

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-228**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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NDA:	22-288
Submission Date(s):	12NOV2008
Brand Name	Bepreve™
Generic Name	Bepotastine Besilate Ophthalmic Solution 1.5%
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
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OCP Division	DCP4
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Applicant	ISTA Pharmaceuticals®, Inc.
Relevant IND(s)	IND 66,864
Submission Type; Code	Original NDA; 505(b)(1) application; 1S (new molecular entity)
Formulation; Strength(s)	Bepotastine Besilate Ophthalmic Solution 1.5%
Indication	Treatment of ocular itching associated with allergic conjunctivitis in patients age 3 years or older

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## **1. EXECUTIVE SUMMARY**

Bepotastine besilate is a selective histamine H<sub>1</sub>-receptor antagonist. Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is a sterile ophthalmic solution of bepotastine besilate proposed for the treatment of itching associated with signs and symptoms of allergic conjunctivitis in patients aged 3 years or older. The proposed dosage and route of administration for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is as follows: instill one drop into the affected eye(s) twice a day (BID). Bepotastine besilate (also known as TAU-284 and SNJ-1773) was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. as a treatment for allergic rhinitis. An oral preparation of bepotastine besilate (Talion® tablets, Mitsubishi Tanabe Pharma Corporation [formerly Tanabe Seiyaku Company, Ltd.]) was approved in Japan in July 2000 and launched in October 2000. In January 2002, the additional indication of pruritus/itching accompanying urticaria and other skin diseases was approved in Japan.

The applicant submitted clinical pharmacology data for bepotastine from the Japanese development programs, including a Phase 1 pharmacokinetic (PK) study examining systemic exposure following bepotastine besilate ophthalmic solutions 1.0% and 1.5% instilled as repeated doses (QID) over a 7 day period (Study SNJ-TO-02), as well as data from multiple Phase 1 studies from the oral development program. To support the safety and efficacy of Bepreve™ (bepotastine besilate ophthalmic solution), 1.5%, the applicant conducted one Phase 2/3 (single site) and one Phase 3 (multisite), placebo-controlled, double-masked, randomized conjunctival allergen challenge (CAC) efficacy studies with bepotastine besilate ophthalmic solutions 1.0% and 1.5% in male and female subjects aged 10 years and older who have a positive history of allergic conjunctivitis (Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P). Both pivotal trials evaluated the clinical efficacy of two bepotastine besilate ophthalmic solutions (1.0% and 1.5%) at each of two durations of action (8 hours, considered acceptable for a drug intended for dosing BID, and 16 hours, considered acceptable for a drug intended for dosing QD) by having 5 subject visits over approximately 7 weeks. In addition, a Phase 3 multisite, double-masked, randomized, placebo-controlled, parallel-group study (CL-SAF-0405071-P) evaluated the safety of bepotastine besilate ophthalmic solution 1.5% administered 2 times per day (BID) for 6 weeks in healthy, normal volunteers 3 years of age and older.

### **1.1. Recommendation**

The clinical pharmacology information provided by the Applicant is acceptable.

### **1.2. Phase IV Commitments**

No phase IV commitments are recommended.

### **1.3. Summary of Important Clinical Pharmacology Findings**

Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is a sterile ophthalmic solution of bepotastine besilate proposed for the treatment of itching associated with signs and symptoms of allergic conjunctivitis in patients aged 3 years or older. The proposed dosage and route of administration for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is as follows: instill one drop into the affected eye(s) twice a day (BID). 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; C<sub>max</sub> values for 1.0% and 1.5% bepotastine besilate were  $5.138 \pm 2.503$  ng/mL and  $7.335 \pm 1.876$  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  $101.3 \pm 3.5$  ng/mL. This is over 10 times that of the C<sub>max</sub> 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 to 88% of the bepotastine besilate dose was excreted in urine by 24 hours.

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

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Concurrence:

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Division File: NDA 22-288  
HFD-520 (CSO/Rodriguez)  
HFD-520 (MO/Wadhwa)  
HFD-520 (Chambers, Boyd)  
HFD-880 (Lazor, Reynolds, Bonapace)

## 2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

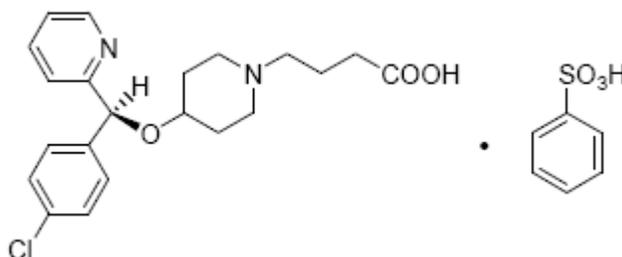
### 2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is a sterile, clear colorless to pale yellow aqueous solution containing bepotastine besilate as the active ingredient. Bepreve™ ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8 and an osmolality of approximately 290 mOsm/kg.

