CLINICAL REVIEW

Application Type	NDA
Submission Number	22-288
Submission Code	Original
Letter Date	11/12/08
Stamp Date	11/12/08
PDUFA Goal Date	9/12/09
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	4/27/09
Established Name	bepotastine besilate ophthalmic solution 1.5%
(Proposed) Trade Name	Bepreve
Therapeutic Class	H1 antagonist
Applicant	Ista Pharmaceuticals, Inc.
Priority Designation	S
Formulation	topical ophthalmic
Dosing Regimen	1 drop twice daily
Indication	treatment of itching associated with allergic conjunctivitis
Intended Population	patients > 2 years old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 22-228 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of bepotastine besilate ophthalmic solution 1.5% for the treatment of itching associated with allergic conjunctivitis.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Postmarketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

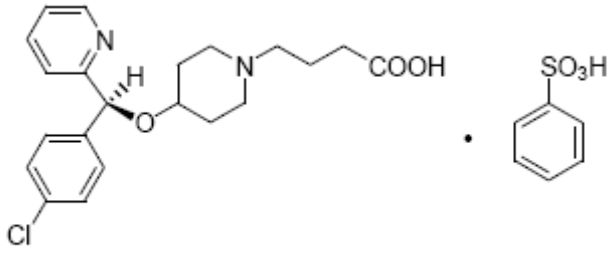
1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Chemical Structure of Bepotastine Besilate



Bepotastine besilate (+)-(S)-4-{4-[(4-Chlorophenyl)(2-pyridyl)methoxy] piperidino} butyric acid monobenzenesulfonate was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. as a treatment for allergic rhinitis. Bepotastine besilate is a relatively selective histamine H_1 receptor antagonist and has an inhibitory action on eosinophilic infiltration to inflammatory sites.

2.2 Table of Currently Available Treatments for Proposed Indication

Approved Drugs For Indication of Itching

Brand Name	Name of Drug	NDA
Alocril	nedocromil	21-009
Acular	ketorolac	19-700
Optivar	azelastine	21-127
Alamast	pemirolast	21-079
Pataday	olopatanol	21-545
Elestat	epinastine	21-565

2.3 Availability of Proposed Active Ingredient in the United States

Bepotastine is not an approved product in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Adverse events for this class of drugs (topical H1 antagonists) are well known. Refer to Section 2.2 for currently approved products. Common side effects seen with this class include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, and taster perversion/bitter taste. There was adequate AE evaluation for bepotastine in the submitted trials.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

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.

2.6 Other Relevant Background Information

Studies CL-S&E-0409071 (7/23/07-SPA response and 12/3/07 SPA final response) and CL-SAF-0405071 (7/23/07 SPA response) were performed under SPA. There was an EOP 2 Meeting on 8/15/07, SPA Meeting on 9/17/08, and pre-NDA Meeting on 8/4/08.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for this study. This inspection was conducted between 02/20/2009-03/10/2009. In general, Protocols CL-S&E-0409071, ISTA-BEPO-CS01, and CL-SAF-0405071-P appear to have been conducted adequately and the data in support of the NDA appear reliable. The final classification of the Sponsor inspection of ISTA Pharmaceuticals Inc. is NAI. A total of six of the Sponsor's CI files were reviewed in depth (Dr. Macejko, Dr. Bergmann, Dr. Torkildsen, Dr. Michaelson, Dr. Kurata, and Dr. Dao). The final classifications of the Clinical Investigator inspections of Dr. Torkildsen and Dr. Michaelson are Voluntary Action Indicated (VAI). While regulatory violations occurred at these sites, the safety and efficacy data from these sites are considered reliable. The preliminary classifications of the Clinical Investigator inspections of Dr. Bergmann and Dr. Macejko are NAI. Upon receipt of the EIRs for Dr. Bergmann and Dr. Macejko an addendum to the clinical inspection summary will be done.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trial was not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no investigators with proprietary interest or with any significant interest in the drug product in any of the 3 studies (ISTA-BEPO-CS01, CL-S&E-0409071, or CL-SAF-0405071).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The composition of vehicle and bepotastine besilate ophthalmic solution 1% and 1.5% are:

Bepotastine besilate ophthalmic solution 0.0% (vehicle)

Component	Concentration (%w/v)
Sodium chloride	(b) (4)
Monobasic sodium phosphate dihydreate	
BAK	0.005
Sodium hydroxide, 1N	qs to pH 6.8
Purified water	qs

Bepotastine besilate ophthalmic solution 1%

Component	Concentration (%w/v)
Bepotastine besilate	1.0
Sodium chloride	(b) (4)
Monobasic sodium phosphate dihydreate	
BAK	0.005
Sodium hydroxide, 1N	qs to pH 6.8
Purified water	qs

Bepotastine besilate ophthalmic solution 1.5%

Component	Concentration (%w/v)
Bepotastine besilate	1.5
Sodium chloride	(b) (4)
Monobasic sodium phosphate dihydreate	
BAK	0.005
Sodium hydroxide, 1N	qs to pH 6.8
Purified water	qs

The osmolarity of all investigational products was adjusted to produce essentially equivalent osmolarities for all three ophthalmic solutions. All drug formulations utilized were manufactured by (b) (4) All subjects within a treatment group received investigational product from a single lot number and all medication was stored at room temperature. The active and vehicle study drug bottles were identical in appearance and packaged in identical containers.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Bepotastine besilate formulation did not cause ocular inflammation or histopathologic changes in rabbits or dogs. There are some data that suggest that Bepreve may have an affinity for melanin binding based on the observation of presence in the iris in an ocular toxicity study and to pigmented tissues in a radiolabeled study. This association with melanin appears to be reversible, reaching levels below limit of detection when given enough time for clearance after dosing (e.g. 30 days after single dose of radiolabeled compound, bepotastine besilate was no longer detected in pigmented tissues).

The pivotal study for the proposed indication was a 26 week study in dogs using 4 and 8X per day dosing with the 1.5% TAU-284 solution. The 4X/day dosing paradigm was determined to be the NOAEL based on decreases in A and B wave amplitude in ERGs in the 8X/day dose group. When considering systemic exposures seen in this study, the identified NOAEL for ERG endpoints provides a 15X safety factor over that of anticipated systemic exposures seen with topical ocular use in humans. Several short term ocular toxicity studies demonstrated that

bepotastine besilate solutions up to 2% in concentration were well tolerated in various animal species.

The exec-CAC concluded that bepotastine besilate did not significantly induce neoplasms in 2 year dietary carcinogenicity studies in mice (at margin of exposure relative to human after ophthalmic use of 353) or in rats (at a margin of exposure relative to human of 200) .

Pregnancy category C is recommended for this product due to the observation of a rare skeletal malformation seen in the fertility/early embryo development study in rats at the 1000 mg/kg dose. The approximate margin of exposure for the 200 mg/kg/day NOAEL identified in this study was 3,300X that of anticipated human systemic exposure with topical ocular use. In rats given oral doses of 100 mg/kg/day, an increased incidence of stillborns were observed (~200X human systemic exposure for ocular use). At the 1000 mg/kg/day dose level in this same study, an increase in stillborns, decreased survival and decreased rate of development were observed in pups. There were no effects observed in rats treated with 10 mg/kg/day (representing a maximal systemic concentration approximately 18 times that anticipated for topical ocular use in humans).

From a radio-labeled study in pregnant rats, it is recognized that bepotastine besilate can rapidly distribute to the yolk sac/placenta and to the fetus. Bepotastine besilate was transferred to the yolk sac/placenta at levels nearly equivalent to maternal maximal plasma concentration, ~33-55% of bepotastine besilate was transferred to the developing fetus. At 24 hours following a single oral administration of 3 mg/kg, ~ 5.9% and 3.1% of maximal plasma TAU-284 concentrations were detected in the brain and liver of the fetus at 24 hours post-dose. Bepotastine besilate was also noted to be transferred to milk in lactating rats, with milk concentrations being 1.5 to 2 times maximal plasma concentrations by 1 hour post-dose and reaching levels below the limit of detection by 48 hours post-dose.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Bepotastine is a histamine H1-receptor antagonist.

4.4.2 Pharmacodynamics

See section 4.4.3

4.4.3 Pharmacokinetics

The proposed dosage and route of administration for bepotastine besilate ophthalmic solution, 1.5% is as follows: instill one drop into the affected eye(s) twice a day. The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1.0% and 1.5% ophthalmic solution was evaluated in a multiple-dose pharmacokinetic (PK) study in 12 healthy adults (Study SNJ-TO-02). Additional data from multiple Phase 1 studies from the

Japanese oral development program were also submitted in this application. The clinical pharmacology findings from these studies are summarized as follows:

- Following ophthalmic administration of bepotastine besilate bilaterally four times daily for seven days in healthy male subjects, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentrations were suggestive of a dose dependent increase in exposure; Cmax values for 1.0% and 1.5% bepotastine besilate were 5.138 ± 2.503 ng/mL and 7.335 ± 1.876 ng/mL, respectively. Plasma concentrations at 24 hours post-instillation were the below quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups. Following a single, oral 10 mg dose of bepotastine besilate in healthy subjects, the maximum plasma concentration of bepotastine was 101.3 ± 3.5 ng/mL. This is over 10 times that of the Cmax attained following one drop of 1.5% bepotastine besilate ophthalmic solution instilled to both eyes four times daily. Thus, the potential for adverse effects resulting from systemic exposure following administration of bepotastine besilate ophthalmic solution, 1.5% is low.
- The plasma protein binding of bepotastine in humans was approximately 55% and independent of bepotastine concentration following oral administration.
- *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes and bepotastine does not inhibit the activity of CYP3A4, CYP2C9, and CYP2C19. Thus, bepotastine besilate has a low potential for drug interactions via inhibition of CYP3A4, CYP2C9, and CYP2C19.
- Following single oral doses ranging from 2.5 to 40 mg in healthy male volunteers, approximately 76-88% of the bepotastine besilate dose was excreted in urine by 24 hours.

