CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 213-978
Drug Name:	OC-1 (Varenicline) nasal spray.
Indication(s):	Signs and symptoms of dry eye disease
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Keywords:

Multi-center, randomization, clinical studies

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1 EXECUTIVE SUMMARY

The Applicant submitted the New Drug Application (NDA) for OC-01 (Varenicline tartrate) nasal spray to treat the signs and symptoms of dry eye disease (DED). Three studies, ONSET-1, ONSET-2, and MYSTIC were among five evaluated for the efficacy assessment. The other two studies, IMPERIAL and (b) (4), were not reviewed for efficacy. IMPERIAL was a Phase 2 trial that enrolled 18 subjects and was prematurely terminated. (b) (4)

Efficacy Assessment
ONSET-2 was a Phase 3, multicenter, randomized, controlled, double-masked study, including a total of 758 subjects of age ≥ 22 years with a diagnosis of DED. An equal number of subjects were randomly assigned to receive OC-01 0.6 mg/mL, OC-01 1.2 mg/mL or placebo (OC-01 Vehicle). Efficacy was evaluated based on the primary endpoint of the percentage of patients achieving a ≥10-millimeter increase in Schirmer's tear test scores at Day 28 from the baseline. Demonstration on this endpoint alone is sufficient for efficacy claim based on FDA Guidance. The study showed that the percentage of subjects with success on the primary endpoint was higher in both of the treatment arms compared to the placebo arm (the percentage difference between 0.6 mg/ml arm and placebo arm = 16.2%, 95% CI = [8.41%, 24.07%]; the percentage difference between 1.2 mg/ml arm and placebo arm = 19.6%, 95% CI [11.63%, 27.67%]). The first secondary endpoint of the change in mean eye dryness score (EDS) from baseline to 5 minutes after treatment administration in the Controlled Adverse Environment (CAE) Chamber at Day 28 among the OC-01 arms was not significantly different from the placebo arm (least square mean difference between 0.6 mg/ml arm vs placebo arm = -2.9, 95% CI [-7.35, 1.55] and least square mean difference between 1.2 mg/ml arm vs placebo arm = -1.6, 95% CI [-6.19, 2.92]). Under the pre-specified statistical test hierarchy, formal testing of subsequent secondary endpoints was stopped due to the lack of statistical significance for the first secondary endpoint. ONSET-2 provides evidence to support the efficacy of OC-01.

ONSET-1 was a Phase 2b, multicenter, double-masked, placebo-controlled study that randomized a total of 182 subjects of age ≥ 22 years with a diagnosis of DED to receive OC-01 0.12 mg/mL, OC-01 0.6 mg/mL, OC-01 1.2 mg/mL, or placebo (OC-01 Vehicle) with an allocation ratio of 1:1:1:1. Efficacy was evaluated based on the primary sign endpoint of the change in Schirmer's test score from the Baseline to Day 28 in the study eye. In addition to this sign endpoint, demonstration on a symptom endpoint is also required for efficacy claim based on FDA guidance. The study demonstrated a statistically significant improvement in the primary efficacy endpoint among the OC-1 treatment arms compared to the placebo arm (the least square mean difference of change between the OC-1 0.6 mg/ml arm and the placebo arm = 7.7, 95% CI [3.8, 11.7] and least square mean difference of change between the OC-1 1.2 mg/ml arm and the placebo arm = 7.5, 95% CI [3.4, 11.6]). There was no formal testing for the dose of OC-01 0.12 mg/ml.

The secondary symptom endpoint of the change in EDS from baseline to Day 28 in the study eye among the OC-01 0.6 mg/ml arm was superior to the placebo arm (least square mean difference of change between the OC-1 0.6 mg/ml arm and the arm = -12.7, 95% CI [-23.2, -2.2]).

Therefore ONSET-1 provides evidence to support the efficacy of OC-01 0.6 mg/ml in both sign and symptom endpoints.

MYSTIC, a Phase 2, single-center, masked, placebo-controlled study, randomized a total of 123 subjects of age ≥ 22 with a diagnosis of DED to receive OC-01 0.6 mg/mL, OC-01 1.2 mg/mL, and placebo (OC-01 Vehicle). Efficacy was evaluated based on the primary endpoint of the change from the baseline in Schirmer's test score at Day 84 in the study eye. The study showed a significant improvement in the primary endpoint among the OC-1 treatment arm compared to the placebo arm (least square mean difference of change between the OC-1 0.6 mg/ml arm and the placebo arm = 4.3, 95% CI [0.32, 8.31]; least square mean difference of change between the OC-1 1.2 mg/ml arm and the placebo arm = 4.7, 95% CI [0.50, 8.9]). MYSTIC supports the efficacy of OC-01 in a sign endpoint.

Conclusions

In conclusion, ONSET-2 and ONSET-1 each demonstrated independent evidence for efficacy but on different endpoints, and MYSTIC is supportive, thus the data from the OC-01 (varenicline) nasal spray clinical development program provided substantial evidence of efficacy. There was consistent evidence by the Schirmer's score, either in the proportion with more than 10mm increase or in the changes from baseline in all three studies. However, for symptoms only ONSET-1 study showed statistically significant reduction in mean EDS from baseline to Day 28 compared to that of placebo but this symptom endpoint is not statistically significant in ONSET-2 and therefore not confirmed.

2 INTRODUCTION

2.1 Overview

The Applicant submitted an Original New Drug Application (NDA) for OC-01(varenicline) nasal spray to treat the signs and symptoms of dry eye disease. OC-01 is an aqueous solution of varenicline tartrate. DED is a multifactorial, age-related, chronic, progressive ocular surface disease resulting in severe pain, visual impairment, tear film hyperosmolarity, and inflammation.

The NDA included five studies. Three of the studies ONSET-1, ONSET-2, and MYSTIC were evaluated for efficacy. ONSET-2 was a Phase 3, ONSET-1 was a Phase 2b and MYSTIC was a Phase 2 study. The detail descriptions of the study designs are given in Section 3.2. The other two studies IMPERIAL and (b) (4) were considered inadequate to support efficacy. IMPERIAL was a Phase 2 trial that enrolled 18 subjects and was prematurely terminated. (b) (4).

ONSET-1 included a 0.1% OC-01 dose arm whereas the ONSET-2 included a 0.6 mg/mL dose arm. However, the Applicant confirmed that ONSET-1 and ONSET-2 used the equivalent doses (0.1% varenicline tartrate salt = 0.6 mg/mL free base and 0.2% varenicline tartrate salt = 1.2 mg/mL free base) of varenicline tartrate and FDA concurred with the equivalence (Meeting Minutes, 03/26/2019).

2.2 Data Sources

In the review, we used mainly the ADSL and ADEF and ADOC datasets. The Applicant used the same data file names for all studies and put them into different folders named by the studies. Data sets that we have used for the review are available in the following links:

- ONSET-1 (OPP-002): \\CDSESUB1\evsprod\NDA213978\0001\m5\datasets\opp-002\analysis\adam\datasets
- ONSET-2 (OPP-101): \\CDSESUB1\evsprod\NDA213978\0001\m5\datasets\opp-101\analysis\adam\datasets and \\CDSESUB1\evsprod\NDA213978\0026\m5\datasets\opp-002\analysis\adam\datasets
- MYSTIC (OPP-004): \\CDSESUB1\evsprod\NDA213978\0001\m5\datasets\opp-004\analysis\adam\datasets

While reviewing the NDA, the Applicant reported an error in a derived variable corresponding to the end date of the Schirmer's Test. The end date for the test was calculated as one day later than it should have been. On August 16, 2021, the Applicant submitted the revised adeff.xpt data for the ONSET-1 study.

Data processing codes to convert the Study Data Tabulation Model (SDTM) to Analysis Data Model (ADaM) were included in the following links:

- ONSET-1 (OPP-002): \\CDSESUB1\evsprod\NDA213978\0001\m5\datasets\opp-002\analysis\adam\programs

- ONSET-2 (OPP-101): \\CDSESUB1\evsprod\NDA213978\0001\m5\datasets\opp-101\analysis\adam\programs
- MYSTIC (OPP-004): \\CDSESUB1\evsprod\NDA213978\0001\m5\datasets\opp-004\analysis\adam\programs

Data analysis SAS codes were provided in the following links.

- ONSET-1 (OPP-002): \\CDSESUB1\evsprod\NDA213978\0013\m5\datasets\opp-002\analysis\adam\program
- ONSET-2 (OPP-101): \\CDSESUB1\evsprod\NDA213978\0013\m5\datasets\opp-101\analysis\adam\program
- MYSTIC (OPP-004): \\CDSESUB1\evsprod\NDA213978\0013\m5\datasets\opp-004\analysis\adam\program

We analyzed the data using R 3.6.0. We reproduced the Applicant's results using predefined methods and used additional statistical methods to assess the robustness of the inference the Applicant made.

We used datasets and documents including the following as the guidance for data analysis:

- Codebooks for datasets of ONSET-1, ONSET-2, and MYSTIC
- Applicant's data processing and analyses codes
- Analysis Data Reviewer's Guide
- Data definition documents
- Randomization schemes and codes

We reviewed documents for ONSET-1, ONSET-2, and MYSTIC that include but not limited to:

- Complete Study Reports (CSR)
- Integrated Assessment of Clinical Efficacy
- Study Protocols (all versions)
- DSMB Charters
- Statistical Analysis Plans (all versions)
- Draft label

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted the SAS codes and the tabulation data. We verified the reproducibility of a few important variables within the analysis datasets using the codes and SDTM dataset. We do not have any concern regarding the analysis datasets.

The Applicant provided a randomization schedule that included a listing of subject ID by treatment arm for ONSET-1, ONSET-2, and MYSTIC. The listing included a list of subjects, time and date of randomization, randomization number, and the treatment arms. A sample of

subjects from the listing were checked for the consistency in the data. We do not have any concern regarding the randomization of the study subjects.

According to the Applicant's description, the studies had monitors or a designee who made routine site visits to review the protocol compliance, assessed Investigational Product (IP) accountability, monitored subject safety, and ensured that the study was being conducted according to the pertinent regulatory requirements.

