CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

SUMMARY REVIEW

Deputy Division Director and Cross-Discipline Team Leader Review: NDA 210913

Date	August 13, 2018
From	Wiley A. Chambers, M.D., William M. Boyd, M.D.
Subject	Deputy Division Director and Cross-Discipline Team Leader Review
NDA#	NDA 210913
Applicant	Sun Pharma Global FZE
Date of Submission	October 16, 2017
PDUFA Goal Date	August 16, 2018
Proprietary Name / Established (USAN) names	Cequa (cyclosporine ophthalmic solution) 0.09%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye)
Action:	Approval

1. Summary

Throughout this review, Cequa (cyclosporine ophthalmic solution) 0.09% is alternately referred to as OTX-101 ophthalmic solution.

In two multicenter, randomized, adequate and well-controlled clinical studies there was a statistically significant, higher percentage of eyes with a clinically significant increase in tear production ($\geq$ 10 mm from baseline in Schirmer's wetting) in patients with keratoconjunctivitis sicca at Day 84 favoring Cequa. This effect was replicated in the studies and seen in approximately 17% of Cequa-treated patients versus approximately 9% of vehicle-treated patients in each study.

Adequate and well controlled studies support the safety of Cequa (cyclosporine ophthalmic solution) 0.09% for the increase of tear production in patients with keratoconjunctivitis sicca. In clinical trials, 769 subjects received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated subjects were female (83%). The most common adverse reactions reported were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of the patients were blepharitis, eye irritation, headache, and urinary tract infection.

The benefits of using this drug product outweigh the risks for the increase in tear production in patients with keratoconjunctivitis sicca (dry eye).

2. BENEFIT-RISK ASSESSMENT

NDA 210913 Benefit-Risk Assessment Framework

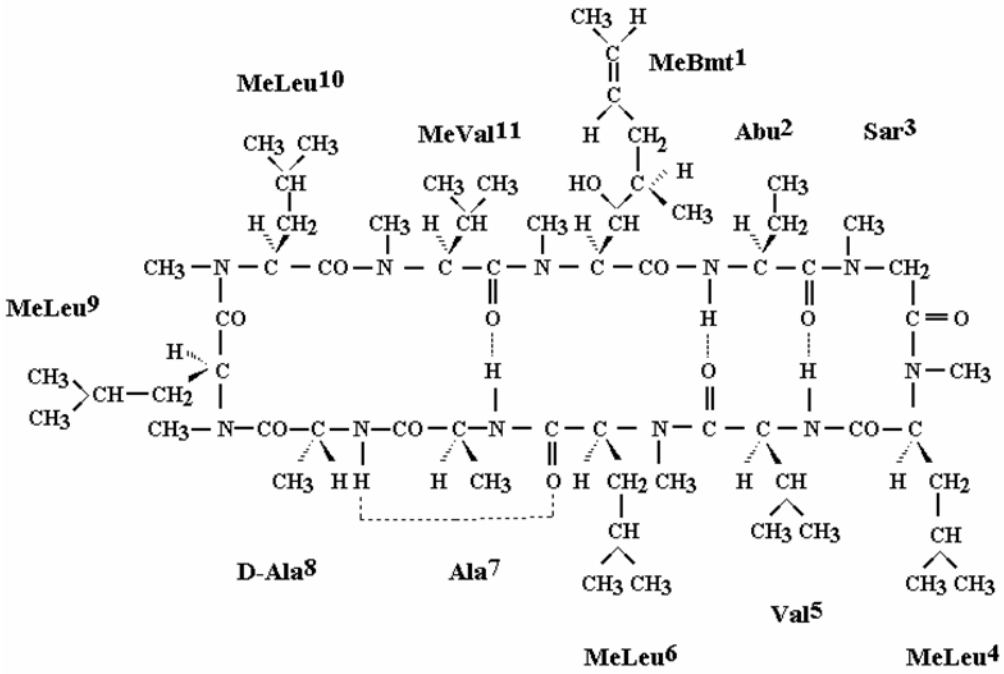
Benefit-Risk Integrated Assessment
The data contained in this submission establishes the efficacy of Cequa (cyclosporine ophthalmic solution) 0.09% by demonstrating that in dry eye patients, there was a statistically significant, higher percentage of eyes with clinically significant increases in tear production. The most common adverse reactions were transient. Those reported in greater than 5% of subjects were pain on instillation of drops (22%) and conjunctival hyperemia (6%). The potential benefits of Cequa (cyclosporine ophthalmic solution) 0.09% through an increase in tear production outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The health and function of the cornea is dependent on a thin tear film layer made up of an aqueous, mucin, lipids, lysozymes, immunoglobulins, glucose, and salts. In keratoconjunctivitis sicca (dry eye), one or more of the components is deficient.	Keratoconjunctivitis sicca (dry eye) is a potentially debilitating condition which can impede the activities of daily living and can be associated with anterior segment damage to the eye.
Current Treatment Options	Currently available treatments for keratoconjunctivitis sicca (dry eye) include the use of OTC demulcents, an Rx topical calcineurin inhibitor (cyclosporine ophthalmic emulsion) and/or a lymphocyte function-associated antigen-1 (LFA-1) antagonist.	This product, if approved, would provide an alternative product to increase tear production.
Benefit	Increases of $\geq$ 10 mm from baseline in Schirmer's wetting in dry eye patients are a clinically relevant benefit. This level of increased tear production has been shown to be correlated with decreased corneal staining.	Two multicenter, randomized, adequate and well-controlled clinical studies demonstrated a statistically significant, higher percentage of eyes with clinically significant increases in tear production.
Risk and Risk Management	The most common adverse reactions reported in subjects were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Systemic adverse events are not expected because blood concentrations of cyclosporine after twice daily topical administration of 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.	The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of cyclosporine ophthalmic solution could be monitored with local slit lamp examinations.