Based on the assessment of systemic exposure information for bepotastine besilate ophthalmic solution, 1.5%, the regulatory requirement for submission of in vivo bioavailability data has been adequately addressed.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study Identifier	Objective of the Study	Study Design	Test Products	# 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% 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%, 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-	Efficacy and safety of	Multi-center,	Bepotastine	130	CAC induced	3 single doses

0409071 Safety and Efficacy Phase 3	bepotastine ophthalmic solution 1% 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	double-masked, randomized, vehicle-controlled, CAC study	besilate ophthalmic solution 1%, 1.5%, or vehicle one drop at Visit 3A, Visit 4, and visit 5		allergic conjunctivitis	received over a period of 7 weeks
CL-SAF-0405071 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

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

The support of clinical safety and efficacy for bepotastine besilate ophthalmic solution consisted of 3 clinical studies conducted in the US. One safety study (CL-SAF-0405071-P) and two efficacy studies (ISTA-BEPO-CS01 and CL-S&E-0409071-P) were performed.

ISTA-BEPO-CS01: A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Two Concentrations (1% and 1.5%) Bepotastine Besilate Ophthalmic Solution in the CAC Model of Acute Allergic Conjunctivitis

The primary objective of this study was to establish the efficacy of bepotastine besilate ophthalmic solution 1% and 1.5% compared to vehicle in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis at 15 minutes, 8 hours, and 16 hours following investigational product instillation. This was a single-center, double-masked, randomized, vehicle-controlled, CAC study planned for patients with a demonstrated history of allergic conjunctivitis who were ≥ 10 years of age. This study consisted of a total of 5 visits, conducted over approximately 7 weeks.

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. Itching

and redness scales were based on a 5-unit (9 steps) grading scale with half unit (one step) increments allowed. 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). Subject-evaluated secondary efficacy variables included: lid swelling (0-3 unit scale, whole unit increments only), nasal symptoms (rhinorrhea, ear or palate pruritis, nasal pruritis and nasal congestion; each graded on a 0-4 unit scale, whole unit increments only), and tearing (graded absent or present). The subjective grades for individual nasal symptoms were added together to make a composite or total nasal score (0-16 units). All investigator evaluations were recorded for both eyes. As a safety measure the following were also monitored: corrected distance visual acuity test utilizing an ETDRS chart, slit lamp biomicroscopy examination, and adverse events (reported, elicited, and observed).

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 hyperemia in at least 2 out of the 3 vessel beds examined during two screening visits. At Visit 1, 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 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 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 continued to Visit 3A. 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 (bepotastine 1%, bepotastine 1.5%, or vehicle). There was no stratification of subjects on the basis of any demographic feature. The two week interval between CAC tests at Visits 3, 4, and 5 was pre-determined to be a sufficient washout period to minimize or eliminate potential bias in the test results due to drug carryover. Currently marketed over the counter anti-allergy eye drops (i.e. antihistamine/ vasoconstrictor combination products like Visine-A™ or Naphcon-A) were administered to subjects if needed at the end of each visit, after all evaluations were completed (relief medication).

Subjects in each treatment group received 3 doses of investigational product during the course of participation in this study. At Visits 3A, 4, and 5, a trained technician instilled 1 drop of the assigned investigational product 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 investigational product instillation during Visit 3A, 4, and 5, respectively. The test investigational product (bepotastine besilate ophthalmic solution 1% or 1.5% or wehicle) was dosed as one drop in each subject 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.

Study ISTA-BEPO-CS01: List of Investigator

Site No.	Principal Investigator	Location	No. of Subjects Enrolled
1	Gail Torkildsen, MD	Andover, MA	107

Study Schedule

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

[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.

Inclusion Criteria

- at least 10 years of age of either sex and any race
- provided written informed consent and signed HIPAA form. Subjects who are under the age of 18 will need to sign an assent form as well as having a parent or legal guardian sign an informed consent
- been willing and able to follow all instructions and attend all study visits
- for females capable of becoming pregnant agreed to have urine pregnancy testing performed at screening (must be negative); must not have been lactating; and must have agreed to use a medically acceptable form of birth control throughout the study duration and for at least one week prior to the first visit and for one month after the last dose of study investigational product. Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)
- had a positive history of ocular allergies and a positive skin test reaction to cat hair, cat dander, grasses, ragweed, and/or trees within the past 24 months
- had a calculated best-corrected visual acuity of 0.7 logMAR or better in each eye as measured using an ETDRS chart
- had a positive bilateral CAC reaction (≥ 2 itching and ≥ 2 redness in two of the three vessel beds) within 10 minutes of instillation of the last titration of allergen at Visit 1
- had a positive bilateral CAC reaction (≥ 2 itching and ≥ 2 redness in two of the three vessel beds) in at least two out of three time points at Visit 2
- been able and willing to avoid all disallowed medication for the appropriate washout period and during the study
- avoid wearing contact lenses for at least 3 days prior to and during the study trial period

Exclusion Criteria

- had known contraindications or sensitivities to the use of any of the study medications(s) or their components
- had any ocular condition that, in the opinion of the investigator, could have affected the subject's safety or trial parameters (particularly narrow angle glaucoma, clinically significant blepharitis, follicular conjunctivitis, iritis, pterygium or a diagnosis of dry eye)

- had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months
- had a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease
- had an active ocular infection (bacterial, viral or fungal), a positive history of an ocular herpetic infection, or preauricular lymphadenopathy at any visit
- manifested signs or symptoms of clinically active allergic conjunctivitis in either eye at the start of Visits 1, 2, 3, 4, or 5 (defined as the presence of any itching or >1 redness in any vessel bed)
- used any of the following disallowed medications during the period indicated prior to study enrollment: systemic or ocular H1 antihistamines, H1 antihistamine-vasoconstrictor drug combinations, decongestants, immunotherapeutic agents, monoamine oxidase inhibitors, artificial tears, lid scrubs, mast cell stabilizers, prostaglandins or prostaglandin derivatives, or ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs) within 7 days; or inhaled, ocular or topical corticosteroids within 2 weeks; or depo-corticosteroids within 45 days [Note: Currently marketed over the counter anti-allergy eye drops (i.e. antihistamine/ vasoconstrictor combination products like Visine-A™ or Naphcon-A®) may have been administered to subjects at the end of each visit, after all evaluations were completed, ie. rescue medication].
- had any significant illness [e.g. any autoimmune disease, or severe cardiovascular disease (including arrhythmias)] the investigator feels could expect to interfere with the subject's safety or study parameters and/or put the subject at any unnecessary risk. This includes but is not limited to: alcohol or drug abuse, poorly controlled hypertension or poorly controlled diabetes, a history of status asthmaticus, a known history of persistent moderate or severe asthma, or a known history of moderate to severe allergic asthmatic reactions to any of the study allergens
- had planned surgery (ocular or systemic) during the trial period or within 30 days after
- had used an investigational drug or device within 30 days of the study or be concurrently enrolled in another investigational drug or device study within 30 days of the study
- been a female who was pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration and for at least one week prior to the first visit and for one month after the last dose of investigational product, or had a positive urine pregnancy test at Visit 1
- had IOP <5 mmHg or >22 mmHg or any type of glaucoma.

C-S&E-0409071-P: A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Evaluation of the Onset and Duration of Action of Two Concentrations of Bepotastine Besilate Ophthalmic Solution (1% and 1.5%) in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis

The primary objective of this study was to establish the safety and efficacy of bepotastine besilate ophthalmic solution 1% and 1.5% compared to vehicle in alleviating the signs and symptoms of allergic conjunctivitis at 15 minutes, 8 hours, and 16 hours following

investigational product instillation using the CAC model of allergic conjunctivitis in subjects with a history of allergic conjunctivitis. This was a multi-center, double-masked, randomized, vehicle-controlled, CAC study planned for approximately 130 subjects with a demonstrated history of allergic conjunctivitis who were ≥10 years of age. This study was conducted at 5 sites and consisted of 5 visits, completed over approximately 7 weeks.

The primary efficacy measures, secondary efficacy measures, and study procedures were the same as for Study ISTA-BEPO-CS01. The only additional measure performed was patient ocular comfort scores were measured. A difference in subject-assessed ocular comfort scores between each concentration of bepotastine besilate ophthalmic solution as compared with vehicle of ≥1.0 unit was considered clinically significant. Any subject-assessed ocular comfort grade of 3 was reported as an adverse event and relatedness to investigational product was evaluated by the investigator and recorded. In addition, investigators independently documented any significant complaint of ocular discomfort as an AE.

Study CL-S&E-0409071: List of Investigators

Site No.	Principal Investigator	Location	No. of Subjects Enrolled
1	Thomas T. Macejko, MD	Fairfield, OH	26
2	Edward J. Meier, MD	Mason, OH	27
3	Mark T. Bergman, MD	Cincinnati, OH	35
4	Eugene B. McLaurin, MD	Memphis, TN	22
5	Fred K. Kurata, MD	Los Angeles, CA	20
TOTAL			130

Study Schedule

Procedure	Visit 1 Day -21 ± 3	Visit 2 Day -14 ± 3	Visit 3 Day 0		Visit 4 Day 14 ± 3	Visit 5 Day 28 ± 3
			Visit 3A	Visit 3B		
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]
Pre-CAC Allergic Signs and Symptoms Assessments	X	X	X		X	X
Screening CAC	X	X				
Medication History Update		X	X	X	X	X
Randomization of Study Subjects			X			
Investigational Product Instillation			X		X	X
Ocular Comfort Examination			X[3]		X[3]	X[3]
Investigational Product Efficacy CAC Test				X[4]	X[5]	X[6]
Intraocular Pressure (IOP)	X[7]					X[7]
Dilated Funduscopy	X[7]					X[7]
AE Queries			X	X	X	X
Exit from Study						X

1 The visual acuity and biomicroscopy examinations 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 second exit slit-lamp examination.

3 Evaluated upon investigational product instillation and 5 minutes (±0.5 minutes) after investigational product instillation.

4 Sixteen (16) hours post investigational product instillation.

5 Eight (8) hours post investigational product instillation.

6 Fifteen (15) minutes post investigational product instillation.

7 Performed following post CAC assessments. IOP measurements were done using Goldmann tonometry.

Inclusion/Exclusion criteria were identical to Study ISTA-BEPO-CS01. The process of allergen titration during the first 2 visits was identical to Study ISTA-BEPO-CS01. Then, the first dose

was administered at Visit 3A, 16 hours prior to a CAC, and the second dose was administered at Visit 4, 8 hours prior to a CAC. The last dose was administered at Visit 5, 15 minutes prior to a CAC.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is treatment of itching associated with allergic conjunctivitis.

6.1.1 Methods

The support for efficacy for bepotastine besilate ophthalmic solution comes from two studies: ISTA-BEPO-CS01 and CL-S&E-0409071.