No unmasking occurred in any of the studies prior to the databases lock.

Dates related to the SAP for all three studies are organized in Table 1. ONSET-2 SAP had an addendum on April 15, 2020 that explained how the missing data due to COVID-19 pandemic would be treated in the analysis.

Table 1 Dates related to SAPs for ONSET-2, ONSET-1, and MYSTIC studies.

	ONSET-2 (OPP-101)	**ONSET-1 (OPP-002)**	**MYSTIC (OPP-004)**
SAP Finalized	April 29, 2020	October 4, 2018	December 23, 2019
Database lock	February 17, 2021	October 15, 2018	January 07, 2020
Last subject follow-up	March, 2021	September 26, 2018	November 22, 2019

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The comparative study designs and endpoints are summarized in Table 3. The studies were similar in objectives, study arms, study population, and the study eye definition.

Table 2 Comparative description of ONSET-2, ONSET-1, and MYSTIC

	ONSET-2 (OPP-101)	**ONSET-1 (OPP-002)**	**MYSTIC (OPP-004)**
Objective	To evaluate the safety and effectiveness of OC-01 nasal spray as compared to placebo on signs and symptoms of DED	Same as ONSET-2	Same as ONSET-2
Study Design	A Phase 3, multicenter, randomized, placebo-controlled, double-masked study Eligible subjects were randomly assigned to one of two treatment arms or placebo.	A Phase 2b, multicenter, randomized, double-masked, placebo-controlled study Eligible subjects were randomly assigned to one of three treatment arms or placebo.	A Phase 2, single-center, randomized, masked, placebo-controlled study Eligible subjects were randomized to one of the two treatment arms or placebo.

	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	Randomization was stratified by three factors: baseline Schirmer's Test Score (STS), baseline Eye Dryness Score (EDS), and study sites. The study used block randomization.	No stratifications were considered during randomization.	No stratifications were considered during randomization.
Treatment arms	• OC-01 0.6 mg/mL • OC-01 1.2 mg/mL • Placebo (OC-01 Vehicle) Subjects self-administered their treatments BID for 28 days.	• OC-01 0.12 mg/mL (0.02%) • OC-01 0.6 mg/mL (0.1%) • OC-01 1.2 mg/mL (0.2%) • Placebo (OC-01 Vehicle) Subjects self-administered their treatments BID for 28 days	• OC-01 0.6 mg/mL (0.1%) • OC-01 1.2 mg/mL (0.2%) • Placebo (OC-01 Vehicle) Subjects self-administered their treatments BID for 84 days.
Sample Size with randomization ratio to the study arms	758 subjects were randomized with ratio 1:1:1	182 subjects were randomized with ratio 1:1:1:1	123 subjects were randomized with ratio 1:1:1
Study population	Subjects of age ≥ 22 with a diagnosis of DED who met the eligibility criteria	Subjects of age ≥ 22 with a diagnosis of DED who met the eligibility criteria. The eligibility criteria were similar to that of ONSET-2.	Subjects of age ≥ 22 with a diagnosis of DED. The eligibility criteria for the study subject population were nearly identical to those for the Phase 2b (ONSET-1) and Phase 3 (ONSET-2) studies
Eligibility Criteria	Inclusion criteria included subjects who: • Used and/or desired to use an artificial tear substitute • Had an Ocular Surface Disease Index score of ≥ 23 with ≤ 3	Same as ONSET-2	Similar to ONSET-1

	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	• Diagnosed to have DED • Best corrected visual acuity (BCVA) was of 0.7 logarithm of the minimum angle of resolution (logMAR) or better • Had normal lid/lash anatomy, blinking function and closure as determined by the Investigator • Not pregnant Exclusion criteria include: • Clinically significant corneal epithelial defects • Chronic or recurrent epistaxis, coagulation disorders • Nasal or sinus surgery • Vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal airway obstruction		
Study Eye	The eye that met all the inclusion and exclusion criteria. If both eyes qualified, then the study eye was the eye with the greatest increase in tear production with stimulation by a cotton swab at the Screening Visit. If there was no difference in stimulated tear production, the eye with the lower baseline	Same as ONSET-2	Same as ONSET-2

	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	STS at screening was the study eye. If there was no difference for either of the measures, the right eye was used as the study eye.		
Primary Efficacy Endpoint	Percentage of subjects who achieve ≥10 mm improvement in the study eye on STS from baseline at Day 28	Change in STS from the baseline in the study eye at Day 28	Change from baseline in the study eye on STS at Day 84.
Secondary Efficacy Endpoints	The secondary endpoint included mean changes from baseline in the following: • EDS at 5 minutes after treatment administration in the Controlled Adverse Environment (CAE) Chamber at Day 28 • EDS at Day 28 • STS in the study eye at Day 28 • Inferior Corneal Fluorescein Staining (CFS) in the study eye at Day 28 • EDS at Day 14 • EDS at Day 7 • Nasal CFS in the study eye at Day 28 • Temporal CFS in the study eye at Day 28 • Central CFS in the study eye at Day 28 • Superior CFS in the study eye at Day 28 • Total CFS in the study eye at Day 28	Change in EDS from baseline to Day 28 in the study eye EDS 5 minutes post treatment in CAE at Day 21 in the study eye	The percent of subjects who achieved ≥10 mm improvement in STS from baseline at Day 28 and 84. Change from baseline in the study eye on Schirmer's Test at Day 28.

According to the DED Guidance for Industry[1], studies needed to establish a statistically significant difference between the investigational treatment and vehicle for at least one objective prespecified sign of dry eye (mean group score of tests versus vehicle) and at least one subjective prespecified symptom of dry eye (mean group score), or a statistically significant difference between the percentage of patients achieving a 10-millimeter increase or more in Schirmer's tear test scores. Efficacy for a sign and efficacy for a symptom do not have to be demonstrated in the same clinical trials, but each should *be demonstrated in more than one clinical trial.*

The primary endpoint of the change from baseline in the study eye in STS for ONSET-1 and MYSTIC is considered as an objective sign endpoint. The secondary endpoints of the change from baseline in EDS was listed as the subjective symptom endpoint in the guidance.

ONSET-2 used the standalone endpoint of a 10mm change in Schirmer which is acceptable to support approval for the full indication for the treatment of DED signs and symptoms as conveyed to the Applicant at the February 25, 2019 meeting (Agency meeting minutes 03/26/2019).

3.2.2 Statistical Methodologies

A discussion of statistical methodologies is given in **Table 3**.

Table 3 Statistical methodology description for studies

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
Primary efficacy Analysis	The unit of analysis was the study eye. The primary endpoint was analyzed using a Cochran-Mantel-Haenszel test comparing each treatment arm to placebo controlling for the stratification factors of study site, baseline STS [≤5, >5], and baseline EDS [<60, ≥60]. Because there were two comparisons of 0.6 mg/mL vs. placebo and 1.2 mg/mL vs. placebo, the overall familywise error rate was protected	The unit of analysis was the study eye. The primary efficacy analysis compared the differences in means of the 0.6 mg/mL and 1.2 mg/mL arms against placebo using the analysis of covariance (ANCOVA) model. The baseline STS, baseline STS with a cotton swab nasal stimulation, and study sites were covariates. Least square means, the mean difference and their corresponding Dunnett-	The unit of analysis was the study eye. The analysis of covariance (ANCOVA) model was used to compare each dose of OC-01 to placebo. The model contained baseline Schirmer's Test and treatment arm as covariates. Least square means, the mean difference and their corresponding 95% confidence intervals (CIs) were reported.

[1] Dry Eye: Developing Drugs for Treatment Guidance for Industry; https://www fda.gov/media/144594/download

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	using Hochberg's approach. If the p-values for both comparisons were <0.05, the null hypotheses were rejected for both treatment arms to conclude that both doses of OC-01 were superior to placebo. If not, the smaller of the two p-values was tested at the 0.025 level; if the null hypothesis was rejected, the dose of OC-01 with p<0.025 would be shown superior to placebo. The odds ratio and the success proportion differences were reported with 95% confidence intervals.	corrected 95% confidence interval (CI) were reported. Endpoints were tested in a hierarchical order with 0.6 mg/mL first and then 1.2 mg/mL doses of OC-01. The 0.12 mg/mL arm was not compared to placebo formally.	There was no pre-specified adjustment for multiple testing. The results will be interpreted with Bonferroni corrections
Secondary efficacy analysis	A hierarchical procedure was used to test the primary and 11 secondary efficacy endpoints to control overall familywise error rate for the 0.6 mg/mL dose and 1.2 mg/mL dose of OC-01 against placebo. If the null hypothesis for the primary endpoint for a given dose was rejected, the secondary endpoints in the order specified above were to be tested to maintain the overall two-sided type I error rate of 0.05.	The first secondary efficacy endpoint of mean change in EDS from baseline to Day 28 in the study eye was evaluated using an ANCOVA model. ANCOVA model included baseline EDS and study sites as covariates. The second secondary efficacy endpoint mean EDS at 5 minutes post treatment in the CAE at Day 21 in the study eye was analyzed using an ANCOVA model including baseline	The secondary endpoints of the percentage of subjects who achieved ≥10 mm improvement in study eyes at Day 84 and 28 from baseline were assessed using a Cochran-Mantel-Haenszel (CMH) test comparing treatment arms to placebo. CMH used baseline STS (≤5 vs. >5) as the stratification factor. The other secondary endpoints evaluating the mean change from baseline were analyzed

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	If the p-value from a test for both comparisons were <0.05 for the first secondary endpoint, both doses would be claimed superior to placebo and the testing would progress to the next comparison in the above sequence. If one dose arm was concluded to be superior to placebo for the primary endpoint, the secondary endpoints were to be tested in the order specified above using the type I error of 0.025 for that dose only. The pairwise treatment arm differences (0.6 mg/mL dose vs. placebo and 1.2 mg/mL dose vs. placebo) were compared on these 11 secondary endpoints using an analysis of covariance (ANCOVA). The ANCOVA model included treatment arm, study site, baseline STS, and baseline EDS as covariates. For the corneal staining analyses for each location, the ANCOVA model also included the baseline corresponding location corneal staining score as another covariate.	EDS and study sites as covariates in the model. For both models, the mean differences were calculated and reported with its 95% CI.	by the ANCOVA model with treatment, and relevant baseline variables as covariates. Least squares mean for each treatment and their corresponding 95% confidence intervals (CIs) were reported.

