CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of NDA 210913

Application Type	NDA
Application Number(s)	210913
Priority or Standard	S
Submit Date(s)	October 16, 2017
Received Date(s)	October 16, 2017
PDUFA Goal Date	August 16, 2018
Division / Office	DTOP / OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	June 19, 2018
Established Name	cyclosporine ophthalmic solution, 0.09%
(Proposed) Trade Name	Cequa
Therapeutic Class	calcineurin inhibitor immunosuppressant
Applicant	Sun Pharma Global FZE
Formulation(s)	Topical ophthalmic solution
Dosing Regimen	One drop in each eye twice daily approximately 12 hours apart
Indication(s)	To increase tear production in patients with keratoconjunctivitis sicca
Intended Population(s)	Patients ≥ 18 years old

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

NDA 210913 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of OTX-101 ophthalmic solution 0.09%, Cequa, dosed twice daily to increase tear production in patients with keratoconjunctivitis sicca.

Throughout this review, Cequa (cyclosporine ophthalmic solution) 0.9% may alternately be referred to as OTX-101 ophthalmic solution 0.09%

1.2 Risk Benefit Assessment

The results from Study OTX-101-2016-001, along with the supportive data from Study OTX-101-2014-001, demonstrate a statistically significant and clinically significant difference between OTX-101 ophthalmic solution 0.09% and vehicle to increase tear production in patients with keratoconjunctivitis sicca.

The most frequent ocular adverse events were instillation site pain (22%) and conjunctival hyperemia (6%). The most frequent non-ocular adverse event was headache (2%).

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product.

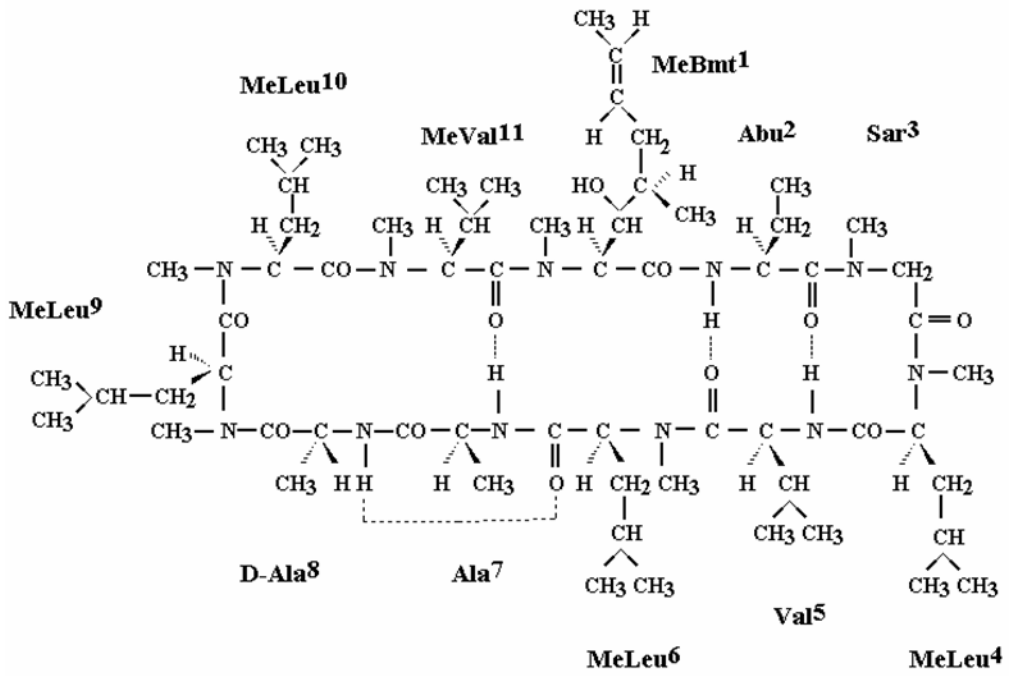
1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Phase 4 clinical study commitments.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Chemical Structure of cyclosporine



Molecular Formula: $C_{62}H_{111}N_{11}O_{12}$

Chemical Name: Cyclosporine A

Cyclo-[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

[R-[R*,R*-(E)]]-Cyclic-(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-alfa-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl)

Cyclo-(MeBmt[1]-Abu[2]-Sar[3]-MeLeu[4]-Val[5]-MeLeu[6]-Ala[7]-D-Ala[8]-MeLeu[9]-MeLeu[10]-MeVal[11]), where MeBmt = (4R)-4-[(E)-2-butenyl]-4,N-dimethyl-L-threonine [(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(N-methylamino)-6-octenoicacid)]

(3S,6S,9S,12R,15S,18S,21S,24S,30S,33S)-30-Ethyl-33-[(1R,2R,4E)-1-hydroxy-2-methyl-4-hexen-1-yl]-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,28-nonamethyl-

1,4,7,10,13,16,19,22,25,28,3 1-undecaazacyclotritriacontane-2,5,8,11,14,17,20,23,26,29,32-undecone

30-ethyl-33-[(4E)-1-hydroxy-2-methylhex-4-en-1-yl]-1,4,7,10,12,15,19,25,28-nonamethyl-6,9,18,24-tetrakis(2-methylpropyl)-3,21-bis(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan

Contains:
Active: cyclosporine, USP (0.9 mg/mL)
Inactives: polyoxyl hydrogenated castor oil; octoxynol-40; sodium phosphate monobasic, dihydrate; sodium phosphate dibasic, anhydrous (b) (4); polyvinylpyrrolidone; hydrochloric acid; sodium hydroxide (to adjust pH); and water for injection

Cyclosporine is an immunomodulator with anti-inflammatory effects that has been developed for the indication to increase tear production in patients with keratoconjunctivitis sicca (KCS).

2.2 Tables of Currently Available Treatments for Proposed Indication

Approved Drugs for Indications Associated with Dry Eye Disease

Indication:	**To increase tear production**	
Restasis	cyclosporine ophthalmic emulsion	NDA 50-790
Indication:	**To treat signs and symptoms of dry eye disease**	
Xiidra	lifitegrast ophthalmic solution	NDA 208073

2.3 Availability of Proposed Active Ingredient in the United States

Cyclosporine, in a topical ophthalmic emulsion formulation, (Restasis) was approved in the United States to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS in patients 16 years of age and older in December 2002.

Cyclosporine, in oral formulation, (Sandimmune) was approved in the United States for the prophylaxis of organ rejection in kidney, liver, and heart allogenic transplants in 1983. In 1995, the oral formulation, Neoral, was approved and in 1997, the additional indications: 1) treatment of patients with active rheumatoid arthritis and 2) treatment of adult non-immunocompromised patients with severe recalcitrant, plaque psoriasis were approved.

2.4 Important Safety Issues With Consideration to Related Drugs

Adverse events for topical ophthalmic cyclosporine (topical immunosuppressant with anti-inflammatory effects) are well known. Refer to Section 2.2 of this review for currently approved products. Common side effects seen with topical ophthalmic cyclosporine include: ocular burning, conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance.

There was adequate AE evaluation for cyclosporine ophthalmic solution (OTX-101) 0.9% in the submitted trials.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On October 28, 2013, a Pre-IND meeting was held for the clinical development plan for cyclosporine (OTX-101) ophthalmic solution, Pre-IND 118,954.

The IND was submitted on July 23, 2014.

On October 6, 2015, an End-of-Phase 2 (EOP2) meeting was held on the development of OTX-101 ophthalmic solution. The agency pointed out that Study OTX-101-2014-001 failed to meet its pre-specified co-primary efficacy endpoints (a sign and a symptom of dry eye) and that any additional analyses (increase in tear production) would be considered post hoc. The agency recommended that the sponsor conduct at least one additional trial in which the drug product demonstrates an increase in tear production.

On February 1, 2016, a guidance meeting was held to discuss additional clinical and chemistry/ manufacturing development issues.

On April 24 2017, a Pre-NDA meeting was held to discuss the content and format of the planned 505(b)(2) NDA for OTX-101 ophthalmic solution 0.09% for the indication to increase tear production in patients with KCS.

