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RESEARCH**

APPLICATION NUMBER:

210913Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA Number	210913
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Submission Date	10/16/2017
Submission Type	505(b)(2); Standard Review
Brand Name	CEQUA
Generic Name	OTX-101 (Cyclosporine Ophthalmic Solution 0.09%)
Dosage Form and Strength	Ophthalmic solution containing cyclosporine 0.9 mg/mL
Route of Administration	Topical Ocular
Proposed Indication	Increase tear production [REDACTED] (b) (4) [REDACTED] associated with keratoconjunctivitis sicca (dry eye)
Applicant	Sun Pharma Global FZE
Associated IND	IND 118954
OCP Review Team	Xiaohui (Tracey) Wei, Ph.D. Philip M. Colangelo, Pharm. D, Ph.D.

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1. Executive Summary

OTX-101 Ophthalmic Solution is a nanomicellar formulation of cyclosporine at a concentration of 0.09% for topical ocular administration to increase tear production (b) (4) associated with keratoconjunctivitis sicca (KCS), also referred to as dry eye disease (DED). The Applicant's proposed dosing is to instill one drop of CEQUA™ twice daily (approximately 12 hours apart) into each eye using a single-use container in patients 18 years of age and older.

OTX-101 0.09% ophthalmic solution strength was selected from the Phase 2b/3 dose-ranging study (OTX-101-2014-001) and demonstrated to be safe and effective in two pivotal clinical studies (Phase 2b/3 study of OTX-101-2014-001 and Phase 3 study of OTX-101-2016-001). Results of the pivotal studies showed that OTX-101 0.09% as compared to vehicle demonstrated statistically significant and clinically relevant increased tear production ($p \leq 0.0021$ from OTX-101-2014-001 study, $p < 0.0001$ from OTX-101-2016-001 study), (b) (4) OTX-101 0.09% was generally well tolerated by healthy volunteers and patients with KCS.

The key clinical pharmacology review questions center on evaluation of the systemic exposure of cyclosporine following topical administration of OTX-101 0.09% ophthalmic solution. As from the Applicant, blood concentrations of cyclosporine after twice daily topical administration of OTX-101 0.09% in humans for 8 days were either not detectable or were marginally above the lower limit of assay quantitation (LLOQ) of 0.100 ng/mL (0.101 to 0.195 ng/mL).

1.1. Recommendations

The Office of Clinical Pharmacology Division of Clinical Pharmacology IV has reviewed the information contained in NDA 210913. The clinical pharmacology information supports the use of OTX-101 0.09% in patients with KCS [see Table 1.1.1] and the clinical pharmacology review team recommends approval of this NDA.

Table 1.1.1. Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or Supportive evidence of effectiveness	The primary evidence of effectiveness for OTX-101 0.09% in patients with KCS comes from one Phase 2b/3 study [OTX-101-2014-001] and one Phase 3 study [OTX-101-2016-001].
General dosing instructions	Instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye using a single-use container in patients 18 years of age and older. CEQUA can be used concomitantly with artificial tears, allowing a 15 minute interval between products.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Due to the low systemic exposure of cyclosporine following topical administration of OTX-101 0.09%, no dose individualization is warranted based on intrinsic and extrinsic factors.
Labeling	The labeling is under review.

1.2. Post Marketing Requirements and Commitments

None.

2. Summary of Clinical Pharmacology Assessment

2.1. Pharmacology and Clinical Pharmacokinetics

Cyclosporine is an immunosuppressive agent, and when given systemically, is used to prevent rejection in solid organ transplant patients. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, topical administration of cyclosporine is thought to suppress the immune-based inflammation of the ocular surface, and allow the lacrimal glands to increase tear production, thus potentiating the return of a more stable tear film (b) (4).

Blood concentrations of cyclosporine after twice daily topical administration of OTX-101 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. While numerically greater values were observed after multiple doses compared to a single dose, the maximum blood level observed was no greater than 0.200 ng/mL. This value is 3000 to 4000-fold lower than the C_{max} of cyclosporine after oral administration of Neoral[®] and 7 to 13-fold lower than the C_{max} of cyclosporine following oral administration of Sandimmune[®].

2.2. Dosing and Therapeutic Individualization

2.2.1. General Dosing

The Applicant proposes to instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye using a single-use container in patients 18 years of age and older. CEQUA can be used concomitantly with artificial tears, allowing a 15 minute interval between products.

2.2.2. Therapeutic Individualization

Due to the low systemic exposure of cyclosporine following topical administration of OTX-101 0.09% in adult patients, no dose adjustment is warranted for intrinsic (e.g., age, sex, hepatic/renal impairment) and extrinsic factors (e.g., smoking, concomitant medicines).

2.3. Outstanding Issues

None.