**Structural Formula:**  $C_{21}H_{25}ClN_2O_3 \cdot C_6H_6O_3S$

**Chemical Structure:**



**Chemical Name:** (+)-(S)-4- {4-[(4-Chlorophenyl)(2-pyridyl)methoxy] piperidino} butyric acid monobenzenesulfonate

**Compendial Name:** Bepotastine Besilate

**International Nonproprietary Name (INN):** Bepotastine

**Company Laboratory Code:** TAU-284, SNJ-1773

**Chemical Abstract Service (CAS) Registry Number:** 190786-44-8

**Molecular Weight:** 547.06

The qualitative and quantitative composition of the proposed Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% drug product is shown in Table 2.2-1.

Table 2.2-1 Composition of Bepotastine Besilate Ophthalmic Solution, 1.5%

Component	Function	%, w/w
Bepotastine Besilate	Active ingredient	1.5%
Sodium Chloride		(b) (4)
Monobasic Sodium Phosphate, Dihydrate		
Benzalkonium Chloride	Preservative	0.005%
Sodium Hydroxide	pH adjustment	Adjust pH to 6.8
Water for Injection	Solvent	QS to 100 mL

Source: Section 3.2.P.1

*2.1.2. What is the proposed mechanism of drug action and therapeutic indication?*

Bepotastine is a selective histamine H<sub>1</sub>-receptor antagonist. Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is proposed for the treatment of itching associated with signs and symptoms of allergic conjunctivitis in patients aged 3 years or older.

*2.1.3. What is the proposed dosage and route of administration?*

The proposed dosage and route of administration for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% is as follows: instill one drop into the affected eye(s) twice a day (BID).

**2.2. General Clinical Pharmacology**

*2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?*

The applicant submitted clinical pharmacology data for bepotastine from the Japanese development programs, including a Phase 1 pharmacokinetic (PK) study examining systemic exposure following bepotastine besilate ophthalmic solutions 1.0% and 1.5% instilled as repeated doses (QID) over a 7 day period (Study SNJ-TO-02), as well as data from multiple Phase 1 studies from the oral development program. To support the safety and efficacy of Bepreve™ (bepotastine besilate ophthalmic solution), 1.5%, the applicant conducted one Phase 2/3 (single site) and one Phase 3 (multisite), placebo-controlled, double-masked, randomized conjunctival allergen challenge (CAC) efficacy studies with bepotastine besilate ophthalmic solutions 1.0% and 1.5% in male and female subjects aged 10 years and older who have a positive history of allergic conjunctivitis (Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P). Both pivotal trials evaluated the clinical efficacy of two bepotastine besilate ophthalmic solutions (1.0% and 1.5%) at each of two durations of action (8 hours, considered acceptable for a drug intended for dosing BID, and 16 hours, considered acceptable for a drug intended for dosing QD) by having 5 subject visits over approximately 7 weeks. In addition, a Phase 3 multisite, double-masked, randomized, placebo-controlled, parallel-group study (CL-SAF-0405071-P) evaluated the safety of bepotastine besilate ophthalmic solution 1.5% administered 2 times per day (BID) for 6 weeks in healthy, normal volunteers 3 years of age and older. Design features of the relevant studies conducted in the Bepreve™ (bepotastine besilate ophthalmic solution), 1.5% development program are summarized in Table 2.2.1-1.