2.6 Other Relevant Background Information

The clinical development program for OTX-101 ophthalmic solution was initiated by Ocular Technologies SARL when it filed IND 118,954 on July 23, 2014. In January 2017, Ocular Technologies SARL was acquired along with all the rights to OTX-101 ophthalmic solution by Sun Pharma Global FZE, the applicant of this NDA.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) audit was requested. Refer to the DSI review and to the Cross Discipline Team Leader memorandum for additional information.

3.2 Compliance with Good Clinical Practices

All clinical trials were conducted in accordance with Good Clinical Practice (GCP).

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no principal investigators with proprietary interest or any significant interest in the drug product in any of the clinical studies.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Composition of Cyclosporine Ophthalmic Solution 0.09% Formulation

Component	Function	Theoretical Composition per mL	Theoretical Percent Weight per Volume
Cyclosporine, USP[b]	Active ingredient	0.9 mg	0.09
Polyoxyl (b) (4) hydrogenated castor oil[c], USP/NF	(b) (4)		
Octoxynol-40, in-house			
Sodium phosphate, monobasic, dehydrate, USP/NF			
Sodium phosphate, dibasic, anhydrous, USP/NF			
(b) (4) (b) (4)			
Polyvinylpyrrolidone[d], USP/NF			
Hydrochloric Acid (b) (4) USP/NF	QS[e] to adjust pH, if required		
Sodium hydroxide (b) (4) USP/NF	QS[e] to adjust pH, if required		
Water for injection, USP/NF	Vehicle	QS[e] to 100% target volume	

[b] USP/NF=United States Pharmacopeia/National Formulary
(b) (4)
[e] QS=Quantity Sufficient

The drug product is a sterile, unit dose, non-preserved clear, colorless ophthalmic solution containing cyclosporine and various excipients. (b) (4) Each vial contains a 0.25 mL fill in a 0.9 mL (b) (4) vial.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Nonclinical Pharmacology/Toxicology

Cyclosporine was not mutagenic/genotoxic in the Ames test, V79-HGPRT test, micronucleus test in mice and Chinese hamsters, chromosome-aberration tests in Chinese hamster bone-marrow, mouse dominant lethal assay, and DNA-repair test in sperm from treated mice. In fertility and general reproductive performance studies in rats, cyclosporine did not impair fertility at an oral dose of up to 15 mg/kg/day for 9 weeks in males and 2 weeks in females prior to mating.

See Pharmacology/Toxicology review for additional nonclinical information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Cyclosporine is an immunosuppressive agent when administered systemically. In patients, whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS, cyclosporine ophthalmic solution is thought to act as a calcineurin inhibitor immunosuppressant. The exact mechanism of action is not known.

4.4.2 Pharmacodynamics

Refer to the Pharmacokinetics section (4.4.3) and the Pharm/Tox review.

4.4.3 Pharmacokinetics

Blood concentrations of cyclosporine, in samples collected, after BID topical administration of OTX-101 ophthalmic solution 0.09% in humans for up to 7 days, and once on Day 8, were either not detectable or were marginally above the LLOQ of 0.100 ng/mL (0.101 to 0.195 ng/mL) for up to 2 hours after a single dose, and up to 4 hours after multiple doses.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
OTX-101-2014-001	Multicenter, Randomized,	History of KCS	Cyclosporine 0.05%	1 drop OU	12 weeks	Cyclosporine 0.05%=151

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
Safety and efficacy	double-masked, vehicle controlled		Cyclosporine 0.09% Vehicle	BID		Cyclosporine 0.09%=152 Vehicle=152
OTX-101-2016-001 Safety and efficacy	Multicenter, Randomized, double-masked, vehicle controlled	History of KCS	Cyclosporine 0.09% Vehicle	1 drop OU BID	12 weeks	Cyclosporine 0.09%=372 Vehicle=373

5.2 Review Strategy

The submitted clinical study report and protocol for the studies identified in Section 5.1 above were reviewed and formed the primary basis of safety and efficacy for this application.

5.3 Discussion of Individual Studies/Clinical Trials

Study OTX-101-2014-001

Title: A Randomized, Multicenter, Double-masked, Vehicle-Controlled, Dose-Ranging Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca

Study Design

This study was a prospective, multicenter, double-masked, vehicle-controlled, dose-ranging study designed to evaluate 2 concentrations of OTX-101 ophthalmic solution, 0.05% and 0.09%, against vehicle in patients with KCS. A total of 455 patients were randomized and 426 completed the study. Randomization was at a ratio of 1:1 (OTX-101 0.05%: OTX-101 0.09%: OTX-101 Vehicle). Patients received 1 drop of masked study medication in each eye BID for 12 weeks.

Inclusion Criteria

For inclusion into the trial, subjects were required to fulfill all the following criteria:

1. Age 18 years or older on the date of informed consent.
2. Provided signed informed consent prior to participation in any study-related procedures.
3. Patient-reported history of KCS for a period of at least 6 months.
4. Clinical diagnosis of bilateral KCS supported by OTX-101-2014-001 study assessments.
5. Lissamine green conjunctival staining sum score of ≥ 3 to ≤ 9 out of a total possible score of 12 (scoring excluded superior zones 2 and 4) in the same eye at Screening and Baseline.
6. Global symptom score ≥ 40 at both Screening and Baseline.
7. Snellen VA of better than 20/200 in each eye.
8. Willing to discontinue use of current dry eye therapy (including artificial tears or ocular lubricants) during the study from the start to the run-in period.

9. Female subjects of childbearing potential were required to have a negative urine pregnancy test at Screening. Women of childbearing potential (i.e., women who were neither menopausal for one year nor surgically sterile) were to use an acceptable form of contraception throughout the study.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

1. Use of cyclosporine ophthalmic emulsion 0.05% (Restasis) within 3 months prior to Screening.
2. Previous treatment failure (lack of efficacy) on cyclosporine ophthalmic emulsion 0.05% (Restasis).
3. Diagnosed with Sjögren's disease > 5 years prior to Screening.
4. Clinical diagnosis or any history of seasonal and/or perennial allergic conjunctivitis.
5. Use of systemic and topical medications that were known to cause dry eye within 7 days prior to Screening and throughout the study period. These included the following medications:

- Immunomodulators (permitted if dose was stable for 3 months prior to screening and did not change during the study period)
- Antihistamines (included over-the-counter [OTC])
- Cholinergics
- Antimuscarinics
- Tricyclic antidepressants
- Phenothiazines
- Retinoids
- Systemic corticosteroids (intranasal, topical dermatologic, or inhaled administration of corticosteroids was permitted).

6. Oral omega-3 fatty acids (permitted if dose was stable for 3 months prior to Screening and did not change during the study period).
7. Use of any topical ophthalmic medications, prescription (including antiglaucoma medications) or OTC (including artificial tears), other than the assigned study medication during the study period.
8. Had current active eye disease other than KCS (i.e., any disease for which topical or systemic ophthalmic medication was necessary).
9. History of herpes keratitis.
10. Unstable macular disease (e.g., age-related macular degeneration, diabetic maculopathy). Stable macular disease was defined as no reduction in central VA within 6 months prior to Screening.
11. Diagnosis of chronic uveitis or any chronic or potentially recurrent ocular conditions (e.g., episcleritis, scleritis).
12. Corneal transplant (e.g., penetrating keratoplasty, lamellar keratoplasty, Descemet's stripping endothelial keratoplasty [DSEK]).