3. Background

Chemical Structure of cyclosporine



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

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.

Cyclosporine, when administered topically to the cornea is an immunomodulator that has been developed to increase tear production in patients with keratoconjunctivitis sicca (KCS). Cyclosporine, in an oral formulation, (Sandimmune) was approved in the United States for the prophylaxis of organ rejection in kidney, liver, and heart allogenic transplants in 1983. Cyclosporine, in an oral formulation, Neoral, was approved and in 1997 with additional indications: 1) treatment of patients with active rheumatoid arthritis and 2) treatment of adult non-immunocompromised patients with severe recalcitrant, plaque psoriasis.

The applicant has filed this application as a 505(b)(2) NDA application. The clinical support for the application is based on adequate and well controlled studies conducted by the applicant. The nonclinical ocular safety is based on nonclinical studies conducted by the applicant. Portions of the labeling are supported by a published literature reference for peri-/post-natal development and fertility. The systemic safety support is based on reference to Sandimmune (NDA 50573) and Neoral (NDA 50715) for which the applicant does not have a right to reference.

Potential adverse events associated with the use of topical ophthalmic cyclosporine (various formulations) are well known. 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.

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 while Study OTX-101-2014-001failed to meet its pre-specified co-primary efficacy endpoints (a sign and a symptom of dry eye) additional post hoc analyses (increase in tear production) should be conducted. In addition, 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.

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

4. Product Quality

Cequa (cyclosporine ophthalmic solution) 0.09% is a clear, preservative-free, formulation of 0.09% cyclosporine in unit dose (b) (4) vials.

