assessment
- Concomitant medication review

10.5. Early Discontinuation Visit

If the subject is discontinuing the study early, procedures performed will include the following:

- Collect and document all used and unopened study medication materials, if available; otherwise arrange for the subject to return them
- AE assessment
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- Corrected Snellen VA
- Slit lamp examination
- IOP
- Ophthalmoscopy/dilated fundus examination

11. STATISTICS

11.1. General Considerations

This is an extension of Protocol OTX-101-2016-001 that will evaluate the safety of OTX-101 0.09% ophthalmic solution in subjects with KCS when dosed twice per day for one year.

Subjects in Protocol OTX-101-2016-001 were randomly assigned to OTX-101 0.09% or its vehicle in a 1:1 ratio. However, all subjects enrolling in this extension study will be assigned to OTX-101 0.09%.

A biostatistician will perform statistical analyses as agreed with the Sponsor according to the Statistical Analysis Plan. Any additional or supplemental data analysis performed independently by an Investigator shall be submitted to the Sponsor for review.

No efficacy analyses will be performed. Safety analyses will be performed using the safety analysis population. Definitions for all of the analysis populations can be found in Section 11.5.

11.2. Definition of Baseline Measurements

Baseline measurements will be the last measurement for the corresponding variable prior to the first randomized dose on Day 0 of Protocol OTX-101-2016-001.

11.3. Handling of Missing Data

No missing efficacy data will be imputed. The reasons for missing data will be recorded.

11.4. Determination of Sample Size

In accordance with the ICH E1A Guidance, safety data for a minimum of 100 subjects treated for one year is recommended for inclusion in applications for marketing approval. The masking of subject treatment assignments in Study OTX-101-2016-001 will be maintained until the database for that study has been locked, so qualified subjects receiving OTX-101 0.09% or vehicle may be enrolled in Study OTX-101-2016-002. Approximately [redacted] subjects will enroll in Study OTX-101-2016-002 of which it is anticipated that at least [redacted] will have been randomly assigned to OTX-101 0.09% in Study OTX-101-2016-001.

11.5. Analysis Populations

Two populations will be used for analysis.

11.5.1. Safety Analysis Populations

The safety population will include all patients enrolled in Study OTX-101-2016-002 who have received at least one dose of the study medication.

11.5.1.1. One Year Safety Population

Certain analyses will include only those subjects with a total of 1 year of exposure to active drug in Studies OTX-101-2016-001 and OTX-101-2016-002. The combined safety data from both protocols will be analyzed for this population.

11.6. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for the safety analysis populations. Summary tables will be supported with individual subject data listings.

11.7. Efficacy Analysis

Not applicable

11.7.1. Hypothesis Testing

Not Applicable

11.8. Safety Analyses

Safety and tolerability data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings. For all subjects enrolled in Study OTX-101-2016-002, the safety data recorded during Study OTX-101-2016-001 will be merged to produce a dataset encompassing one year of exposure to treatment.

AEs that occurred during the run-in period on vehicle of Protocol OTX-101-2016-001 will be summarized separately from AEs that occur from the first dose of double-masked treatment on Day 0 of that protocol to the Day 364 or Day 448 visit of Protocol OTX-101-2016-002.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and/or its contracted agents will utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with FDA regulations and the ICH Good Clinical Practice (GCP) guidance.

The study will be monitored by the Sponsor or its designee to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, with ICH GCP, and with the applicable regulatory requirements.

To insure compliance with GCP and all applicable regulatory requirements, the Sponsor or its agent may conduct a quality assurance audit at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to: a review of all informed consent forms, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the study medication receipt, storage, and administration. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the findings of the audit.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Institutional Review Board Approval

The IRB must review, approve, and provide continuing review of the clinical study protocol, protocol amendments, the informed consent documents, subject recruitment advertisements, and any other written information to be provided to the subjects. Initial IRB approval is an affirmative decision that the clinical study has been reviewed and may be conducted at the clinical site within the constraints set forth by the IRB, the institution, GCP, and applicable regulatory requirements. A copy of the IRB approval letter for the protocol, the informed consent, the intended advertising, and any written material to be provided to the subject must be submitted to the Sponsor or its designee prior to release of investigational supplies to the clinical site. Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines. The IRB must be notified of completion or termination of the study. The clinical site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

13.2. Ethical Conduct of the Study

This clinical study will be conducted in accordance with the protocol, including all statements regarding confidentiality, and in compliance with ICH guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

13.3. Subject Information and Consent

A sample informed consent form containing the required elements of informed consent will be provided by the Sponsor or its designee. Any changes made to this sample must be approved by the Sponsor prior to submission to the IRB. After approval by the Sponsor, the informed consent form must be submitted to and approved by the IRB. The informed consent form must be written in a language in which the subject is fluent. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation.

