STATISTICAL ANALYSIS PLAN

PROTOCOL 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
PROTOCOL NUMBER:	OTX-101-2016-002
STUDY DRUG:	OTX-101 Ophthalmic Solution
DEVELOPMENT PHASE:	Phase 3
SPONSOR:	Sun Pharma Global (FZE) 
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	adverse event
BID	twice daily
DOB	date of birth
FDA	Food and Drug Administration
eCRF	electronic case report form
HLA-DR	human leukocyte antigen-DR
ICH	International Council for Harmonisation
IFN-γ	interferon gamma
IL	interleukin
IOP	intraocular pressure
IRB	Institutional Review Board
LFU	lacrimal function unit
KCS	keratoconjunctivitis sicca
MMP	matrix metalloproteinase
NDA	New Drug Application
PT	Preferred Term
SAE	serious adverse event
SOC	System Organ Class
TEAE	treatment-emergent adverse event
VA	visual acuity

1. INTRODUCTION

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).

KCS 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 connect 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 (1) disrupt corneal barrier function (interleukin [IL] 17, matrix metalloproteinase [MMP]-3 and MMP-9), (2) sensitize corneal and ocular surface nerve endings (IL-1β and IL-6), (3) cause epithelial cell death (apoptosis, interferon gamma [IFN-γ]) and loss of mucus-producing goblet cells (IFN-γ), and (4) 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, 2014). 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 therapies for the treatment of KCS. To meet this unmet medical need, Sun Pharma Global (FZE), the Sponsor is developing OTX-101, a new nanomicellar formulation of cyclosporine for the treatment of KCS.

2. STUDY DESCRIPTION

2.1. Primary Objective

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

2.2. 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 visual acuity (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 an additional 12 weeks, and a total of 52 weeks.

Subjects will self-administer study medication topically to both eyes twice daily (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 for Visit 9 the window will be +14 days. Both eyes will be assessed at each visit. Adverse events (AEs) and concomitant medications will be documented at each study visit from signing of informed consent to Day 364.

A total of approximately 700 subjects will be enrolled in Protocol OTX-101-2016-001 (approximately 350 subjects in each treatment arm) 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 300 subjects in Protocol OTX-101-2016-002.

Treatment Assignment

All subjects will receive: OTX-101 0.09%

2.3. 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 VA of better than 20/200 in both eyes at Visit 5 (Day 84) of Protocol OTX-101-2016-001.

2.4. Exclusion Criteria

1. Any AE reported in Protocol OTX-101-2016-001 that has not resolved.
5. Use of Restasis or any topical cyclosporine preparation following Visit 5 of Protocol OTX-101-2016-001.
6. 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.
7. Current active eye disease other than KCS (i.e., any disease for which topical or systemic ophthalmic medication is necessary).
8. History of herpes keratitis.
9. 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.
10. Diagnosis of chronic uveitis.
11. Corneal transplant following Visit 5 of Study OTX-101-2016-001.
12. Corneal refractive surgery following Visit 5 of Study OTX-101-2016-001.
13. Non-laser glaucoma surgery following Visit 5 of Study OTX-101-2016-001.
14. Lagophthalmos or clinically significant eyelid margin irregularity of the study eye whether congenital or acquired.
15. Presence of conjunctivochalasis (i.e., mechanical blockage of the lower lid punctum by redundant conjunctiva).
16. Presence of pterygium in either eye.
17. Unwilling to discontinue use of contact lenses during the duration of the study.
18. Preplanned elective surgery or hospitalization during the study period.
19. HIV-positive.
20. Unable to reliably report symptoms and history.

21. 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.
22. Women who are pregnant or breastfeeding.

2.5. Permitted Medications and Treatments

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 electronic case report form (eCRF).

Preservative-free artificial tears may be used *ad libitum* (as desired).

2.6. Prohibited Medications and Treatments

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.

2.7. 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.

3. 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.

3.1. Background Characteristics

3.1.1. 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.

3.1.2. 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.

3.2. Urine Pregnancy Test

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

3.3. 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.

3.4. Safety Assessments

Safety will be assessed at each visit by corrected Snellen VA, slit lamp examination, intraocular pressure (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).

3.4.1. 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 $\geq$ 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.

3.4.2. 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.

3.4.3. 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.

3.4.4. 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.

3.5. Adverse and Serious Adverse Events

3.5.1. 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.

3.5.2. Serious Adverse Event

A serious adverse event (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.

3.5.3. 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.

3.5.4. 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

4. SAMPLE SIZE AND POWER CONSIDERATIONS

In accordance with the International Council for Harmonisation (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 300 subjects will enroll in Study OTX-101-2016-002 of which it is anticipated that at least 150 will have been randomly assigned to OTX-101 0.09% in Study OTX-101-2016-001.

5. ANALYSIS POPULATIONS

Three populations will be used for analysis.

5.1. Safety Analysis Populations

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

Summaries will be presented by the following groups of subjects:

1. subjects assigned to the OTX-101 0.09% arm in Study OTX-101-2016-001; i.e., those subjects with 12 months exposure to active drug.
2. subjects assigned to the Vehicle arm in Study OTX-101-2016-001; i.e., those subjects with at least 9 months of exposure to active drug.

6. HANDLING OF MISSING DATA

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

7. STATISTICAL ANALYSIS

All statistical analyses and reporting will be performed using the SAS® System Version 9.3 or later.

Unless otherwise specified, continuous variables will be summarized with descriptive statistics (n, mean, median, standard deviation, standard error, minimum, and maximum), and categorical variables will be summarized with counts and percentages.

