CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

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/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
Biometrics Division:	IV
Statistical Reviewer:	Mushfiqur Rashid, Ph.D.
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Medical Division:	Division of Anti-infective and Ophthalmology Products
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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.

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