6.1.2 Demographics

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

Parameter	Bepotastine 1% (N=36)	Bepotastine 1.5% (N=35)	Vehicle (N=36)	Total Randomized Subjects (N=107)
Gender				
Male	22	17	19	58
Female	14	18	17	49
Age				
Mean	39.3	44.3	40.9	41.7
Race				
African-American	0	1	1	2
Asian	0	0	2	2
Caucasian	35	31	33	99
Other	1	3	0	4
Ethnicity				
Hispanic/Latino	2	4	4	10
Non-Hispanic	34	31	32	97
Iris Color				
Blue	11	11	12	34
Brown	15	17	19	51
Green	3	1	2	6
Hazel	7	6	3	16

Reviewer's Comments:

Comparison of demographics in the ITT population for bepotastine besilate ophthalmic solution 1.5% to vehicle revealed a lack of statistically significant difference with regards to age (p = 0.305), gender (p = 0.814), ethnicity (p = 1.000), race (p = 0.14, or eye color (p = 0.716).

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

Parameter	Bepotastine 1% (N=44)	Bepotastine 1.5% (N=43)	Vehicle (N=43)	Total Randomized Subjects (N=130)
Gender				
Male	25	21	29	75
Female	19	22	14	55
Age				
Mean	34.8	33.3	33.3	33.8
Race				
African-American	2	6	4	12
American Indian	1	0	0	1
Asian	8	8	6	22
Caucasian	33	29	32	94
Other	0	0	1	1
Ethnicity				
Hispanic/Latino	0	0	2	2
Non-Hispanic	44	43	41	128
Iris Color				
Blue	22	38	26	86
Brown	42	34	42	118
Green	8	10	10	28
Hazel	16	4	6	26
Other	0	0	2	2

Reviewer's Comments:

Comparison of demographics in the ITT population for bepotastine besilate ophthalmic solution 1.5% to vehicle revealed a lack of statistically significant difference with regards to age (p=0.789), gender (p=0.164), ethnicity (p= 0.486), race (p=0.923), or eye color (p=0.132).

6.1.3 Patient Disposition

The safety population was defined as all subjects who received at least one dose of test agent. 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.

Study ISTA-BEPO-CSO1: Patient Disposition

	Bepotastine 1%	Bepotastine besilate 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

Study ISTA-BEPO-CSO1: Patient Withdrawals

Subject No.	Treatment Group	Reason For Withdrawal
1026-025	Vehicle	Subject decision/non-compliance-missed Visit 3B and Visit 4
1045-040	Bepotastine 1.5%	Subject decision/non-compliance-missed Visit 3B and Visit 4
1064-052	Bepotastine 1.5%	Unacceptable baseline itching and redness at Visit 5
1140-063	Bepotastine 1.5%	Subject decision/non-compliance-missed Visit 3B and Visit 4

There were a total of 6 patients which were excluded from the PP group. Two patients had protocol violations and were therefore excluded from the PP population. Subject 1024-020 in the bepotastine besilate ophthalmic solution 1% treatment group was noted by the sub-investigator to have a pterygium in their right eye at Visit 1. Although the pterygium was grounds for excluding this subject, the sub-investigator allowed the subject to continue their participation in the study because they noted the pterygium was minor. At Visit 3A prior to enrollment, the Principal Investigator observed the pterygium and allowed the subject to continue their participation in the study. After study completion, the subject's enrollment in the study despite the pterygium was considered a protocol violation. The second protocol violation was Subject 1150-002, in the bepotastine besilate ophthalmic solution 1% treatment group, who failed to complete Visit 3B within the required time frame and missed Visit 4. Four subjects discontinued early from the study and were also excluded from the PP population.

Study CL-S&E-0409071: Patient Disposition

	Bepotastine 1%	Bepotastine besilate 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

Study CL-S&E-0409071: Patient Withdrawals

Subject No.	Treatment Group	Reason For Withdrawal
1003-050	Vehicle	Subject decision/non-compliance
2001-066	Vehicle	Subject decision/non-compliance
3016-010	Vehicle	Subject decision/non-compliance
3028-027	Bepotastine 1.5%	Subject decision/non-compliance
3057-002	Bepotastine 1.5%	Exclusion criteria*
4007-125	Bepotastine 1.5%	Subject decision/non-compliance
4045-128	Vehicle	Subject decision/non-compliance
5003-110	Vehicle	Subject decision/non-compliance
5005-111	Bepotastine 1.5%	Subject decision/non-compliance
5012-099	Bepotastine 1.5%	Exclusion criteria*
5016-098	Vehicle	Subject decision/non-compliance
5031 -097	Bepotastine 1%	Subject decision/non-compliance
5034-101	Vehicle	Subject decision/non-compliance

*Subjects manifested signs or symptoms of clinically active allergic conjunctivitis (defined as any ocular itching or an ocular redness score >1, for any vessel bed) at the start of the study visit.

Thirteen subjects became classified as discontinued/ withdrawn over the course of the study. The remaining 117 subjects comprised the PP population.

Reviewer's Comment:
Reviewed CRFs and appears that the majority of the patient discontinuations in Study CL-S&E-0409071 were patient no-shows.

6.1.4 Analysis of Primary Endpoint(s)

For Studies ISTA-BEPO-CSO1 and CL-S&E-0409071-P:
The primary efficacy variables were:

- Ocular itching evaluated by the subject at 3, 5, and 7 minutes post challenge (0-4 unit [nine step] scale, allowing half unit [one step] increments)
- Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit [9 step] scale, allowing half unit [one step] increments)

The average score of each subject's eyes was the unit used for comparison between bepotastine and vehicle for all analyses. Clinical significance required at least a 1 unit change for the majority of time points at a study visit during the treatment period. Clinical success at a study visit required achievement of both statistical and clinical significance for a majority of time points. Clinical efficacy for ocular itching and conjunctival redness was considered to have been achieved by showing clinical success at Visit 5 as well as at Visit 3B and/or Visit 4. All hypothesis testing was conducted with a type I error α=0.05 using 2-sided tests, with corrections for multiple comparisons as appropriate. To adjust for comparisons, p-values $\leq$ 0.0125 (at Visit 5) and $\leq$ 0.00625 (at Visit 3B or Visit 4) at any observation time point signified a statistically significant difference. Primary efficacy analyses were done on the protocol-compliant (i.e., PP population). An analysis of efficacy for subjects also was conducted on the ITT population (defined as all randomized subjects regardless of whether or not the subject received Test Agent) using a LOCF method.

Ocular Itching Analysis

Study ISTA-BEPO-CSO1: Ocular Itching (ITT Population With LOCF)

Visit	Bepotastine 1%		Bepotastine 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	0.002	0.9	<0.001
5 min post-CAC	0.8	<0.001	1.0	<0.001
7 min post-CAC	0.8	<0.001	1.0	<0.001
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	**0.9**	**<0.001**	**1.3**	**<0.001**
5 min post-CAC	**1.0**	**<0.001**	**1.5**	**<0.001**
7 min post-CAC	**1.0**	**<0.001**	**1.4**	**<0.001**
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	**1.3**	**<0.001**	**1.4**	**<0.001**
5 min post-CAC	**1.4**	**<0.001**	**1.4**	**<0.001**
7 min post-CAC	**1.3**	**<0.001**	**1.3**	**<0.001**

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

Visit	Bepotastine 1%		Bepotastine 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	<0.001	1.0	<0.001
5 min post-CAC	0.9	<0.001	1.1	<0.001
7 min post-CAC	0.9	<0.001	1.1	<0.001
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	**1.0**	**<0.001**	**1.4**	**<0.001**
5 min post-CAC	**1.1**	**<0.001**	**1.7**	**<0.001**
7 min post-CAC	**1.0**	**<0.001**	**1.5**	**<0.001**
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	**1.4**	**<0.001**	**1.5**	**<0.001**
5 min post-CAC	**1.4**	**<0.001**	**1.5**	**<0.001**
7 min post-CAC	**1.3**	**<0.001**	**1.5**	**<0.001**

Study CL-S&E-0409071-P: Ocular Itching (ITT Population With LOCF)

Visit	Bepotastine 1%		Bepotastine 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	0.6	0.0055	0.6	0.0051
5 min post-CAC	0.7	0.0006	0.7	0.0021
7 min post-CAC	0.8	0.0001	0.8	0.0003
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	**1.2**	**<0.001**	**1.3**	**<0.001**
5 min post-CAC	**1.3**	**<0.001**	**1.3**	**<0.001**
7 min post-CAC	**1.2**	**<0.001**	**1.2**	**<0.001**
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	**1.4**	**<0.001**	**1.5**	**<0.001**
5 min post-CAC	**1.5**	**<0.001**	**1.6**	**<0.001**
7 min post-CAC	**1.3**	**<0.001**	**1.4**	**<0.001**

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

Visit	Bepotastine 1%		Bepotastine 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	0.0114	0.6	0.0074
5 min post-CAC	0.7	0.0007	0.8	0.0008
7 min post-CAC	0.8	0.0005	0.7	0.0016
Visit 4 (Day 14)-CAC at 8 hours post-dosing				
3 min post-CAC	**1.2**	**<0.001**	**1.3**	**<0.001**
5 min post-CAC	**1.3**	**<0.001**	**1.3**	**<0.001**
7 min post-CAC	**1.1**	**<0.001**	**1.2**	**<0.001**
Visit 5 (Day 28)-CAC at 15 minutes post-dosing				
3 min post-CAC	**1.4**	**<0.001**	**1.5**	**<0.001**
5 min post-CAC	**1.4**	**<0.001**	**1.6**	**<0.001**
7 min post-CAC	**1.2**	**<0.001**	**1.4**	**<0.001**

Ocular Itching Assessment Grades
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-A mild continuous itch (can be localized) without desire to rub
2.5-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

Study ISTA-BEPO-CSO1: Mean Ocular Itching Scores (ITT with LOCF Population)

Visit	Bepotastine 1% N=36	Bepotastine 1.5% N=35	Vehicle N=36
Visit 2			
3 Minutes Post-Challenge	2.52	2.57	2.35
5 Minutes Post-Challenge	2.73	2.81	2.76
7 Minutes Post-Challenge	2.75	2.82	2.81
Visit 3b			
3 Minutes Post-Challenge	1.44	1.16	2.10
5 Minutes Post-Challenge	1.58	1.34	2.37
7 Minutes Post-Challenge	1.44	1.31	2.27
Visit 4			
3 Minutes Post-Challenge	1.15	0.73	2.06
5 Minutes Post-Challenge	1.29	0.80	2.33
7 Minutes Post-Challenge	1.27	0.82	2.23
Visit 5			
3 Minutes Post-Challenge	0.56	0.49	1.87
5 Minutes Post-Challenge	0.72	0.71	2.07
7 Minutes Post-Challenge	0.70	0.67	1.95