Schedule of Visits and Assessments

Table 4: Schedule of Procedures

Procedures	Screening Days -17 to -15	Run-In Period 14 to 17 Days	Baseline Day 0	Day 14 (± 3)	Day 28 (± 3)	Day 42 (± 3)	Day 56 (± 3)	Day 84[a] (+ 7)	Early Discontinuation
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	
Informed consent	X								
Inclusion/exclusion criteria	X		X						
Demographics	X								
Medical/ocular history	X								
Concomitant medication history/review	X		X	X	X	X	X	X	X
Urine pregnancy test[b]	X							X	X
Run-in period with vehicle[c]	X	X							
Symptom frequency/severity rating	X		X	X	X	X	X	X	X
Snellen visual acuity[d]	X		X	X	X	X	X	X	X
Slit lamp examination	X		X	X	X	X	X	X	X
Fluorescein staining of the cornea	X		X	X	X	X	X	X	X
TBUT[e]	X		X	X	X	X	X	X	X
Lissamine green conjunctival staining[f]	X		X	X	X	X	X	X	X
Schirmer's test (unanesthetized)[g]			X					X	X
IOP[h]	X				X		X	X	X
Ophthalmoscopy/dilated fundoscopy	X							X	X

Table 4: Schedule of Procedures (Continued)

Procedures	Screening Days -17 to -15	Run-In Period 14 to 17 Days	Baseline Day 0	Day 14 (± 3)	Day 28 (± 3)	Day 42 (± 3)	Day 56 (± 3)	Day 84[a] (+ 7)	Early Discontinuation
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	
Randomization			X						
Study medication distribution			X		X		X		
Run-in medication distribution	X								
Study medication administration[i]			X ◄	———	———	———	———	► X	
Evaluation of subject comfort and tolerability[h]			X					X	
Patient satisfaction with treatment rating[k]					X		X	X	X
Adverse event assessment[l]	X		X	X	X	X	X	X	X
Study medication accountability[m]			X		X		X	X	X

AE = adverse event; BID = twice daily; IOP = intraocular pressure; TBUT = tear break-up time; VA = visual acuity;

[a] Several procedures are performed in a different order on the Day 84 Visit than at the prior visit. Please refer to Protocol Section 10.5 in Appendix 16.1.1 for the order of procedures for this visit.

[b] Women of childbearing potential only.

[c] The run-in period commences on the day of screening. The first dose of run-in study medication will be instilled at the clinical site.

[d] If the corrected or uncorrected VA is 20/40 or better, no additional refraction is necessary. If corrected or uncorrected VA is worse than 20/40, then an updated refraction must be performed. This refraction must be used for all VA assessments during the study. The subject must wear the same glasses, if applicable, at each visit.

[e] During the 2- to 2 1/2-minute waiting period between instillation of fluorescein and measurement of corneal staining, the TBUT test can be performed.

[f] Lissamine greening conjunctival staining should be performed approximately 5 minutes after corneal staining.

[g] Schirmer's test (unanesthetized) should be performed at least 5 minutes after lissamine green conjunctival staining to allow for any reflex tearing to subside.

[h] Measure IOP using Goldmann applanation tonometry.

[i] The first dose of study medication (Day 0) and the morning dose on Day 84 will be administered by the subject (or caregiver) at the site; otherwise subjects (or caregiver) will administer study medication BID at home. At Day 84, because subjects (or caregiver) will dose at the site at this visit, the visit should be scheduled in the morning, and subjects should be reminded at scheduling and confirmation not to dose at home prior to coming to the site.

[j] The evaluation of comfort and tolerability will be performed at 3 minutes and 10 minutes after the dose of study medication at the site.

[k] This will be performed prior to visual acuity assessment at the visits indicated.
[l] Collection of AEs extends from signing of informed consent until the last study visit.
[m] Clinical site personnel will document all received and returned medication at Day 0 (run-in medication) and Days 28, 56, and 84 (randomized study medication). Study medication accountability will be performed by the monitor at each applicable monitoring visit.

Primary Efficacy Endpoints

The co-primary efficacy variables were mean change from baseline at Day 84 for:

- Total conjunctival staining score in the designated study eye
- Global symptom score (i.e., the square of the product of modified SANDE frequency and severity scores)

Secondary Endpoints

- Mean change from baseline in tear break-up time (TBUT) in the study eye from baseline to Day 84
- Mean change from baseline in total corneal fluorescein staining score in the study eye at Day 84
- Patient satisfaction with treatment score (5-point ordinal scale) at Day 84
- Mean change from baseline in Schirmer's test score (categorized) at Day 84 (average of both eyes)
- Proportion of subjects demonstrating a ≥ 30% reduction in total conjunctival staining score in the study eye from baseline to Day 84
- Mean change from baseline at Days 14, 28, 42 and 56 in the study eye for:
  - Total conjunctival staining score
  - Global symptom score
  - TBUT
  - Total corneal fluorescein staining score
- Patient satisfaction with treatment score (5-point scale) at Days 28 and 56

Investigators

Principal Investigator	**Site Number**	**Number of Subjects Randomized**
Marc Abrams, MD Abrams Eye Center 2322 East 22nd Street, Suite 102 Cleveland, OH 44115	01	15
Jason Bacharach, MD North Bay Eye Associates 104 Lynch Creek Way, Suites 12 & 15 Petaluma, CA 94954	02	7
John Branch, MD Southern Eye Associates 300 E FM 2410, Suite 190 Harker Heights, TX 76548	03	0
Leonard Cacioppo, MD Hernando Eye Institute	04	15

Principal Investigator	Site Number	Number of Subjects Randomized
14543 Cortez Blvd. Brooksville, FL 34613		
Douglas Day, MD Coastal Research Associates, LLC 11205 Alpharetta Highway, Suite J-3 Roswell, GA 30076	05	28
David Evans Total Eye Care 6060 Primacy Pkwy #200 Memphis, TN 38119	06	42
J. Brian Foster The Eye Associates of Manatee 6002 Pointe West Blvd Bradenton, FL 34209	07	1
Michael Grodin, DO Katzen Medical Associates, P.C. 1209 York Rd, Suite 200 Lutherville, MD 21093	08	12
Robert Haverly, MD Laser Eye Surgery of Erie 311 West 24th St. Erie, PA 16502	09	7
Jerry Hu, MD Texas Eye and Laser Center 1872 Norwood Dr. Hurst, TX 76054	10	0
Gary Jerkins, MD Nashville Vision Associates 4306 Harding Pike, Suite 202 Nashville, TN 37205	11	10
Michael Jones, MD Quantum Vision Centers 3990 N. Illinois St. Swansea, IL 62226	12	0
Shane Kannarr, OD Kannarr Eye Care 2521 N. Broadway St. Pittsburg, KS 66762	13	19
Michael Korenfeld, MD Comprehensive Eye Care Ltd. 901 E. 3rd St. Washington, MO 63090	14	13
Bradley Kwapiszeski, MD Heart of America Eye Care. P.A. 8901 W. 74th Street, Suites 285 & 281	15	8

Principal Investigator	Site Number	Number of Subjects Randomized
Shawnee Mission, KS 66204		
Jodi Luchs, MD South Shore Eye Care 2185 Wantagh Avenue Wantagh, NY 11793	16	17
Joseph Martel, MD Martel Medical Eye Group 11216 Trinity River Drive Rancho Cordova, CA 95670	17	43
Matthew Paul, MD Danbury Eye Physicians & Surgeons, P.C. 69 Sand Pit Road Danbury, CT 06810-4005	18	13
William Rand, MD Rand Eye Institute 5 W. Sample Road Deerfield Beach, FL 33064	19	19
Charles Reilly, MD R&R Research 5430 Fredericksburg Road, Ste. 100 San Antonio, TX 78229	20	19
John Rowda, DO Nature Coast Clinical Research 6122 West Corporate Oaks Drive Crystal River, FL 34429	21	9
Kenneth Sall, MD Sall Research Medical Center, Inc. 11423 187th St., Suite 200 Artesia, CA 90701	22	21
Barry Schechter, MD Florida Eye Microsurgical Institute 1717 Woolbright Rd. Boynton Beach, FL 33426	23	15
Lee Shettle, DO Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	24	27
Stephen Smith, MD Eye Associates of Ft. Myers 4225 Evans Ave. Ft. Myers, FL 33901	25	10
Robert Smyth-Medina, MD North Valley Eye Medical Group 1550 Indian Hills Road, #341 Mission Hills, CA 91345	26	24

Principal Investigator	Site Number	Number of Subjects Randomized
Gregory Sulkowski, MD Taustine Eye Center 1169 Eastern Pkwy., Suite 3427 Louisville, KY 40217	27	10
Joseph Tauber, MD Tauber Eye Center 4400 Broadway Street Kansas City, MO 64111	28	4
Michael Tepedino, MD Cornerstone Eye Care 400 E. Hartley Drive High Point, NC 27262	29	16
Melissa Toyos, MD Toyos Clinic 2204 Crestmoor Rd. Nashville, TN 37203	30	2
David Wirta, MD Aesthetic Eye Care Institute David Wirta, MD and Associates 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	31	29

Study OTX-101-2016-001

Title: A Randomized, Multicenter, Double-masked, Vehicle-Controlled Study of the Safety and Efficacy of OTX-101 in the Treatment of Keratoconjunctivitis Sicca

Study Design
This study was a randomized, multicenter, double-masked, vehicle-controlled study designed to compare the safety and efficacy of OTX-101 ophthalmic solution, 0.09% with placebo (vehicle) in patients with a history of KCS. A total of 744 patients were randomized and 708 completed the study. Randomization was at a ratio of 1:1 (OTX-101 0.09%: OTX-101 Vehicle). Patients received 1 drop of masked study medication in each eye BID for 12 weeks.

