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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

Clinical Studies

NDA/Serial Number:	22,288 (original)
Drug Name:	Bepotastine besilate ophthalmic solution 1.5% and 1.0% (Bepreve)
Indication(s):	Treatment of itching (b) (4) associated with allergic conjunctivitis
Applicant:	ISTA Pharmaceuticals, Inc.
Date(s):	Stamp date: November 12, 2008 PDUFA date: September 11, 2009
Review Priority:	Standard
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Keywords: Conjunctival Allergen Challenge Model, Ocular Itching, Conjunctival Redness.

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA 22288 submission, the applicant is seeking approval for Bepotastine Besilate Ophthalmic Solution (Bepreve) as an eye drop treatment for ocular itching (b) (4) associated with allergic conjunctivitis. The applicant has submitted two phase 3 conjunctival allergen challenge (CAC) studies: ISTA-BEPO-CS01 and CL-S&E-0409071-P. In addition, the applicant has submitted a safety study (CL-SAF-0405071-P).

These studies have demonstrated that: (1) Both Bepreve 1.5% and Bepreve 1.0% achieved the pre-defined clinical and statistical significance in the primary endpoint of ocular itching; (2) Bepreve 1.5% had numerical advantage (in terms of point estimate of treatment effect) over Bepreve 1.0% in the primary endpoint of ocular itching; (3) Both Bepreve 1.5% and Bepreve 1.0% failed in the primary endpoint of conjunctival redness; (4) There were no serious ocular adverse events reported in patients dosed with either Bepreve 1.0% or 1.5%.

It is recommended that Bepreve 1.5% be approved for the treatment of ocular itching associated with allergic conjunctivitis.

1.2 Brief Overview of Clinical Studies

Both the phase 3 CAC studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) were identical in design except that (1) study ISTA-BEPO-CS01 was a single centered whereas and CL-S&E-0409071-P was a multi-centered and (2) the multicenter trial included an assessment of ocular comfort.

Both studies were double-masked, randomized, vehicle-controlled efficacy and safety studies. They evaluated the onset and duration of action of Bepreve 1.5% and Bepreve 1.0% in patients with acute allergic conjunctivitis using the conjunctival allergen challenge (CAC) model of acute allergic conjunctivitis. Study subjects were randomized in a 1:1:1 ratio to one of there test agents (vehicle, Bepreve 1.0%, and Bepreve 1.5%). In Study ISTA-BEPO-CS01, 107 subjects from one US site were randomized: 36 in the Vehicle group, 36 in the Bepreve 1.0% group, and 35 in the Bepreve 1.5% group. In Study CL-S&E-0409071-P, 130 subjects from 5 US sites were randomized: 43 in the Vehicle group, 43 in the Bepreve 1.0% group, and 44 in the Bepreve 1.5% group.

These two studies included 5 visits in a period over approximately 7 weeks: Visit 1 (Day -21) for an allergen titration CAC test, Visit 2 (Day -14) for an allergen confirmation CAC test, Visit 3A (Day 0) for randomization and the first instillation of the assigned test agent, Visit 3B (Day 1) for a duration of action CAC test 16 hours post instillation of test agent, Visit 4 (Day 14) for the second instillation of test agent and a duration of action CAC test 8 hours post instillation of test agent, and Visit 5 (Day 28) for the third

instillation of test agent and an onset of action CAC test 15 minutes post instillation of test agent.

The primary objectives of both studies were to establish the efficacy and safety of Bepreve 1.0% and 1.5% compared with vehicle in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis when dosed 15 minutes prior to a CAC (for onset of action), 8 hours prior to a CAC (for duration of action acceptable for a drug indicated for twice-daily dosing), or 16 hours prior to a CAC (for duration of action acceptable for a drug indicated for once-daily dosing) in subjects with a history of allergic conjunctivitis.

The primary efficacy variables were subject-evaluated ocular itching at 3, 5, and 7 minutes post CAC and investigator-evaluated conjunctival redness at 7, 15, and 20 minutes post CAC.

In order to demonstrate clinical significance for the primary endpoints (ocular itching and conjunctival redness) at a given visit, Bepreve 1.5% or Bepreve 1.0% must demonstrate clinical superiority over vehicle by at least 0.5 unit (point-estimate) for all time points and at least 1.0 unit (point-estimate) for the majority (2/3) of time points.

Statistical significance was considered to have been demonstrated for Bepreve 1.5% or Bepreve 1.0% by showing statistical significance for the primary efficacy variables (ocular itching and conjunctival redness) at majority (2/3) of the time points at Visit 5 (Day 28) and either at Visit 3B (Day 1) or at Visit 4 (Day 14).

Efficacy of treatment with Bepreve 1.5% or Bepreve 1.0% was considered to have been demonstrated in each primary endpoint if both the clinical significancy and the statistical significancy were achieved at Visit 5 (Day 28) and either at Visit 3B (Day 1) or at Visit 4 (Day 14).

1.3 Statistical Issues and Findings

The efficacy data from the two phase-3 CAC studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) demonstrated that both Bepreve 1.5% and Bepreve 1.0% achieved statistically significant reductions in the primary endpoint of ocular itching. However, both Bepreve 1.5% and Bepreve 1.0% did not show statistically significant reductions in the other primary endpoint of redness associated with allergic conjunctivitis.

The efficacy data from Study ISTA-BEPO-CSO1 (single site trial) showed that only Bepreve 1.5% achieved clinical significance and statistical significance in treating ocular itching at all visits (Day 1, Day 14, and Day 28). Furthermore, in both studies, Bepreve 1.5% had numerical advantage (in terms of the point estimate) over Bepreve 1.0% at Visit 4 (Day 14) and Visit 5 (Day 28). Therefore, Bepreve 1.5% is recommended as the more efficacious dose.

Robustness of the Efficacy Results for the Primary Endpoint of Ocular Itching:

The primary efficacy analysis in the two phase 3 studies was based on the ITT population using the last observation carried forward (LOCF) method for imputing missing data. There are concerns in using LOCF method that can potentially bias the results. The applicant conducted sensitivity analyses using alternative population analysis sets (the PP population and the ITT population with observed data only). The sensitivity analysis results were consistent with those of the primary analysis. The applicant also conducted analyses using different imputation methods for missing data for the ITT population. The imputation methods were Monte Carlo Markov Chain (MCMC) imputation, and the Visit 2 (Day -14: baseline) observations carried forward imputation. The treatment effect of Bepreve 1.5% and Bepreve 1.0% for the ocular itching indication continued to be significant according to the pre-defined clinical and statistical criteria. Furthermore, the sensitivity analysis results using multiple alternative statistical testing procedures (e.g., t-test, Wilcoxon rank sum test, etc.) were also consistent with the primary analysis results.