3. Comprehensive Clinical Pharmacology Review

3.1. Overview of the Product and Regulatory Background

OTX-101 is a topical immunomodulator indicated to increase tear production (b) (4) (b) (4) associated with keratoconjunctivitis sicca (KCS; dry eye).

The clinical development of OTX-101 0.09% ophthalmic solution included a total of four clinical trials conducted with cyclosporine ophthalmic solution, 0.09% following topical administration: one Phase 1 study in healthy volunteers (OTX-101-2016-003), one Phase 2b/3 study in patients with KCS (OTX-101-2014-001), and two Phase 3 studies in patients with KCS (OTX-101-2016-001, OTX-101-2016-002). Studies OTX-101-2014-001 and OTX-101-2016-001 are the pivotal studies to provide the primary evidence of effectiveness for OTX-101 0.09% in patients with KCS.

The Division agreed with the Applicant's proposed development program based on 505(b)(2) pathway. There were multiple milestone meetings between the Division and the Applicant during the development process including a pre-IND meeting on October 28, 2013, an end of Phase 2 meeting on October 6, 2016, and a pre-NDA meeting on April 24, 2017.

The Applicant has requested a waiver for the conduct of clinical studies in all pediatric age groups because studies are impossible or highly impractical due to few children with the disease. This waiver request was granted by the Division of Transplant and Ophthalmology Products.

3.2. General Pharmacology and Pharmacokinetic Characteristics

Table 3.2.1. Summary of Pharmacokinetics

Pharmacology	
Mechanism of Action	OTX-101 acts as a topical immunomodulator and is thought to suppress the immune-based inflammation of the ocular surface, and allow the lacrimal glands to increase tear production, thus potentiating the return of a more stable tear film (b) (4)
Active Moieties	Cyclosporine
General Information	
Bioanalysis	Validated LC-MS/MS method to determine cyclosporine concentrations in blood (See Appendix 4.1).

Healthy vs. Patients	The systemic exposure of cyclosporine following topical administration of OTX-101 was only determined in healthy volunteers and no data are available in patients.
Drug exposure at steady state following the therapeutic dosing regimen	Blood concentrations of cyclosporine after BID topical administration of OTX-101 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 4 hours after multiple doses. [Study OTX-101-2014-001]
Range of effective dose or exposure	The proposed dose is one drop twice daily (approximately 12 hours apart) into each eye. No exposure-response relationship for efficacy was identified due to negligible systemic absorption.
Maximally tolerated dose (MTD) or exposure	The maximally tolerated dose was not explored as systemic exposure is negligible following topical administration of OTX-101. The whole blood concentrations of cyclosporine (0.100 to 0.200 ng/mL) determined after dosing of OTX-101 are 3000 to 4000 -fold lower than the C _{max} of cyclosporine after oral administration of Neoral [®] , and are 7 to 13-fold lower than the C _{max} of cyclosporine following oral administration of Sandimmune [®] .
Dose Proportionality	Dose proportionality was not explored as systemic exposure is negligible following topical administration of OTX-101.
Accumulation	The level of systemic exposure was numerically higher after multiple doses compared to a single dose. However, the maximum blood level observed was no greater than 0.200 ng/mL. [Study OTX-101-2014-001]
Variability	Variability was not explored as systemic exposure is negligible following topical administration of OTX-10.
Bioavailability	N/A
T_{max}	N/A
Volume of Distribution	N/A
Plasma Protein Binding	NA
Substrate transporter systems [in vitro]	N/A
Half-life	N/A
Fraction metabolized (% dose)	N/A
Primary metabolic pathway(s) [in vitro]	N/A

Primary excretion pathways (% dose) ±SD	N/A
Inhibition/Induction of metabolism	Cyclosporine is an inhibitor of CYP3A
Inhibition/Induction of transporter systems	Cyclosporine is an inhibitor of multidrug efflux transporter P-glycoprotein (MDR1/P-gp), organic anion transporter polypeptides OATP1B1 and OATP1B3, the breast cancer resistance protein, BCRP, and a weak inhibitor of the multidrug resistance proteins, MRP1 and MRP2.

3.3. Clinical Pharmacology Review Questions

3.3.1. Was cyclosporine systemically absorbed following the topical administration of OTX-101 ophthalmic solution, 0.09% in humans?

The systemic absorption of cyclosporine following the topical application of OTX-101 ophthalmic solution, 0.09% was negligible in healthy subjects.