Study CL-S&E-0409071-P: Mean Ocular Itching Scores (ITT with LOCF Population)

Visit	Bepotastine 1% N=44	Bepotastine 1.5% N=43	Vehicle N=43
Visit 1-Baseline	0	0	0
10 Minutes post-challenge	3.3	3.22	3.23
Visit 2			
Pre-CAC	0.0	0.0	0.01
3 Minutes Post-Challenge	2.57	2.51	2.63
5 Minutes Post-Challenge	2.99	2.99	2.9
7 Minutes Post-Challenge	3.05	3.07	3.05
Visit 3a			

Pre-CAC	0	0	0
Visit 3b			
3 Minutes Post-Challenge	1.27	1.23	1.83
5 Minutes Post-Challenge	1.42	1.44	2.15
7 Minutes Post-Challenge	1.19	1.23	2.02
Visit 4			
Pre-CAC	0	0	0
3 Minutes Post-Challenge	0.96	0.89	2.18
5 Minutes Post-Challenge	1.01	0.95	2.27
7 Minutes Post-Challenge	0.94	0.87	2.1
Visit 5			
Pre-CAC	0	0	0
3 Minutes Post-Challenge	0.42	0.4	1.85
5 Minutes Post-Challenge	0.6	0.46	2.07
7 Minutes Post-Challenge	0.64	0.51	1.93

Reviewer's Comment:

In order to demonstrate clinical significance in a CAC study, the difference between groups should ***be at least one unit on a scale from 0-4 at a majority of the time points evaluated****. This endpoint was duplicated in two trials only at the 8 hours post-dosing CAC with both concentrations of drug (bepotastine 1% and 1.5%). However, bepotastine besilate ophthalmic solution 1.5% produced greater clinical response than bepotastine besilate ophthalmic solution 1% in reducing ocular itching at both 8-hour and 16- hour duration-of-action time points versus vehicle. Therefore, the data supports bepotastine 1.5% at bid dosing for the treatment of itching associated with allergic conjunctivitis.*

Conjunctival Redness Analysis

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

Time of Post-CAC Observation	Bepotastine 1%		Bepotastine 1.5%	
	Difference in Mean Redness Grades (Vehicle – Active)	P value	Difference in Mean Redness Grades (Vehicle – Active)	P value
Visit 3B				
7 min post-CAC	0.4	0.012	0.2	0.208
15 min post-CAC	0.3	0.048	0.0	0.755
20 min post-CAC	0.2	0.102	-0.1	0.711
Visit 4				
7 min post-CAC	0.4	0.014	0.4	0.029
15 min post-CAC	0.3	0.071	0.4	0.062
20 min post-CAC	0.3	0.083	0.3	0.137
Visit 5				
7 min post-CAC	0.8	<0.001	0.6	0.004
15 min post-CAC	0.6	<0.001	0.4	0.039
20 min post-CAC	0.5	<0.001	0.3	0.151

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

Time of Post-CAC Observation	Bepotastine 1%		Bepotastine 1.5%	
	Difference in Mean Redness Grades (Vehicle – Active)	P value	Difference in Mean Redness Grades (Vehicle – Active)	P value
Visit 3B				
7 min post-CAC	0.4	0.0053	0.1	0.5472
15 min post-CAC	0.4	0.0168	0.1	0.3882
20 min post-CAC	0.4	0.0407	0.1	0.5000
Visit 4				
7 min post-CAC	0.5	0.0006	0.2	0.1067
15 min post-CAC	0.3	0.0356	0.1	0.3598
20 min post-CAC	0.3	0.1026	0.1	0.5909
Visit 5				
7 min post-CAC	0.6	0.001	0.4	0.0031
15 min post-CAC	0.5	0.0020	0.4	0.0114
20 min post-CAC	0.2	0.1485	0.2	0.2251

Conjunctival Redness Assessment Grades
0-None
1-Mild-Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal
2-Moderate-More apparent dilation of blood vessels; vessels color is more intense (redder); involves the majority of the vessels bed
3-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-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

Study ISTA-BEPO-CSO1: Mean Conjunctival Hyperemia Scores (ITT with LOCF Population)

Visit	Bepotastine 1% N=44	Bepotastine 1.5% N=43	Vehicle N=43
Visit 2			
7 Minutes Post-Challenge	2.01	2.03	2.10
15 Minute Post-Challenge	2.21	2.29	2.25
20 Minutes Post-Challenge	2.19	2.28	2.25
Visit 3b			
7 Minutes Post-Challenge	1.42	1.63	1.79
15 Minutes Post-Challenge	1.53	1.81	1.81
20 Minutes Post-Challenge	1.47	1.78	1.70
Visit 4			
7 Minutes Post-Challenge	1.26	1.30	1.67
15 Minutes Post-Challenge	1.56	1.47	1.84
20 Minutes Post-Challenge	1.55	1.52	1.84
Visit 5			
7 Minutes Post-Challenge	1.11	1.37	1.91
15 Minute Post-Challenge	1.45	1.65	2.05
20 Minutes Post-Challenge	1.44	1.62	1.95

Study CL-S&E-0409071-P: Mean Conjunctival Hyperemia Scores (ITT with LOCF Population)

Visit	Bepotastine 1% N=44	Bepotastine 1.5% N=43	Vehicle N=43
Visit 1-Baseline	0.52	0.63	0.58
10 minutes post-challenge	2.6	2.68	2.6
Visit 2			
Pre-CAC	0.65	0.67	0.63
7 Minutes Post-Challenge	2.41	2.46	2.4
15 Minute Post-Challenge	2.49	2.59	2.53
20 Minutes Post-Challenge	2.52	2.6	2.5

Visit 3a			
Pre-CAC	0.61	0.63	0.6
Visit 3b			
7 Minutes Post-Challenge	1.46	1.8	1.89
15 Minutes Post-Challenge	1.6	1.85	1.99
20 Minutes Post-Challenge	1.62	1.87	1.98
Visit 4			
Pre-CAC	0.6	0.69	0.63
7 Minutes Post-Challenge	1.35	1.59	1.8
15 Minutes Post-Challenge	1.57	1.76	1.88
20 Minutes Post-Challenge	1.59	1.77	1.84
Visit 5			
Pre-CAC	0.49	0.6	0.56
7 Minutes Post-Challenge	1.28	1.42	1.85
15 Minute Post-Challenge	1.51	1.59	1.97
20 Minutes Post-Challenge	1.64	1.67	1.87

Reviewer's Comment:
Neither concentration of bepotastine was found to provide a clinically significant reduction in redness compared to vehicle at any study visit during the treatment period.

6.1.5 Analysis of Secondary Endpoints(s)

Studies ISTA-BEPO-CSO1 and CL-S&E-0409071-P:
The secondary efficacy variables for both studies included:

Ocular symptom scores:

- Ciliary and episcleral redness evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit (nine step) scale, with half unit (one step) increments allowed)
- Chemosis evaluated by the investigator at 7, 15, and 20 minutes post challenge (0-4 unit (one step) scale, with half unit (one step) increments allowed)
- Lid swelling evaluated by the subject at 7, 15, and 20 minutes post challenge (0-3 unit scale, whole unit increments only)
- Tearing evaluated by the subject at 7, 15, and 20 minutes post challenge (graded absent or present)
- Ocular mucous discharge evaluated by the investigator at 7, 15, and 20 minutes post challenge (graded absent or present)

Non-ocular symptom scores:

- Rhinorrhea, ear or palate pruritus, nasal pruritus, and nasal congestion evaluated by the subject at 7, 15, and 20 minutes post challenge (0-4 unit scale, whole unit increments only)
- A composite score of rhinorrhea, ear or palate pruritus, nasal pruritus, and nasal congestion evaluated by the subject at 7, 15, and 20 minutes (0-16 unit scale)

Clinical significance required at least a 1 unit change for the majority of time points at a study visit during the treatment period. Clinical success at a study visit required achievement of both statistical and clinical significance for a majority of time points. Clinical efficacy for secondary efficacy variables was considered to have been achieved by showing clinical success at Visit 5 as well as at Visit 3B and/or Visit 4.

Reviewer's Comment:
None of the secondary endpoints achieved clinical success (i.e., both statistical and clinical significance) as defined in the trial protocol in either study.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

See section 6.1.2.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In order to demonstrate clinical significance in a CAC study, the difference between groups should be at least one unit on a scale from 0-4 at all the time points evaluated. This endpoint was duplicated in two trials only at the 8 hours post-dosing CAC with both concentrations of drug (bepotastine 1% and 1.5%). However, bepotastine 1.5% produced greater clinical response than bepotastine 1% in reducing ocular itching at both 8-hour and 16- hour duration-of-action time points. Therefore, the data supports bepotastine 1.5% at bid dosing for the treatment of itching associated with allergic conjunctivitis.

Study ISTA-BEPO-CS01: Percentage of Eyes With No Itching at Various Post-CAC Times (ITT with LOCF Population)

Time of CAC After Treatment	**Bepotastine 1%**			**Bepotastine 1.5%**		
	3 mins.	5 mins.	7 mins.	3 mins.	5 mins.	7 mins.
15 minutes	38.9	41.7	47.2	58.7	45.7	48.6
8 hours	9.7	9.7	11.1	29.9	28.7	27.3
16 hours	8.3	9.7	12.5	22.9	20.0	17.2

Reviewer's Comment:
The above post hoc subgroup analysis further supports that bepotastine 1.5% has a greater clinical response compared to the 1%.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated for the clinical efficacy studies. The duration of treatment for the subjects in these trials was three single doses at three separate visits.