In the two phase 3 studies, multiplicity adjustments (for controlling overall 0.05 type I error rate) were made because two concentrations of Bepreve were tested (1.0% and 1.5%), multiple primary endpoints were assessed (ocular itching and conjunctival redness), and both studies only required that statistical significance be achieved at the onset of action of CAC test (Visit 5) and at 1 of the 2 durations of action CAC tests (8-hour or 16-hour). The requirements for statistical significance pre-specified in the protocol were p-value ≤ 0.00625 at the 8-hour (Day 14: Visit 4) and 16-hour duration (Day 1: Visit 3B) of CAC tests and p-value ≤ 0.0125 at the onset of action CAC test (Day 28: Visit 5) for a majority (2/3) of time points. However, the multiplicity adjustments criteria applied in this submission do not adjust for the majority of the time points within a visit. In order to adjust multiplicity correctly for the majority (2/3) of time points, the proposed type I error rates 0.0125 and 0.00625 have to be divided by 3 because there are three different ways to win. Therefore, type I error rates will be 0.0042 and 0.0021 for Visit 5 (Day 28) and Visit 3B (Day 1) /Visit 4 (Day 14) respectively. With these type I error rate adjustments, the efficacy conclusions remain the same.

2 INTRODUCTION

According to the applicant, bepotastine besilate is an anti-allergic drug possessing highly selective histamine H1 receptor antagonistic action and, in addition, inhibitory action on eosinophilic infiltration to inflammatory sites. It was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. as a treatment for allergic rhinitis. An oral preparation of bepotastine besilate [Talion tablets, Mitsubishi Tanabe Pharma Corporation (formerly Tanabe Seiyaku Company, Ltd.)] was approved in Japan in July 2000 as a treatment for allergic rhinitis (10mg po bid for up to 4 weeks). In January 2002, the additional indication of pruritus/itching accompanying urticaria and other skin diseases was approved in Japan. Currently, Bepotastine is not an approved product in the U.S. for any indication. There are approved drugs for the proposed indications in the U.S.

Bepotastine besilate was developed under IND 66,864. There was an end of phase 2/pre-Phase 3 meeting on August 15, 2007. The multicenter phase 3 study protocol (CL-S&E-0409071-P) was submitted to the Agency for review under special protocol assessments (SAP). The SPA responses for Study CL-S&E-040907-P were dated on July 23, 2007 (SPA response) and December 3, 2007 (final response). The pre-NDA meeting was held on August 4, 2008..

Data sets and all modules containing clinical study reports were submitted electronically. This reviewer focused on the review of the two phase 3 studies ISTA-BEPO-CS01 and CL-S&E-0409071-P. The full electronic path for the study results according to CDER EDR naming convention is as follows:

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The data sets were adequately documented.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Introduction

In this NDA, the applicant has submitted data from two Phase 3 studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) in patients with allergic conjunctivitis.

3.1.2 Study Designs

Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P were identical in design except that 1) study ISTA-BEPO-CS01 was a single centered whereas and CL-S&E-0409071-P was a multi-centered and 2) the multicenter trial included an assessment of ocular comfort. Both studies were double-masked, randomized, vehicle-controlled, evaluation of the onset and duration of action of Bepreve 1.5% and Bepreve 1.0% in the conjunctival allergen challenge (CAC) model of acute allergic conjunctivitis planned for patients with a demonstrated history of allergic conjunctivitis. Patients (≥ 10 years of age) who demonstrated history of allergic conjunctivitis were eligible for the study. This study consisted of a total of 5 visits, conducted over approximately 7 weeks.

Subjects were evaluated during screening for a consistent allergic response to a defined allergen as judged by grades of 2.0 units or greater for ocular itching and for hyperemia in at least 2 out of the 3 vessel beds examined during two screening visits. At Visit 1 (Day -21), allergen instilled in each eye of subjects was titrated for the induction of an ocular allergic response to obtain the lowest concentration of allergen that produced an allergic response. Any subject who met the criteria for an allergic response continued to Visit 2 (Day -14) at which time the allergen of the same identity and dose used in the previous visit was instilled in each subject eye and an ocular allergic response was confirmed. Itching at Visit 2 (Day -14) was subject-assessed at 3, 5, and 7 minutes post CAC. Redness was investigator-assessed at 7, 15, and 20 minutes post CAC. Only subjects who met the study criteria for a positive CAC reaction at Visits 1 and 2 were allowed to continue to Visit 3A (Day 0). At Visit 3A a computer-generated randomization list was used to assign the subjects (in 1:1:1 proportions) to one of three treatment groups (Bepreve 1.0%, Bepreve 1.5%, or vehicle).

At Visits 3A (Day 0), 4 (Day 14), and 5 (Day 28), a trained technician instilled 1 drop of the assigned test agent into both eyes of each subject. CAC was performed, using the previously validated allergen dose for each subject at: 16 hours (duration-of-action acceptable for drugs intended to be dosed QD), 8 hours (duration-of-action acceptable for drugs intended to be dosed BID), or 15 minutes (onset of action) post test agent instillation during Visit 3A (Day 0), 4 (Day 14), and 5 (Day 28), respectively.

The test agents (Bepreve 1.0% or Bepreve 1.5% or vehicle) were dosed as one drop in each eye at each of Visits 3B, 4, and 5, always at the same concentration for an individual subject. Signs and symptoms of allergic conjunctivitis were then graded over a 20-minute period following the CAC. The severity of allergy symptoms was evaluated independently by subjects, using a self-reported standardized severity scale, and the severity of allergic signs independently by investigators. Using slit lamp biomicroscopy and accompanying photographic standards, investigators evaluated subjects' allergic response using a 5-point scale, with 0.5 unit increments allowed, for ciliary hyperemia, conjunctival hyperemia, and episcleral hyperemia. Chemosis also was evaluated by investigators on a 5-point (nine-step) scale with 0.5 unit increments allowed. Investigators additionally evaluated mucous discharge, which was rated as either absent or present. All investigator evaluations were recorded for both eyes.