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	The difference in the mean for each comparison was calculated and reported along with its 95% confidence interval (CI) using the Hochberg test.		
Analysis populations	Intent-to-Treat (ITT): Included all randomized subjects. The ITT population was considered the primary analysis population for efficacy outcomes. Modified ITT (mITT): Three mITT Populations were defined by centers excluded because of being impacted by the Coronavirus disease-2019 (COVID-19) pandemic. Three mITT populations were defined as follows: − mITT-1 excluded Sites 48 and 51 − mITT-2 excluded Sites 45 and 48 − mITT-3 excluded Site 51 Safety Population: The Safety Population included all randomized subjects who received at least one dose of the IP. The statistical analysis of safety data was performed using the Safety Population. Per Protocol (PP): The PP Population included all	Intent-to-Treat: Included all randomized subjects. ITT was considered as the primary analysis population Safety Population: The Safety Population included all randomized subjects who received at least one dose of the Investigational Product (IP).	Intent-to-Treat: The ITT Population included all randomized subjects. The ITT population weas considered the primary analysis population for efficacy endpoints. The Per Protocol (PP) Population included subjects in the ITT Population who did not have significant protocol deviations and had at least one post-baseline visit. Sensitivity analyses were performed on the PP Population. The Safety Population included all randomized subjects who received at least one dose of the IP. Safety was evaluated base on Safety Population. The ITT and Safety population were identical for this study.

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	subjects in the ITT Population with post baseline data, excluding subjects who had major protocol deviations. Protocol deviations were assessed prior to database lock.		
Intercurrent events	Subjects may have been discontinued at any time prior to their completion of the study or study treatment due to the following reasons: • Non-fatal AEs • Protocol violations • Administrative reasons (e.g., lost to follow-up) • Physicians decision • Subjects non-compliance • Death • Study termination by the Sponsor • Subjects consent withdrawal Subjects who terminated early were asked to complete the safety assessments prior to exit. Discontinued subjects from the study were not replaced.	Subjects discontinued the study due to the following events: • AEs • Unmasking • Protocol violations • Administrative reasons (e.g., inability to continue, lost to follow-up) • Study termination by the Sponsor • Subjects consent withdrawal Subjects who terminated early were asked to complete the safety assessments prior to exit. Subjects who are terminated early from the study were not replaced.	Same as ONSET-1
Handling missing observations for primary endpoint analysis	Missing at Day 28 (Visit 4) were considered Missing at Random (MAR). The Statistical Analysis Plan (SAP) specified multiple imputation for handling MAR data.	Missing values were not imputed in the primary analysis. Assuming MAR, the study excluded missing observations from the analysis.	Missing observations were removed from efficacy analyses. Sensitivity for the efficacy analysis were performed using last-observation-carried-forward (LOCF)

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
	Missing due to COVID-19 were regarded as MAR and three mITT Populations were defined (see Analysis Populations above) because the pandemic had different effects on three centers that enrolled subjects. Sensitivity analyses for efficacy were performed using Last Observation Carried Forward (LOCF) procedure to impute missing data on both the ITT and mITT Populations.		imputation method to impute missing data on both the ITT and PP Populations.
Interim analysis	There was no interim analysis.	There was no interim analysis.	There was no interim analysis.
Adjustment for multiplicity	Yes	Yes	No
Planned Subgroup Analyses	All primary and secondary efficacy endpoints will be summarized for the overall population and for the following subgroups: • Baseline anesthetized Schirmer's score (<5, >5) • Baseline EDS (< 60, ≥ 60) • Baseline inferior corneal staining (< 1.5, ≥ 1.5)	Primary and secondary efficacy measures were summarized overall and for the following subgroups: • Baseline inferior corneal staining (< 1.5, ≥ 1.5) • Baseline EDS (< 60, ≥ 60)	Not planned
Deviation from planned analysis	No	No	The SAP specified multiple imputation for handling missing efficacy data if more than 5% of data were missing and LOCF if less than 5% were missing. In the submission, more than 5% of data were missing,

Study Name	ONSET-2 (OPP-101)	ONSET-1 (OPP-002)	MYSTIC (OPP-004)
			however LOCF was used as a sensitivity analysis.
Alternative methodologies adopted by the reviewer	There were 88 strata due to the stratification factors of 22 sites, baseline STS (≤5, >5), and baseline EDS (<60, ≥60). Due to the large number of strata, the data were sparse. For the stratified analyses, strata which had ≤1 observation were excluded from the analysis. In addition, the 0 cell counts were adjusted with 0.5. We assessed the sensitivity of CMH stratified analysis with such sparse data by conducting the analysis without adjustment for stratification and adjusted for the propensity score due to those stratified factors. For the propensity score adjustment, we enumerated the probability of being assigned to a study arm given the different values of the stratified factor for each subject and used the propensity score as a covariate in place of multiple stratified factor variables.	We have evaluated the sensitivity of primary analysis results by imputing the missing change from baseline in STS at Day 28 (Visit 5) to zero. We analyzed the imputed data following the primary analysis method.	We have evaluated the sensitivity of primary analysis results by imputing the missing change from baseline in STS at Day 84 to zero. We analyzed the imputed data following the primary analysis method.
Safety Analysis	Not evaluated by the statistical reviewers	Not evaluated by the statistical reviewers	Not evaluated by the statistical reviewers

3.2.2.1 Disposition

The subject disposition for ONSET-2 is summarized in Table 4.

Table 4 Subject disposition Study: ONSET-2 (OPP-101)

Category	OC-01 0.6 mg/mL N=260 n (%)	OC-01 1.2 mg/mL N=246 n (%)	Placebo N=252 n (%)	Total N=758 n (%)
Randomized	260	246	252	758
ITT Population[a]	260 (100.0)	246 (100.0)	252 (100.0)	758 (100.0)
Safety Population[b]	260 (100.0)	245 (99.6)	251 (99.6)	756 (99.7)
Per-protocol Population[c]	252 (96.9)	240 (97.6)	248 (98.4)	740 (97.6)
mITT-1 Population[d]	227 (87.3)	216 (87.8)	220 (87.3)	663 (87.5)
mITT-2 Population[e]	235 (90.4)	221 (89.8)	228 (90.5)	684 (90.2)
mITT-3 Population[f]	248 (95.4)	238 (96.7)	242 (96.0)	728 (96.0)
ITT-COVID-19 Population[g]	37 (14.2)	33 (13.4)	34 (13.5)	104 (13.7)
Subjects completed treatment	251 (96.5)	230 (93.5)	242 (96.0)	723 (95.4)
Subjects discontinued treatment	9 (3.5)	16 (6.5)	10 (4.0)	35 (4.6)
Reasons for discontinuation from the treatment				
Non-fatal adverse event	5 (1.9)	8 (3.3)	4 (1.6)	17 (2.2)
Lost to follow up	2 (0.8)	1 (0.4)	2 (0.8)	5 (0.7)
Withdraw by subject	1 (0.4)	6 (2.4)	2 (0.8)	9 (1.2)
Subject non-compliance	0	1 (0.4)	1 (0.4)	2 (0.3)
Protocol violation	0	0	1 (0.4)	1 (0.1)
Physician decision	1 (0.4)	0	0	1 (0.1)
Subjects completed the study[h]	245 (94.2)	223 (90.7)	240 (95.2)	708 (93.4)
Subjects discontinued from the study	15 (5.8)	23 (9.3)	12 (4.8)	50 (6.6)
Reasons for discontinuation from the study				
Lost to follow up	6 (2.3)	12 (4.9)	6 (2.4)	24 (3.2)
Non-fatal adverse event	4 (1.5)	1 (0.4)	0	5 (0.7)
Withdraw by subject	3 (1.2)	9 (3.7)	3 (1.2)	15 (2.0)
Physician decision	2 (0.8)	0	0	2 (0.3)
Protocol violation	0	0	1 (0.4)	1 (0.1)
Subject non-compliance	0	1 (0.4)	0	1 (0.1)
Death	0	0	1 (0.4)	1 (0.1)
Other	0	0	1 (0.4)	1 (0.1)
Subjects completed both the study treatment and the study	245 (94.2)	216 (87.8)	235 (93.3)	696 (91.8)
Subjects discontinued either treatment or the study	15 (5.8)	30 (12.2)	17 (6.7)	62 (8.2)
Subjects with significant ocular history	191 (73.5)	180 (73.2)	195 (77.4)	566 (74.7)

Percentages were calculated based on all randomized subjects. Source: Statistical Reviewer's analysis

Abbreviation: COVID-19 = Coronavirus disease-2019; ITT = intent-to-treat; mITT = modified intent-to-treat
a The ITT Population included all randomized subjects.
[b] The Safety Population included all randomized subjects who received at least one dose of IP.
[c] The Per Protocol Population included all subjects in the ITT Population with post-baseline (Visit 1) data, excluding subjects who had major protocol deviations.
[d] The mITT-1 Population was defined as randomized subjects excluding Sites 48 and 51.
[e] The mITT-2 Population was defined as randomized subjects excluding Sites 45 and 48.
[f] The mITT-3 Population was defined as randomized subjects excluding Site 51.
[g] The ITT-COVID-19 Population was defined as randomized subjects of Sites 45, 48, and 51 who were impacted by COVID-19.
[h] Consistent with the Applicant's reported ongoing subjects + the completed subjects

ONSET-2 randomized 758 subjects to receive 0.6 mg/mL OC-01 nasal spray (N=260), 1.2 mg/mL OC-01 (N=246), or placebo (N=252). All these subjects were included in the ITT population. Among the randomized subjects, two subjects did not receive the IP and were excluded in the Safety Population.