6.1.10 Additional Efficacy Issues/Analyses

Study CL-S&E-0409071-P and Ocular Comfort Evaluation:

Ocular comfort was evaluated each time subjects received investigational product (ie, at visits16 hours, 8 hours, and 15 minutes before the CAC). Drop comfort for each eye was subject-assessed using a 4-point scale (0-3 unit scale, 7-step grading scale) with half-unit (1-step) increments allowed, at 2 time points: upon investigational product instillation and again 5 ± 0.5 minutes later. Mean comfort grades and the difference in mean grades (bepotastine [1% and 1.5%] compared with vehicle) were presented for each eye and for all eyes for all treatment groups at each study visit. Subject-assessed comfort grades of 3 were to be recorded as an AE and relatedness to investigational product was evaluated. In addition, any significant complaint of discomfort following drop instillation was also to be recorded as an AE. Since ocular comfort, distinct from ocular discomfort, may or may not relate to safety of the investigational product, a difference in mean grades ≥1.0 unit (comparing bepotastine [1% or 1.5%] with vehicle) was considered clinically significant but not clinically meaningful in the absence of a substantial increase in ocular AEs considered related to bepotastine besilate investigational product.

Ocular Comfort Grades

0-Comfortable; discomfort absent
1-Generally comfortable; mild discomfort
2-Some discomfort, but tolerable; moderate discomfort
3-Severely uncomfortable or intolerable

Study CL-S&E-0409071: Ocular Comfort Evaluation Immediately After Instillation of Study Medication

Visit	Vehicle	Bepotastine 1%	Bepotastine 1.5%
Visit 3A			
N	86	88	86
Mean value (sd)	0.14 (0.37)	0.16 (0.37)	0.14 (0.35)
Difference		0.03	0
P value		0.654	1
Visit 4			
N	76	86	78
Mean value (sd)	0.05 (0.23)	0.12 (0.43)	0.05 (0.21)
Difference		0.06	0
P value		0.250	0.969
Visit 5			
N	72	86	76
Mean value (sd)	0.03 (0.17)	0.06 (0.24)	0.08 (0.42)
Difference		0.03	0.05
P value		0.359	0.333

Study CL-S&E-0409071: Ocular Comfort Evaluation 5 Minutes After Instillation of Study Medication

Visit	Vehicle	Bepotastine 1%	Bepotastine 1.5%
Visit 3A			
N	86	88	86
Mean value (sd)	0.13 (0.35)	0.19 (0.41)	0.23 (0.45)
Difference		0.06	0.1
P value		0.302	0.105
Visit 4			
N	76	86	78
Mean value (sd)	0.13 (0.41)	0.05(0.21)	0.08 (0.23)
Difference		-0.09	-0.05
P value		0.094	0.308
Visit 5			
N	72	86	76
Mean value (sd)	0	0.09 (0.31)	0.09 (0.35)
Difference		0.09	0.09
P value		0.018	0.029

Reviewer's Comment:
There were no significant differences in ocular comfort scores between bepotastine 1% or 1.5% and vehicle at any of the time points. Ocular comfort was also assessed in Study CL-SAF-0405071, see section 7.4.5 for details.

7 Review of Safety

Safety Summary

7.1 Methods

Clinical Studies Used to Evaluate Safety

Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P:
As a safety measure, the following safety variables were monitored:

- Distance visual acuity utilizing an ETDRS chart at the beginning of each visit. For subjects under the age of 18, this also was performed approximately 15 minutes post investigational product instillation at Visit 3A and Visit 4, and approximately 40 minutes post investigational instillation at Visit 5.
- Slit lamp biomicroscopy conducted by the investigator at the beginning of each visit. For subjects under the age of 18, this also was performed approximately 15 minutes post investigational product instillation at Visit 3A and Visit 4, and approximately 40 minutes

post investigational product instillation at Visit 5. For all subjects, Visit 5 also included a post-CAC exit slit-lamp exam.

- IOP following the post-CAC assessments at Visit 1 and Visit 5.
- Dilated fundoscopy conducted by the investigator following the post-CAC assessments at Visit 1 and Visit 5.
- Adverse events (reported, elicited, and observed).
- Ocular comfort examination conducted upon investigational product instillation and 5 ± 0.5 minutes after investigational product instillation at Visit 3A, Visit 4, and Visit 5 (only for study CL-S&E-0409071-P).

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: Treatment Emergent Ocular Adverse Events (Safety Population)

	Vehicle N=36	**Bepotastine 1% N=36**	**Bepotastine 1.5% N=35**
Total Ocular AEs	**3**	**0**	**2**
Eye irritation	2 (both rated mild)	0	1 (rated mild)
Conjunctival cyst	0	0	1 (rated mild)
FBS	1 (rated moderate)	0	0

Study ISTA-BEPO-CS01: Treatment Emergent Non-Ocular Adverse Events (Safety Population)

	Vehicle N=36	**Bepotastine 1% N=36**	**Bepotastine 1.5% N=35**
No. of Subjects With Non-ocular AEs	**2**	**9**	**7**
Dysgeusia	0	6	3
Respiratory, thoracic, and mediastinal disorders	1	1	3
GI disorders	1	0	2
Nasopharyngitis	0	2	0
Lymphadenopathy	0	1	0
Anxiety	0	0	1
Cyst removal	0	1	0

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 1.5% group, and none were reported for the bepotastine 1% group. Of the 5 treatment-emergent ocular adverse events reported, none were rated as severe in intensity.

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 1% group and 7/35 (20%) subjects were in the bepotastine 1.5% group. Of the 18 subjects who experienced a non-ocular treatment-emergent adverse event, 12 subjects were classified as mild and 6 subjects were classified as moderate. There were no subjects who experienced an AE that was considered severe by the investigator.

Of the 18 subjects who experienced a non-ocular treatment-emergent adverse event, 9 subjects reported one or more experiences of dysgeusia (distortion or decrease of the sense of taste). While there were no reports of dysgeusia in the vehicle group, 6/36 (16.7%) of subjects in the bepotastine 1% group and 3/35 (8.6%) subjects in the bepotastine 1.5% group reported dysgeusia. All of the events were classified as mild with one exception, a report of dysgeusia in the bepotastine 1.5% group that was classified as moderate.

In addition, subjects receiving bepotastine experienced no clinically significant changes from baseline in visual acuity, intraocular pressure, dilated fundoscopy or slit-lamp biomicroscopy safety measurements. No other safety-related issues were reported during this study.

Reviewer's Comment:
Non-ocular treatment-emergent adverse events occurred in greater frequency in the bepotastine treatment groups compared to vehicle because of the greater incidence of dysgeusia in these groups. No trends were apparent with respect to all other non-ocular adverse events by system/organ/class.

Study CL-S&E-0409071-P: Treatment Emergent Ocular Adverse Events (Safety Population)

	Bepotastine 1% N=44	**Bepotastine 1.5% N=43**	**Vehicle N=43**
Total Ocular AEs	**4**	**3**	**2**
Eye irritation	2	2	1
Dry eye	1	0	0
Eye pain	0	0	1
Eye pruritis	1	0	0
Keratitis	0	1	0

Study CL-S&E-0409071-P: Treatment Emergent Non-Ocular Adverse Events (Safety Population)

	Bepotastine 1% N=44	**Bepotastine 1.5% N=43**	**Vehicle N=43**
Total Non-ocular AEs	**15**	**9**	**7**
Nasopharyngitis	5	3	3
Taste perversion	2	2	0
Nasal congestion	1	2	0
Lower respiratory tract infection	0	0	1
HA	1	0	0
Migraine	1	0	0
Cough	1	0	0
Pharygeolaryngeal pain	1	0	0
Postnasal drip	0	1	0
Nausea	1	0	0
Rash	0	0	1
Foot fracture	0	0	1
Joint sprain	0	1	0
Road traffic accident	0	0	1
Rotator cuff syndrome	1	0	0

There were no SAEs or deaths reported in the safety population. There were a total of 40 treatment emergent AEs (9 ocular events and 31 non-ocular events) reported during the course of the study for 32 subjects across all 5 study sites. More AEs occurred in the bepotastine 1% group (19 AEs in 15 subjects) than in the bepotastine 1.5% group (12 AEs in 10 subjects) or vehicle treatment group (9 AEs in 7 subjects). 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. There was no apparent dose relationship with respect to frequency of AEs. In addition, there were also no apparent trends with respect to type of AE across treatment groups.

Reviewer's Comment:
More AEs occurred in the bepotastine 1% treatment group (19 AEs) than in the bepotastine 1.5% treatment group (12 AEs) or placebo treatment group (9 AEs). However, there were no apparent trends with respect to the type of AE across treatment groups.

The main support of safety for bepotastine 1.5% came from study CL-SAF-0405071 "A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Bepotastine Besilate Ophthalmic Solution 1.5% Used Twice Daily in Healthy, Normal Volunteers". This trial was conducted at 6 sites in the US. 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 normal ocular health. Randomization was at a ratio of 2:1 (active: vehicle) and subjects were not stratified by age group. This study consisted of 4 visits conducted over approximately 43 days for all study participants except for a subset of subjects who underwent ocular endothelial cell counts (ECC). At 1 of the 6 study sites,

a sub-population of subjects ≥10 years of age who agreed to undergo specular microscopy at Visit 1 (baseline) and again at Visit 5 (Day 84 + 7) was identified. To be enrolled, a baseline ECC of ≥2200 cells/mm2 was necessary. All subjects who did not undergo endothelial cell counts at Visit 1 exited the clinical trial at Visit 4. The planned pediatric population was approximately 12 subjects in each of 3 age groups (3 years old, 4 years old, and 5 years old) and 20-25 subjects in each of 3 age ranges (6-9 years old, 10-12 years old, and 13-17 years old).

Subjects were given a diary and instructed to record the time and date of every dose daily and completed diary pages were collected at each subsequent visit (ie, Visit 2 through Visit 4). For subjects under age 13, a parent or legal guardian who observed the drug instillation completed the dosing diary. Any subject who had taken greater than 75% of investigational product as determined from diary entries was considered as study drug compliant. Subjects or their representatives were instructed on proper drop instillation at Visit 1. Thereafter, all doses of investigational product were administered by the subject (or parent/ legal guardian) except for 1 dose at Visit 2 and Visit 3. At Visit 2 and Visit 3, a trained technician administered a single drop to both eyes and drop comfort was subject-evaluated within 1 minute and again 5 ± 0.5 minutes later using a predefined grading scale.