Table 2.2.1-1 Summary of the Bepotastine Besilate Ophthalmic Solution, 1.5% Clinical Development Program

<b>Study</b>	<b>Study Design</b>	<b>Study Objective</b>	<b>Test Product(s); Dosage Regimen; Route of Administration; Treatment Duration</b>	<b>Population</b>	<b># Subjects</b>
<b>ISTA-BEPO-CS01</b>	Phase 2/3, single center, double-masked, randomized, placebo-controlled, CAC study	Efficacy and safety of bepotastine besilate ophthalmic solution 1.0% and 1.5% compared to placebo in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis at 15 minutes, 8 hours, and 16 hours following medication instillation	TP: Bepotastine besilate ophthalmic solution 1.0%, 1.5%, or Placebo; Dose: One drop at Visit 3A, Visit 4, and Visit 5; Route: ophthalmic; Duration: 7 weeks	CAC-induced allergic conjunctivitis patients	107
<b>CL-S&amp;E-0409071-P</b>	Phase 3, multi-center, double-masked, randomized, placebo-controlled, CAC study	Efficacy and safety of bepotastine besilate ophthalmic solution 1.0% and 1.5% compared to placebo in alleviating the signs and symptoms of CAC-induced allergic conjunctivitis at 15 minutes, at 8 hours, and at 16 hours following investigational product instillation	TP: Bepotastine besilate ophthalmic solution 1.0%, 1.5%, or Placebo; Dose: One drop at Visit 3A, Visit 4, and Visit 5; Route: ophthalmic; Duration: 7 weeks	CAC-induced allergic conjunctivitis patients	130
<b>CL-SAF-0405071-P</b>	Phase 3, multi-center, randomized, double-masked, vehicle-controlled, parallel-group study	Evaluate the safety of bepotastine besilate ophthalmic solution 1.5% in healthy, normal volunteers	TP: Bepotastine besilate ophthalmic solution 1.5% or Placebo; Dose: one drop BID; Route: ophthalmic; Duration: 6 weeks to 12 weeks	Healthy subjects	861
<b>SNJ-TO-02</b>	Phase 1, open-label study	Investigate the safety and PK of 1.0% and 1.5% SNJ-1773 ophthalmic solutions	TP: SNJ-1773 1.0% or 1.5%; Dose: one drop QID; Route: ophthalmic; Duration: 7 days	Healthy subjects (Japanese)	12

TP, test product

Source: Table 5.2 Tabular Listing of Clinical Studies

2.2.2. *What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy variables for both efficacy CAC trials were ocular itching and conjunctival hyperemia (redness). The primary efficacy variable of ocular itching was evaluated by subjects at 3, 5, and 7 minutes post-CAC, while conjunctival hyperemia was investigator-evaluated at 7, 15, and 20 minutes post-CAC. Severity scales for both measures were based on a 5-point (nine-step) scale with half unit (one step) increments allowed (e.g. grades 0 through 4). The average score of each subject's eyes was used for comparison between bepotastine besilate ophthalmic solutions (1.0% and 1.5%) and the placebo ophthalmic solution.

Clinical efficacy for both primary efficacy variables required demonstration of clinical and statistical significance at Visit 5 (the onset of action CAC test) and at Visit 3B (the 16 hour duration of action CAC test) or Visit 4 (the 8 hour duration of action CAC test). The studies consisted of six 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. Only subjects who met the study criteria for a positive CAC reaction at Visits 1 and 2 continued to Visit 3A (Day 0). At Visits 3A, 4, and 5, investigational product was instilled, and conjunctival allergen challenge (CAC) was performed, using the previously validated allergen dose for each subject, at: 16 hours (assessed at Visit 3B or Day 1; 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. Signs and symptoms of allergic conjunctivitis were then graded over a 20-minute period following the CAC.

Secondary efficacy variables included rhinorrhea, nasal congestion, tearing, ciliary and episcleral hyperemia, chemosis, ocular mucous discharge, eyelid swelling, nasal pruritus, and ear or palate pruritus, and a total non-ocular (principally nasal) composite symptom scores.

2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

The active moiety bepotastine was appropriately identified and measured in plasma and urine for purposes of assessment of systemic exposure following ocular and oral administration by a validated high performance liquid chromatographic (HPLC) method with UV-detection.

2.2.4. *Exposure-Response*

2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

Summaries of treatment differences for ocular itching and conjunctival hyperemia (both eyes averaged) for both pivotal studies combined are presented in Tables 2.2.4.1-1 and 2.2.4.1-2. Based on the applicant's analyses of Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P, both bepotastine besilate ophthalmic solutions (1.0% and 1.5%) were efficacious for reduction of ocular itching, but not conjunctival hyperemia, in the CAC model compared to placebo with a

duration of action of at least 8 hours. In addition, clinical benefit was seen with bepotastine besilate ophthalmic solution 1.5% for reduction of CAC-induced ocular itching compared to placebo for a duration of action of at least 16 hours. Neither concentration of bepotastine besilate ophthalmic solution (1.0% or 1.5%) demonstrated clinical efficacy compared with placebo in reducing conjunctival hyperemia at any visit.