Discontinuation from the study treatment in the OC-1 1.2 mg/ml arm was higher compared to the OC-1 0.6 mg/ml or placebo. Thirty-five subjects discontinued treatment prior to treatment completion, of which 9 subjects (3.5%) were from the 0.6 mg/mL OC-01 arm, 16 subjects (6.5%) were from the 1.2 mg/mL OC-01 arm, and 10 subjects (4.0%) were from the placebo arm. The most common reasons for treatment discontinuation were non-fatal Adverse Events (AEs) (2.2%), withdrawal by subjects (1.2%), and lost to follow up (0.7%).

Subjects discontinuing from the study treatment and the study was higher in the OC-1 1.2 mg/ml arm (30 [12.2%]) compared to the other arms. The distribution of discontinuations from the treatment, discontinuations from the study, and discontinuation reasons were similar between the 0.6 mg/mL OC-01 and placebo arms.

The distribution of subjects with significant ocular history was balanced across the study arms.

Table 5 Subjects disposition. Study: ONSET-1(OPP-002).

	OC-01 0.12 mg/mL N=47 n (%)	OC-01 0.6 mg/mL N=48 n (%)	OC-01 1.2 mg/mL N=44 n (%)	Placebo N=43 n (%)	Total N=182 n (%)
Analysis population					
Randomized (ITT Population)	47 (100)	48 (100)	44 (100)	43 (100)	182 (100)
Treated (Safety Population)	47 (100)	48 (100)	44 (100)	43 (100)	182 (100)
Study completion					
Subjects completed the study	47 (100)	46 (96)	40 (91)	43 (100)	176 (97)
Subjects discontinued the study	0	2 (4)	4 (9)	0	6 (3)
Reasons for discontinuation					
Non-fatal adverse event	0	1 (2)	3 (7)	0	4 (2)
Withdraw by Investigator due to prohibited medication	0	0	1 (2)	0	1 (1)
Withdraw by subject	0	1 (2)	0	0	1 (1)

Denominators were the number of randomized subjects. Abbreviations: ITT = intent-to-treat. Source: Statistical Reviewer's analysis

The Subject disposition for ONSET-1 is summarized in Table 5. The percentage of subjects discontinuing the study in the OC-01 1.2 mg/ml arm was 9%, which was larger than the percentages in other arms.

Table 6 Subjects disposition. Study: MYSTIC(OPP-004)

	OC-01 0.6 mg/mL (N=41) n (%)	OC-01 1.2 mg/mL (N=41) n (%)	Placebo (N=41) n (%)	Overall (N=123) n (%)
Intent-To-Treat Population	41.0 (100)	41.0 (100)	41.0 (100)	123 (100)
Safety Population	41.0 (100)	41.0 (100)	41.0 (100)	123 (100)
Per-Protocol Population	35.0 (85.4)	33.0 (80.5)	34.0 (82.9)	102 (82.9)
Completed the study	36.0 (87.8)	29.0 (70.7)	32.0 (78.0)	97.0 (78.9)
Discontinued from the study	5.00 (12.2)	12.0 (29.3)	9.00 (22.0)	26.0 (21.1)
Primary Reason for Discontinuation				
Lost to follow-up	4.00 (9.8)	4.00 (9.8)	5.00 (12.2)	13.0 (10.6)
Non-fatal adverse event	1.00 (2.4)	3.00 (7.3)	3.00 (7.3)	7.00 (5.7)
Subject non-compliance	0 (0)	1.00 (2.4)	0 (0)	1.00 (0.8)
Withdraw by subject	0 (0)	4.00 (9.8)	1.00 (2.4)	5.00 (4.1)

Denominators were the number of randomized subjects. Source: Statistical Reviewer's analysis

In MYSTIC, the highest percentage of discontinuations from the study was observed in the OC-01 1.2 mg/mL arm (12/41[29.3%]) compared to that of the OC-01 0.6 mg/ml and the placebo arms. The distribution of discontinuation from the study were not comparable across the study arms (Table 6).

3.2.2.2 Demographics

Table 7 Demographic characteristics of the study population for studies ONSET-1 (OPP-002), ONSET-2 (OPP-101), and MYSTIC (OPP-004)

Study Name	Characteristics	OC-01 0.12 mg/mL	OC-01 0.6 mg/mL	OC-01 1.2 mg/mL	Placebo	Overall
ONSET-2 (OPP-101)						
	Group size		**N=260**	**N=246**	**N=252**	**N=758**
	Age (Years)					
	Mean (SD)		59.6 (12.8)	58.4 (13.0)	58.4 (13.3)	58.8 (13.0)
	Range (min, max)		22, 91	22, 91	23, 95	22, 95
	Quartiles (25th, median, 75th)		52, 61, 69	50, 59, 68	51, 59, 68	51, 60, 68
	Male, n (%)		66.0 (25.4)	65.0 (26.4)	51.0 (20.2)	182 (24.0)
	Race, n (%)					
	White		219 (84.2)	200 (81.3)	211 (83.7)	630 (83.1)
	Black or African American		27.0 (10.4)	34.0 (13.8)	28.0 (11.1)	89.0 (11.7)
	Asian		10.0 (3.8)	7.00 (2.8)	5.00 (2.0)	22.0 (2.9)
	American Indian or Alaska Native		0 (0)	1 (0.4)	3 (1.2)	4 (0.5)
	Multiple		3.0 (1.2)	2.0 (0.8)	5.0 (2.0)	10.0 (1.3)
	Other		1.00 (0.4)	2 (0.8)	0 (0)	3 (0.4)
	Ethnicity, n (%)					
	Hispanic or Latino		27.0 (10.4)	37.0 (15.0)	36.0 (14.3)	100 (13.2)
	Not Hispanic or Latino		233 (89.6)	209 (85.0)	216 (85.7)	658 (86.8)
ONSET-1 (OPP-002)						
	Group Size	**N=47**	**N=48**	**N=44**	**N=43**	**N=182**
	Age (years)					
	Mean (SD)	64.2 (12.7)	66.5 (9.4)	67.4 (10.6)	64.0 (10.3)	65.5 (10.8)
	Range (min, max)	24, 89	49, 88	22, 84	32, 89	22, 89
	Quartiles (25th, median, 75th)	58, 65, 73	60, 65, 73	64, 68, 73	57, 63, 71	59, 66, 72

	Male, n (%)	11 (23)	14 (29)	9 (20)	11 (26)	45 (25)
	Race, n (%)					
	White	42 (89)	39 (81)	36 (82)	40 (93)	157 (86)
	Black or African-American	2 (4)	4 (8)	6 (14)	2 (5)	14 (8)
	Asian	3 (6)	4 (8)	0	1(2)	8 (4)
	Others	0	1 (2)	2 (4)	0	3(2)
	Ethnicity, n (%)					
	Not Hispanic or Latino	39 (83)	45 (94)	42 (95)	38 (88)	164 (90)
	Hispanic or Latino	8 (17)	3 (6)	2 (5)	5 (12)	18 (10)
MYSTIC (OPP-004)						
	Group size		**N=41**	**N=41**	**N=41**	**N=123**
	Age (Years)					
	Mean (SD)		51.4 (13.2)	54.2 (11.8)	55.8 (13.2)	53.8 (12.8)
	Range (min, max)		28, 74	28, 74	26, 77	26, 77
	Quartiles (25^{th}, median, 75^{th})		42, 51, 62	48, 56, 61	48, 57, 65	45, 56, 63
	Male, n (%)		9 (22.0)	6 (14.6)	8 (19.5)	23 (18.7)
	Race, n (%)					
	Other		41 (100.0)	41 (100.0)	41 (100.0)	123 (100.0)
	Ethnicity, n (%)					
	Hispanic or Latino		41 (100.0)	41 (100.0)	41 (100.0)	123 (100.0)
	Significant ocular history, n (%)					
	Yes		16 (39.0)	17 (41.5)	17 (41.5)	50 (40.7)

Source: Reviewer's analysis

In ONSET-1, ONSET-2, and MYSTIC, subjects were predominantly female. Overall, 75% of subjects in ONSET-1, 76% of subjects in ONSET-2, and 80% of the subject in MYSTIC were female. The male and female ratio appeared to be balanced across the study arms and across the studies.

In all three studies, the age distribution was similar across the study arms. The overall age distribution across studies was different. ONSET-1 subjects were the oldest and MYSTIC subjects were the youngest (mean ages in ONSET-1, ONSET-2, and MYSTIC were 65.5, 60.0 and 54.8 respectively).

We observed a discrepancy between the Applicant's reported frequencies in race. The discrepancy was due to the fact that we considered the multiple races as an individual category.

Most of the subjects in ONSET-1 and ONSET-2 were White (86% and 83% respectively). MYSTIC did not have any White subjects in the study. Race distribution were balanced across the study arms in all three studies (Table 7).

3.2.2.3 Baseline Characteristics of Disease

Table 8 Baseline disease characteristics (Safety Population). Study: ONSET-2 (OPP-101)

	OC-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=245	Placebo N=251	Overall N=756
Schirmer's Test Score (mm)[a]				
Mean (SD)	5.14 (2.95)	5.39 (2.93)	4.89 (2.89)	5.14 (2.93)
Range (min, max)	0, 10	0, 10	0, 10	0, 10
Quartiles (25th, median, 75th)	3, 5, 7	3, 5, 8	2, 5, 7	3, 5, 8
Schirmer's Test Score with cotton swab stimulation (mm)[a]				
Mean (SD)	27.6 (8.27)	28.1 (8.33)	27.8 (8.16)	27.8 (8.25)
Range (min, max)	8, 35	7, 35	8, 35	7, 35
Quartiles (25th, median, 75th)	21, 30, 35	21, 33, 35	22, 31, 35	21, 31, 35
Eye Dryness Score (mm)[b]				
Mean (SD)	58.5 (22.05)	59.3 (22.61)	58.1 (22.35)	58.6 (22.31)
Range (min, max)	2, 100	4, 99	3, 100	2, 100
Quartiles (25th, median, 75th)	42, 63, 76	43, 64, 76	42, 62, 77	42, 63, 76
Best Corrected Visual Acuity (logMAR)[a]				
Mean (SD)	0.11 (0.14)	0.13 (0.15)	0.13 (0.16)	0.12 (0.15)
Range (min, max)	-0.3, 0.52	-0.2, 0.6	-0.18, 0.62	-0.3, 0.62
Quartiles (25th, median, 75th)	0.0, 0.1, 0.2	0.02, 0.12, 0.24	0.02, 0.10, 0.22	0.02, 0.10, 0.22
Ora Calibra Ocular Discomfort Scale (grade)[a]				
Mean (SD)	2.8 (0.88)	2.8 (1.05)	2.8 (0.97)	2.8 (0.96)
Range (min, max)	0, 4	0, 4	0, 4	0, 4
Quartiles (25th, median, 75th)	2.0, 3.0, 3.0	2.0, 3.0, 4.0	2.0, 3.0, 3.0	2.0, 3.0, 3.0
Ocular Surface Disease Index[b]				
Mean (SD)	51.31 (19.46)	52.43 (18.76)	50.94 (18.86)	51.55 (19.02)
Range (min, max)	18.8, 100	25, 100	25, 100	18.8, 100
Quartiles (25th, median, 75th)	34.5, 50.0, 66.7	37.5, 50.0, 66.7	35.4, 47.9, 63.6	35.4, 50.0, 64.6
Corneal fluorescein staining (score)[a]				
Mean (SD)	6.4 (2.16)	6.3 (2.19)	6.2 (2.05)	6.3 (2.13)
Range (min, max)	2, 14	2, 15	2, 13	2, 15
Quartiles (25th, median, 75th)	5, 6, 8	5, 6, 7	5, 6, 8	5, 6, 8