The Applicant conducted one Phase 1 study, OTX-101-2016-003, to investigate the clinical pharmacokinetics of cyclosporine following topical administration of OTX-101 ophthalmic solution in healthy volunteers. Results from this study showed that blood concentrations of cyclosporine after twice daily (BID) topical administration of cyclosporine 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. While numerically greater values were observed after multiple doses compared to a single dose, the maximum blood level observed was no greater than 0.200 ng/mL (See section 4.2). The whole blood concentrations of cyclosporine (0.100 to 0.200 ng/mL) determined after dosing of OTX-101 Ophthalmic Solution at the intended clinical dose (0.09%, BID, OU), are 3000 to 4000-fold lower than the C_{max} (655 to 1802 ng/mL) of cyclosporine following oral administration of Neoral (Neoral® Package Insert), and are 7 to 13-fold lower than the C_{max} of cyclosporine (1.4 to 2.7 ng/mL) following oral administration of Sandimmune (Sandimmune® Package Insert).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of one drop of CEQUA twice daily (approximately 12 hours apart) instilled into each eye using a single-use container in patients 18 years of age and older is appropriate for the general patient population.

The Applicant conducted a Phase 2b/3 dose-ranging study (OTX-101-2014-001) to assess the efficacy and safety of OTX-101 0.09% and OTX-101 0.05% Ophthalmic Solution versus Vehicle. OTX-101 0.09% was selected in the Phase 3 study (OTX-101-2016-001) based on the dose-response trend observed for OTX-101 0.09% on the Schirmer's test and measures of ocular surface improvement (decreased conjunctival and corneal staining) in the dose-ranging Phase 2b/3 study. OTX-101 0.09% appeared to be more effective than OTX-101 0.05% in increasing tear production. The comparison of OTX-101 0.09% against Vehicle showed notable differentiation ($P = 0.0069$), whereas the comparison between the OTX-101 0.05% and Vehicle groups did not ($P = 0.1279$). An apparent dose response was also demonstrated in the analysis of mean change from baseline in Schirmer's test score (adjusted least squares means were 3.05 for OTX-101 0.09% versus Vehicle ($P = 0.0003$) and 2.22 for OTX-101 0.05% versus Vehicle ($P = 0.0076$)).

In the Phase 3 study (OTX-101-2016-001), OTX-101 0.09% as compared to Vehicle demonstrated statistically significant and clinically relevant increased tear production as measured by increased Schirmer's test scores (Table 3.3.2-1), (b) (4)

Table 3.3.2-1. Proportion of Eyes with Increase from Baseline in Schirmer's Test of ≥ 10 mm on Day 84 - Both Eyes (ITT Population)

Parameter	OTX-101-2014-001			OTX-101-2016-001		
	OTX-101 0.09%	Vehicle	Treatment Difference ^a	OTX-101 0.09%	Vehicle	Treatment Difference ^a
N ^b	152	152	–	371	373	–
Eyes responding, n (%) ^c	51 (16.8)	26 (8.6)	(8.2)	123 (16.6)	69 (9.2)	(7.3)
95% CL (%)	[12.6, 21.0]	[5.4, 11.7]	[3.0, 13.5]	[13.9, 19.3]	[7.2, 11.3]	[3.9, 10.7]
P-value	–	–	0.0021	–	–	< 0.0001

CL = 95% upper and lower confidence limits; ITT = intent-to-treat

^a Generalized estimating equations 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 the response probability in the 2 groups is the same. Positive estimates of the difference favor response in the OTX-101 group.

^b N = Number of subjects in the intent-to-treat population.

^c n = number of subjects with only one eye + 2 times number of subjects with both eyes responding. Denominator is 2 times the number of subjects.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Since the systemic absorption of cyclosporine was negligible following the topical application of OTX-101 ophthalmic solution, 0.09% in healthy volunteers, dose individualization is not necessary based on intrinsic and extrinsic factors.

4. Appendix

4.1 Summary of Bioanalytical Method Validation and Performance

Cyclosporine whole blood concentrations were determined using a validated, liquid chromatography with tandem mass spectrometry (LC/MS/MS) method. The validated detection range for cyclosporine was 0.100 ng/mL to 100 ng/mL in human blood. Results from the validated assay are listed in Table 4.1-1.

Table 4.1-1. Summary of Analytical Methods for Quantification of Cyclosporine in Human Whole Blood

Method	ARCYC2
Matrix	Blood
Clinical Studies Supported	OTX-101-2016-003
Standard Curve Range (LLOQ-ULOQ)	0.100 - 100 ng/mL
QC Samples	0.300, 40.0, 80.0 ng/mL
Accuracy (%)	Within $\pm 15\%$ deviation from the nominal concentration
Precision (%)	$\leq 15\%$
Short-term matrix stability (Human Whole Blood)	Up to 20 hours
Freeze-thaw stability	5 cycles
Extract stability (Human Whole Blood Extracts)	Up to 30 hours
Long-term stability	49 days at -20°C or -70°C storage

Reviewer comment: The validation and performance of the bioanalytical method was deemed acceptable by the reviewer.