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. At Visits 1-3, the procedure was performed pre-instillation and approximately 15 minutes post instillation of investigational product. Biomicroscopy was performed only once at Visit 4 and Visit 5. Slit-lamp biomicroscopy included an evaluation of the lid and lid margin (using a 0-4 scale for erythema, swelling); conjunctiva (including the palpebral and/or bulbar using a 0-4 scale for hyperemia, chemosis); cornea (using a 0-3 scale for edema and erosion; and using a 0-4 scale for corneal epithelial condition); lens (using a 0-4 scale); and anterior chamber (using a 0-4 scale for cells and flare). For all biomicroscopy parameters, half-grade answers (e.g. 0.5, 1.5, 2.5, and 3.5) were allowed.
- ECC conducted on subjects 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.
- IOP conducted on subjects 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 exam

Ocular comfort assessments were performed at Visit 2 and Visit 3 using a 0-3 unit grading scale (half-unit increments allowed). Any subject-assessed ocular comfort grade of 3 was to be reported as an AE and relatedness to investigational product was to be evaluated by the investigator and recorded. In addition, investigators independently documented any significant complaint of ocular discomfort as an AE. A difference of >1.0 unit in subject-assessed ocular comfort scores between the bepotastine besilate ophthalmic solution 1.5% group and the vehicle group was considered clinically significant but was not clinically meaningful in the absence of a substantial increase in ocular AEs considered related to bepotastine besilate investigational product.

Inclusion Criteria

- >=3 years of age at Visit 1 of either sex and any race
- provided written informed consent and signed HIPAA form. Subjects who were at least 7 years of age and less than 18 years of age also needed to sign an assent form. In addition, all subjects below the age of 18 years were required to have a parent or legal guardian sign the informed consent
- was willing and able to follow all instructions and attend all study visits; for females capable of becoming pregnant agreed to have urine pregnancy testing performed at screening (must be negative), Visit 4 and Visit 5 (for those subjects undergoing endothelial cell count procedures); must not have been lactating; and must have agreed to use a medically acceptable form of birth control (Acceptable forms of birth control were spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence was considered an acceptable form of birth control) throughout the study duration and for at least 1 week prior to the first visit and for 1 month after the last dose of investigational product. Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)
- had ocular health within normal limits, including a calculated best-corrected (if necessary) visual acuity of 0.3 logMAR or better, in each eye as measured using an ETDRS chart. For subjects under 10 years old who were developmentally unable to use the ETDRS chart, a best attempt at visual acuity preferably was made using the LEA symbols; other methods of estimating visual acuity were employed if necessary. For these subjects, 20-foot Snellen equivalent units of 20/63 or better in both eyes was required.
- For those subjects undergoing ocular ECC subjects had a baseline (Visit 1) ocular endothelial cell density ≥2200 cells/mm^2.

Exclusion Criteria

- had known contraindications or sensitivities to the use of any of the investigational product(s) or their components
- had ocular surgical intervention within 3 months prior to Visit 1 or during the study and/or a history of refractive surgery within the past 6 months

- had an active ocular disorder with the exception of refractive disorders
- had a known history of retinal detachment, diabetic retinopathy, or progressive retinal disease
- had the presence of an active ocular infection (bacterial, viral, or fungal), positive history of an ocular herpetic infection, or preauricular lymphadenopathy at any visit
- had prior (within 5 days of beginning study treatment), current or anticipated use of ophthalmic agents other than investigational product during study participation;
- had prior (within 5 days of beginning study treatment), current or anticipated use of contact lenses during study participation
- had prior (within 14 days of beginning study treatment), current or anticipated use of certain systemic medications, such as corticosteroids or antihistamines, during study participation, which could have confounded study data or interfered with the subject's study participation
- had prior (within 7 days of beginning study treatment) or currently active illness (eg, upper respiratory tract infection)
- had prior (within 30 days of beginning study treatment) or anticipated concurrent use of an investigational drug or device
- had a condition or a situation which, in the investigator's opinion, put the subject at increased risk, confounded study data, or interfered significantly with the subject's study participation
- had planned surgery (ocular or systemic) during the trial period or within 30 days after the study period ended
- had body weight <5th percentile for their age (only for subjects < 12 years)
- was currently breast feeding or planning to breast feed during the study period
- was a female who was currently pregnant, was planning a pregnancy, or had a positive urine pregnancy test at Visit 1
- had IOP < 5 mmHg or >22 mmHg or any type of glaucoma.

List of Investigators for Study CL-SAF-0405071

Site No.	Principal Investigator	Location	No. of Subjects Enrolled
1	Stacy L. Ackerman, MD	Philadelphia, PA	110
2	Thomas K. Mundorf, MD	Charlotte, NC	109
3	Tushina A. Reddy, MD	Las Vegas, NV	105
4	Eugene E. Protzko, MD	Havre de Grace, MD	126
5	Jung T. Dao, MD	Meza, AZ	110
6	Clifford Michaelson, MD	Andover, MA	301
TOTAL			**861**

Study Schedule

Assessments Performed	Visit 1 (Day 1)	Visit 2 (Day 8±2)	Visit 3 (Day 22±3)	Visit 4 (Day 43+3)	Visit 5[1] (Day 84+7)
Informed Consent/HIPAA/Assent[2]	X				
Medical & Ophthalmic History	X				
Urine Pregnancy Test[3]	X			X	X[4]
Body Weight Determination[5]	X				
Physical Exam[6]	X			X	X[4]
Visual Acuity[7, 8]	X	X	X	X	X[4]
Biomicroscopy[9]	X	X	X	X	X[4]
Specular Microscopy (Ocular Endothelial Cell Counts)[4, 10]	X				X[4]
Intraocular Pressure[10]	X			X	X[4]
Ophthalmoscopy (Dilated)[11]	X			X	X[4]
Instill Investigational Product at Office	X	X	X		
Ocular Comfort Examination[12]		X	X		
Dispense Study Treatment[13]	X		X		
Dispense Dosing Diary	X				
Collection of Returned Study Treatment			X	X	
Collection of Completed Dosing Diary Pages[14]		X	X	X	
Assessment of Adverse Events	X	X	X	X	X[4]
Assessment of Concomitant Medications	X	X	X	X	X[4]
Exit				X[1]	X[4]

1 Only for subjects who underwent ocular endothelial cell counts.
2 Assent was taken from subjects at least 7 years of age and less than 18 years of age.
3 Was conducted on females of child-bearing potential. Child-bearing potential was defined as any female who had her first menses, had not had a hysterectomy, bilateral tubal ligation or bilateral oophorectomy, and had not been post-menopausal for at least 12 months.
4 Limited to subjects who underwent ocular endothelial cell counts at 1 site.
5 The investigator referred to **Appendix 3 of the study protocol**, located in Appendix 16.1.1, for subjects <12 years of age only.
6 Physical examination included vital signs, body weight, general health, head, eyes, ears, nose, throat (HEENT), heart, lungs, abdomen, neurologic evaluation, condition of extremities, back, and skin, and any other comments.
7 If correction was necessary, best-corrected visual acuity was determined.
8 For subjects under 10 years of age who were developmentally unable to use ETDRS chart, a best attempt at obtaining visual acuity was made preferably by using a LEA symbols visual acuity chart (measured as 20-foot Snellen equivalent units).
9 Evaluated prior to and approximately 15 minutes post investigational product instillation at Visits 1-3, and once at Visit 4 and Visit 5.
10 Age ≥10 years old (if possible).
11 Dilated, to observe the posterior pole.
12 Evaluated upon investigational product instillation and 5 ± 0.5 minutes after investigational product instillation.
13 An extra bottle of investigational product may have been dispensed to subjects during the study treatment period.
14 Individual completed diary pages were collected from subject dosing diaries at Visit 2 and Visit 3.

Study CL-SAF-0405071: Patient Demographics (Safety Population)

Parameter	Bepotastine besilate 1.5% (N=575)	Vehicle (N=286)
Gender		
Male	208	108
Female	367	178
Age		
Mean	34.5	34.2
(Range 3-84 years old)		
Race		
African-American	37	18
American Indian	3	0
Asian	7	4
Caucasian	487	240
Native Hawaiian	5	3
Other	36	21
Ethnicity		
Hispanic	44	30
Non-Hispanic	531	256
Iris Color		
Blue	344	152
Brown	517	278
Green	96	58
Hazel	187	84
Other	6	0

*Safety population defined as subjects who received at least 1 dose of investigational product.

Reviewer's Comment:

The demographics of subjects in the safety population were well-balanced between the 2 treatment groups. There were no significant differences between the bepotastine 1.5% and the placebo groups with regards to age, gender, ethnicity, eye color, or race.

7.1.2 Adequacy of Data

The main study to support the safety of bepotastine besilate 1.5% was Study CL-SAF-0405071. This was a was a multi-center, randomized, double-masked, vehicle-controlled, parallel-group safety study in healthy subjects using bepotastine besilate 1.5% bid for 6 weeks. The safety population comprised 861 subjects (safety population defined as receiving at least one dose of drug), of which 801 completed the study.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Three studies are used to support the safety and efficacy of bepotastine. The main support for the safety of bepotastine besilate 1.5% comes from Study CL-SAF-0405071.

Study	Test Products	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
ISTA-BEPO-CS01	Bepotastine 1% OR Bepotastine 1.5% OR Vehicle One drop at Visit 3A, Visit 4, and visit 5	107	CAC induced allergic conjunctivitis	Study duration 7 weeks but only received 3 drops during study
CL-S&E-0409071	Bepotastine 1% OR Bepotastine 1.5% OR Vehicle One drop at Visit 3A, Visit 4, and visit 5	130	CAC induced allergic conjunctivitis	Study duration 7 weeks but only received 3 drops during study
CL-SAF-0405071	Bepotastine 1.5% OR Vehicle BID daily for 6 weeks	861	Healthy	6 weeks of treatment for all subjects and 6 additional weeks of study duration for ECC group

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Treatment Duration (Safety Population) for Study CL-SAF-0405071

Treatment Group	Mean Treatment Duration (Days, +/- sd)
Bepotastine besilate 1.5% (N=572)	40.4 (6.7)
Age 3-9 (N=47)	42.0 (0.4)
Age 10-17 (N=40)	41.2 (5.6)
Age >=18 (N=485)	40.1 (7.1)
Vehicle (N=286)	40.6 (6.5)
Age 3-9 (N=25)	42.0 (0.4)
Age 10-17 (N=15)	42.1 (0.3)
Age >= 18 (N=246)	40.3 (6.9)

*Treatment duration was defined as the number of days between the first and last instillation of masked investigational product.

Number of Compliant Subjects Per Age Group

	Bepotastine			Vehicle		
Age	3-9	10-17	>18	3-9	10-17	>18
Number Randomized	47	40	485	25	15	246
Number That Completed Study	47 (100%)	39 (97.5%)	452 (92.6%)	25 (100%)	15 (100%)	232 (94.3%)

*A completed subject is defined as one who has completed all study visits and received at least 75% of scheduled doses.