Source: Reviewer's analysis
Abbreviations: logMAR = logarithm of the minimum angle of resolution; max = maximum; min = minimum.
SD = standard deviation
[a] Study eye.
[b] Both eyes.

The baseline disease characteristics were balanced across the study arms in ONSET-2 (Table 8)

Table 9 Baseline disease characteristics of the study eye based on safety population. Study: ONSET-1 (OPP-002)

Baseline assessment	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43	Overall N=182
Schirmer's test (mm)					
Mean (SD)	5.2 (3.1)	4.8 (2.7)	5.5 (3.0)	4.5 (2.9)	5.0 (2.9)
Range (min, max)	0, 10	1, 10	0, 10	0, 10	0, 10
Quartiles (25th, median, 75th)	3, 5, 8	2, 5, 7	4, 5, 8	2, 4, 7	3, 5, 7
Cotton swab Schirmer's test (mm)					
Mean (SD)	28.2 (7.3)	29.2 (7.8)	29.6 (7.5)	25.9 (7.0)	28.3 (7.5)
Range (min, max)	14, 35	10, 35	10, 35	15, 35	10, 35
Quartiles (25th, median, 75th)	20, 30, 35	22, 34, 35	24, 34, 35	20, 25, 35	21, 32, 35
Eye Dryness Score (mm)[a]					
Mean (SD)	65.6 (20.1)	63.7 (18.4)	53.5 (22.4)	65.2 (17.7)	62.1 (20.2)
Range (min, max)	10, 100	27, 98	5, 96	33, 98	5, 100
Quartiles (25th, median, 75th)	51, 68, 83	52, 66, 80	33, 56, 72	51, 66, 80	48, 65, 79
Ora Calibra Ocular Discomfort Scale					
Mean (SD)	2.8 (0.9)	2.7 (0.9)	2.5 (1.0)	2.7 (0.9)	2.7 (0.9)
Range (min, max)	1, 4	0, 4	1, 4	1, 4	0, 4
Quartiles (25th, median, 75th)	2, 3, 4	2, 3, 3	2, 3, 3	2, 3, 3	2, 3, 3
Visual acuity (logMAR)					
Mean (SD)	0.12 (0.13)	0.11 (0.16)	0.13 (0.17)	0.09 (0.12)	0.11 (0.15)
Range (min, max)	-0.1, 0.4	-0.2, 0.5	-0.2, 0.6	-0.2, 0.4	-0.2, 0.6
Quartiles (25th, median, 75th)	0.0, 0.1, 0.2	0.0, 0.1, 0.2	0.0, 0.1, 0.2	0.0, 0.1, 0.2	0.0, 0.1, 0.2
Ocular Surface Disease Index [a]					
Mean (SD)	53.8 (17.0)	49.7 (15.7)	45.5 (15.0)	51.7 (16.6)	50.2 (16.2)
Range (min, max)	25, 100	25, 79	25, 75	25, 83	25, 100
Quartiles (25th, median, 75th)	42, 50, 63	35, 51, 61	33, 42, 57	35, 53, 67	35, 50, 61
Corneal fluorescein staining					
Mean (SD)	5.9 (1.6)	6.7 (2.1)	6.9 (2.4)	6.7 (2.4)	6.6 (2.2)
Range (min, max)	4, 10	4, 12	4, 14	4, 14	4, 14
Quartiles (25th, median, 75th)	5, 6, 7	5, 6, 9	5, 7, 8	5, 6, 8	5, 6, 8

Source: Statistical Reviewers analysis. logMAR = logarithm of the minimum angle of resolution. Source: Reviewer's analysis.

[a] Both eyes

In ONSET-1, Baseline cotton swab Schirmer's test (mm) level, treatment arms were not comparable to the placebo arm (mean [SD] in OC-01 0.6 mg/ml = 29.2 [7.8], OC-01 1.2 mg/ml = 29.6 [7.5], and placebo = 25.9 [7.0]). The baseline Eye Dryness Score (mm) of OC-1 1.2

mg/ml arm was not comparable to the other two arms (mean [SD] in OC-01 0.6 mg/ml = 63.7 [18.4], in OC-01 1.2 mg/ml = 53.5 [22.4], and placebo = 65.2 [17.7]) (Table 9).

Table 10 Baseline disease characteristics of the study eye based on safety population. Study: MYSTIC (OPP-004).

Baseline Assessment Category Statistic	OC-01 0.6 mg/mL N=41	OC-01 1.2 mg/mL N=41	Placebo N=41	Total N=123
Schirmer's Test score (mm)				
Mean (SD)	5.5 (2.46)	5.4 (2.47)	5.3 (2.04)	5.4 (2.32)
Range (min, max)	0, 9	0, 9	0, 9	0, 9
Quartiles (25th, median, 75th)	4.0, 5.0, 8.0	4.0, 6.0, 7.0	4.0, 6.0, 7.0	4.0, 6.0, 7.0
Cotton swab Schirmer's Test score (mm)				
Mean (SD)	20.3 (7.53)	19.6 (7.27)	19.5 (8.07)	19.8 (7.58)
Range (min, max)	10, 35	9, 35	9, 35	9, 35
Quartiles (25th, median, 75th)	16, 18, 25	15, 17, 22	14, 17, 25	15, 17, 25
Best Corrected Visual Acuity score (logMAR)				
Mean (SD)	0.18 (0.20)	0.18 (0.16)	0.24 (0.21)	0.20 (0.19)
Range (min, max)	-0.18, 0.64	-0.10, 0.62	-0.06, 0.56	-0.18, 0.64
Quartiles (25th, median, 75th)	0.03, 0.16, 0.27	0.04, 0.20, 0.28	0.12, 0.18, 0.42	0.04, 0.16, 0.30
Corneal Fluorescein Staining – total score (grade)				
Mean (SD)	4.6 (1.92)	6.0 (3.34)	5.8 (3.78)	5.5 (3.14)
Range (min, max)	2, 10	2, 15	2, 15	2, 15
Quartiles (25th, median, 75th)	3.0, 4.0, 6.0	4.0, 5.0, 8.0	3.0, 4.0, 6.0	3.0, 4.0, 6.0

Abbreviations: logMAR = logarithm of the minimum angle of resolution; max = maximum; min = minimum; SD = standard deviation.

Overall, the distribution of baseline disease characteristics such as the Schirmer's test score, Cotton Swab Schirmer's test score, the Best Corrected Visual Acuity (BCVA), fluorescein corneal staining was balanced across the studies and across the study arms within studies.

Across studies some of the baseline diseases characteristics were not comparable. The EDS was lower in ONSET-2 compared to ONSET-1. The BCVA appeared to be different in MYSTIC compared to ONSET-1 and ONSET-2 (the overall mean [SD] in logMAR scale in MYSTIC = 0.20 [0.2] , ONSET-1 = 0.11 [0.15], and ONSET-2 = 0.12 [0.15]) (Table 8, Table 9, and Table 10).

3.2.3 Results and Conclusions

3.2.3.1 ONSET-2 (OPP-101)

Table 11 The primary endpoint of the observed percent of subjects who achieve ≥ 10 mm improvement in STS at Visit 4b (Day 28) from Baseline in the study eye in the ITT analysis population.

Adjustments		OC-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=246	Placebo N=252
	n (%)	100 (38.5)	103 (41.9)	56 (22.2)
Primary Analysis				
CMH	Proportion difference (95% CI)[a]	16.2 (8.41, 24.07)	19.6 (11.63, 27.67)	Reference
	Odds ratio (95% CI)[a]	2.47 (1.61, 3.80)	2.51 (1.67, 3.77)	Reference
	p-value[b]	<0.0001	<0.0001	
Sensitivity Analysis				
Unadjusted	Proportion difference (95% CI)	16.2 (8.10, 24.33)	24.0 (11.4, 27.86)	Reference
	Odds ratio (95% CI)	2.18 (1.49, 3.24)	2.52 (1.71, 3.74)	Reference
Propensity score adjusted	Proportion difference (95% CI)	16.4 (8.51, 24.33)	19.4 (11.30, 27.45)	Reference
	Odds ratio (95% CI)	2.2 (1.5, 3.28)	2.49 (1.69, 3.70)	Reference
	p-value	<0.0001	<0.0001	
CMH (LOCF)	n (%)	123 (47.3)	121 (49.2)	70 (27.8)
	Proportion difference (95% CI)[a]	19.5 (11.1, 27.9)	21.4 (12.9, 29.9)	Reference
	Odds ratio (95% CI)[a]	2.52 (1.70, 3.75)	2.4 (1.66, 3.55)	Reference
	p-value	<0.0001	<0.0001	

- Column header counts were the number of randomized subjects. All comparisons were made to placebo arm. The ITT Population included all randomized subjects. Subjects who early terminated before or were missing at Visit 4b were considered failure to achieve ≥10 mm improvement.
- Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EDS = Eye Dryness Score.
- ITT = intent-to-treat; STS = Schirmer's Test Score
- [a] The CMH test compared each of the treatment arms to placebo controlling for study site, baseline STS ($_{\leq}$5, >5], and baseline EDS (<60, $_{\geq}$60]. These logit estimators use a correction of 0.5 in every cell of those tables that contain a zero. Tables with a zero row or a zero column were not included in computing the logit estimators.
- Source: Reviewer's analysis

From the CMH stratified analysis, the odds of achieving ≥10 mm improvement on STS from the Baseline at Day 28 (Visit 4b) in the study eye among the 0.6 mg/ml arm was 2.5 times higher compared to that of the placebo (OR = 2.47, 95% CI: [1.61, 3.80]). The odds of achieving ≥10 mm improvement on STS from baseline to Visit 4b (Day 28) in the study eye among OC-1 1.2 mg/ml arm was 2.5 times higher compared to that of the Placebo arm (OR = 2.51, 95% CI: [1.67, 3.77]) (Table 11).