Results of a 2-sample t-test comparing the differences in reduction of ocular itching response between the two bepotastine besilate ophthalmic solution strengths (1.0% and 1.5%) indicated that there was no statistically significant difference between the two active formulations in reducing ocular itching compared with placebo, although the 1.5% strength approached statistical superiority to 1.0% ( $P \leq 0.05$ ) at Visit 4.

Table 2.2.4.1-1. Summary of Treatment Differences for Ocular Itching Following Ophthalmic Administration of Bepotastine Besilate 1.0%, 1.5% and Placebo in Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P – Per Protocol Population<sup>a</sup>

Visit	Treatment	N	Treatment Difference (Placebo – Active)		
			Time Points		
			3 min	5 min	7 min
5 (15 min)	Bepotastine besilate 1.0%	78	1.4	1.4	1.3
	Bepotastine besilate 1.5%	70	1.5	1.6	1.4
	1.0%/1.5% Comparison <sup>bc</sup>		0.28	0.22	0.24
4 (8 hr)	Bepotastine besilate 1.0%	74	1.1	1.2	1.1
	Bepotastine besilate 1.5%	64	1.4	1.5	1.3
	1.0%/1.5% Comparison <sup>bd</sup>		0.07	0.05	0.06
3B (16 hr)	Bepotastine besilate 1.0%	78	0.6	0.8	0.9
	Bepotastine besilate 1.5%	68	0.8	1.0	0.9
	1.0%/1.5% Comparison <sup>bc</sup>		0.18	0.31	0.75

<sup>a</sup> ITT populations (both observed data and LOCF) showed similar results.

<sup>b</sup> Compared using 2-sample t-test.

<sup>c</sup> p = 0.0019

<sup>d</sup> p = 0.0023

<sup>e</sup> p = 0.0932

Source: Integrated Summary of Efficacy

Table 2.2.4.1-2. Summary of Treatment Differences for Conjunctival Hyperemia Following Ophthalmic Administration of Bepotastine Besilate 1.0%, 1.5% and Placebo in Studies ISTA-BEPO-CS01 and CL-S&E-0409071-P – Per Protocol Population<sup>a</sup>

Visit	Treatment	N	Treatment Difference (Placebo – Active)		
			Time Points		
			3 min	5 min	7 min
5	Bepotastine besilate 1.0%	78	0.7	0.5	0.4
	Bepotastine besilate 1.5%	70	0.6	0.4	0.3
	1.0%/1.5% Comparison <sup>bc</sup>		0.25	0.35	0.62
4	Bepotastine besilate 1.0%	74	0.4	0.3	0.2
	Bepotastine besilate 1.5%	64	0.3	0.3	0.2
	1.0%/1.5% Comparison <sup>bd</sup>		0.50	0.91	0.83
3B	Bepotastine besilate 1.0%	78	0.4	0.3	0.3
	Bepotastine besilate 1.5%	68	0.1	0.1	0
	1.0%/1.5% Comparison <sup>bc</sup>		0.03	0.08	0.06

<sup>a</sup> ITT populations (both observed data and LOCF) showed similar results.

<sup>b</sup> Compared using 2-sample t-test.

<sup>c</sup> p = 0.1618

<sup>d</sup> p = 0.0047

<sup>e</sup> p < 0.0001

Source: Integrated Summary of Efficacy

For further discussion of the efficacy comparison of the two bepotastine besilate ophthalmic solution strengths, refer to the Medical Officer's and Biostatistician's reviews of NDA 22-288.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Summaries of treatment-emergent adverse events reported the pivotal trials for bepotastine besilate are presented in Tables 2.2.4.2-1 and 2.2.4.2-2. Based on the applicant's analysis of safety, in Study ISTA-BEPO-CS01 there were no significant differences in the safety profiles between the two bepotastine besilate formulations. In Study CL-S&E-0409071-P, more adverse events occurred in the bepotastine besilate ophthalmic solution 1.0% treatment group (19/44) than in the bepotastine besilate ophthalmic solution 1.5% treatment group (1/43). However, there were no apparent trends with respect to the type of adverse events across treatment groups.