Of the 861 subjects enrolled, 127 were pediatric subjects. Of the pediatric subjects, 72 were 3-9 years of age and 55 were 10-17 years of age.

7.2.2 Explorations for Dose Response

In Study CL-SAF-0405071 only one dose (bepotastine besilate 1.5% BID) was used.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

See section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of bepotastine given by the topical route of administration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drugs (topical H1 antagonists) are well known. Refer to Section 2.2 for currently approved products. Common side effects include for this class include: headache, asthenia, blurry vision, eye burning/stinging upon instillation, eye pain, cold/flu symptoms, cough, fatigue, dry eye, foreign body sensation, lid edema, keratitis, hyperemia, nausea, phayrngitis, pruritis, rhinitis, sinusitis, sore throat, taste perversion/bitter taste. There was adequate AE evaluation for this product.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during study CL-SAF-0405071.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported during study CL-SAF-0405071.

7.3.3 Dropouts and/or Discontinuations

Study CL-SAF-0405071: Subject Disposition

	Bepotastine besilate 1.5%	**Vehicle**
Number of Randomized subjects	575	286
Number of Subjects in Safety Population *	575	286
Number of Pediatric Subjects in Safety Population	87	40

Patients that Underwent ECC-Baseline	133	69
Patients that Underwent ECC- Day 84	125	68
Number of Subjects Completed Study**	532 (92.5%)	269 (94.1%)
Reason For Withdrawal		
AE	6	6
Protocol Violation	3	0
Subject Decision/Non-Compliance	32	10
Other	2	1

*Safety population defined as subjects who received at least 1 dose of investigational product.
**A completed subject is defined as one who has completed all study visits and received at least 75% of scheduled doses.

Twelve subjects withdrew from the study early with an AE being listed as the reason for study discontinuation (six in bepotastine group and six in the vehicle group).

Study CL-SAF-0405071: Patient Withdrawals Due to Adverse Events

Subject Number	Treatment Group	AE Leading to Discontinuation
3010-541	Bepotastine	Intermittent headaches associated with study drops
3018-549	Vehicle	Sinusitis and ear infection
3076-604	Vehicle	Neck and shoulder pain subsequent to car accident
3079-607	Bepotastine	Intermittent HTN worsening over 20 days of dosing and non-ocular allergies
3098-625	Bepotastine	Pneumonia
3102-629	Bepotastine	Intermittent headache and earache
5084-842	Vehicle	Sinusitis
6059-053	Vehicle	Eyelid pain and eyelid margin crusting
6110-093	Bepotastine	Bronchitis and ocular stinging and photophobia
6241-209	Vehicle	Eye irritation, redness, blurred vision, and burning upon instillation
6300-259	Vehicle	Three styes
6318-274	Bepotastine	Eye irritation

7.3.4 Significant Adverse Events

No serious adverse events were reported during study CL-SAF-0405071.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study CL-SAF-0405071: Overview of Adverse Events (Safety Population)

	Bepotastine N=575	**Vehicle N=286**
Total Number of AEs	336	115
Total Number of Treatment-Emergent Ocular AEs	65	35
Total Number of Treatment Emergent Non-Ocular AEs	248	58
Number of Subjects Reporting >=1 AE	216	68
Subjects Discontinuing Investigational Product Due to AE	6	6

Study CL-SAF-0405071: Treatment Emergent Ocular Adverse Events (Safety Population)

	Bepotastine besilate 1.5% N=575	**Vehicle N=286**
Eye disorders		
Eye irritation	27	6
Dry eye	6	5
Ocular hyperemia	2	4
Asthenopia	1	3
Eye pain	2	2
Eye puritis	3	1
Lacrimation increased	3	0
Photophobia	2	1
Conjunctival cyst	1	1
Conjunctival hemorrhage	0	2
Eyelid margin crusting	1	1
Eyelid pain	1	1
FBS	2	0
Punctate keratitis	1	1
Abnormal sensation in eye	0	1
Eye discharge	0	1
Eye swelling	1	0
Eye edema	1	0
Eyelid pruritis	1	0
Glare	1	0
Keratitis	1	0
Vision blurred	0	1
Vitreous floaters	1	0
Vascular Disorders		
Hyperemia	2	0

General disorders		
Sensation of pressure	0	1
Infections		
Hordeolum	0	1
Injury		
Contusion	0	1
Skin disorders		
Photosenstivity reaction	1	0

Study CL-SAF-0405071: Treatment Emergent Non-Ocular Adverse Events (Safety Population)

	Bepotastine besilate 1.5% N=575	**Vehicle N=286**
Nervous system disorders		
Taste perversion	84	4
Bad taste	45	1
Headache	20	7
After taste	14	2
Nerve compression	0	1
Parosmia	1	0
Taste abnormality	1	0
Taste bitter	1	0
Taste metallic	1	0
Infections		
Nasophayngitis	12	5
Influenza	3	0
Sinusitis	1	2
Bronchitis	2	0
UTI	1	1
Ear infection	0	1
Folliculitis	1	0
Herpes zoster	1	0
Pharyngitis	0	1
Pneumonia	1	0
Tooth abscess	0	1
Vaginal infection	1	0
Viral pharyngitis	0	1
Respiratory disorders		
Nasal congestion	5	0
Rhinorrhea	3	2
Cough	2	2
Post-nasal drip	4	0
Pharngolaryngeal pain	1	1
Sneezing	2	0

Wheezing	2	0
Asthma	1	0
Sinus congestion	1	0
Musculoskeletal		
Back pain	1	1
Plantar fasciitis	1	1
Tendonitis	1	1
Arthralgia	1	0
Musculoskeletal pain	0	1
Neck pain	0	1
Osteoarthritis	1	0
Pain in extremity	1	0
GI disorders		
GERD	2	0
Tooth impacted	1	1
Abdominal pain	0	1
Dry mouth	1	0
Nausea	1	0
Paresthesia oral	0	1
Vomiting	0	1
Injury and poisoning		
Contusion	1	1
Accident	1	0
Animal bite	0	1
Fall	1	0
Joint sprain	1	0
Limb injury	0	1
Procedural pain	1	0
Road traffic accident	1	0
Tendon rupture	0	1
Skin disorders		
Drug eruption	1	0
Eczema	0	1
Rash	1	0
Urticaria	0	1
Ear disorders		
Ear pain	1	0
Eustachian tube obstruction	1	0
Tinnitus	1	0
Cardiac disorders		
Extrasystole	1	0
General disorders		
Chest pain	1	0

Immune system disorders		
Hypersensitivity	1	0
Metabolism disorder		
Hypercholesterolemia	0	1
Vascular disorders		
HTN	1	0

***Treatment-emergent adverse events were defined as those occurring during the 6-week dosing period.**

The 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 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 <0.0001).

There were very few subjects reporting treatment-emergent ocular AEs in the pediatric age subgroups. There were no AEs reported in the 3-9 years of age group and only 3 AEs reported in the 10-17 years of age group, all of which were eye disorders (2 AEs were in the vehicle treatment group, 1 AE in the bepotastine 1.5% treatment group). The type and pattern of occurrence of treatment-emergent non-ocular AEs related to the investigational product in the 2 pediatric age subgroups were similar to those observed in the overall safety population. In the 3-9 years of age subgroup, there were only 4 subjects reporting AEs, and all of these AEs were taste-related. In the 10-17 years of age subgroup, there were 7 subjects reporting AEs; 6 of these AEs were taste-related and 1 AE was a headache.

Reviewer's Comment:
Four adverse events occurred in ≥2% of subjects in the bepotastine besilate ophthalmic solution 1.5% treatment group: taste disturbance upon instillation, eye irritation, headache, and nasal pharyngitis. The most frequently reported AEs in this study were related to the taste response of subjects to the investigational product. There was a considerable variation in the frequency of taste-related issues reported as AEs between sites: the percentage of subjects in the bepotastine besilate ophthalmic solution 1.5% treatment group reporting a taste-related AE varied from 0% (investigative site 5) to 42% (investigative site 6).

In addition, subjects receiving bepotastine 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).

7.4.2 Laboratory Findings

Pregnancy tests were administered as a safety measure. All females of childbearing potential had negative pregnancy test results at both Visit 1 and Visit 4 (and at Visit 5 for those female subjects enrolled in the ECC subpopulation).

7.4.3 Vital Signs

Study CL-SAF-0405071: Summary of Vital Signs (Visit 1)

Vital Sign	Bepotastine 1.5%	Vehicle
Weight		
N	575	286
Mean (sd)	162.23 (54.77)	160.38 (54.11)
Heart Rate		
N	575	286
Mean (sd)	72.26 (9.55)	72.2 (10.32)
Blood Pressure-systolic		
N	575	286
Mean (sd)	119.43 (15.60)	118.96 (15.34)
Blood pressure-diastolic		
N	575	286
Mean (sd)	75.58 (9.72)	74.88 (9.35)

Study CL-SAF-0405071: Summary of Vital Signs (Visit 4)

Vital Sign	Bepotastine 1.5%	Vehicle
Weight		
N	547	274
Mean (sd)	160.74 (54.76)	159.77 (54.26)
Heart Rate		
N	547	274
Mean (sd)	72.7 (10.00)	72.68 (10.17)
Blood Pressure-systolic		
N	547	274
Mean (sd)	118.8 (14.77)	117.85 (15.54)
Blood pressure-diastolic		
N	547	274
Mean (sd)	75.33 (9.59)	75.06 (9.32)

Study CL-SAF-0405071: Summary of Vital Signs (Visit 5)

Vital Sign	Bepotastine 1.5%	Vehicle
Weight		
N	125	68
Mean (sd)	173.98 (45.12)	169.9 (41.75)
Heart Rate		
N	125	68
Mean (sd)	71.38 (9.14)	68.15 (8.29)

Blood Pressure-systolic		
N	125	68
Mean (sd)	119.06 (11.45)	118.32 (9.91)
Blood pressure-diastolic		
N	125	68
Mean (sd)	77.38 (8.16)	76.88 (7.97)

Vital signs (weight, heart rate, and blood pressure) were measured during Visit 1 and Visit 4 for all subjects in the safety population and during Visit 1 and Visit 5 for those subjects in the ECC subpopulation.

Reviewer's Comment:
There were no clinically significant differences between the vehicle treatment group and the bepotastine 1.5% treatment group at any of the study visits.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained.