Subject-evaluated assessments included both ocular and nasal allergic symptoms. Both the right and left eyes were independently evaluated for itching (using a 5-point scale with 0.5 unit increments allowed) and lid swelling (using a 4-point scale with whole unit increments only). Tearing was rated by subjects as either absent or present. Nasal symptoms were evaluated by subjects on a 5-point scale, with whole unit increments only, for rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion. Subject-evaluated assessments of ocular itching occurred at 3, 5, and 7 minutes post-allergen challenge. All other assessments, including investigator-evaluated assessments and subject-evaluated ocular and nasal symptom assessments, occurred at 7, 15, and 20 minutes post-challenge.

Inclusion/Exclusion Criteria:

See clinical review for details.

Study Schedule

The first dose of the test agents was administered at Visit 3A (Day 0), 16 hours prior to a CAC, and the second dose was administered at Visit 4 (Day 14), 8 hours prior to a CAC. The last dose was administered at Visit 5 (Day 28), 15 minutes prior to a CAC. The detailed study schedules are summarized in the following table:

Table 1: Detailed Study Schedules

Procedure	Visit 1 (Day -21 ± 3)	Visit 2 (Day -14 ± 3)	Visit 3A (Day 0)	Visit 3B (Day 1)	Visit 4 (Day 14 ± 3)	Visit 5 (Day 28 ± 3)
Informed Consent/Assent/ HIPAA	X					
Demographic Data	X					
Medical and Medication History	X					
Pregnancy Test (for females of childbearing potential)	X					X
Visual Acuity	X	X	X[1]		X[1]	X[1]
Biomicroscopy	X	X	X[1]		X[1]	X[1,2]
Intraocular Pressure	X[3]					X[3]
Dilated Fundoscopy	X[3]					X[3]
Screening Conjunctival Allergen Challenge (CAC)	X	X				
Medication History Update		X	X	X	X	X
Randomization of study subjects			X			
Investigational product Instillation			X		X	X
Drug Efficacy CAC				X[4]	X[5]	X[6]
Adverse Event Queries				X	X	X
Exit from Study						X

Source: Clinical Study Report:CL-S & E-0409071-P, Page 29

[1] The visual acuity and biomicroscopy exams were performed on subjects < 18 years of age at the following times: prior to investigational product instillation at all visits, approximately 15 minutes after investigational product instillation at Visit 3A and Visit 4, and approximately 40 minutes after investigational product instillation bilaterally at Visit 5.

[2] Including a 2nd exit slit-lamp exam.

[3] Performed following post-CAC assessments. The IOP measurements were performed using Goldmann tonometry.

[4] Sixteen (16) hours post investigational product instillation.

[5] Eight (8) hours post investigational product instillation.

[6] Fifteen (15) minutes post investigational product instillation.

Comparison of Study Designs:

Table 2 provides a comparison of study designs in CAC studies ISTA-BEPO-CS01, C-S&E-0409071-P and CL-SAF-0405071-P:

Table 2: Brief Summary of Clinical Studies

Study Identifier	**Objective of the Study**	**Study Design**	**Test Products**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
ISTA-BEPO-CS01 Safety and Efficacy Phase 2/3	Efficacy and safety of bepotastine besilate ophthalmic solution 1.0% and 1.5% compared to vehicle in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis at 15 mins., 8 hours, and 16 hours following mediation instillation	Single center, double-masked, randomized vehicle-controlled , CAC study	Bepotastine besilate ophthalmic solution 1.0%, 1.5%, or vehicle one drop at Visit 3A, Visit 4, and visit 5	107	CAC induced allergic conjunctivitis	3 single doses received over a period of 7 weeks
CL-S&E-0409071-P Safety and Efficacy Phase 3	Efficacy and safety of bepotastine ophthalmic solution 1.0% and 1.5% compared to vehicle in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis at 15 mins., 8 hours, and 16 hours	Multi-center, double-masked, randomized, vehicle-controlled, CAC study	Bepotastine besilate ophthalmic solution 1.0%, 1.5%, or vehicle one drop at Visit 3A, Visit 4, and visit 5	130	CAC induced allergic conjunctivitis	3 single doses received over a period of 7 weeks
CL-SAF-0405071-P Safety Phase 3	Evaluate the safety of bepotastine besilate ophthalmic solution 1.5% in healthy, normal volunteers	Multi-center, randomized, double-masked, vehicle-controlled, parallel-group study	Bepotastine besilate ophthalmic solution 1.5% or vehicle BID	861	Healthy	Treatment BID for 6 weeks for all subjects and subjects which participated in measuring endothelial cell counts were followed for an additional 6 weeks after stopping treatment

Primary Efficacy Variables:

The primary efficacy variables were subject-evaluated ocular itching at 3, 5, and 7 minutes post CAC and investigator-evaluated conjunctival redness at 7, 15, and 20 minutes post CAC. Ocular itching and conjunctival redness scales were based on a 5-unit grading scale with half unit (one step) increments. The endpoint measurement was calculated by averaging the scores from both eyes of each subject.

The Ocular Itching Assessment Grades are described as follows:

Table 3: Ocular Itching Assessment Grades

Grade	Assessment
0	None
0.5	An intermittent tickle sensation possible localized in the corner of the eye
1.0	An intermittent tickle sensation involving more than just the corner of the eye
1.5	Intermittent all-over itching sensation
2.0	Moderate, diffuse continuous itch with desire to rub
3.0	A severe itch with desire to rub
3.5	Severe itch improved with minimal rubbing
4.0	Incapacitating itch with an irresistible urge to rub

The Conjunctival redness assessment grades are described in the following table:

Table 4: Conjunctival redness assessment grades

Grade	Assessment
0	None
1.0	Mild-Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal
2.0	Moderate-More apparent dilation of blood vessels; vessels color is more intense (redder); involves the majority of the vessels bed
3.0	Severe-Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red, may be less red or pink in presence of chemosis, is not quandrantic
4.0	Extremely severe-Large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed

Secondary Efficacy Variables:

The secondary efficacy variables were evaluated at 7, 15, and 20 minutes post CAC and included: investigator-evaluated ciliary redness, episcleral redness, and chemosis (0-4 unit scales, allowing half unit increments), and ocular mucous discharge (graded absent or present).

Analysis Populations:

The analysis populations are described in sections below:

The ITT population was defined as all randomized subjects regardless of whether or not the subject received test agent. The PP population was defined as randomized subjects that had no significant protocol deviations or any incomplete patient data. The safety population was defined as all subjects who received at least one dose of test agent.