Schedule of Visits and Assessments

Table 3: Schedule of Procedures

Procedures / Day	Screening -20 to -14	Run-In [a] 14 to 20 days	Baseline 0	Visit 3 28 ± 3	Visit 4 56 ± 3	Visit 5 [b] 84 + 7	Early Discontinuation
Informed consent	X						
Inclusion/exclusion criteria	X		X				
Demographics	X						
Medical/ocular history	X						
Concomitant medication history/review	X		X	X	X	X	X
Urine pregnancy test [c]	X		X			X	X
Run-in period with vehicle		X					
SANDE Symptom frequency/severity rating	X		X	X	X	X	X
OSDI questionnaire			X			X	X
Corrected Snellen visual acuity [d]	X		X	X	X	X	X
Slit lamp examination	X		X	X	X	X	X
Fluorescein staining of the cornea	X		X	X	X	X	X
Lissamine green conjunctival staining [e]	X		X	X	X	X	X
Schirmer's test (unanesthetized) [f]			X			X	X
Intraocular pressure [g]	X					X	X
Ophthalmoscopy/dilated fundoscopy	X					X	X
Randomization			X				
Study medication distribution			X	X	X		
Run-in medication distribution	X						
Study medication administration [h]			X				
Adverse event assessment [i]	X		X	X	X	X	X
Study medication accountability [j]			X	X	X	X	X

AE = adverse event; BID = twice daily; OSDI = Ocular Surface Disease Index; SANDE = Symptom Assessment iN Dry Eye.
[a] The run-in period commenced on the day of the Screening Visit. The first dose of vehicle was instilled at the clinical site.
[b] Several procedures were performed in a different order at Visit 5 than at the prior visits. Please refer to Appendix 16.1.1, Protocol Section 10.5 for the order of procedures for this visit.
[c] Women of childbearing potential only.
[d] Refraction must have been within 6 months of the Screening Visit; this refraction was to be used for all visual acuity assessments for the duration of the study. The subject was to wear the same glasses, if applicable, at each visit.
[e] Lissamine green conjunctival staining was to be performed approximately 5 minutes after corneal staining.
[f] Schirmer's test (unanesthetized) was to be performed at least 5 minutes after lissamine green conjunctival staining to allow for any reflex tearing to subside.
[g] Measured intraocular pressure using Goldmann applanation tonometry.
[h] The first dose of study medication (Day 0) was administered by the subject at the site; otherwise subjects self-administered study medication BID at home.
[i] Collection of AEs extended from signing of informed consent until the last study visit.
[j] Clinical site personnel documented all received and returned medication at Day 0 (run-in medication) and Days 28, 56, and 84 (randomized study medication). Study medication accountability was performed by the monitor at each applicable monitoring visit.

Inclusion Criteria

For inclusion into the trial, patients were required to fulfill all the following criteria:

1. Age 18 years or older on the date of informed consent.
2. Provided signed written consent prior to participation in any study-related procedures.
3. Subject-reported history of KCS for a period of at least 6 months.
4. Clinical diagnosis of bilateral KCS.
5. Lissamine green conjunctival staining sum score of ≥ 3 to ≤ 9 out of a total possible score of 12 (scoring excluded superior zones 2 and 4) in the same eye at both the Screening and Baseline Visits.
6. Global symptom score (modified SANDE) ≥ 40 at both the Screening and Baseline Visits.
7. Corrected Snellen VA of better than 20/200 in each eye.
8. Willing to discontinue use of current dry eye therapy (including artificial tears or ocular lubricants) during the study as of the run-in period.
9. Women of childbearing potential (i.e., female subjects who were not either postmenopausal for at least one year or surgically sterile) were required to have a negative urine pregnancy test at the Screening and Baseline Visits.
10. Women of childbearing potential and men who had partners of childbearing potential had to agree to use an acceptable form of contraception throughout the study.

Exclusion Criteria

Any of the following were regarded as a criterion for exclusion from the trial:

1. Use of cyclosporine ophthalmic emulsion 0.05% (Restasis) within 3 months prior to the Screening Visit.
2. Previous treatment failure (lack of efficacy) with cyclosporine ophthalmic emulsion 0.05% (Restasis).
3. Diagnosis of Sjögren's disease > 5 years prior to the Screening Visit.
4. Clinical diagnosis or any history of seasonal and/or perennial allergic conjunctivitis.
5. Use of systemic or topical medications within 7 days prior to the Screening Visit or during the study period that were known to cause dry eye. These included the following medications:
   - Immunomodulators (permitted if dose was stable for 3 months prior to the Screening Visit and did not change during the study period)
   - Antihistamines (including over-the-counter [OTC])
   - Cholinergics
   - Antimuscarinics
   - Tricyclic antidepressants
   - Phenothiazines
   - Retinoids
   - Systemic corticosteroids (intranasal, topical dermatologic, or inhaled administration of corticosteroids was permitted).
6. Oral omega-3 fatty acids (permitted if dose was stable for 3 months prior to the Screening Visit and did not change during the study period).
7. Use of any topical ophthalmic medications, prescription (including anti-glaucoma medications) or OTC (including artificial tears), other than the assigned study medication during the study period.

8. Current active eye disease other than KCS (i.e., any disease for which topical or systemic ophthalmic medication was necessary).
9. History of herpes keratitis.
10. Unstable macular disease (e.g., age-related macular degeneration, diabetic maculopathy). Stable macular disease was defined as no reduction in central VA within 6 months prior to the Screening Visit.
11. Diagnosis of chronic uveitis or any chronic or potentially recurrent ocular condition (e.g., episcleritis, scleritis).
12. Corneal transplant (e.g., penetrating keratoplasty, lamellar keratoplasty, Descemet's stripping endothelial keratoplasty [DSEK]).
13. Corneal refractive surgery (e.g., laser-assisted in situ keratomileusis [LASIK], photorefractive keratectomy [PRK], limbal relaxing incision [LRI]) within 6 months prior to the Screening Visit or postoperative refractive surgery symptoms of dryness that had not resolved.
14. Cataract surgery within 3 months prior to the Screening Visit.
15. Non-laser glaucoma surgery at any time; glaucoma laser procedures within 3 months prior to the Screening Visit.
16. Presence of punctal plugs or past history of permanent punctal occlusion (e.g., cautery).
17. Lagophthalmos or clinically significant eyelid margin irregularity of either eye whether congenital or acquired.
18. Presence of conjunctivochalasis (i.e., mechanical blockage of the lower lid punctum by redundant conjunctiva).
19. Presence of pterygium in either eye.
20. Unwillingness to discontinue use of contact lenses during the duration of the study.
21. Preplanned elective surgery or hospitalization during the study period.
22. HIV positive.
23. Inability to reliably report symptoms and/or history.
24. Known hypersensitivity or contraindication to the study medication(s) or their components.
25. History or presence of chronic generalized systemic disease that the Investigator felt might increase the risk to the subject or confound the results of the study.
26. Severe/serious ocular condition or any other unstable medical condition that, in the Investigator's opinion, might preclude study treatment or follow-up.
27. Women who were pregnant or breastfeeding.
28. Participation in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.
29. Previous randomization into Study OTX-101-2014-001 or into this study (OTX-101-2016-001).