We can reproduce the Applicant's efficacy finding. The results were robust against different unadjusted and Propensity Score adjusted methods and missing value imputations.

Table 12 The secondary endpoints in ONSET-2. Source: Statistical Reviewer's Analysis

	OC-01 0.6 mg/mL N=260	**OC-01 1.2 mg/mL N=246**	**Placebo N=252**
EDS in CAE at Week 4 (Day 21) at 5 Minutes Post-Treatment for mITT-2			
n	187	171	169
Mean (SD)	-10.3 (26.18)	-9.3 (25.78)	-6.5 (24.23)
Range (min, max)	-81, 62	-75, 54	-78, 78
LS mean change from baseline			
LS mean (SE)	-10.3 (1.62)	-9.0 (1.75)	-7.4 (1.74)
95% CI	-13.49, -7.15	-12.48, -5.61	-10.84, -4.00
Treatment comparison			
LS mean difference (SE)	-2.9 (2.27)	-1.6 (2.32)	
95% CI	-7.35, 1.55	-6.19, 2.92	
p-value	0.2008	0.4818	
Change from the Baseline in EDS at Day 28 in ITT			
Mean change from baseline			
Mean (SE)	-19.5 (1.71)	-22.54 (1.76)	-14.9 (1.74)
Range (min, max)	-17.0 (-92.0, 52.0)	-22.0 (-89.0, 68.0)	-12.0 (-78.0, 59.0)
LS mean change from baseline			
LS mean (SE)	-20.3 (1.6)	-22.8 (1.7)	-15.8 (1.6)
95% CI	-24.2, -16.4	-26.8, -18.7	-19.7, -12.0
LS mean difference			
LS mean difference (SE)	-4.5 (2.1)	-6.94 (2.1)	-
95% CI	-8.6, -0.35	-11.1, -2.7	
p-value	0.033	0.001	
Change from the Baseline in EDS at Day 28 in ITT (LOCF)			
Mean change from baseline			
Mean (SE)	-19.4 (1.7)	-23.1 (1.8)	-15.2 (1.7)

Range (min, max)	-16.5 (-92.0, 52.0)	-22.0 (-89.0, 68.0)	-12.0 (-78.0, 59.0)
LS mean change from baseline			
LS mean (SE)	-20.2 (1.68)	-23.1 (1.76)	-16.2 (1.66)
95% CI	-24.2, -16.3	-27.3, -19.0	-20.2, -12.3
LS mean difference			
LS mean difference (SE)	-4.02 (2.1)	-6.88 (2.17)	-
95% CI	-8.22, 0.17	-11.15, -2.62	-
p-value	0.0598	0.015	-
Change from the Baseline in EDS at Day 14 in ITT			
Mean change from baseline			
Mean (SE)	-15.6 (1.4)	- 15.7(1.4)	-12.9 (1.4)
Range (min, max)	-12.5 (-86.0, 42.0)	-12.0 (-79.0, 44.0)	-11.0 (-94.0, 65.0)
LS mean change from baseline			
LS mean (SE)	-15.3 (1.4)	-15.0 (1.5)	-13.0 (1.4)
95% CI	-18.7, -11.94	-18.6, -11.52	-16.3, -9.69
LS mean difference			
LS mean difference (SE)	-2.3 (1.8)	-2.03 (1.8)	-
95% CI[a]	-5.86, 1.25	-5.65, 1.58	-
p-value[b]	0.20	0.27	-

Column header counts were the number of randomized subjects. All comparisons made were in reference to the Placebo arm.

The first secondary endpoint of the mean change from baseline in EDS at 5 minutes after treatment administration in the Controlled Adverse Environment (CAE) Chamber at Day 28 among the OC-01 arm was not significantly different from that of the placebo arm (Table 12).

With the predefined rule of test hierarchy, testing of the secondary endpoint in the OC-01 arm should not proceed. Despite the fact, we have included the second secondary endpoint of change in mean EDS score at Day 28 and from baseline in Table 12 as, this endpoint has a central role in ONSET-1 to support the efficacy.

3.2.3.2 ONSET-1 (OPP-002)

Table 13 The change in Schirmer's Test Score in the study eye at Day 28 from Baseline. Study: ONSET-1(OPP-002), Population ITT, Source: Reviewer's analysis

	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Mean change from baseline (mm)				
N	47	46	40	43
Mean (SD)	10.0 (9.5)	11.8 (8.9)	11.4 (9.3)	3.2 (5.6)
Range (min, max)	-5, 34	-2, 29	-3, 31	-4, 26
Quartiles (25^{th}, median, 75^{th})	3, 7, 15	5, 10, 15	5, 8, 19	0, 2, 5
LS mean change from baseline (mm)				
LS mean (SE)	10.1 (1.2)	11.4 (1.3)	11.1 (1.3)	3.7 (1.3)
95% CI	7.7, 12.5	8.9, 13.9	8.5, 13.7	1.1, 6.2
LS mean difference (mm)				
LS mean difference (SE)	6.4 (1.8)	7.7 (1.8)	7.5 (1.9)	-
95% CI	--	3.8, 11.7	3.4, 11.6	-
p-value	--	<0.001	<0.001	-
Mean change from baseline (mm) missing changes imputed to zero				
N	47	48	44	43
Mean (SD)	10.0 (9.53)	11.3 (9.04)	10.4 (9.41)	3.21 (5.55)
Range (min, max)	7.0 (-5.0, 34.0)	10.0 (-2.0, 29.0)	7.0 (-3.0, 31.0)	2.0 (-4.0, 26.0)
LS mean change from baseline (mm)				
LS mean (SE)	10.08 (1.24)	10.99 (1.23)	10.05 (1.28)	3.66 (1.31)
95% CI	6.99 , 13.16	7.94, 14.04	6.87, 13.23	0.42, 6.91
LS mean difference (mm)				
LS mean difference (SE)	6.41 (1.79)	7.32 (1.79)	6.38 (1.34)	-
95% CI	2.87, 9.95	3.78, 10.86	2.75, 10.01	-
p-value		<0.001	<0.001	-
Mean change from baseline (mm) based on revised adeff.xpt data[a]				
N	47	46	40	43
Mean (SD)	10.0 (9.5)	11.8 (8.9)	11.4 (9.3)	3.2 (5.6)
Range (min, max)	-5, 34	-2, 29	-3, 31	-4, 26
Quartiles (25^{th}, median, 75^{th})	3, 7, 15	5, 10, 15	5, 8, 19	0, 2, 5
LS mean change from baseline (mm)				
LS mean (SE)	10.1 (1.2)	11.4 (1.3)	11.1 (1.3)	3.7 (1.3)

95% CI	7.7, 12.5	8.9, 13.9	8.5, 13.7	1.1, 6.2
LS mean difference (mm)				
LS mean difference (SE)	6.4 (1.8)	7.7 (1.8)	7.5 (1.9)	-
95% CI	-	3.8, 11.7	3.4, 11.6	-
p-value	-	<0.001	<0.001	-
≥ 10-mm increase in Schirmer's Test Score (% of eyes) at Day 28[b]				
N	47	48	40	43
Proportions	21.0 (44.7%)	25.0 (52.1%)	19.0 (47.5%)	6.00 (14.0%)
Proportion difference (95% CI)	31.0 (11.2, 50.8)	38.1(20.6, 55.6)	33.4(12.6, 54.2)	-
Odds ratio (95% CI)	5.1 (1.9, 15.6)	7.5 (2.8, 22.9)	5.6 (2.0, 17.6)	-
p-value	0.002	<0.001	0.002	

All comparisons were made to placebo arm. Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error; STS = Schirmer's Test Score.

[a] The analysis was based on revised adeff.xpt that the Sponsor submitted on August 16, 2021 (data EDR link: \\CDSESUB1\evsprod\NDA213978\0026\m5\datasets\opp-002\analysis\adam\datasets)

[b] Post hoc analysis. Imputation method LOCF. In the proposed label, ONSET-1 primary endpoint was reported using the same measurement scale as ONSET-2 endpoint.

ONSET-1 showed the superiority of both OC-1 0.6 mg/mL and 1.2 mg/mL nasal spray compared to placebo for the mean change at Day 28 (Visit 5) in STS (with anesthesia) from baseline in the study eye.

Subjects treated with OC-01 nasal spray showed statistically superior mean increases in tear film production compared to subjects treated with the placebo (vehicle nasal spray) (least squares [LS] mean change from baseline Schirmer's score [95% CI] in arms 0.6 mg/ml = 11.4 [8.9-13.9], 1.2 mg/ml = 11.1[8.5-13.7], and placebo = 3.7 [1.1, 6.2]). The changes at Day 28 (Visit 5) from baseline in STS in 0.6 mg/ml and 1.2 mg/ml arms were similar.

We can reproduce the Applicant's analysis results. The primary analysis results were robust to various strategies for handling missing data. Both uncorrected (submitted primarily) and the revised version of adeff.xpt data provided identical results.