4.2 Individual Clinical Pharmacology Report Reviews

OTX-101-2016-003: An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of OTX-101 Nanomicellar Ophthalmic Solution in Healthy Volunteers

An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of OTX-101 Nanomicellar Ophthalmic Solution in Healthy Volunteers

Date(s): 21 September 2016– 09 October 2016

Sponsor: Sun Pharma Global FZE c/o Point Guard Partners, LLC

Testing Site:

(b) (4)

Analytical Site:

(b) (4)

OBJECTIVES

The objectives of this study were:

- To evaluate the ocular and systemic safety of OTX-101 nanomicellar ophthalmic solution 0.09%.
- To evaluate the systemic absorption of OTX-101 nanomicellar ophthalmic solution 0.09%.

METHODS

Trial Design

This was an open-label, single-arm, single-center study conducted in 16 healthy subjects. After screening/qualification, subjects received one drop of OTX-101 nanomicellar ophthalmic solution 0.09% topically into each eye (OU), twice a day (BID) for 7 days, and once on Day 8, instilled by clinic staff.

Pharmacokinetic Assessments

Blood samples were obtained at following time points after the instillation of study medications on both Day 1 and Day 8: 0.5 hour prior to the drug administration, and at approximately 0.25, 0.5, 1, 2, 4, 8 and 12 hours post dose.

Bioanalytical Method

Cyclosporine whole blood concentrations were determined using a validated, liquid chromatography with tandem mass spectrometry (LC/MS/MS) method. The validated detection range for cyclosporine was 0.100 ng/mL to 100 ng/mL in human blood.

Reviewer Comment: The performance of the bioanalytical methods for Cyclosporine in human whole blood has been evaluated by the Applicant (Refer to Section 4.1). The bioanalytical method is acceptable.

RESULTS AND CONCLUSIONS

Pharmacokinetic Results

Sixteen healthy subjects were enrolled, one of which was discontinued after the first day for non-compliance. Thus, information was available after a single dose for 16 subjects, and after 7.5 days of dosing for 15 subjects (248 total sampling times available).

Of these samples, 87.1% (216/248) were below the lower limit of quantitation (LLOQ) (0.100 ng/mL). Of the 32 samples above LLOQ, all were between 0.100 and 0.200 ng/mL. Only 4 subjects had ≥ 3 consecutive whole blood cyclosporine concentrations $\geq$ LLOQ. Due to this sparse data, pharmacokinetic analysis was limited. For these 4 subjects, the mean $\pm$ standard deviation (SD) maximum concentration (C_{max}) on day 8 was 0.173 $\pm$ 0.020 ng/mL.

Individual values for the 32 samples above LLOQ are shown in Table 1. On Day 1, 3 of 16 subjects (18.8%) had values ranging from 0.106 to 0.187 ng/mL at 0.5 to 2.0 hours after dosing. On Day 8, 10 of 15 subjects (66.7%) had values ranging from 0.101 to 0.195 ng/mL at 0.25 to 4.0 hours after dosing. There were no subjects with values above LLOQ in the blood samples just prior to the dosing on Day 8.

Table 1: Study OTX-101-2016-003: Cyclosporine Whole Blood Concentrations (ng/mL) for Observations Above Lower Limit of Quantitation (0.100 ng/mL) in Healthy Subjects

Subject No.	Day 1 (Hours)			Day 8 (Hours)				
	0.5	1.0	2.0	0.25	0.5	1.0	2.0	4.0
1	---	0.127	0.143	---	---	0.122	0.159	---
3	---	---	---	---	---	---	0.102	---
4	---	---	---	---	---	0.106	0.102	---
6	---	---	---	---	0.101	0.167	0.195	0.138
7	---	---	---	---	---	0.109	---	---
8	---	---	---	---	---	---	0.104	---
12	---	0.187	0.172	---	---	0.112	0.119	---
13	---	---	---	---	---	0.168	0.162	0.118
14	0.160	0.150	0.106	0.115	0.151	0.181	0.143	0.124
15	---	---	---	---	0.103	0.129	0.147	0.110

Safety Results

The Test Drug (OTX-101 ophthalmic solution 0.09%) was well-tolerated following repeated daily BID administration as a single full eye drop of 0.09% solution administered to each eye of the healthy adult subjects.

REVIEWER'S ASSESSMENT

This study evaluated the systemic absorption of OTX-101 nanomicellar ophthalmic solution 0.09%. We concur with the Applicant's following conclusions:

- Following BID topical administration of cyclosporine ophthalmic solution, 0.09% in humans for up to 7 days, and once on Day 8, blood concentrations of cyclosporine 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.

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/

XIAOHUI WEI
07/11/2018

PHILIP M COLANGELO
07/11/2018