Release Specification of the Drug Substance:

Summary of Justification of Drug Substance Specifications

Test	Acceptance Criteria	Justification
Description/Appearance	White or almost white powder	Physical examination of the dry powder drug substance allows for inspection of any color changes or gross visible contamination that may indicate the need for further investigation and action, as appropriate.
Identity	Retention time of the principle peak in the chromatogram of the tested substance corresponds to the retention time of the peak in chromatogram of the reference standard.	Identification is confirmed by comparison of the retention time of the principle peak of the drug substance test sample and standard solution via High Performance Liquid Chromatography (HPLC). This method enables discrimination between compounds of other related structures that may be present.
Assay	(b) (4)	The proposed assay acceptance criterion is based on the current version of the USP monograph.
Particle Size[a]	(b) (4) % NMT 50 µm (b) (4) % NMT 100 µm	The acceptance criteria for particle size ensure flowability of the final API for use in further processing and manufacturing of final drug product dosage forms.
Related Substances Any individual impurity Total Impurities	 ≤ (b) (4) % ≤ (b) (4) %	The acceptance criteria have been established in accordance with USP monograph.
Residual Solvents: (b) (4)	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm	Acceptance criteria were established per the (b) (4) DMF and USP<467>, Ph Eur Chapter 5.4 and ICHQ3C.
Microbial Quality: Total aerobic bacteria Yeasts and molds	 ≤ (b) (4) CFU/g ≤ (b) (4) CFU/g	Acceptance criteria are aligned with USP <61> and <62>

[a] Accepted on the basis of supplier (b) (4) COA

SOURCE: Module 2.3.S

Description and Composition of the Drug Product

Component	Function	Theoretical Composition per mL	Theoretical Percent Weight per Volume[a]
Cyclosporine, USP[b]	Active Ingredient	(b) (4)	0.09
Polyoxyl (b) (4) Hydrogenated Castor Oil[c], USP/NF	(b) (4)		
Octoxynol-40, In-House			
Sodium Phosphate Monobasic, Dihydrate, USP/NF			
Sodium Phosphate Dibasic Anhydrous, USP/NF			
(b) (4)			
Polyvinylpyrrolidone[d], USP/NF			
Hydrochloric Acid (1N) USP/NF	QS[d] to adjust pH, if required		
Sodium Hydroxide (1N) USP/NF	QS[d] to adjust pH, if required		
Water for Injection, USP/NF	(b) (4)		

[a] Rounded to two decimal places

[b] USP/NF=United States Pharmacopeia/National Formulary

(b) (4)

SOURCE: Module 2.3.P

Specifications for OTX-101 Ophthalmic Solution

Test	Acceptance Criteria	Analytical Method
Appearance	Clear, colorless solution, essentially free from visible particulate matter	Visual
Identification[a]	Retention time of the sample conforms to the retention time of the standard	HPLC
	The FTIR spectrum of the sample matches that of the standard.	FT-IR
Cyclosporine Assay	(b) (4)% of label claim	HPLC
(b) (4) Each specified unidentified product RRT (b) (4) RRT (b) (4) Any unspecified impurity Total impurities	(b) (4)	HPLC
pH	6.5-7.2	USP<791>
Osmolality	160-190 mOsm/kg	USP<785>
Viscosity	(b) (4) cP	USP<911>
Sterility	No evidence of microbial growth	USP<71>
Micelle Size Determination	Zavg (b) (4) nm, PdI NMT (b) (4)	Light Scattering
Particulate Matter	Number of particles ≥ (b) (4) NMT 50/mL Number of particles ≥ (b) (4) NMT 5/mL Number of particles ≥ (b) (4) NMT 2/mL	USP<789>
Uniformity of Dosage Units[b]	Complies	USP<905>
Weight Loss[b]	NMT (b) (4)% w/w	Gravimetric

[a] Test not performed on stability.
[b] Test performed only on stability.

(b) (4)

SOURCE: Module 3.2.P.5.1

Drug Product Container Closure

The container closure system for OTX-101 Ophthalmic Solution consists of the following components: (b) (4)

(b) (4)

Two (2) cards of the five (5) labeled (b) (4) vials are packaged in a pre-printed polyfoil aluminum pouch. Six (6) sealed pouches are then packaged in secondary packaging that consists of a standard paperboard carton that is appropriately printed or labeled. Refer to Table 1 for additional details on container closure system materials and supplier/manufacturers.