Table 2.2.4.2-1. Treatment-Emergent Adverse Events Reported in Study ISTA-BEPO-CS01

Adverse Event	Bepotastine Besilate 1.0% (N = 36)		Bepotastine Besilate 1.5% (N = 35)	
	N	%	N	%
<i>Ocular AEs</i>				
Eye Irritation	0	0	1	2.9
Conjunctival Cyst	0	0	1	2.9
Foreign Body Sensation	0	0	0	0
<i>Non-Ocular AEs</i>				
Dysgeusia	6	16.7	3	8.6
Respiratory, thoracic, and mediastinal disorders (all)	1	2.8	3	8.6
Gastrointestinal Disorders (all)	0	0	2	5.7
Nasopharyngitis	2	5.6	0	0
Lymphadenopathy	1	2.8	0	0
Anxiety	0	0	1	2.9
Cyst Removal	1	2.8	0	0

Source: Clinical Study Report ISTA-BEPO-CS01

Table 2.2.4.2-2. Treatment-Emergent Adverse Events Reported in Study CL-S&E-0409071-P

Adverse Event	Bepotastine Besilate 1.0% (N = 44)		Bepotastine Besilate 1.5% (N = 43)	
	N	%	N	%
<i>Ocular AEs</i>				
Eye Irritation	2	4.5	2	4.7
Dry Eye	1	2.3	0	0
Eye Pain	0	0	0	0
Eye Pruritis	1	2.3	0	0
Keratitis	0	0	1	2.3
<i>Non-Ocular AEs</i>				
Nasopharyngitis	5	11.4	3	7.0
Taste Perversion	2	4.5	2	4.7
Nasal Congestion	1	2.3	2	4.7
Headache	1	2.3	0	0
Migraine	1	2.3	0	0
Cough	1	2.3	0	0
Pharyngolaryngeal Pain	1	2.3	0	0
Postnasal Drip	0	0	1	2.3
Nausea	1	2.3	0	0
Joint Sprain	0	0	1	2.3
Rotator Cuff Syndrome	1	2.3	0	0

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

For further discussion of the safety comparison of the two bepotastine besilate ophthalmic solution strengths, refer to the Medical Officer’s review of NDA 22-288.

*2.2.4.3. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

There are no unresolved dosing or administration issues. The proposed dose and dosing regimen for Bepreve™ (bepotastine besilate ophthalmic solution), 1.5%, one drop into the affected eye(s) twice a day (BID), is consistent with the known relationship between dose-response for reduction of ocular itching. Both bepotastine besilate ophthalmic solutions (1.0% and 1.5%) were efficacious for reduction of ocular itching, and clinical benefit was seen with bepotastine besilate ophthalmic solution 1.5% for reduction of CAC-induced ocular itching compared to placebo for a duration of action of at least 16 hours. Since there were no significant differences in the safety profiles between the two bepotastine besilate formulations, selection of the 1.5% strength is acceptable from a clinical pharmacology perspective, based on the applicant’s analyses. For further discussion of the efficacy comparison of the two bepotastine besilate ophthalmic solution strengths, refer to the Medical Officer’s and Biostatistician’s reviews of NDA 22-288.

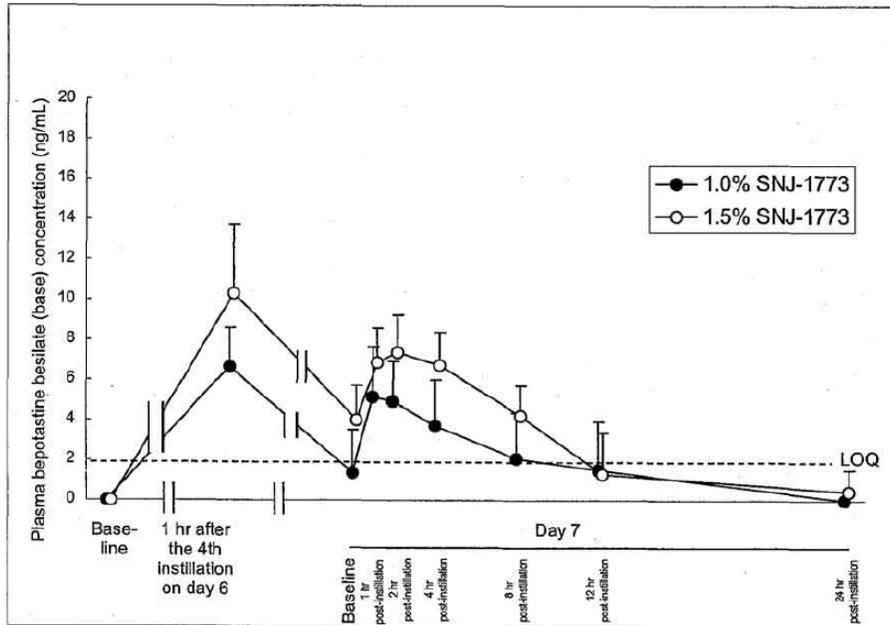
## 2.2.5. *What are the PK characteristics of the drug and its major metabolite?*