It is the responsibility of the Investigator to inform each subject, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits, and to document the informed consent process in the subject's research chart and medical record, if applicable. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign, and date the current IRB-approved version of the informed consent form. The original informed consent form is to be retained by the clinical site, and a copy is to be given to the subject.

13.4. Subject Confidentiality and Confidentiality of Data

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the clinical site, the Sponsor and its authorized agents, the IRB, and FDA and relevant regulatory agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. No information that can be related to a specific individual subject will be released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

13.5. Study Monitoring

The study will be monitored by the Sponsor or its designee in accordance with current GCP. The study monitor(s) are responsible for monitoring whether the study is conducted according to applicable Clinical Research SOPs, the protocol, and other written instructions and regulatory guidelines. Monitoring visits may occur as required and could include a study initiation visit, a monitoring visit(s), and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct. The Investigator will be responsible for making sure that clinical site personnel are provided adequate training on conducting their designated tasks.

This study will utilize electronic document capture (EDC). During this centralized monitoring, data are reviewed by the monitors as entered by the site, and the monitors will flag any abnormalities, trends, or safety signals for Medical Monitor review and monitor follow-up onsite, if necessary.

During visits to the clinical site, the monitor may review the source documents, eCRFs, signed informed consent forms, study medication storage conditions, and the reporting procedures for AEs and SAEs. All data generated during this study and the medical records/documents from which they originated are subject to inspection by the Sponsor and/or its designee, the FDA, and other regulatory agencies. The Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities.

Upon completion of the study, the clinical monitor will conduct a final visit (close-out) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the study medication and other supplies have been accounted for, perform final study medication accountability (see Section 8.5.3) and ensure that the Investigators are aware of their responsibilities once the study ends.

13.6. Case Report Forms and Study Records

The eCRF exists within an EDC system with controlled access managed by the Sponsor or its authorized representatives for this study. Study personnel will be appropriately trained in the use of eCRFs and application of electronic signatures before the start of the study and prior to being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail.

The Investigator will attest that the information contained in the eCRFs is true by providing electronic signature within the EDC system prior to database lock. After database lock, the Investigator will receive a copy of the subject data (e.g., CD-ROM, or other appropriate media) for archiving at the study site.

At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

13.7. Protocol Violations/Deviations

The Investigator should not deviate from the requirements of this protocol without prior written approval of the Medical Monitor, with the exception of a medical emergency.

Protocol deviations should be reported to the IRB in accordance with IRB guidelines.

All changes to the protocol will be made by the Sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

13.8. Access to Source Documentation

A trial-related monitoring audit, review by the IRB, and/or regulatory inspection may be conducted at any time during or after completion of a study (Section 12). The Investigator must provide direct access to study documentation. The audit may include, but is not limited to, a review of all informed consent forms; a review of medical records; a review of regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the study medication receipt, storage, and administration.

13.9. Data Generation and Analysis

Management of data and the production of the clinical study report will be the responsibility of the Sponsor or its designee.

During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Such clarifications and corrections will be discussed with, and approved by, clinical site personnel and appropriately documented. Prior to database lock, data listings will be generated and anomalous values investigated.

13.10. Retention of Data

Investigators should retain study-related records at the site until informed by the Sponsor. The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current clinical site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the clinical site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

If it becomes necessary for the Sponsor, its designee, or the FDA or relevant regulatory authorities to review any documentation relating to the study, the Investigator must permit access to such records.

13.11. Publication and Disclosure Policy

All information concerning OTX-101 ophthalmic solution and the operations of the Sponsor, such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of the Sponsor. The Investigator agrees to use this information solely for the purposes of accomplishing this study and agrees not to use it for any other purposes without the written consent of the Sponsor.

The publication policy is addressed in a separate agreement.

At the conclusion of the study, after the data are analyzed, a final study report will be prepared. The Sponsor will provide the Investigators with a summary of the results.

14. LIST OF REFERENCES

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