Table 1: Packaging Components and Supplier Information for the OTX-101 Ophthalmic Solution Container Closure System

Packaging Component	Material	Material Description	Supplier/Manufacturer	DMF No. (if available)
0.9 mL Unit Dose Vial	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Label placed on (b) (4) vial tab	Adhesive used on label	(b) (4)		

Packaging Component	Material	Material Description	Supplier/Manufacturer	DMF No. (if available)
Polyfoil Aluminum Pouch[a]	Foil Used for Polyfoil Aluminum Pouch	(b) (4)		

SOURCE: Module 3.2.P.7.

From the Office of Product Quality Review dated 7/19/2018:

Inspections
All the facilities are acceptable based on the profile. No additional pre-approval inspection is required at this review cycle. Therefore, the overall recommendation of "Approve" was entered for the NDA into Panorama by OPF on 5/9/2018.

Post approval inspection for (b) (4) is recommended due to previous recalls associated with OOS results, failing to meet in-process controls, exceeding impurity levels at stability, and reported consumer complaints of drug product mix up.

Summary of Drug Substance Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)	(b) (4)	(b) (4)	• Medium	• Approve
		(b) (4) (b) (4)	• High	• Approve with post approval Inspection
		Profile Code: CSN		

Summary of Drug Product Facility Information:

Establishment Name and Address	FEI Number	Responsibilities andprofile codes	Initial Assessment	Final Recommendation
Laboratoire Unither ZI de la Guerie F-50211 Coutances Cedex France	3006974616	Drug product manufacturer, analytical testing, release, packaging, stability testing and alternate site for release SLO	• High	• Approve
(b) (4)			• Medium	• Approve
			• Medium	• Approve

Recommendation and Conclusion on Approvability from OPQ

NDA 210913, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Cequa (cyclosporine) ophthalmic solution. All information requests and review issues have been addressed. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 5/9/2018. Therefore, NDA 210913 is recommended for approval from Product Quality perspective.

Reference ID: 4306102

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 8/6/2018:

The applicant has filed a 505(b)(2) NDA application and relies upon Sandimmune (NDA 050573) and Neoral (NDA 050715) for most aspects of systemic safety support, a published literature reference for peri-/post-natal development and fertility and original nonclinical studies conducted by the Applicant to support ocular safety and distribution.

Cyclosporine is a calcineurin inhibitor immunosuppressant agent when administered systemically. 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 act as a partial immunomodulator. The exact mechanism of action is not known.

A pivotal 26-week ocular toxicity study was conducted in rabbits with Cequa (cyclosporine ophthalmic solution) 0.09%. Cequa did not produce toxicity at dosing regimens approximately 2-fold higher than the proposed clinical dose, on a per eye basis.

A bridge to the listed drugs (LDs) was established based on a dose comparison between the Applicant's proposed dosing regimen and the approved maintenance doses for the listed oral drug formulations (Neoral and Sandimmune), which provided adequate systemic safety support for this application.

Bilateral BID administration of Cequa would result in a daily dose of (b) (4) µg/eye/day or a total daily dose of (b) (4) µg. It should be noted that the recommended daily maintenance doses of Neoral and Sandimmune (~ 10 mg/kg/day; up to ~600 mg/day for 60 kg person) are 6830 times higher than the total daily dose of Cequa; therefore, there are no systemic safety concerns beyond those established for the approved oral formulations.

A bridge to the published literature used to support nonclinical studies of fertility and peri-/post-natal development (Ryffell, 1983) was established based on a dose comparison between the Applicant's proposed dosing regimen and the NOAEL found in those studies.

Bilateral BID administration of Cequa would result in a daily dose of (b) (4) µg/eye/day or a total daily dose of (b) (4) µg/day ((b) (4) µg/kg in a (b) (4) kg adult). The NOAEL established for fertility and peri-/post-natal development in the published literature is 15 mg/kg [Human Equivalent Dose (HED): (b) (4) µg/kg in a (b) (4) kg adult] resulting in a dose margin of approximately (b) (4) -fold over the HED. The total dose of the cyclosporine following ocular administration of Cequa is much lower than that of the NOAEL. As such, reliance on this study for fertility and peri-/post-natal safety support is scientifically appropriate.

6. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology review dated 7/11/2018:

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 Cmax of cyclosporine after oral administration of Neoral and 7 to 13-fold lower than the Cmax of cyclosporine following oral administration of Sandimmune.

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).

7. Sterility Assurance

From the original Office of Product Quality Review, Microbiology subsection, dated 7/19/2018:

Cequa (cyclosporine Ophthalmic Solution) 0.09% is supplied as a single-use 0.9 ml (b) (4) vial with a 0.25 ml fill. The drug product is supplied as a package of six (6) sealed polyfoil aluminum pouches, each containing two (2) cards of five (5) vials.

The application is recommended for approval from the standpoint of Product Quality Microbiology:

- The applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product.
- The applicant has provided adequate descriptions of the manufacturing facility and equipment used in the manufacturing of commercial batches and the manufacturing process is consistent with regulatory expectations for a sterile pharmaceutical product.
- The applicant's environmental monitoring program is consistent with regulatory expectations for a pharmaceutical product manufactured by (b) (4) The applicant has met regulatory expectations for validating the (b) (4) ability to retain a bacterial challenge from the subject drug product.
- The holding period times are not excessive, and the provided microbiological data support the proposed manufacturing process times. There is minimal risk of microbial proliferation in the product during these holding times.
- The applicant has met regulatory expectations for the performance of process simulations in support of the (b) (4) of the subject drug product.
- The applicant has met regulatory expectations for the product release specification.
- The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

- The applicant's proposed 24-month expiry is acceptable based on the provided microbial test data.
- The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.
- The applicant has met regulatory expectations regarding the information related to issues of product quality microbiology provided in the product labeling.

8. Clinical/Statistical- Efficacy

From the original Medical Officer Review dated 8/8/2018:

Primary Data Used to Evaluate Efficacy

Protocol	Study Design	Subject Population	Treatment Group	Dosing Regimen	Study Duration	Number of Subjects
OTX-101-2014-001 Safety and efficacy	Multicenter, Randomized, double-masked, vehicle controlled	History of KCS	Cyclosporine 0.05% Cyclosporine 0.09% Vehicle	1 drop OU BID	12 weeks	Cyclosporine 0.05%=151 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

Reference ID: 4306102

Study OTX-101-2014-001

The original 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)

(b) (4)

At the EOP2 meeting, the applicant 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 with both eyes averaged demonstrated statistical significance ($p = 0.0069$) for OTX-101 0.09%. The applicant proposed conducting a phase 3 study (Study OTX-101-2016-001) to confirm the post hoc findings; using 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

Percentage of Eyes with ≥10mm Increase in Schirmer's Day 84	OTX-101 0.09%	Vehicle	Treatment Difference[a]
N[b]	152	152	8.2%
n, number of eyes responding[c]	51	26	***p* = 0.0021**
% of eyes	16.8	8.6	[3.0. 13.5]

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.
[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

Study OTX-101-2016-001

The primary efficacy endpoint 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

Percentage of Eyes with ≥10mm Increase in Schirmer's Day 84	OTX-101 0.09%	Vehicle	Treatment Difference[a]
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

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.

Efficacy Summary Statement

In two multicenter, randomized, adequate and well-controlled clinical studies there was a statistically significant ($p<0.01$) higher percentage of eyes with clinically significant increases of (≥ 10 mm from baseline in Schirmer's) wetting at Day 84 favoring Cequa. This effect was seen in approximately 17% of Cequa-treated patients versus approximately 9% of vehicle-treated patients.