7.4.5 Special Safety Studies

Specular microscopy was used to measure the ocular endothelial cell density. 202 subjects were enrolled into the ECC subpopulation which was comprised of 133 subjects in the bepotastine 1.5% group and 69 subjects in the vehicle group. Overall, 193 ECC subjects (95.5%) completed the dosing regimen and underwent specular microscopy at Visit 5. This included 125 subjects (94.0%) in the bepotastine 1.5% and 68 subjects (98.5%) in the vehicle group. The mean age (SD) of all subjects was 38.3 (12.8) years with a range of 12 to 68 years. All evaluations were performed at a single site on the ECC subpopulation at Visit 1 and at Visit 5.

Comparison of the mean endothelial cell density counts (cells/mm2) between the bepotastine 1.5% treatment group and the vehicle treatment group showed no significant difference at Visit 1 (p=0.22) or at Visit 5 (p=0.14). The difference from baseline (Visit 5–Visit 1) also was calculated for each of the subjects, then averaged to give the mean difference for the entire group. The mean endothelial cell density increased from baseline (Visit 5–Visit 1) in both the vehicle and the bepotastine besilate ophthalmic solution 1.5% groups. The increases from baseline in the endothelial cell density [mean difference (SD)] were similar for the two treatment groups, 202 (328) cells/mm2 in the vehicle group and 260 (376) cells/mm2 in the bepotastine besilate ophthalmic solution 1.5% group. These increases in endothelial cell density relative to baseline were not significantly different between the vehicle and the bepotastine besilate ophthalmic solution 1.5% groups (P=0.29).

Study CL-SAF-0405071: Summary of Endothelial Cell Density Counts

Visit	Bepotastine 1.5%	Vehicle
Visit 1 (Baseline)		
N	133	69
Mean (sd)	2766 (256)	2722 (224)
P value	0.22	
Visit 5 (12 weeks)		
N	125	68
Mean (sd)	3014 (428)	2921 (404)
P value	0.14	
Difference from baseline	260 (376)	202 (328)
P value	0.29	

Reviewer's Comment:
There were no clinically significant differences in endothelial cell density between the bepotastine 1.5% and vehicle.

Ocular comfort was subject-assessed upon investigational product instillation and 5 ± 0.5 minutes later at Visit 2 and Visit 3 utilizing a 4-point (7-step) grading scale with half-unit (1-step) increments allowed. Mean grades for each eye separately, and for all eyes combined, were calculated by treatment group at both time points for the two study visits. A clinically significant difference in group mean comfort score relative to the mean score in the placebo group was defined in the protocol as a difference >1.0 unit.

Ocular Comfort Grades
0-Confortable; discomfort absent
1-Generally comfortable; mild discomfort
2-Some discomfort, but tolerable; moderate discomfort
3-Severely uncomfortable or intolerable

Study CL-SAF-0405071: Ocular Comfort Evaluation Upon Instillation of Study Medication

	Vehicle	Bepotastine 1.5%
Visit 2		
N	506	1028
Mean value (sd)	0.07 (0.26)	0.13 (0.35)
Difference		0.06
P value		0.12
Visit 3		
N	492	996
Mean value (sd)	0.06 (0.23)	0.1 (0.33)
Difference		0.04
P value		0.55

Study CL-SAF-0405071: Ocular Comfort Evaluation 5 Minutes After Instillation

	Vehicle	Bepotastine 1.5%
Visit 2		
N	506	1028
Mean value (sd)	0.02 (0.13)	0.06 (0.25)
Difference		0.04
P value		0.23
Visit 3		
N	492	996
Mean value (sd)	0.04 (0.17)	0.05 (0.22)
Difference		0.01
P value		0.35

Reviewer's Comment:
There were no observed significant differences in ocular comfort scores between bepotastine 1.5% and vehicle at any of the time points.

Physical examinations (general health; head, eyes, ears, nose, and throat; heart; lungs; abdomen; neurologic evaluation; condition of extremities; back; and skin) were conducted during Visit 1 and Visit 4 for all subjects in the safety population and during Visit 1 and Visit 5 for those subjects in the ECC subpopulation. There were no clinically significant abnormal findings in, or differences between, the placebo treatment group and the bepotastine besilate ophthalmic solution 1.5% treatment group, either in the safety population or in the ECC subpopulation, at any of the study visits.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not observed.

7.5.2 Time Dependency for Adverse Events

The total number of AEs was greatest in the Day 1 to Day 8 period and decreased thereafter in both the bepotastine besilate ophthalmic solution 1.5% and the vehicle treatment groups.

Study CL-SAF-0405071: Adverse Events as a Function of Time

	Days 1-8	Days 9-22	Days 23-44	Days 44-84
Bepotastine 1.5%				
Total AEs	222	55	37	17
Eye irritation	22	3	2	0
Dry eye	3	1	1	1
Other eye disorders	15	6	4	2
Taste-related AEs	131	16	3	0
Headaches	16	4	0	0
Other	1	0	0	0
Vehicle				
Total AEs	57	23	18	15
Eye irritation	5	1	1	1
Dry eye	3	1	1	0
Other eye disorders	11	9	1	1
Taste-related AEs	6	1	2	0
Headaches	7	0	0	0
Other	0	1	0	1

Reviewer's Comment:
The data does not show evidence of a delayed toxicity or increased safety risks associated with duration of exposure to bepotastine 1.5% dosed BID for 6 weeks.

7.5.3 Drug-Demographic Interactions

The demographics of subjects in the safety population were well-balanced between the 2 treatment groups; there were no significant differences between the bepotastine besilate ophthalmic solution 1.5% and the vehicle groups with regards to age, gender, ethnicity, eye color, or race.

7.5.4 Drug-Disease Interactions

Bepotastine besilate 1.5% was evaluated for the treatment of allergic conjunctivitis, and no drug-disease interaction was performed.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between bepotastine and any of the concomitant medications allowed in those studies. The low systemic absorption of bepotastine would limit the potential for drug interaction.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of bepotastine in topical preparations, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

This drug was tested on a pediatric population. Height was not collected as part of this protocol.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Bepotastine is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

On March 11, 2009 a 4 month safety update was submitted to the NDA (Sequence 008). ISTA conducted a literature review for the period of August 1, 2008 through February 15, 2009 and also obtained translations of 9 additional nonclinical studies performed by Senju Pharmaceuticals Co., Ltd.

It was reported that ISTA had not conducted any clinical studies with Bepreve since the completed Phase 3 studies that were fully reported in the NDA. In this amendment, 7 US articles, 12 abstracts/posters, and 15 Japanese articles were submitted. The 7 US articles included 2 articles regarding the oral administration of bepotastine, 3 pharm/tox articles, and 2 articles about the VAS questionnaire and the use of H1 anti-histamines. The 15 Japanese articles were all regarding the use of bepotastine oral tablets (Talion) for various uses. In addition, 9 abstracts for non-clinical study reports were submitted.

No new safety issues relating to bepotastine 1.5% were found.

8 Post-marketing Experience

Bepotastine besilate as an oral formulation (Talion tablets, Mitsubishi Tanabe Pharma Corporation [formerly Tanabe Seiyaku Company, Ltd.]) has been marked in Japan since October 2000, first as a treatment for allergic rhinitis and then in a broadened labeling for prurigo, eczema, and cutaneous pruritus. In a post-marketing reporting of voluntary patient summaries from Japanese physicians (TNB-PMS-01), including adverse events, the safety experience was summarized for almost 6 years of marketing of Talion tablets. In that time, approximately 6,127,000 5-mg bepotastine besilate tablets and approximately 110,325,000 10-mg bepotastine

besilate tablets were distributed in Japan. Eighty-nine of 4453 patients (2.00%) experienced 95 adverse events in the post-marketing surveillance report, which does not exceed the adverse event rate during clinical studies prior to approval (9.47%). The two most common adverse events were drowsiness (59 of 4453 patients, 1.32%) and upper abdominal pain (6 of 4453 patients, 0.13%). All other adverse events were seen in no more than 4 patients (frequency <0.1%) and none was judged to be serious.

The long-term use of Talion tablets was investigated as part of another post-market surveillance study conducted in Japan from October 2000 to March 2004 (TNB-PMS-02). Long-term drug use for the treatment of allergic rhinitis was defined as patients who had been using the drug continuously beyond 4 weeks of administration. Eight of 1153 patients (0.69%) experienced 9 adverse events after shifting to long-term administration of Talion tablets. The incidence of adverse events were as follows: "drowsiness" and "dry mouth" (each 3 of 1153 patients, 0.26%), "upper abdominal pain," "facial edema" and "pharyngeal dryness" (each 1 of 1153 patients, 0.09%). Adverse event rates of geriatric (≥65 years) patients were compared with those of non-geriatric (<65 years) patients as another feature of TNB-PMS-02. The incidence of patients ≥65 years with adverse events (17 of 873 patients, 2%) was not significantly different from the incidence of patients <65 years with adverse events (72 of 3580 patients, 2%) using Fisher's direct method ($P = 1.00$).

Finally, a retrospective analysis of the safety of Talion tablets in pediatric patients (ages 5-14 years old) in Japan was completed. Adverse events were confirmed in 14 of 1,316 pediatric patients (1.1%). The most common were drowsiness (5/1316 patients, 0.4%), thirst (2/1316 patients, 0.2%), and urticaria (2/1316 patients, 0.2%). All events were considered mild. No difference in the incidence of adverse events was observed in average daily dose by body weight, indicating that oral bepotastine besilate has been safely administered in Japan over a wide range of doses (0.1 mg/kg to 1.5 mg/kg).

9 Appendices

9.1 Literature Review/References

A pub med search did not reveal any new information on bepotastine.

9.2 Advisory Committee Meeting Labeling

Since this is a NME (new molecular entity) there was an advisory committee on June 26, 2009. The following questions were presented to the committee:

1. Do you think adequate safety and efficacy for bepotastine ophthalmic solution has been demonstrated for the treatment of itching due to allergic conjunctivitis?

The committee voted 7-Yes and 0-No.

2. If yes, on which study(ies) are you basing your decision?

All committee members stated they based their decision on Studies ISTA-BEPO-CS01 CL-S&E-0409071, and CL-SAF-0405071.

3. If no, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

Not applicable.

4. Do you have any suggestions concerning the proposed draft labeling of the product?

There were no suggestions regarding the proposed draft labeling.

6 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS))

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONAL D WADHWA
08/17/2009

WILLIAM M BOYD
08/18/2009