Definition of Baseline:

Baseline measurements will be the last measurement for the corresponding variable prior to the first dose of OTX-101 0.09%. For those initially randomized to OTX-101 0.09%, baseline would be the day of randomization (Day 0). For those initially randomized to Vehicle, baseline would be the day of the first dose of OTX-101 0.09% in the extension phase.

Out of Window and Unscheduled Visits:

Data will be presented according to the assigned visit in the database.

7.1. Subject Disposition

Subject disposition, including the number of subjects entering the extension phase and completing the extension phase will be tabulated. The percentage of subjects treated and completing the study will be based on the total number entering the extension phase. A subject data listing will be provided.

The total number and percentage of subjects included in each of the analysis datasets will be summarized with percentages based on the total number of subjects entering the extension phase. A subject data listing will be provided.

Discontinuations and the reasons for discontinuation from the study will be summarized for all subjects. Summaries will include the number and percentage of subjects. Reasons for discontinuation following the receipt of study drug will include the following:

- Withdrawal by Subject
- Lost to Follow-up
- Adverse Event
- Pregnancy
- Death
- Physician Decision
- Protocol Deviation
- Other

A subject data listing will be provided.

7.2. Demographic and Baseline Characteristics

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

Continuous variables such as age will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), and categorical variables such as gender, race, ethnicity, and iris color will be summarized using counts and percentages of subjects.

Age will be determined as the whole integer number of years from the date of birth (DOB) to the date of the screening visit, i.e., the truncated integer difference between the DOB and Visit 1.

7.3. Concomitant Medications

A subject data listing will be provided. Medications used prior to the first dose of OTX-101 0.09%, but stopped prior to first dose will be indicated separately from those used concomitantly with OTX-101 0.09% on the listing.

7.4. Ocular and Other Medical History

A subject data listing will be provided.

7.5. Treatment Compliance and Exposure

The % compliance on OTX-101 0.9% will be summarized over all visits by the categories of <70% and ≥70%.

Duration of drug exposure will be calculated for each subject as the last date of dosing minus the first date of dosing + 1. The number and percentage of subjects will be summarized according to the following duration-of-exposure categories: '< 3 mon (90 days), '3 to < 6 mon', '6 mon to < 9 mon', '9 to < 12 mon', and '≥12 mon (360 days)'. A subject data listing will be provided.

7.6. Adverse Events

A treatment-emergent adverse event (TEAE) is one that was experienced on or after the day of first dose of OTX-101 0.09% in Study OTX-101-2016-002; or if experienced prior to first dose, worsened after first dose.

An overall summary will be presented which gives the number and percentage of subjects within each cohort that experienced a TEAE, experienced any treatment-related TEAE, permanently discontinued treatment due to a TEAE, experienced a treatment emergent SAE, and that died.

In summary tables, AEs occurring in both eyes will be summarized once at the greater intensity and relationship to study drug.

Events that are possibly or probably related will be counted as an event related to study drug.

The number and percentage of subjects experiencing one or more events within a Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) class without regard to intensity, relationship, or seriousness will be tabulated by cohort. In addition, tables will display events by SOC, PT, and maximum intensity or closest relationship to treatment.

The number of deaths and SAEs will also be presented, and AEs leading to premature discontinuation from the study will be listed and tabulated.

A glossary listing that shows the verbatim terms assigned to each SOC and PT will be provided.

A listing of TEAEs by cohort ordered by subject, SOC, PT, and onset date will be provided.

A listing of serious TEAEs by cohort ordered by subject, SOC, PT, and onset date will be provided.

7.7. Visual Acuity

Descriptive statistics of the observed and change from baseline Snellen VA expressed as equivalent logMAR will be tabulated for each eye by visit (see definition of baseline in Section 7) and cohort. Only the results from visits during the extension plus the appropriate baseline visit will be presented. A subject data listing will be provided.

7.8. Intraocular Pressure

Descriptive statistics of the observed and change from baseline IOP will be tabulated for each eye by visit and cohort. Only the results from visits during the extension plus the appropriate baseline visit will be presented. A subject data listing will be provided.

7.9. Ophthalmoscopy/Dilated Fundoscopy

The observations of ocular ophthalmoscopy and dilated fundoscopy will be summarized in frequency tables based on the ordinal or categorical scales for each measure for each eye by time point and cohort. Only the results from visits during the extension will be presented. A subject data listing will be provided.

7.10. Slit Lamp Examination

The observations of slit lamp examination will be summarized in frequency tables based on the ordinal or categorical scales for each measure for each eye by time point and cohort. Only the results from visits during the extension will be presented. A subject data listing will be provided.

8. CHANGES FROM THE PROTOCOL

None.

9. INTERIM ANALYSIS

At the pre-New Drug Application (NDA) meeting with the Division of Transplantation and Ophthalmology Products (24 April 2017), it was recommended for the evaluation of longer-term exposure to OTX-101 0.09% that data from ≥ 100 subjects who were enrolled in OTX-101-2016-002 and had completed 6 months of exposure to study drug be submitted at the time of the NDA filing.

Of the 258 subjects who were enrolled in Study OTX-101-2016-002 and exposed to OTX-101 0.09%, a subset of 165 subjects had ≥ 6 months of total OTX-101 exposure from their combined participation in Study OTX-101-2016-001 and Study OTX-101-2016-002 and for whom ≥ 6 months of data were monitored and cleaned as of the data cutoff (DCO) of 12 May 2017. This subset also included data from subjects who prematurely discontinued from Study OTX-101-2016-002.

Safety data from this subset were presented in the Summary of Clinical Safety (Module 2.7.4) and Integrated Summary of Safety (Module 5.3.5.3) in the NDA.

10. TABLES AND LISTINGS

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Table 1: 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