9. Safety

From the original Medical Officer Review dated 8/8/2018:

Pooled Data

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

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 (31)**	**94 (18)**	**37 (24)**	**28 (18)**	**125 (34)**	**66 (18)**
Instillation site pain	114 (22)	21 (4)	23 (15)	5 (3.3)	90 (24)	16 (4)
Conjunctival hyperemia	30 (6)	19 (4)	0	0	30 (8)	19 (5)
Eye irritation	6 (1)	6 (1)	3 (2)	1 (0.7)	3 (1)	5 (1)
Blepharitis	5 (1)	0	0	0	5 (1)	0
Eye pruritus	2 (0.4)	8 (1.5)	1 (1)	4 (2.6)	1 (0.3)	5 (1)
Foreign body sensation	2 (0.4)	5 (1)	1 (1)	0	1 (0.3)	5 (1)
Vitreous floaters	2 (0.4)	5 (1)	1 (1)	2 (1.3)	1 (0.3)	3 (0.8)
NON-OCULAR	**70 (13)**	**65 (12)**	**21 (14)**	**32 (21)**	**49 (13)**	**33 (9)**
Headache	8 (1.5)	2 (0.4)	2 (1)	0	6 (2)	2 (0.5)
Urinary tract infection	6 (1)	4 (1)	2 (1)	2 (1)	4 (1)	2 (0.5)
Bronchitis	5 (1)	3 (0.6)	2 (1)	2 (1)	3 (1)	1 (0.3)
Sinusitis	4 (1)	5 (1)	0	0	4 (1)	5 (1)
Upper respiratory tract infection	4 (1)	5 (1)	3 (2)	2 (1)	1 (0.3)	2 (0.5)
Nasopharyngitis	1 (0.2)	5 (1)	1 (1)	4 (3)	0	1 (0.3)

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%).

Exposure

There is adequate exposure to assess the safety profile of OTX-101 ophthalmic solution 0.09%.

Mean Duration of Exposure in Individual Studies – Safety Population

	Pooled Data		OTX-101-2014-001		OTX-101-2016-001	
Exposure (weeks)	**OTX-101 0.09% (N=524)**	**Vehicle (N=524)**	**OTX-101 0.09% (N=152)**	**Vehicle (N=152)**	**OTX-101 0.09% (N=372)**	**Vehicle (N=372)**
N	520	519	152	151	368	368
Mean (SD)	11.8 (2.4)	12.2 (1.3)	11.6 (2.43)	12.0 (1.8)	11.9 (2.4)	12.3 (1.0)
Min, Max	0,15	1,15	1, 13	1, 14	0,15	3, 15

Min=minimum, Max=maximum

Deaths

One death was reported during the development of OTX-101. Subject number (b) (6) in study OTX-1010-2016-001 experienced a fatal serious adverse event (SAE) two days following initiation of study medication. The cause of death is listed as unknown. 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) (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 applicant and/or medical monitor agrees with the Investigator's assessment of causality. This death does not appear related to drug product.

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

Safety Summary Statement

Adequate and well controlled studies support the safety of Cequa (cyclosporine ophthalmic solution) 0.09% for the increase of tear production in patients with keratoconjunctivitis sicca.

In clinical trials, 769 subjects received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated subjects were female (83%). The most common adverse reactions reported in greater than 5% of subjects were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of the patients were blepharitis, eye irritation, headache, and urinary tract infection.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

11. Pediatrics

The safety and efficacy of Cequa (cyclosporine ophthalmic solution) 0.09% have not been established in pediatric patients below the age of 18. This drug product triggers PREA as a new dosage form. The applicant requested a full waiver of pediatric studies because studies are impractical and highly impossible for the proposed indication. Dry eye syndrome does not exist in a significant number of pediatric patients and therefore studies would be impractical. The Pediatric Review Committee (PeRC,) in their 6/13/2018 meeting, concurred with the applicant's plan for a full waiver of pediatric studies.

12. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 7/5/2018:

The Applicant conducted two pivotal efficacy studies to evaluate OTX-101: OTX-101-2014-001 and OTX-101-2016-001. These studies are hereafter referred to as Study 14 and Study 16, respectively.

Studies 14 and 16 were multi-center, randomized, double-masked, vehicle-controlled, superiority studies. Study 14 randomized 455 subjects in a 1:1:1 ratio to OTX-101 0.05%, OTX-101 0.09%, or vehicle. In Study 16, a total of 745 subjects were randomized in a 1:1 ratio to OTX-101 0.09% or vehicle. In both studies, subjects were instructed to administer study medication topically to both eyes twice daily for 12 weeks. The primary efficacy evaluations were conducted at Day 84.