Primary Efficacy Endpoint

- A clinically meaningful improvement (increase of ≥ 10 mm) from baseline in Schirmer's test (unanesthetized) at Day 84 based on data for both eyes

Secondary Endpoints

Frequency and intensity components of the SANDE global symptom score at Day 84

- Mean change from baseline in lissamine green conjunctival staining score (excluding superior zones) at Day 84 based on data for both eyes
- Mean change from baseline in Schirmer's test (unanesthetized) at Day 84 based on data for both eyes
- Mean change from baseline in central corneal staining score at Day 84 based on data for both eyes
- Complete clearing of central corneal fluorescein staining at Day 84 based on data for both eyes
- Mean change from baseline in SANDE global symptom score at Day 84
- Mean change from baseline in the visual related function subscale (Items 6-9) of the OSDI questionnaire at Day 84
- Complete clearing of lissamine green conjunctival staining in the temporal zone at Day 84 based on data for both eyes
- Repeated measures analysis of all time points for:
  - Lissamine green conjunctival staining score (excluding superior zones)
  - Total fluorescein corneal staining score
  - SANDE global symptom score
- Mean change from baseline at Day 84 for the total OSDI score and for each of its subscales
- The frequency and intensity components of the SANDE global symptom score at Day 84

Investigators

Principal Investigator	**Site Number**	**Number of Subjects Randomized**
Marc Abrams, MD Abrams Eye Center 2322 East 22nd Street, Suite 102 Cleveland, OH 44115	01	31
Jason Bacharach, MD North Bay Eye Associates 104 Lynch Creek Way, Suites 12 & 15 Petaluma, CA 94954	02	10
Robert Benza, MD Apex Eye 7850 Camargo Rd. Cincinnati, OH 45243	27	30
Mark Bergmann, MD Apex Eye 6507 Harrison Ave., Suite E Cincinnati, OH 45247	28	26
Leonard Cacioppo, MD Hernando Eye Institute 14543 Cortez Blvd. Brooksville, FL 34613	03	8
Bill Christie, MD Scott and Christie Eyecare Associates 105 Brandt Dr. #201 Cranberry Township, PA 16066	46	25
Douglas Day, MD Coastal Research Associates 11205 Alpharetta Highway, Suite J-3 Roswell, GA 30076	04	9
David Evans, OD Total Eye Care 6060 Primacy Pkwy #200 Memphis, TN 38119	05	30
William Faulkner, MD Cincinnati Eye Institute 1945 CEI Dr. Cincinnati, OH 45242	39	3
Damien Goldberg, MD Wolstan & Goldberg Eye Associates 23600 Telo Ave., Suite 100 Torrance, CA 90505	29	23

Principal Investigator	Site Number	Number of Subjects Randomized
Robert Haverly, MD Laser Eye Surgery of Erie 311 West 24th St. Erie, PA 16502	06	12
Edward Holland, MD Cincinnati Eye Institute 580 S. Loop Rd #200, Edgewood, KY 41017	44	3
John Hovanesian, MD Harvard Eye Associates 24401 Calle De La Louisa, Suite 300 Laguna Hills, CA 92653	43	4
Gary Jerkins, MD Nashville Vision Associates 4306 Harding Pike, Suite 202 Nashville, TN 37205	07	30
Shane Kannarr, OD Kannarr Eye Care 2521 N. Broadway St Pittsburg, KS 66762	08	15
Kathleen Kelley, MD Price Vision Group 9002 N Meridian St #100 Indianapolis, IN 46260	40	26
Bruce Koffler, MD Koffler Vision Group 120 N Eagle Creek Dr # 431, Lexington, KY 40509	47	15
Michael Korenfeld, MD Comprehensive Eye Care Ltd. 901 E. 3rd St. Washington, MO 63090	09	8
Bradley Kwapiszeski, MD Heart of America Eye Care, P.A. 8901 W. 74th Street, Suites 285 & 281 Shawnee Mission, KS 66204	10	10
Benjamin Lambright, MD Nature Coast Clinical Research 6122 W. Corporate Oaks Dr. Crystal River, FL 34429	16	18
William Lipsky, MD Advanced Laser Vision & Surgical Institute 11550 Fuqua St., Suite 215 Houston, TX 77034	30	24

Principal Investigator	Site Number	Number of Subjects Randomized
Thomas LoBue, MD LoBue Laser & Eye Medical Centers 40700 California Oaks Rd. #106 Murrieta, CA 92562	35	6
Jodi Luchs, MD South Shore Eye Care 2185 Wantagh Avenue Wantagh, NY 11793	11	11
Ranjan Malhotra, MD Ophthalmology Associates 12990 Manchester Road Suite 200 St. Louis, MO 63131	31	29
Joseph Martel, MD Martel Medical Eye Group 11216 Trinity River Drive Rancho Cordova, CA 95670	12	45
Frank McDonald, MD Levenson Eye Associates 751 Oak Street, Suite 200 Jacksonville, FL 32204	32	21
Satish Modi, MD Alterman, Modi & Wolter 23 Davis Ave. Poughkeepsie, NY 12603	33	16
Thomas Mundorf, MD Mundorf Eye Center 1718 E 4th St. #703 Charlotte, NC 28204	49	1
Yen Nieman, MD Texan Eye/Keystone Research Ltd. 5717 Balcones Dr. Austin, TX 78731	37	1
William Rand, MD Rand Eye Institute 5 W. Sample Road Deerfield Beach, FL 33064	14	12
Charles Reilly, MD R & R Research 5430 Fredericksburg Road, Ste. 100 San Antonio, TX 78229	15	3
Kyle Rhodes, MD Revolution Research, Inc. Lake Travis Eye and Laser Center 401 Ranch Rd 620 S. #210 Lakeway, TX 78734	45	18

Principal Investigator	Site Number	Number of Subjects Randomized
Kenneth Sall, MD Sall Research Medical Center, Inc. 11423 187th St., Suite 200 Artesia, CA 90701	17	17
Reginald Sampson, MD Hull Eye Center 1739 W Avenue J Lancaster, CA 93534	41	43
Michael Savetsky, MD Foothill Eye Institute 210 S Grand Ave #106 Glendora, CA 91741	38	5
Barry Schechter, MD Florida Eye Microsurgical Institute 1717 Woolbright Rd. Boynton Beach, FL 33426	18	8
Andrew Schwartz, MD Fifth Avenue Eye Associates 1034 Fifth Avenue New York, NY 10028	42	11
John Sheppard, MD Virginia Eye Consultants 241 Corporate Blvd. Norfolk, VA 23502	48	2
Lee Shettle, DO Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	19	18
Stephen Smith, MD Eye Associates of Ft. Myers 4225 Evans Ave Ft. Myers, FL 33901	20	5
Robert Smyth-Medina, MD North Valley Eye Medical Group 1550 Indian Hills Road, #341 Mission Hills, CA 91345	21	30
Robert Sorenson, MD Inland Eye Specialists 3953 W. Stetson Ave Hemet, CA 92545	34	4
Gregory Sulkowski, MD Taustine Eye Center 1169 Eastern Pkwy., Suite 3427 Louisville, KY 40217	22	6

Principal Investigator	Site Number	Number of Subjects Randomized
Joseph Tauber, MD Tauber Eye Center 4400 Broadway Street Kansas City, MO 64111	23	28
David Wirta, MD Aesthetic Eye Care Institute David Wirta, MD and Associates 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	26	25

See Section 6 of this review for efficacy results and Section 7 for safety.

6 REVIEW OF EFFICACY

Efficacy Summary

6.1 Indication

The proposed indication is to increase tear production (b) (4) associated with KCS.

6.1.1 Methods

The primary support for efficacy for cyclosporine ophthalmic solution 0.09% comes from two studies: OTX-101-2014-001 and OTX-101-2016-001. All the studies used the control adverse environment (CAE) model to determine the efficacy of OTX-101 ophthalmic solution 0.09%. The CAE model creates a controlled environment to evaluate the signs and symptoms of dry eye.