Table 14 The change in Eye Dryness Score at Day 28 (Visit 5) from the Baseline (Secondary Endpoint) in ONSET-1

At Day 28 (Visit 5)	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Mean change from baseline				
N	47	46	40	43
Mean (SD)	-13.7 (25.5)	-19.5 (33.6)	-8.3 (27.8)	-7.8 (24.8)
Range (min, max)	-69, 55	-79, 48	-74, 49	-58, 51
Quartiles (25^{th}, median, 75^{th})	-32, -14, 1	-47, -23, 5	-23, -3, 7	-24, -9, 3
LS mean change from baseline (scale)				
LS mean (SE)	-11.4 (3.6)	-19.0 (3.7)	-15.4 (4.0)	-5.6 (3.8)
95% CI	-18.6, -4.2	-26.2, -11.7	-23.3, -7.5	-13.1, 1.8
LS mean difference (scale)				
LS mean difference (SE)	-5.4 (5.2)	-12.7 (5.3)	-9.2 (5.6)	--
95% CI[a]	--	-23.2, -2.2	-20.3, 2.0	--
p-value[b]	--	0.018	0.10	--

Column header counts were the number of randomized subjects. All comparisons made were in reference to placebo arm.

Subjects treated with 0.6 mg/mL OC-01 nasal spray showed a statistically superior reduction in mean EDS at Day 28 from the Baseline compared to subjects treated with the placebo (LS mean change -19.0; 95% CI: -26.2, -11.7, P-value = 0.021). Subjects treated with 1.2 mg/mL OC-01 nasal spray was not statistically different than placebo (LS mean change -15.4 [CI : -23.3, -7.5], p-value = 0.10).

3.2.3.3 MYSTIC (OPP-004)

Table 15 The change in Schirmer's Test Score in study eye at Day 84 from the Baseline. Study: MYSTIC (OPP-004).

	OC-01 0.6 mg/mL N=41	OC-01 1.2 mg/mL N=41	Placebo N=41
ITT (Based on available observations) [a]			
Change from baseline (mm)			
Mean (SE)	10.6 (1.38)	11.0 (1.52)	6.3 (1.44)
Range (min, max)	-3, 31	-5, 31	-1, 24
LS mean change from baseline (mm)			
LS mean (SE)[b]	10.6 (1.39)	11.0 (1.53)	6.3 (1.46)

95% CI	7.87, 13.39	7.93, 13.99	3.34, 9.11
Treatment comparison (mm)			
LS mean difference (SE)	4.3 (2.01)	4.7 (2.11)	—
95% CI	0.32, 8.31	0.50, 8.9	—
p-value	0.035	0.029	—
LOCF (ITT)			
Change from baseline (mm)			
Mean (SE)	10.6 (1.29)	11.0 (1.29)	6.0 (1.29)
Median (Min, Max)	8.00 (-3.00, 31.0)	9.00 (-5.00, 31.0)	4.00 (-2.00, 24.0)
LS mean change from baseline (mm)			
LS mean (SE)[b]	10.8 (1.29)	11.0 (1.29)	6.0(1.29)
95% CI	8.21, 13.32	8.40, 13.52	3.44, 8.55
Treatment comparison (mm)			
LS mean difference (SE)	4.76 (1.83)	4.96 (1.83)	—
95% CI	1.15, 8.38	1.35, 8.60	—
p-value	0.01	0.007	—
Per-Protocol analysis population			
Change from baseline (mm)			
Mean (SE)	10.9 (1.34)	10.7 (1.38)	6.06 (1.36)
Median (Min, Max)	8.00 (-3.00, 31.0)	10.0 (-5.00, 31.0)	4.00 (-1.00, 24.0)
LS mean change from baseline (mm)			
LS mean (SE)[b]	10.9 (1.35)	10.7 (1.39)	6.1 (1.38)
95% CI	8.24, 13.60	7.94, 13.45	3.35, 8.81
Treatment comparison (mm)			
LS mean difference (SE)	4.8 (1.92)	4.6 (1.95)	-
95% CI	1.01, 8.66	0.72, 8.49	-
p-value	0.013	0.02	-
ITT population with missing changes replaced by zero.			
Change from baseline (mm)			
Mean (SE)	9.05 (1.28)	7.76 (1.28)	4.88 (1.28)
Median (Min, Max)	7.00 (-3.00, 31.0)	5.00 (-5.00, 31.0)	3.00 (-1.00, 24.0)
LS mean change from baseline (mm)			
LS mean (SE)[b]	9.04 (1.29)	7.79 (1.29)	4.89 (1.29)
95% CI	6.49, 11.58	5.24, 10.34	2.34, 7.43
Treatment comparison (mm)			
LS mean difference (SE)	5.15 (1.8)	2.9 (1.8)	-
95% CI	0.55, 7.74	-0.70, 6.50	-
p-value	0.02	0.11	-

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error; STS = Schirmer's Test Score

[a] Planned efficacy analysis

[b] LS means were derived from ANCOVA model with treatment and baseline STS as covariates.

The primary efficacy and sensitivity analysis are given in Table 15. The mean change from baseline showed increased tear film production for both OC-01 treatment arms relative to placebo through Day 84 (Visit 6) (LS mean difference from placebo in OC-01 0.6 mg/ml = 4.3, p-value = 0.035 and in OC-01 1.2 mg/ml = 4.7, p-value = 0.029).

The results of the primary analysis were robust against different strategies to handle missing data in the ITT Population and the PP Population and partially supported by the reviewer's sensitivity analysis method of replacing the missing changes from baseline to zero.

In the ITT Population using the LOCF imputation method, subjects treated with OC-01 (varenicline) nasal spray showed mean increases in tear film production compared with subjects treated with placebo (LS mean change from baseline STS in the 0.6 mg/mL is 4.8 p-value = 0.01 and in the 1.2 mg/ml is 4.96, p-value = 0.007)

In the PP population, subjects treated with OC-01 showed mean increases in tear film production compared with subjects treated with placebo (LS mean change from baseline STS in the 0.6 mg/mL is 4.8 p-value = 0.013 and in the 1.2 mg/ml was 4. 6, p-value = 0.02)

Assuming the missing subjects status remain unchanged, only OC-01 0.6 mg/ml appeared to be superior in tear film production compared to placebo (LS mean change from baseline in OC-01 0.6 mg/ml = 5.15, p-value = 0.02)

We did not report the secondary endpoint analysis of MYSTIC study. The difference in the proportion of subjects with at least 10 mm improvement in STS from baseline at Day 84 among the OC-01 study arms was not statistically different from placebo in the ITT analysis population.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race, Age, Baseline STS, Baseline EDS and Baseline Inferior CFS

Table 16 Subgroup analyses of the primary endpoint of observed percent of subjects who achieve at least 10 mm improvement on STS from Baseline to Visit 4b in the study eye among the subgroups of sex, race, age, Baseline STS, Baseline EDS, and Baseline

Subgroups	C-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=246
Sex		
Female	2.6 (1.70, 4.06)	2.2 (1.44, 3.53)
Male	1.3 (0.54, 3.20)	3.2 (1.42, 7.64)
Test for Interaction with treatment. Reference Sex; Female	0.49 (0.18, 1.3)	1.5 (0.61, 4.07)
p-value	0.151	0.35
Race		
White	2.4 (1.56, 3.72)	2.95 (1.92, 4.58)
Non-White	1.52 (0.6, 3.8)	1.15 (0.45, 3.0)
Test for Interaction with treatment. Reference Race; Non-White	1.5 (0.54, 4.2)	2.6 (0.93, 7.15)
p-value	0.40	0.064
Age (years)		
≥ 65	3.31 (1.65, 7.00)	4.65 (2.30, 9.94)
< 65	1.87 (1.16, 3.02)	1.86 (1.16, 3.01)
Test for Interaction with treatment. Reference age ≥65	0.54 (0.22, 1.26)	0.42 (0.17, 0.97)
p-value	0.16	**0.046**
Baseline STS (mm)		
> 5	2.03 (1.06, 3.93)	2.13 (1.16, 3.96)
≤ 5	3.3 (1.88, 6.2)	3.74 (2.08, 6.91)
Test for Interaction with treatment. Reference STS ≤ 5	0.64 (0.28, 1.47)	0.61 (0.26, 1.3)
p-value	0.30	0.24
Baseline EDS		
≥ 60	2.02 (1.17, 3.52)	1.89 (1.08, 3.33)
< 60	3.7 (1.87, 7.62)	5.03 (2.59, 10.18)
Test for Interaction with treatment. Reference EDS < 60	0.64 (0.27, 1.48)	0.386 (0.16, 0.89)
p-value	0.30	**0.02**

Baseline Inferior CFS		
≥ 1.5	2.24 (1.33, 3.80)	3.29 (1.96, 5.63)
< 1.5	2.80 (1.37, 5.85)	3.16 (1.40, 5.76)
Test for Interaction with treatment. Reference CFS < 1.5	0.85 (0.35, 2.02)	1.4 (0.58, 3.47)
p-value	0.72	0.43
Used Artificial tears*		
Yes	1.74 (0.72, 4.35)	2.13 (0.85, 5.48)
No	2.74 (1.68, 4.55)	2.96 (1.80, 4.91)
Test for Interaction with treatment. Reference "No"	0.65 (0.25, 1.70))	0.76 (0.28, 2.00)
p-value	0.38	0.57

* The artificial tear use frequency may not be completely recorded

The effect of OC-01 1.2 mg/ml on efficacy appear to be different within the <64 years old age arm compared to the subjects of ≥ 65 age arm. Among subjects who received treatment of 1.2 mg/ml, subjects who were of age <65 year had 58% less odds of success in the primary endpoint compared to the subject of age ≥ 65 (p-value = 0.046). The differential effect of treatment was not evident in OC-01 0.6 mg/ml receiving subjects.

Similarly, the effect of OC-01 1.2 mg/ml on efficacy varies by the baseline EDS level. Among subjects who received treatment of 1.2 mg/ml, subjects with baseline EDS ≥ 60 had 61% less odds to observe a success in the primary endpoint compared to the subject of baseline EDS <60 (p-value = 0.02). The differential effect of treatment was not evident in OC-01 0.6 mg/ml receiving subjects.

The effect of OC-1 across the subgroups of sex, race, baseline STS, Baseline Inferior CFS were similar for both dose levels.