Study 14 had co-primary endpoints of sign and symptom. The sign primary endpoint was the mean change from baseline in total conjunctival staining score. The symptom primary endpoint was the mean change from baseline in global symptom score. On the other hand, Study 16 had a single primary endpoint associated with tear production: response rate in the Schirmer's test score defined as the proportion of eyes achieving $\geq$ 10 mm increase from baseline in the Schirmer's test score. The selection of the primary endpoint in Study 16 was based on the positive results of the Schirmer's test score in Study 14.

For the filing of this NDA submission, the Applicant proposed to use the response rate in the Schirmer's test score as a single primary endpoint. This proposal was considered acceptable by the Division of Transplant and Ophthalmology Products (DTOP) at the End-of-Phase 2 meeting. The DTOP also agreed that the analysis results of this endpoint for Study 14 can be considered supportive.

In both studies, the response rate in the Schirmer's test score was significantly higher in the OTX-101 0.09% group compared to that in the vehicle group: 16.8% vs. 8.6% in Study 14 and 16.6% vs. 9.2% in Study 16

Reference ID: 4306102

(Table 1). The differences in the response rates (OTX-101 - vehicle) were statistically significant: 8.2% [95% CI: (1.9%, 14.6%)] in Study 14 and 7.3% [95% CI: (3.3%, 11.3%)] in Study 16.

Table 1: Proportion of eyes with ≥10 mm increase from baseline in the Schirmer's test score at Day 84

	OTX-101-2014-001		OTX-101-2016-001	
	OTX-101 0.09% N = 152	Vehicle N = 152	OTX-101 0.09% N = 371	Vehicle N = 373
Number of eyes	304	304	742	746
Eyes with ≥10-mm increase, n (%) [1]	51 (16.8%)	26 (8.6%)	123 (16.6%)	69 (9.2%)
Difference [95% CI] [2]	8.2% [1.9%, 14.6%]		7.3% [3.3%, 11.3%]	
P-value for Difference [2]	0.0113		0.0003	

[1] All randomized and treated subjects were included in the analysis. Missing values were treated as failures;
[2] Based on a generalized estimating equation model including treatment as a sole factor. Observations from the left and right eyes of the same subject were treated as repeated measures; CI: confidence interval.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Cequa, and granted conditional acceptance on 2/6/2018. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA completed a formal review of the package insert and container labeling on 5/2/2018. Their recommendation regarding the container (vial) labels was not transmitted to the applicant. The vials are too small to include this information; the foil pouch has been revised.

> Designate an area for inclusion of the lot number, expiration date and name of manufacturer/packer/ drug distributor on each plastic single-use vial. We also recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

OPDP
The Office of Prescription Drug Promotion (OPDP) completed reviews of the package insert (7/31/2018) and carton and containers (8/1/2018) but had no additional suggested revisions.

FINANCIAL DISCLOSURE
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

OSI
A routine Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated 5/29/2018:

The clinical sites of (b) (6) were inspected in support of this NDA. The clinical sites of were selected for inspection because of their relatively large enrollments and lack of previous inspections.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
(b) (6)	OTX-101-2014-001 Subjects: (b) (6)	(b) (6)	NAI
	OTX-101-2016-001 Subjects: (b) (6)	(b) (6)	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of the inspections of (b) (6) was No Action Indicated (NAI).

13. Labeling

NDA 210913 Cequa (cyclosporine ophthalmic solution) 0.09% is recommended for approval to increase tear production in patients with keratoconjunctivitis sicca (dry eye) with the labeling attached as an Appendix in this review.

14. Regulatory Action

NDA 210913 Cequa (cyclosporine ophthalmic solution) 0.09% will be approved to increase tear production in patients with keratoconjunctivitis sicca (dry eye). There are no recommended postmarketing risk evaluation and management strategies (i.e. REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

8 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/

WILLIAM M BOYD
08/13/2018

WILEY A CHAMBERS
08/13/2018