6.1.2 Demographics

Studies OTX-101-2014-001 and OTX-101-2016-001: (ITT Population)

	Study OTX-101-2014-001			Study OTX-101-2016-001	
	OTX-101 0.05%	OTX-101 0.09%	Vehicle	OTX-101 0.09%	Vehicle
Age					
N	151	152	152	371	373
Mean (SD)	61.9 (13.27)	59.2 (14.55)	59.3 (13.75)	58.4 (14.10)	59.5 (14.68)
Min,Max	23,91	23,85	22,89	18,89	20,90
Gender n (%)					
Female	119 (78.8)	122 (80.3)	120 (78.9)	315 (84.9)	311 (83.4)
Male	32 (21.2)	30 (19.7)	32 (21.2)	56 (15.1)	62 (16.6)
Race n (%)					
White	128 (84.8)	126 (82.9)	120 (78.9)	310 (83.6)	305 (81.8)
Black	11 (7.3)	13 (8.6)	20 (13.2)	41 (11.1)	45 (12.1)
Asian	8 (5.3)	7 (4.6)	3 (2.0)	11 (3.0)	12 (3.2)

Other	3 (2.0)	6 (3.9)	7 (4.6)	8 (2.2)	10 (2.7)
Native Hawaiian/Other Pacific Islander	0	0	2 (1.3)	0	1 (0.3)
American Indian	1 (0.7)	0	0	1 (0.3)	0
Ethnicity n (%)					
Not Hispanic/ Latino	131 (86.8)	123 (80.9)	122 (80.3)	314 (84.6)	319 (85.5)
Hispanic/ Latino	20 (13.2)	29 (19.1)	30 (19.7)	57 (15.4)	54 (14.5)

ITT= intent-to-treat; Min,Max=minimum,maximum; SD=standard deviation

6.1.3 Subject Disposition

The efficacy results are based on the ITT population for all randomized patients enrolled in two safety and efficacy trials, Studies OTX-101-2014-001 and OTX-101-2016-001.

Study OTX-101-2014-001 - Subject Disposition and Primary Reason for Discontinuation

OTX-101 0.05% N=151 n (%)	OTX-101 0.09% N=152 n (%)	Vehicle N=151 n (%)	Reason for Discontinuation
3 (2.0)	7 (4.6)	2 (1.3)	Withdrawal of consent
2 (1.3)	1 (0.7)	3 (2.0)	Adverse event
1 (0.7)	2 (1.3)	3 (2.0)	Lost to follow-up
3 (2.0)	2 (1.3)	0	Other (noncompliance, subject relocated, subject did not meet inclusion criteria, subject unable to attend future study visits, subject decision)

Study OTX-101-2016-001 - Subject Disposition and Primary Reason for Discontinuation

OTX-101 0.09% N=372 n (%)	Vehicle N=373 n (%)	Reason for Discontinuation
14 (3.8)	2 (0.5)	Adverse Event
5[a] (1.3)	4 (1.1)	Withdrawal by subject
4 (1.1)	4 (1.1)	Lost to follow-up
0	2 (0.5)	Protocol deviation

[a]This total includes Subject 26-010 who withdrew consent after baseline assessments and never received study medication.

6.1.4 Analysis of Primary Endpoint(s)

The co-primary efficacy endpoints for Study OTX-101-2014-001 were:

- Mean change from baseline in total lissamine green conjunctival staining score in the study eye at Day 84
- Mean change from baseline in global symptom score at Day 84

(b) (4)

Reviewer's Comments: (b) (4)

At the EOP2 meeting, the sponsor presented results from analyses of the pre-specified secondary endpoint, mean improvement from baseline in Schirmer's test scores which showed that both concentrations of OTX-101 increased tear production. Post hoc analyses of the endpoint, proportion of subjects with increase of ≥ 10 mm increase in Schirmer's scores from baseline with both eyes averaged demonstrated statistical significance ($p = 0.0069$) as compared to vehicle for OTX-101 0.09%. The sponsor proposed conducting a phase 3 study (Study OTX-101-2016-001) to confirm the post hoc findings; using the single primary efficacy endpoint, Schirmer's test score increase of ≥10 mm from baseline to demonstrate efficacy. The Agency recommended an analysis consisting of the percentage of eyes with an increase of ≥10mm without averaging eyes.

Study OTX-101-2014-001 – Post Hoc Analysis (ITT Population)
Percentage of Eyes with Increase of ≥10 mm from Baseline in Schirmer's Test Score

Statistic	OTX-101 0.09%	Vehicle	Treatment Difference[a] *P*-Value[a] [CL]
			0.09% vs. Vehicle
Percentage of Eyes with Increase of ≥10 mm from Baseline in Schirmer's Test at Day 84			
N[b]	152	152	8.2%
n, number of eyes responding[c]	51	26	***p* = 0.0021**
% of eyes	16.8	8.6	[3.9. 10.7]

CL=95% upper and lower confidence limits (unadjusted); ITT=intent-to-treat
[a] Generalized estimating equation logistic model with treatment group as a fixed effect as well as eyes within subject as a repeated measure using a compound symmetric covariance structure. The *P*-value tests the hypothesis that the % of eyes in the 2 groups is the same. Positive estimates of the difference favor response in the OTX-101 group.
[b] Missing data on Day 84 were imputed by baseline carried forward. A total of 25 subjects in the OTX-101 group and 12 subjects in the Vehicle group did not provide post-baseline values.
[c] n=number of subjects with only one eye responding + 2 x the number of subjects.
Source: Table 14.2.1.1

Reviewer's comments: *In this post hoc analysis, OTX-101 0.09% showed statistical significance (p = 0.0021) for the percentage of eyes with increase of ≥10 mm from baseline in Schirmer' s test at Day 84 as compared to vehicle.*

The primary efficacy endpoints for Study OTX-101-2016-001 was:

- A clinically meaningful improvement (increase of ≥ 10 mm) from baseline in Schirmer's test (unanesthetized) at Day 84 based on data for both eyes

Study OTX-101-2016-001 – Single Primary Efficacy Endpoint Results (ITT Population)
Percentage of Eyes with Increase of ≥10 mm from Baseline in Schirmer's Test Score

Statistic	OTX-101 0.09%	Vehicle	Treatment Difference[a] *P*-Value[a] [CL]
			0.09% vs. Vehicle
Percentage of Eyes with Increase of ≥10 mm from Baseline in Schirmer's Test at Day 84			
N[b]	371	373	7.3%
n, number of eyes responding[c]	123	69	***p* < 0.0001**
% of eyes	16.6	9.2	[3.9, 10.7]

CL=95% upper and lower confidence limits (unadjusted); ITT=intent-to-treat
[a] Generalized estimating equation logistic model with treatment group as a fixed effect as well as eyes within subject as a repeated measure using a compound symmetric covariance structure. The *P*-value tests the hypothesis that the % of eyes in the 2 groups is the same. Positive estimates of the difference favor response in the OTX-101 group.
[b] Missing data on Day 84 were imputed by baseline carried forward. A total of 25 subjects in the OTX-101 group and 12 subjects in the Vehicle group did not provide post-baseline values.
[c] n=number of subjects with only one eye responding + 2 x the number of subjects.
Source: Table 14.2.1.1

Reviewer's comments: *Study OTX-101-2016-001confirmed that a greater percentage of eyes in the cyclosporine arm had an increase of ≥10 mm from baseline on the Schirmer's test at Day 84 as compared to vehicle.*

6.1.5 Analysis of Secondary Endpoints(s)

Analysis of the following secondary endpoint in Study OTX-101-2014-001 was what lead the sponsor to propose an alternative clinical development plan which was to pre-specify a single primary efficacy endpoint in a confirmatory phase 3 study:

- Mean change from baseline in Schirmer's test score (categorized) at Day 84 (average of both eyes)

In this analysis, the Schirmer's test scores in mm were converted to a 5-point categorical scale that corresponded with the amount of wetting observed: 1 = < 3 mm, 2 = 3 – 6 mm, 3 = 7 – 10 mm, 4 = 11 – 14 mm, 5 = > 14 mm.