### 2.2.5.1. *Systemic Exposure Following Ocular Administration*

The extent of systemic exposure of bepotastine following topical ophthalmic administration of bepotastine besilate 1.0% and 1.5% ophthalmic solution was evaluated in one multiple-dose pharmacokinetic (PK) study in healthy adults (Study SNJ-TO-02). Study SNJ-TO-02 was a Phase 1 open-label study in 12 healthy adult male who received one drop of 1.0% or 1.5% SNJ-1773 ophthalmic solution to both eyes four times daily for seven days in sequential fashion.

Plasma concentration-time profiles for bepotastine following ophthalmic administration of SNJ-1773 bilaterally four times daily for seven days in healthy male subjects are presented in Figure 2.2.5.1-1. A summary of plasma concentrations of bepotastine following ophthalmic administration of SNJ-1773 bilaterally four times daily for seven days in healthy male subjects is presented in Table 2.2.5.1-1. Following ophthalmic administration of SNJ-1773 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 increased proportional to dose; C<sub>max</sub> values for 1.0% and 1.5% SNJ-1773 following four times daily bilateral ophthalmic administration for 7 days were  $5.138 \pm 2.503$  ng/mL and  $7.335 \pm 1.876$  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.

Figure 2.2.5.1-1. Mean Plasma Concentration-Time Profiles for Bepotastine Besilate Following Ophthalmic Administration of SNJ-1773 Bilaterally Four Times Daily for Seven Days in Healthy Male Subjects



SNJ-1773 = bepotastine besilate ophthalmic solution  
 Source: SNJ-TO-02 Study Report, Section 11.4.1

The estimated maximum total daily dose of bepotastine besilate administered in Study SNJ-TO-02 is approximately 4 mg for the 1.0% solution and 6 mg for the 1.5% solution. The proposed DOSAGE AND ADMINISTRATION of Bepreve™ (bepotastine besilate ophthalmic solution, 1.5%) is to instill one drop into the affected eye(s) twice a day (BID). The estimated maximum total daily dose for this proposed regimen is approximately 3 mg. Thus, the anticipated systemic exposure with the proposed regimen is expected to be less than that observed in Study SNJ-TO-02. In addition, following a single, oral 10 mg dose of bepotastine besilate in healthy subjects, the maximum plasma concentration of bepotastine was  $101.3 \pm 3.5$  ng/mL. This is over 10 times that of the C<sub>max</sub> 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.

2.2.5.2. *What other characteristics of drug absorption, distribution, metabolism, and excretion are known and applicable to the NDA review for the ophthalmic drug product?*

The extent of protein binding of bepotastine was determined from blood samples obtained from healthy adult male volunteers enrolled in a bioequivalence study conducted in Japan to support the oral formulation of bepotastine besilate (Study TNB-TO-04). Subjects received one 10 mg tablet, blood samples were collected at 1 and 2 hours post-dose, and protein binding was determined via ultrafiltration. The plasma protein binding of bepotastine was approximately 55% and independent of bepotastine concentration over a range of 60 to 170ng/mL.

In vitro metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

The urinary excretion of bepotastine was investigated in a Phase 1 single dose escalation study conducted in Japan with the oral formulation of bepotastine besilate (Study TNB-TO-01). Following single oral doses ranging from 2.5 to 40 mg, approximately 76 to 88% of the bepotastine dose was excreted in urine by 24 hours. Two minor metabolites were detected, accounting for about 0.3% and 1% of the original dose and were only observed with bepotastine doses of 20 mg or higher.

### **2.3. Intrinsic Factors**

Not applicable.