Safety Endpoints:

The safety variables for this study included:

- Incidence and frequency of AEs (reported, elicited, and observed).
- Physical examination [an assessment of general health, head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, neurologic evaluation, condition of extremities, back, skin, and vital signs] and pregnancy test (women of childbearing potential only) at Visit 1, Visit 4, and Visit 5.
- Visual acuity using an ETDRS chart at the beginning of each study visit. For subjects < 10 years who were developmentally unable to use the ETDRS chart, a best attempt at visual acuity was made using the LEA symbols.
- Slit lamp biomicroscopy conducted by the investigator at all study visits.
- ECC conducted on subject's age ≥10 years old at Visit 1 and Visit 5. All safety assessment performed at Visit 4 were repeated at Visit 5, in addition to ocular endothelial cell counts.
- Intraocular pressure (IOP) conducted on subject's age ≥10 years old (if possible), at Visit 1, Visit 4, and Visit 5.
- DFE conducted by the investigator at Visit 1, Visit 4, and Visit 5. The presence or absence of clinically significant fundus abnormalities and vitreous pathology were evaluated by comparison to baseline (Visit 1) values using a 0-3 severity scale.
- Ocular comfort examinations.

Sample Size Determination:

In Study ISTA-BEPO-CS01, a sample size of 30 subjects in each treatment group was selected based on 90% power and 0.05 alpha (two-sided) to detect a difference in means of 1.00 unit (the difference between vehicle and one of the bepotastine besilate ophthalmic solution groups). The two-sample t-test was used assuming the common standard deviation of unity.

In Study CL-S&E-0409071-P, a sample size of approximately 40 subjects was selected in each group based on 90% power and 0.05 alpha (two-sided) to detect a difference in means of 1.0 (the difference between vehicle and bepotastine besilate ophthalmic solution 1.0% or the difference between vehicle and bepotastine besilate ophthalmic solution 1.5%). The two-sample t-test was used assuming the common standard deviation of unity.

Statistical Methods:
In order to demonstrate clinical significance, bepotastine besilate ophthalmic solution (1.0% and 1.5%) must demonstrate clinical superiority over vehicle by at least 0.5 (point-estimate) unit (1-step) of a 5-point grading scale for all time points and at least 1.0 (point-estimate) unit (2 steps) for the majority of time points within a visit, measured for both ocular itching and conjunctival redness. Statistical significance was considered to have been demonstrated for bepotastine besilate ophthalmic solution (1.0% and 1.5%) by showing statistical significance for the primary efficacy variables (ocular itching and conjunctival redness) at majority (2/3) of the time points at Visit 5 (Day 28) and either at Visit 3B (Day 1) or Visit 4 (Day 14). Clinical efficacy was considered to have been demonstrated for bepotastine besilate ophthalmic solution (1.0% and 1.5%) by showing clinical and statistical significance for the primary efficacy variables, ocular itching and conjunctival redness, at Visit 5 (Day 28) and either at Visit 3B (Day 1) or Visit 4 (Day 14).

Hypothesis testing (using Wilcoxon rank sum test) was performed on the primary efficacy variables using a Wilcoxon rank sum test at each visit. The null hypotheses were:

● There is no difference in primary efficacy endpoints between bepotastine besilate ophthalmic solution 1.0% and vehicle at the majority of the time points

● There is no difference in primary efficacy endpoints between bepotastine besilate ophthalmic solution 1.5% and vehicle at the majority of the time points

In the primary analysis, the missing data were imputed using the Last Observation Carried Forward (LOCF) method.

Sensitivity analyses on various study populations were performed to examine the robustness of the primary efficacy results: the per protocol (PP) population (observed data), the ITT population with observed data only, the ITT population with baseline values carried forward for imputation of missing, data and the ITT population with Monte Carlo Markov Chain (MCMC) imputation of missing data. Additional sensitivity analyses were also performed using two-sample t-test, Wilcoxon rank sum test for clustered data, and ANCOVA.

Multiplicity adjustments (to control overall type I error rate of 0.05) were made because multiple concentrations of Bepreve were tested (1.0% and 1.5%), multiple primary endpoints were assessed (ocular itching and conjunctival redness), and both CAC trials only required that statistical significance be achieved at 1 of the 2 duration of action CAC tests (8-hour or 16-hour). The requirements for statistical significance therefore were p-value ≤ 0.00625 at the 8-hour and 16-hour duration of CAC tests and p-value ≤ 0.0125 at the onset of action CAC test for a majority of time points.

Statistical Comments:
The multiplicity adjustments criteria applied in this submission do not adjust for the majority of the time points within a visit. In order to adjust multiplicity correctly for the majority (2/3) of time points, the proposed type I error rates 0.0125 and 0.00625 have to be divided by 3 because there are three different ways to win. Therefore, type I error rates will be 0.0042 and 0.0021 for Visit 5 (Day 28) and Visit 3B (Day 1) /Visit 4 (Day 14) respectively.

Patient Disposition and Study populations

In Study ISTA-BEPO-CSO1, a total of four subjects (one in vehicle group, three in the Bepotastine 1.5% group, and none in the Bepotastine 1.0% group) discontinued/ withdrawn over the course of the study. The per-protocol (PP) population, defined prior to database lock as subjects who completed the study without any major protocol violation, was 101 subjects.
study visit).

In Study CL-S&E-0409071-P, a total of thirteen subjects (seven in the vehicle group, five in the Bepotastine 1.5% group, and one in the Bepotastine 1.0% group) discontinued/ withdrawn over the course of the study. The remaining 117 subjects completed the study and comprised the PP population.
The summary of the study population for both studies is presented in Tables 5-6.

Table 5: Patient Disposition (Study ISTA-BEPO-CSO1)

	Bepreve 1.0%	**Bepreve 1.5%**	**Vehicle**	**Total**
Randomized	36	35	36	107
Safety Population	36	35	36	107
ITT Population with LOCF	36	35	36	107
PP Population	35	32	34	101

Data source: Clinical Study Report: ISTA-BEPO-CS01, Page 108 (Table 14.1.1)

Table 6: Patient Disposition (Study CL-S&E-0409071-P)

	Bepreve 1.0%	Bepreve 1.5%	Vehicle	Total
Randomized	44	43	43	130
Safety Population	44	43	43	130
ITT Population with LOCF	44	43	43	130
PP Population	43	38	36	117

Data source: Clinical Study Report:CL-S & E-0409071-P, Page 155 (Table 14.1.1)

Demographic and Baseline Characteristics at Entry:

Baseline demographics for the intent-to-treat (ITT) population for Study ISTA-BEPO-CSO1 are presented in the following table:

Table 7: Study ISTA-BEPO-CSO1: Demographics (ITT Population)

Parameter	**Total Randomized Subjects (N=107)**	**Bepreve 1.0% (N=36)**	**Bepreve 1.5% (N=35)**	**Vehicle (N=36)**
Gender				
Male	58	22	17	19
Female	49	14	18	17
Age				
Mean	41.7	39.3	44.3	40.9
Race				
Caucasian	99	35	31	33
African-American	2	0	1	1
Asian	2	0	0	2
Other race	4	1	3	0
Ethnicity				
Hispanic/Latino	10	2	4	4
Not Hispanic/Latino	97	34	31	32
Iris Color				
Blue	34	11	11	12
Brown	51	15	17	19
Green	6	3	1	2
Hazel	16	7	6	3

Data Source: Clinical Study Report: ISTA-BEPO-CS01, Page 110 (Table 14.1.3.1)

It can be seen that demographics and other characteristics of subjects were well-balanced among the treatment groups for the ITT population. The applicant reported that pairwise comparison of demographics for bepotastine besilate ophthalmic solutions 1.0% and 1.5% to vehicle revealed a lack of statistically significant differences with regards to age (p-value = 0.747 for 1.0%, p-value = 0.305 for 1.5%), gender (p-value = 0.634 for 1.0%, p-value = 0.814 for 1.5%), ethnicity (p-value = 0.674 for 1.0%, p-value = 1.000 for 1.5%), eye color (p-value = 0.514 for 1.0%, p-value = 0.716 for 1.5%), or race (p-value = 0.364 for 1.0%, p-value = 0.145 for 1.5%).

Baseline demographics for the intent-to-treat (ITT) population for Study CL-S&E-0409071-P are presented in the following table:

Table 8: Study CL-S&E-0409071-P: Demographics (ITT Population)

Parameter	Total Randomized Subjects (N=130)	Bepreve 1.0% (N=44)	Bepreve 1.5% (N=43)	Vehicle (N=43)
Gender				
Male	75	25	21	29
Female	55	19	22	14
Age				
Mean	33.8	34.8	33.3	33.3
Race				
Caucasian	94	33	29	32
African-American	12	2	6	4
Asian	22	8	8	6
American Indian	1	1	0	
Other race	1	0	0	1
Ethnicity				
Hispanic/Latino	2	0	0	2
Not Hispanic/Latino	128	44	43	41
Iris Color				
Blue	86	22	38	26
Brown	118	42	34	42
Green	28	8	10	10
Hazel	26	16	4	6
Other	2	0	0	2

Data source: Clinical Study Report:CL-S & E-0409071-P, Page 157 (Table 14.1.3.1)

It can be seen from the above table that demographics and other characteristics of subjects were well balanced among the treatment groups for the ITT population. The applicant reported that comparison of demographics for bepotastine besilate ophthalmic

solutions 1.0% and 1.5% to vehicle revealed a lack of statistically significant differences with regards to age (t-test; p-value 0.62 for 1.0%, p-value=1.0 for 1.5%), gender (Fisher's exact test; p-value=0.378 for 1.0%, p-value=0.125 for 1.5%), ethnicity (Fisher's exact test; p-value=0.24 for 1.0%, p-value=0.49 for 1.5%), race (Fisher's exact test; p-value=0.70 for 1.0%, p-value = 0.65 for 1.5%), or eye color (Fisher's exact test; p-value=0.13 for 1.0%, p-value=0.251 for 1.5%).

3.1.3 Efficacy Results

Efficacy Results of the Primary Efficacy Endpoint of Ocular Itching

The efficacy results for the primary endpoint of ocular itching are presented in Tables 9-10. Both studies demonstrated that both Bepreve 1.5% and Bepreve 1.0% achieved clinical significance (i.e., a ≥ 1.0-unit difference versus vehicle at a majority of time points and a ≥ 0.5-unit difference versus vehicle at all time points) in treating ocular itching for all observation time points at Visit 4 (8 hour duration-of-action) and Visit 5 (onset of action) for the ITT population with LOCF. The p-values (based on both Wilcoxon and t tests) for all observation time points at visit 4 and visit 5 showed highly statistically significant difference (p-value < 0.0042 for visit 4 and p-value < 0.0021 for visit 5 for bepotastine besilate ophthalmic solution (both Bepreve 1.5% and Bepreve 1.0%) as compared to vehicle in treating ocular itching. Thus, for both studies, both Bepreve 1.5% and Bepreve 1.0% achieved statistical significance in treating ocular itching for all observation time points at Visit 4 (8 hour duration-of-action) and Visit 5 (onset of action) for the ITT population with LOCF. According to applicant's criteria, both Bepreve 1.5% and Bepreve 1.0% achieved clinical efficacy (both clinical significance and statistical significance) in treating ocular itching.

It is worth noting that in study ISTA-BEPO-CSO1(single site trial) only Bepreve 1.5% achieved clinical significance and statistical significance in treating ocular itching for visit 3B (Day 1). Furthermore, in both studies, Bepreve 1.5% has numerical advantage (in terms of the point estimate) over Bepreve 1.0% at visit 4 and visit 5.

It is further noted that the per-protocol analysis results performed (Table 11-12) were consistent with those of the primary analysis.

This reviewer conducted a sensitivity analysis of the ITT population with Visit 2 (baseline value) observations carried forward for the missing data. The results of this sensitivity analysis were also consistent with those of the primary analyses.

Table 9: Ocular Itching Grade (Vehicle vs. Active)
(Study ISTA-BEPO-CSO1: ITT Population With LOCF)

	Vehicle vs. Bepreve 1.0%		**Vehicle vs. Bepreve 1.5%**	
Visit	Difference (95% CI)	P value: Wilcoxon test (t-test)	Difference (95% CI)	P value: Wilcoxon test (t-test)
Visit 3B (Day 1)-CAC at 16 hours post dosing				
3 min post-CAC	0.7 (0.3, 1.1)	0.0014 (0.0010)	0.9 (0.4, 1.2)	0.0013 (0.0007)
5 min post-CAC	0.8 (0.4, 1.2)	0.0002 (0.0002)	1.0 (0.5, 1.3)	0.0006 (0.0001)
7 min post-CAC	0.8 (0.4, 1.3)	0.0002 (0.0001)	1.0 (0.4, 1.3)	0.0004 (0.0002)
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	0.9 (0.5, 1.2)	<0.0001 (<0.0001)	1.3 (0.8, 1.6)	<0.0001 (<0.0001)
5 min post-CAC	1.0 (0.6, 1.4)	<0.0001 (<(0.0001)	1.5 (1.0, 1.8)	<0.0001 (<0.0001)
7 min post-CAC	1.0 (0.6, 1.4)	<0.0001 (<0.0001)	1.4 (0.9, 1.7)	<0.0001 (<0.0001)
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	1.3 (1.0, 1.7)	<0.0001 (<0.0001)	1.4 (1.0, 1.7)	<0.0001 (<0.0001)
5 min post-CAC	1.4 (1.0, 1.8)	<0.0001 (<0.0001)	1.4 (0.9, 1.7)	<0.0001 (<0.0001)
7 min post-CAC	1.3 (0.9, 1.7)	<0.0001 (<0.0001)	1.3 (0.8, 1.6)	<0.0001 (<0.0001)