Study OTX-101-2014-001 – Secondary Analysis (ITT Population)
Mean Change from Baseline to Day 84 in Categorized Schirmer's Test Score with Both Eyes Averaged

Statistic	OTX-101 0.09%	OTX-101 0.05%	Vehicle	Adjusted Least Squares Mean, *p*-Value[a] [CL]	
				0.09% vs. Vehicle	0.05% vs. Vehicle
Mean change from baseline to Day 84 in categorized Schirmer's test score with both eyes averaged					
Baseline					
n	152	151	152		
Mean (SD)	3.3 (1.30)	3.1 (1.27)	3.4 (1.25)		
Change from Baseline					
n	140	141	144		
Mean (SD)	0.37 (1.260)	0.41 (1.263)	-0.08 (1.307)	0.46, *p* = **0.003** [0.21, .0.71]	0.39, *p* = **0.0025** [0.21, 0532]
LS mean, SE	0.5, 0.09	0.4, 0.09	0.0, 0.09		

ANCOVA=analysis of variance; CL=95% confidence limits; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error
[a]ANCOVA with baseline and pooled study site as covariates.
Source: Table 14.2.5.1.1

Reviewer's comments: *Both concentrations of OTX-101 showed increased tear production at Day 84.*

6.1.6 Other Endpoints Not applicable.

6.1.7 Subpopulations

The study population was primary female, consistent with the demographics of the condition. The effects observed were consistent in all subpopulations evaluated.

7 REVIEW OF SAFETY

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary data used to evaluate safety was from Studies OTX-101-2014-001 and OTX-101-2016-001.

7.1.2 Categorization of Adverse Events

Routine clinical testing was used to establish the safety of topical ophthalmic drops (i.e., biomicroscopy, visual acuity, etc.). This was adequately addressed in the design and conduct of the clinical trials. All adverse events were coded using a MedDRA dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooled data across two trials (Studies OTX-101-2014-001 and OTX-101-2016-001) was the primary data used to evaluate safety and in the analysis of common adverse events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Mean Duration of Exposure in Individual Studies – Safety Population

	OTX-101-2014-001		OTX-101-2016-001		Pooled Data	
	OTX-101 0.09% (N=152)	Vehicle (N=152)	OTX-101 0.09% (N=372)	Vehicle (N=372)	OTX-101 0.09% (N=524)	Vehicle (N=524)
Exposure (weeks)						
N	152	151	368	368	520	519
Mean (SD)	11.6 (2.43)	12.0 (1.80)	11.9 (2.39)	12.3 (1.04)	11.8 (2.40)	12.2 (1.31)
Min, Max	1, 13	1, 14	0,15	3, 15	0,15	1,15

Min=minimum, Max=maximum

Reviewer's comments: *There is adequate exposure to assess the safety profile of OTX-101 ophthalmic solution 0.09%.*

7.2.2 Explorations for Dose Response

Two concentrations of OTX-101 (0.05% and 0.09%) were evaluated in Study OTX-101-2014-001. Analyses of efficacy data showed OTX-101 0.09% to be more effective as compared to OTX-101 0.05% in affecting tear production. OTX-101 0.09% was selected for development.

See Section 5.3 for more details of the dose-response study.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

The routine clinical testing used to evaluate the safety concerns of topical ophthalmic drops (i.e., biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the clinical trials.

7.3 Major Safety Results

7.3.1 Deaths

One death was reported during the development of OTX-101. Subject experienced a fatal serious adverse event (SAE) two days following initiation of study medication. The cause of death is listed as unknown.

Subject Number	Treatment Group	System Organ Class (Preferred Term)	Ocular/Non-ocular	Severity	Outcome
Study OTX-101-2016-001					
(b) (6)	OTX-101 0.09%	General disorders and administration site conditions (Death)	Non-ocular	Severe	Death

Reviewer's comments: *Per Section 14.2 of the CSR: Subject (b) (6) was a 56-year old white female with ongoing ocular history of KCS since (b) (6) Her medical history was significant for chronic pain syndrome of back and neck since (b) (6) and arthritis of the hip since (b) (6) Concomitant medications taken within 2 weeks prior to the event included oxycodone, potassium, hyaluronic acid with vitamin C, and vitamin B complex. On (b) (6) the subject initiated treatment with OTX-101 0.09% Ophthalmic Solution.*

On (b) (6) the subject experienced an SAE of death. She had passed away sometime during the night due to unknown causes. The event was reported as an SAE because it led to death. The Investigator reported the SAE to be severe in intensity and not related to the study medication. The Sponsor and/or medical monitor agrees with the Investigator's assessment of causality.

7.3.2 Nonfatal Serious Adverse Events

Five subjects in the OTX-101 0.09% treatment group and 6 subjects in the vehicle group reported a nonfatal SAE. Two of the subjects with an SAE withdrew from the study and 9 of the subjects completed the study.

Serious Adverse Events

Subject Number	Treatment Group	System Organ Class (Preferred Term)	Ocular/Non-ocular	Severity	Outcome
Study OTX-101-2014-001					
(b) (6)	Vehicle	Metabolism and nutrition disorders (Hypokalaemia)	Non-ocular	Severe	Resolved
	Vehicle	Injury, poisoning and procedural complications (Humerus fracture)	Non-ocular	Moderate	Ongoing
	Vehicle	Nervous system disorders (Cerebrovascular accident)	Non-ocular	Moderate	Resolved
	Vehicle	Psychiatric disorders (Bipolar disorder)	Non-ocular	Moderate	Resolved
Study OTX-101-2016-001					
(b) (6)	OTX-101 0.09%	Infection and infestation (Pneumonia)	Non-ocular	Severe	Resolved
	OTX-101 0.09%	Neoplasms benign, malignant and unspecified (including cysts and polyps) (Lung neoplasm malignant)	Non-ocular	Severe	Ongoing
	OTX-101 0.09%	Injury, poisoning and procedural complications (Subdural haematoma)	Non-ocular	Moderate	Resolved with sequelae
	OTX-101 0.09%	Musculoskeletal and connective tissue disorders (Spinal column stenosis)	Non-ocular	Mild	Resolved
	OTX-101 0.09%	Renal and urinary disorders (Nephrolithiasis)	Non-ocular	Moderate	Resolved
	Vehicle	General disorders and administration site conditions (Perforated ulcer)	Non-ocular	Severe	Resolved
	Vehicle	Musculoskeletal and connective tissue disorders (Spinal osteoarthritis)	Non-ocular	Moderate	Resolved

7.3.3 Dropouts and/or Discontinuations

Fifteen subjects (2.9%) in the OTX-101 0.09% treatment group and 5 subjects (1.0%) in the vehicle group withdrew from the study due to adverse events.