We did not conduct any subgroup analysis for the studies the ONSET-1 and MYSTIC because of limited sample size. For the planned subgroup analysis, our results were consistent with the Applicant's.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

Table 17 Efficacy Evaluation: A comparative representation of findings.

Study Name	**ONSET-2 (OPP-101)**	**ONSET-1 (OPP-002)**	**MYSTIC (OPP-004)**	**Overall**
Efficacy endpoint analyses	**Primary:** The odds of ≥ 10 mm improvement in STS at Day 28 from the Baseline among 0.6 mg/ml arm were 2.5 times higher compared to that of the placebo arm (OR = 2.47, 95% CI: [1.61, 3.80]). The odds of ≥ 10 mm improvement among OC-1 1.2 mg/ml arm was 2.5 times higher compared to that of the placebo arm (OR = 2.51, 95% CI: [1.67, 3.77]) (Table 11) **Secondary:** The first secondary endpoint of mean change in EDS at 5 minutes after treatment	**Primary:** Both OC-1 0.6 mg/mL and 1.2 mg/mL nasal spray were superior compared to placebo for the mean change at Day 28 in STS (with anesthesia) from baseline in the study eye (Table 13) **Secondary:** Subjects treated with 0.6 mg/mL OC-01 nasal spray was superior in reduction of mean EDS from baseline to Day 28 compared to that with placebo (LS mean change -19.0; 95% CI: -26.2, -11.7, p-value = 0.021) Subjects treated with 1.2 mg/mL OC-01 nasal spray were not	**Primary:** Both OC-1 0.6 mg/mL and 1.2 mg/mL nasal spray were superior compared to placebo for the mean change at Day 84 in STS (with anesthesia) from baseline in the study eye (LS mean difference from placebo in OC-01 0.6 mg/ml = 4.3, p-value = 0.035 and in OC-01 1.2 mg/ml = 4.7, p-value = 0.029) (Table 15) **Secondary:** Difference in proportion of subjects with ≥ 10 mm improvement in STS from Baseline at Day 84 among the OC-01 arms were not statistically	ONSET-2 demonstrated the superiority of the OC-1 to treat the full indication of DED signs and symptoms. ONSET-1 and MYSTIC demonstrated a statistically superior improvements in OC-1 0.6 mg/ml to treat signs at Day 28 and Day 84 from the Baseline. ONSET-1 demonstrated that OC-1 0.6 mg/ml was statistically superior to improving the subjective symptom at Day 28 from baseline. However, the superiority of OC-01 0.6 mg/ml was not evident in the phase 3 pivotal study ONSET-2

	administration in the Controlled Adverse Environment (CAE) Chamber at Day 28 in the OC-1 arms were not statistically different from placebo (LS mean difference for 0.6 mg/ml arm = –2.9 [CI : -7.3, 1.5], p-value = 0.20 and 1.2 mg/ml arm = –1.6 [CI : -6.2, 2.9], p-value = 0.48) According the predefined hierarchy, the other secondary endpoints including mean change in EDS from baseline were not statistically different from the placebo arm (Table 12)	statistically different than placebo (LS mean change -15.4 [CI : -23.3, -7.5], p-value = 0.10) (Table 14)	different than placebo	
Sensitivity analysis due to missing imputation	Efficacy findings were robust against different imputation methods	Robust against missing imputation	OC-01 0.6 mg/ml efficacy is robust against all imputation methods. OC-01 1.2 mg/ml was not robust against	Efficacy findings from studies for dose level OC-01 0.6 mg/ml was robust against missing imputation methods

			the missing imputation with zero change.	
Demographic Characteristics (Table 7)	75% subjects were female Mean age = 60 Year 83% were White Arms were balanced	76% subjects were female Mean age = 65.5 Year 86% were White Arms were balanced	80% subjects were female Mean age = 54.8 Year 0% were White Arms were balanced	Age and race distribution were not comparable across the study
Subjects disposition	Discontinuation from the IP and study were the highest among OC-1 1.2 mg/ml arm. Discontinued from IP in arm 0.6 mg/ml= 9 (3.5%), 1.2 mg/m = 16 (6.5%), and placebo = 10 (4.0%) Discontinuation from the study in arm 0.6 mg/ml = 15 (5.8%), 1.2 mg/m = 23 (9.3%), and placebo = 12 (4.8%). The distribution of discontinuation was balanced across the 0.6 mg/mL OC-01	Subjects discontinued most in the OC-01 1.2 mg/ml arm (4[9%]). Study discontinuation distribution were not balanced across the study arms (Table 5)	The highest discontinuation from the study observed in the OC-01 1.2 mg/mL (12/41[29.3%]) compared to the OC-01 0.6 mg/ml and placebo arms. Distribution of discontinuation from the study were not comparable across the study arms (Table 6)	

	and placebo arms (Table 4)			
Baseline Disease characteristics	The baseline disease characteristics were balanced across the study arms in ONSET-2 (Table 8)	Baseline Cotton swab Schirmer's test (mm) levels OC-1 arms were not comparable to placebo arms (mean [SD] in OC-01 0.6 mg/ml = 29.2 [7.8], OC-01 1.2 mg/ml = 29.6 [7.5], and placebo = 25.9 [7.0]). The baseline Eye Dryness Score (mm) for the study eye across all but the OC-1 1.2 mg/ml arm (mean [SD] in OC-01 0.6 mg/ml = 63.7 [18.4], in OC-01 1.2 mg/ml = 53.5 [22.4], and placebo = 65.2 [17.7]) (Table 9).	The Baseline diseased characteristics were balanced across the study arms in MYSTIC (Table 10).	Across the studies, the Baseline diseases characteristics such as EDS, BCVA were not comparable.
Additional analysis	Propensity score adjusted estimate	Assess the sensitivity of efficacy analysis by imputing all missing values to zero	Assess the sensitivity of efficacy analysis by imputing all missing values to zero (unchanged from baseline)	

Subgroup analysis summary	Among subjects who received treatment of 1.2 mg/ml, subjects who were of age <65 year have 58% less odds to observe the success in the primary endpoint compared to the subject of age ≥ 65 (p-value = 0.046) Among subjects who received treatment of 1.2 mg/ml, subjects who were of baseline EDS ≥ 60 had 61% less odds to observe a success in the primary endpoint compared to the subject of baseline EDS <60 (p-value = 0.02). We did not observe any differential effect of drug in the OC-1 0.6 mg/ml arm in subgroups (Table 16)	Not conducted due to low sample size	Not conducted due to low sample size	

5.1 Statistical Issues

In MYSTIC, the applicant used the available observations instead of the pre-planned ITT analysis population for efficacy analysis. However, from the sensitivity analysis, it was found that the inference was robust when using the ITT population and imputing missing observations in OC-01 0.6 mg/ml arm.

5.2 Collective Evidence

The NDA included 5 studies of which we evaluated three studies (ONSET-1, ONSET-2, and MYSTIC). In ONSET-2, the Applicant assessed the difference in proportion of subjects who achieve ≥10 mm improvement in the study eye on STS from baseline. In ONSET-1 the Applicant evaluated a sign endpoint (mean change in STS at Day 28 from the Baseline) and a symptom endpoint (mean change in EDS at day 28 from the Baseline) to demonstrate the efficacy. In MYSTIC, the Applicant assessed a sign (mean change in STA at Day 84 from the Baseline). In all three studies, subjects were treated with either OC-01 0.6 mg/ml or OC-01 1.2 mg/ml.

ONSET-2 demonstrated the percentage of subjects with success on the primary endpoint was superior in both of the treatment arms compared to the placebo arm (the percentage difference between 0.6 mg/ml arm and placebo arm = 16.2%, 95% CI = [8.41%, 24.07%]; the percentage difference between 1.2 mg/ml arm and placebo arm = 19.6%, 95% CI [11.63%, 27.67%]). The first secondary endpoint of the change in mean eye dryness score (EDS) from baseline to 5 minutes after treatment administration in the Controlled Adverse Environment (CAE) Chamber at Day 28 among the OC-01 arms was not significantly different from the placebo arm (least square mean difference between 0.6 mg/ml arm vs placebo arm = -2.9, 95% CI [-7.35, 1.55] and least square mean difference between 1.2 mg/ml arm vs placebo arm = -1.6, 95% CI [-6.19, 2.92]). Under the pre-specified statistical test hierarchy, formal testing of subsequent secondary endpoints was stopped due to the lack of statistical significance for the first secondary endpoint. ONSET-2 provides evidence to support the efficacy of OC-01 .

ONSET-1 demonstrated a statistically significant improvement in the primary efficacy endpoint of mean change in STS on Day 28 from baseline among the OC-1 treatment arms compared to the placebo arm (the least square mean difference of change between the OC-1 0.6 mg/ml arm and the placebo arm = 7.7, 95% CI [3.8, 11.7] and least square mean difference of change between the OC-1 1.2 mg/ml arm and the placebo arm = 7.5, 95% CI [3.4, 11.6]).. The secondary symptom endpoint of the change in EDS from baseline to Day 28 in the study eye among the OC-01 0.6 mg/ml arm was superior to the placebo arm (least square mean difference of change between the OC-1 0.6 mg/ml arm and the arm = -12.7, 95% CI [-23.2, -2.2]). ONSET-1 provides evidence to support the efficacy of OC-01 0.6 mg/ml in both sign and symptom endpoints

5.3 Conclusions and Recommendations

Based on the totality of evidence from the three adequate and well-controlled studies ONSET-1, ONSET-2, and MYSTIC, the reviewer concludes that, the application demonstrated substantial evidence to support the efficacy of OC-01 0.6 mg/ml to treat the signs and symptoms of DED.

5.4 Labeling Recommendations

We recommend, the label should not include the success in symptom of DED until the Applicant has further supportive evidence of OC-01 efficacy to treat symptom of eye dryness score.

In the label the Applicant used the LOCF imputation method that results a higher proportion in the treatment group than the proposed primary analysis with MAR/MNAR in ONSET-2. However, both of the imputation method provided the same conclusion of the efficacy and therefore acceptable for labeling.

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/

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10/07/2021 06:52:56 PM

GUOXING SOON
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