Table 10: Ocular Itching Grade (Vehicle vs. Active)
(Study CL-S&E-0409071-P: ITT Population With LOCF)

	Vehicle vs. Bepreve 1.0%		**Vehicle vs. Bepreve 1.5%**	
Visit	Difference (95% CI)	P value: Wilcoxon test (t-test)	Difference (95% CI)	P value: Wilcoxon test (t-test)
Visit 3B (Day 1)- CAC at 16 hours post-dosing				
3 min post-CAC	0.6 (0.2,0.9)	0.0064 (0.0055)	0.6 (0.2, 1.0)	0.0049 (0.0051)
5 min post-CAC	0.7 (0.3,1.1)	0.0009 (0.0006)	0.7 (0.3, 1.1)	0.0017 (0.0021)
7 min post-CAC	0.8 (0.4, 1.2)	0.0003 (0.0001)	0.8 (0.4, 1.2)	0.0004 (0.0003)
Visit 4 (Day 14)- CAC at 8 hours post-dosing				
3 min post-CAC	1.2 (0.8, 1.6)	<0.0001 (<0.0001)	1.3 (0.9, 1.7)	<0.0001 (<0.0001)
5 min post-CAC	1.3 (0.9, 1.6)	<0.0001 (<0.0001)	1.3 (1.0, 1.7)	<0.0001 (<0.0001)
7 min post-CAC	1.2 (0.8, 1.5)	<0.0001 (<0.0001)	1.3 (0.9, 1.6)	<0.0001 (<0.0001)
Visit 5 (Day 28)- CAC at 15 minutes post-dosing				
3 min post-CAC	1.4 (1.1, 1.8)	<0.0001 (<0.0001)	1.5 (1.1, 1.8)	<0.0001 (<0.0001)
5 min post-CAC	1.5 (1.1, 1.8)	<0.0001 (<0.0001)	1.6 (1.3, 2.0)	<0.0001 (<0.0001)
7 min post-CAC	1.3 (0.9, 1.7)	<0.0001 (<0.0001)	1.4 (1.1, 1.8)	<0.0001 (<0.0001)

Table 11: Study ISTA-BEPO-CSO1: Ocular Itching (PP)

Visit	Bepreve 1.0%		Bepreve 1.5%	
	Difference in Mean Itching Grades (Vehicle – Active)	P value	Difference in Mean Itching Grades (Vehicle – Active)	P value
Visit 3B (Day 1)-CAC at 16 hours post dosing				
3 min post-CAC	0.7	0.0008(0.0003)	1.0	0.0001(<0.0001)
5 min post-CAC	0.9	0.0001(0.0001)	1.1	0.0001(<0.0001)
7 min post-CAC	0.9	0.0001(<0.0001)	1.1	<0.0001(<0.0001)
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	1.0	<0.0001(<0.0001)	1.4	<0.0001(<0.0001)
5 min post-CAC	1.1	<0.0001(<0.0001)	1.7	<0.0001(<0.0001)
7 min post-CAC	1.0	<0.0001(<0.0001)	1.5	<0.0001(<0.0001)
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	1.4	<0.0001(<0.0001)	1.5	<0.0001(<0.0001)
5 min post-CAC	1.4	<0.0001(<0.0001)	1.5	<0.0001(<0.0001)
7 min post-CAC	1.3	<0.0001(<0.0001)	1.5	<0.0001(<0.0001)

Table 12: Study CL-S&E-0409071-P: Ocular Itching (PP)

Visit	Bepreve 1.0%		Bepreve 1.5%	
	Difference in Mean Itching Grades (Vehicle – Active)	P value	Difference in Mean Itching Grades (Vehicle – Active)	P value
Visit 3B (Day 1)-CAC at 16 hours post-dosing				
3 min post-CAC	0.5	0.0116(0.0114)	0.6	0.006(0.0074)
5 min post-CAC	0.7	0.0012(0.0007)	0.8	0.0011(0.0008)
7 min post-CAC	0.8	0.0012(0.0005)	0.7	0.0018(0.0016)
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	1.2	<0.0001(<0.0001)	1.3	<0.0001(<0.0001)
5 min post-CAC	1.3	<0.0001(<0.0001)	1.3	<0.0001(<0.0001)
7 min post-CAC	1.1	<0.0001(<0.0001)	1.2	<0.0001(<0.0001)
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	1.4	<0.0001 (<0.0001)	1.5	<0.0001 (<0.0001)
5 min post-CAC	1.4	<0.0001 (<0.0001)	1.6	<0.0001 (<0.0001)
7 min post-CAC	1.2	<0.0001 (<0.0001)	1.4	<0.0001 (<0.0001)

Efficacy Results of the Primary Efficacy Endpoint of Conjunctival Redness

The efficacy results for the primary endpoint of conjunctival redness are presented in Tables 13-14.

It can be seen from Table 13 and Table 14, the efficacy data from both studies, both Bepreve 1.5% and Bepreve 1.0% failed to achieve clinical significance (i.e., a ≥ 1.0-unit difference versus vehicle at a majority of time points and a ≥ 0.5-unit difference versus vehicle at all time points) in treating conjunctival redness for all observation time points in none of the visits for the ITT population with LOCF.
As a result, the effectiveness (both clinical significance and statistical significance) of both Bepreve 1.5% and Bepreve 1.0% was not demonstrated in either study.