Subject Discontinuation from Study Due to Adverse Events

Study Site Number	Subject Number	Treatment	System Organ Class (Preferred Term)	Ocular/Non-ocular	Severity
Study OTX-101-2014-001					
14	(b) (6)	OTX-101 0.09%	Musculoskeletal and Connective Tissue Disorders/Back pain	Non-ocular	Moderate

Study Site Number	Subject Number	Treatment	System Organ Class (Preferred Term)	Ocular/Non-ocular	Severity
			Metabolism and Nutrition Disorders/Dehydration	Non-ocular	Moderate
			Nervous System Disorders/ Headache	Non-ocular	Mild
			Infections and Infestations/Urinary tract infection	Non-ocular	Moderate
			Gastrointestinal Disorders/ Vomiting	Non-ocular	Mild
			Gastrointestinal Disorders/ Vomiting	Non-ocular	Moderate
11	(b) (6)	Vehicle	Immune System Disorders/Seasonal allergies	Ocular	Mild
20	(b) (6)	Vehicle	Infections and Infestations/Viral conjunctivitis	Ocular	Moderate
24	(b) (6)	Vehicle	Nervous System Disorders/ Cerebrovascular accident	Non-ocular	Moderate
Study OTX-101-2016-001					
01	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Mild
03	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Moderate
			General Disorders and Administration Site Conditions/ Instillation site reaction	Ocular	Moderate
05	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Mild
07	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Mild
			General Disorders and Administration Site Conditions/ Instillation site pruritus	Ocular	Mild
08	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Moderate
12	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Mild
			Infections and Infestations/ Sinusitis	Non-ocular	Mild
19	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Moderate
			Eye Disorders/Macular fibrosis	Ocular	Mild
19	(b) (6)	OTX-101	Eye Disorders/Eye irritation	Ocular	Mild

Study Site Number	Subject Number	Treatment	System Organ Class (Preferred Term)	Ocular/Non-ocular	Severity
		0.09%			
21	(b) (6)	OTX-101 0.09%	Eye Disorders/Vision blurred	Ocular	Mild
			Eye Disorders/Conjunctival hyperemia	Ocular	Moderate
26	(b) (6)	OTX-101 0.09%	Eye Disorders/Eye pain	Ocular	Mild
29	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Mild
			Nervous System Disorders/ Headache	Non-ocular	Mild
			General Disorders and Administration Site Conditions/ Instillation site pruritus	Ocular	Mild
33	(b) (6)	OTX-101 0.09%	Eye Disorders/Eye pain	Ocular	Mild
39	(b) (6)	OTX-101 0.09%	General Disorders and Administration Site Conditions/ Instillation site pain	Ocular	Mild
44	(b) (6)	OTX-101 0.09%	Respiratory, Thoracic and Mediastinal Disorders/Throat irritation	Non-ocular	Moderate
			Infections and Infestations/Candida infection	Non-ocular	Moderate
23	(b) (6)	Vehicle	Eye Disorders/Foreign body sensation in eyes	Ocular	Severe
29	(b) (6)	Vehicle	Nervous System Disorders/ Headache	Non-ocular	Moderate

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in Section 7.3.3.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Incidence ≥ 1 % Treatment-Emergent Adverse Events by Preferred Term and Treatment

Preferred Term (PT)	Pooled Data		Study OTX-101-2014-001		Study OTX-101-2016-001	
	OTX-101 0.09% (N=524) n (%)	**Vehicle (N=524) n (%)**	**OTX-101 0.09% (N=152) n (%)**	**Vehicle (N=152) n (%)**	**OTX-101 0.09% (N=372) n (%)**	**Vehicle (N=372) n (%)**

OCULAR	**162 (30.9)**	**94 (17.9)**	**37 (24.3)**	**28 (18.4)**	**125 (33.6)**	**66 (17.7)**
Instillation site pain	114 (21.8)	21 (4.0)	23 (15.1)	5 (3.3)	90 (24.2)	16 (4.3)
Conjunctival hyperemia	30 (5.7)	19 (3.6)	0	0	30 (8.1)	19 (5.1)
Eye irritation	6 (1.1)	6 (1.1)	3 (2.0)	1 (0.7)	3 (0.8)	5 (1.3)
Blepharitis	5 (1.0)	0	0	0	5 (1.3)	0
Eye pruritus	2 (0.4)	8 (1.5)	1 (0.7)	4 (2.6)	1 (0.3)	5 (1.3)
Foreign body sensation	2 (0.4)	5 (1.0)	1 (0.7)	0	1 (0.3)	5 (1.3)
Vitreous floaters	2 (0.4)	5 (1.0)	1 (0.7)	2 (1.3)	1 (0.3)	3 (0.8)
NON-OCULAR	**70 (13.4)**	**65 (12.4)**	**21 (13.8)**	**32 (21.1)**	**49 (13.2)**	**33 (8.9)**
Headache	8 (1.5)	2 (0.4)	2 (1.3)	0	6 (1.6)	2 (0.5)
Urinary tract infection	6 (1.1)	4 (0.8)	2 (1.3)	2 (1.3)	4 (1.1)	2 (0.5)
Bronchitis	5 (1.0)	3 (0.6)	2 (1.3)	2 (1.3)	3 (0.8)	1 (0.3)
Sinusitis	4 (0.8)	5 (1.0)	0	0	4 (1.1)	5 (1.3)
Upper respiratory tract infection	4 (0.8)	5 (1.0)	3 (2.0)	2 (1.3)	1 (0.3)	2 (0.5)
Nasopharyngitis	1 (0.2)	5 (1.0)	1 (0.7)	4 (2.6)	0	1 (0.3)

Reviewer's comments: *The most frequent ocular adverse events were instillation site pain (22%) and conjunctival hyperemia (6%). The most frequent non-ocular adverse event was headache (2%).*

7.4.2 Laboratory Findings

No clinically relevant laboratory abnormalities were detected in any of the trials that conducted laboratory evaluation.

7.4.3 Vital Signs

Vital sign parameters were not evaluated in any of the trials.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed.

7.5Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not observed.

7.5.2 Time Dependency for Adverse Events

There were no time dependent adverse events noted.

7.5.3 Drug-Demographic Interactions

The demographics in the safety population included subjects from age 18 and older. There were no significant differences between OTX-101 ophthalmic solution 0.09% and the vehicle group with regards to age, gender, race, or ethnicity.

7.5.4 Drug-Disease Interactions

A review of adverse events revealed no untoward safety issues in each of the subpopulations categorized by concomitant diseases.

7.5.5 Drug-Drug Interactions

No investigations on potential drug-drug interactions were performed. During the clinical development of OTX-101, no drug-drug interactions were reported.

7.6 Additional Safety Evaluations

7.6.1 Carcinogenicity

Because of the low expected absorption of OTX-101 ophthalmic solution 0.09%, a topical ocular preparation, no human carcinogenicity studies were conducted.

In a 78-week carcinogenicity study in mice, orally administered OTX-101 at doses of 1, 4, and 16 mg/kg/day, a statistically significant trend was found for lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. The clinical significance of these findings is not known.

In a 24-months carcinogenicity study in rats, orally administered OTX-101 at doses of 0.5, 2, and 8 mg/kg/day, pancreatic adenomas significantly exceeded the control rate in the low dose level. The clinical significance of these findings is not known.

7.6.2 Human Reproduction and Pregnancy Data

Reproduction studies have been performed in rats and rabbits at maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), oral cyclosporine solution was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cyclosporine has been reported to be excreted in human breast milk following systemic administration. Because many drugs are excreted in human milk, use of OTX-101 ophthalmic solution 0.09% in nursing mothers is not recommended

7.6.3 Pediatrics and Assessment of Effects on Growth

This drug was not tested in a pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no anticipated abuse potential for this product. No withdrawal or rebound effects are anticipated.

7.7 Additional Submissions / Safety Issues

The 120 Day Safety Update was received on February 27, 2018 The submission reported that since the NDA filing, Applicant completed the open-label extension of Study OTX-101-2016-001 (Safety Extension Study OTX-101-2016-002). The study was conducted to evaluate the long-term (52 weeks) safety of OTX-101 0.09% in subjects with keratoconjunctivitis sicca who completed 12 weeks of therapy in Study OTX-101-2016-001. The information contained in the safety update is comparable to the information reviewed for the original NDA. No edits to the labeling were proposed by the applicant based on the 120 Day Safety Update.

8 POSTMARKET EXPERIENCE

OTX-101 ophthalmic solution 0.09% has been not marketed in any country.

9 APPENDICES

9.1 Literature Review References

There was no additional relevant material identified from the literature for this application.

9.2 Labeling Recommendations

See labeling recommendations which follow in the attached appendix.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held.

9.4 Financial Disclosure Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 210913

Submission Date(s): October 16, 2017

Applicant: Sun Pharma Global FZE

Product: cyclosporine ophthalmic solution, 0.09%

Reviewer: Lucious Lim, M.D., M.P.H.

Date of Review: June 19, 2018

Covered Clinical Study (Name and/or Number): Study OTX-101-2014

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 31		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): Study OTX-101-2016

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 45		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

There are no financial interests/arrangements to disclose.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LUCIOUS LIM
08/08/2018

WILLIAM M BOYD
08/08/2018