Table 13: Study ISTA-BEPO-CSO1: Clinical Assessment of Conjunctival Redness (ITT Population With LOCF)

Time of Post-CAC Observation	Bepreve 1.0%		Bepreve 1.5%	
	Difference in Mean Redness Grades (Vehicle – Active)	P value	Difference in Mean Redness Grades (Vehicle – Active)	P value: Wilcoxon test (t-test)
Visit 3B				
7 min post-CAC	0.4	0.0095(0.0148)	0.2	0.2825(0.3564)
15 min post-CAC	0.3	0.0365 (0.0549)	0.0	0.9444(0.7422)
20 min post-CAC	0.2	0.0787 (0.1093)	-0.1	0.4922(0.4171)
Visit 4				
7 min post-CAC	0.4	0.0101(0.0074)	0.4	0.0424(0.0353)
15 min post-CAC	0.3	0.0564(0.0335)	0.4	0.1185(0.0626)
20 min post-CAC	0.3	0.0592(0.0544)	0.3	0.1493(0.0953)
Visit 5				
7 min post-CAC	0.8	<0.0001(<0.0001)	0.6	0.0025(0.0011)
15 min post-CAC	0.6	0.0003(0.0001)	0.4	0.0347(0.0061)
20 min post-CAC	0.5	<0.0007(0.0009)	0.3	0.1235(0.0482)

Table 14: Study CL-S&E-049071-P: Clinical Assessment of Conjunctival Redness (ITT Population With LOCF)

Time of Post-CAC Observation	Bepreve 1.0%		Bepreve 1.5%	
	Difference in Mean Redness Grades (Vehicle – Active)	P value	Difference in Mean Redness Grades (Vehicle – Active)	P value: Wilcoxon test (t-test)
Visit 3B				
7 min post-CAC	0.4	0.0034(0.0053)	0.1	0.6758(0.5472)
15 min post-CAC	0.4	0.0187(0.0168)	0.1	0.5175(0.3882)
20 min post-CAC	0.4	0.0386(0.0407)	0.1	0.6667(0.5000)
Visit 4				
7 min post-CAC	0.5	0.0016(0.0006)	0.2	0.1676(0.1067)
15 min post-CAC	0.3	0.036(0.0356)	0.1	0.3656 (0.3598)
20 min post-CAC	0.3	0.0861(0.1026)	0.1	0.5735(0.5909)
Visit 5				
7 min post-CAC	0.6	0.0001(0.0001)	0.4	0.0023(0.0031)
15 min post-CAC	0.5	0.0013(0.0020)	0.4	0.0109(0.0114)
20 min post-CAC	0.2	0.0962(0.1485)	0.2	0.1997(0.2251)

Analysis of Secondary Endpoints:

The applicant reported that in both studies none of the secondary efficacy variables achieved clinical significance at any study visit for either bepotastine besilate ophthalmic solution (1.0% or 1.5%) compared to vehicle. Clinical efficacy was therefore not realized for reduction of any of these secondary efficacy variables with either active test agent.

Conclusions:

The efficacy data from the two phase-3 studies demonstrated that both Bepreve 1.5% and Bepreve 1.0% achieved statistically significant reductions in the primary endpoint of ocular itching. However, both Bepreve 1.5% and Bepreve 1.0% did not show statistically significant reductions in the primary endpoint of redness associated with allergic conjunctivitis.

Based on the efficacy results in both studies, Bepreve 1.0% and Bepreve 1.5% are effective in treating ocular itching. The data from the single site trial (study ISTA-BEPO-CSO1) showed that only, Bepreve 1.5% achieved clinical significance and statistical significance in treating ocular itching for visit 3B. Furthermore, in both studies, Bepreve 1.5% has numerical advantage (in terms of the point estimate) over Bepreve

1.0% at visit 4 and visit 5. Therefore, Bepreve 1.5% is recommended as the more efficacious dose.

3.2 Evaluation of Safety

This section summarizes safety data for this submission. See clinical review for further details.

The analysis of safety included a summary of the percentage of subjects with specific treatment-emergent adverse events by treatment group. Incidence of ocular and systemic adverse events also was tabulated by MedDRA preferred term and System Organ Class by treatment group. The primary safety variable was the incidence of subjects with any adverse event during the entire study. Incidence was also tabulated by body system, severity, and specific event within each body system, and treatment group. Secondary safety variables included visual acuity, biomicroscopy findings, IOP, and dilated fundoscopy, and were summarized descriptively. In general, descriptive statistics were used without inferential tests for significance.

Study ISTA-BEPO-CS01:

The applicant reported that that non-ocular treatment-emergent adverse events occurred in greater frequency in the bepotastine besilate treatment groups as a whole as compared to vehicle. A total of 18 subjects experienced a non-ocular treatment-emergent adverse event. Of those, 2/36 (5.6%) subjects were in the vehicle group, 9/36 (25%) subjects were in the bepotastine besilate ophthalmic solution 1.0% group and 7/35 (20%) subjects were in the bepotastine besilate ophthalmic solution 1.5% group. Of the 18 subjects who experienced a non-ocular treatment-emergent adverse event, events for 12 subjects were classified as mild and for 6 subjects were classified as moderate. There were no subjects who experienced an AE that was considered severe by the investigator.

According to the applicant, there were no serious adverse events (SAEs) or deaths reported in the safety population. There were a total of 5 subjects with treatment-emergent ocular AEs reported for all three treatment groups: 3/36 (8.3%) were in the vehicle group, 2/35 (5.7%) were in the bepotastine besilate ophthalmic solution 1.5% group, and none were reported for the bepotastine besilate ophthalmic solution 1.0% group. Of the 5 treatment-emergent ocular adverse events reported, none were rated as severe in intensity.

Study CL-S&E-0409071-P:

The applicant reported that there were no SAEs or deaths reported in the safety population. There were a total of 40 treatment emergent AEs reported during the course of the study for 32 subjects across all 5 study sites. Of the 40 treatment emergent AEs reported, 31 were non ocular and 9 were ocular. More AEs occurred in the bepotastine besilate ophthalmic solution 1.0% group (19 AEs in 15 subjects) than in the bepotastine besilate ophthalmic solution 1.5% group (12 AEs in 10 subjects) or vehicle treatment group (9 AEs in 7 subjects). Of the 8 subjects who reported 9 treatment emergent ocular AEs, 4 subjects were in the bepotastine besilate ophthalmic solution 1.0% group, 3 subjects were in the bepotastine besilate ophthalmic solution 1.5% group, and 1 subject was in the vehicle treatment group. Of the 9 treatment emergent ocular AEs, all were classified as mild in severity, except 1 incident each of eye irritation and eye pain, both of which occurred in a single subject in the vehicle treatment group and were classified as moderate.

Study CL-SAF-0405071-P:

Study CL-SAF-0405071-P was a multi-center, randomized, double-masked, placebo-controlled, parallel-group safety study conducted at 6 sites in the United States evaluating the safety of bepotastine besilate ophthalmic solution 1.5% used twice daily in healthy, normal volunteers. This study was planned for approximately 850 subjects in order to ensure 750 completed at end of 6 weeks (Visit 4), 500 in the bepotastine besilate ophthalmic solution 1.5% treatment group and 250 in placebo group. Of the 850 subject total, approximately 105 pediatric subjects were anticipated to complete the study. The dosing regimen for all subjects was 1 drop administered bilaterally, twice daily, for 6 continuous weeks. The target study population was subjects 3 years of age and older with ocular health within normal limits. Randomization was at a ratio of 2:1 (active: vehicle) and subjects were not stratified by age group.

The applicant reported that no deaths occurred during study CL-SAF-040. Furthermore, no serious adverse events were reported during study CL-SAF-0405071.

The applicant further reported that most commonly reported non-ocular AEs were in the taste-related category. The taste-related category includes specific AEs described by the subjects as taste perversion, bad taste, aftertaste, taste abnormality, bitter taste, or metallic taste. In the bepotastine besilate ophthalmic solution 1.5% group, 25.2% of subjects reported at least 1 taste-related AE. This incidence had a statistical significance greater than the 2.4% incidence reported in the vehicle treatment group (p-value <0.0001). In the bepotastine besilate ophthalmic solution 1.5% treatment group, the overall rate of taste-related AEs averaged over all sites was 25.2%.

In addition, subjects receiving bepotastine besilate ophthalmic solution 1.5% did not experience any clinically significant changes from baseline or compared to subjects

receiving vehicle in any of the other safety measurements (visual acuity, intraocular pressure, dilated fundoscopy, slit-lamp biomicroscopy, ocular endothelial cell counts, and ocular comfort evaluations).

According to sponsor, bepotastine besilate ophthalmic solution 1.5% was safe and well tolerated as used in this study, exhibiting an adverse event profile that was similar to that of the vehicle with the exception of taste-related adverse events grouped under the term "taste disturbance upon instillation."

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Examination of Subgroups

The applicant did not perform the analyses of subgroups by site, region, age, sex, and ethnic origin because of small sample sizes in the subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The efficacy data from the two phase-3 CAC studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) demonstrated that both Bepreve 1.5% and Bepreve 1.0% achieved statistically significant reductions in the primary endpoint of ocular itching. However, both Bepreve 1.5% and Bepreve 1.0% did not show statistically significant reductions in the other primary endpoint of redness associated with allergic conjunctivitis.

The efficacy data from Study ISTA-BEPO-CSO1 (single site trial) showed that only Bepreve 1.5% achieved clinical significance and statistical significance in treating ocular itching at all visits (Day 1, Day 14, and Day 28). Furthermore, in both studies, Bepreve 1.5% had numerical advantage (in terms of the point estimate) over Bepreve 1.0% at Visit 4 (Day 14) and Visit 5 (Day 28). Therefore, Bepreve 1.5% is recommended as the more efficacious dose.

Robustness of the Efficacy Results for the Primary Endpoint of Ocular Itching:

The primary efficacy analysis in the two phase 3 studies was based on the ITT population using the last observation carried forward (LOCF) method for imputing missing data. There are concerns in using LOCF method that can potentially bias the results. The applicant conducted sensitivity analyses using alternative population analysis sets (the PP population and the ITT population with observed data only). The sensitivity analysis results were consistent with those of the primary analysis. The applicant also conducted analyses using different imputation methods for missing data for the ITT population. The imputation methods were Monte Carlo Markov Chain (MCMC) imputation, and the Visit 2 (Day -14: baseline) observations carried forward imputation. The treatment effect of Bepreve 1.5% and Bepreve 1.0% for the ocular itching indication continued to be significant according to the pre-defined clinical and statistical criteria. Furthermore, the sensitivity analysis results using multiple alternative statistical testing procedures (e.g., t-test, Wilcoxon rank sum test, etc.) were also consistent with the primary analysis results.

In the two phase 3 studies, multiplicity adjustments (for controlling overall 0.05 type I error rate) were made because two concentrations of Bepreve were tested (1.0% and 1.5%), multiple primary endpoints were assessed (ocular itching and conjunctival redness), and both studies only required that statistical significance be achieved at the onset of action of CAC test (Visit 5) and at 1 of the 2 durations of action CAC tests (8-hour or 16-hour). The requirements for statistical significance pre-specified in the protocol were p-value ≤ 0.00625 at the 8-hour (Day 14: Visit 4) and 16-hour duration (Day 1: Visit 3B) of CAC tests and p-value ≤ 0.0125 at the onset of action CAC test (Day 28: Visit 5) for a majority (2/3) of time points. However, the multiplicity adjustments criteria applied in this submission do not adjust for the majority of the time points within a visit. In order to adjust multiplicity correctly for the majority (2/3) of time points, the proposed type I error rates 0.0125 and 0.00625 have to be divided by 3 because there are three different ways to win. Therefore, type I error rates will be 0.0042 and 0.0021 for Visit 5 (Day 28) and Visit 3B (Day 1) /Visit 4 (Day 14) respectively. With these type I error rate adjustments, the efficacy conclusions remain the same.

5.2 Conclusions and Recommendations

In this NDA 22288 submission, the applicant is seeking approval for Bepotastine Besilate Ophthalmic Solution (Bepreve) as an eye drop treatment for ocular itching (b) (4) associated with allergic conjunctivitis. The applicant has submitted two phase 3 conjunctival allergen challenge (CAC) studies: ISTA-BEPO-CS01 and CL-S&E-0409071-P. In addition, the applicant has submitted a safety study (CL-SAF-0405071-P).

These studies have demonstrated that: (1) Both Bepreve 1.5% and Bepreve 1.0% achieved the pre-defined clinical and statistical significance in the primary endpoint of

ocular itching; (2) Bepreve 1.5% had numerical advantage (in terms of point estimate of treatment effect) over Bepreve 1.0% in the primary endpoint of ocular itching; (3) Both Bepreve 1.5% and Bepreve 1.0% failed in the primary endpoint of conjunctival redness; (4) There were no serious ocular adverse events reported in patients dosed with either Bepreve 1.0% or 1.5%.

It is recommended that Bepreve 1.5% be approved for the treatment of ocular itching associated with allergic conjunctivitis.

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22288	ORIG 1	ISTA PHARMACEUTICALS	BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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