### **2.4. Extrinsic Factors**

*In vitro* studies of the effect of bepotastine besilate on the metabolism of various cytochrome P450 substrates for CYP3A4, CYP2C9, and CYP2C19 demonstrated that bepotastine does not inhibit the activity of CYP3A4, CYP2C9, and CYP2C19. Although certain cytochrome P450 enzymes were not studied (CYP1A2, CYP2C8, CYP2D6), systemic concentrations following ophthalmic administration are expected to be low, such that metabolic drug interactions are not expected with the ophthalmic product.

### **2.5. General Biopharmaceutics**

Not applicable.

### **2.6. Analytical Section**

#### *2.6.1. How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?*

Plasma concentrations of bepotastine were determined via a high performance liquid chromatography (HPLC) method with UV-detection for both the ophthalmic PK study (SNJ-TO-02) and the single oral dose escalation study (TNB-TO-01) (Validation Study Reports SNJ-TO-06 and TNB-HE-03, respectively). Urine concentrations of bepotastine were also determined via HPLC with UV-detection in Study TNB-TO-01.

The analytical methods used for the two studies were similar. For purposes of development of the ophthalmic solution formulation of bepotastine besilate, the HPLC method used for the oral development program was modified and validated in order to obtain more sensitive quantitation at low bepotastine concentrations in human plasma.

#### *2.6.2. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total bepotastine concentrations were measured in plasma of healthy subjects in Studies SNJ-TO-02 and TNB-TO-01. The measurement of total concentrations of bepotastine for purposes of supporting the current application and determining systemic exposure following ophthalmic administration is appropriate.

#### *2.6.3. What bioanalytical methods are used to assess concentrations?*

Plasma and urine concentrations of bepotastine were determined via a high performance liquid chromatography (HPLC) method with UV-detection.

*2.6.3.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

The calibration curve for the HPLC assay utilized for determination of systemic concentrations following ophthalmic administration (Study SNJ-TO-02) ranged from 2 to 300 ng/mL for bepotastine in human plasma. Calibration data were fitted with a linear regression model (no weighting).

The calibration curve for the HPLC assay utilized for Study TNB-TO-01 ranged from 2 to 1000 ng/mL for bepotastine in human plasma. Calibration data were fitted with a linear regression model (weighting unspecified).

The calibration curve for the HPLC assay utilized for Study TNB-TO-01 ranged from 0.05 to 100 µg/mL for bepotastine in human urine. Calibration data were fitted with a linear regression model (weighting unspecified).

In general, the ranges of the assays were sufficient to measure bepotastine concentrations in human plasma and urine for the intended purpose of describing systemic exposure following ophthalmic and oral administration in support of the current application.

*2.6.3.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The lower limit of quantitation for bepotastine in human plasma is 2 ng/mL. The upper limits of quantitation are 300 ng/mL (SNJ-TO-02) and 1000 ng/mL (TNB-TO-01) for the two methods, respectively. The lower limit of quantitation for bepotastine in human urine is 0.05 µg/mL. The upper limit of quantitation is 100 µg/mL.

*2.6.3.3. What are the accuracy, precision, and selectivity at these limits?*

For the HPLC method utilized for the ophthalmic PK Study SNJ-TO-02, intra-day accuracy ranged from 97.8 to 113.5% of nominal with a precision range of 0.9 to 9.0%. The corresponding inter-day accuracy and precision ranges were 94.6% to 98.7% of nominal and 4.4 to 6.3%, respectively. Selectivity against endogenous interferences was demonstrated using blank human plasma samples from six healthy adult male volunteers.

For the HPLC method utilized for the oral PK Study TNB-TO-01, intra-day precision values ranged between 1.8 and 3.7% and accuracy between 96.8 to 98.5%. Inter-day performance and selectivity was not reported.

*2.6.3.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Stability in extraction solution, in plasma at 1) room temperature, 2) approximately 4°C, 3) approximately -20°C, and during freezing and thawing (one, two and three times) was assessed with QC samples (Low and High) conducted in triplicate. All stability tests satisfied the allowable criterion (mean remaining ratio within 100 ± 15%).

*2.6.3.5. What is the QC sample plan?*

For the HPLC method utilized for the ophthalmic PK Study SNJ-TO-02, each analytical run included five QC samples at each of three concentrations, as follows: 5 (Low), 150 (Medium), and 240 (High) ng/mL concentrations.

For the HPLC method utilized for the oral PK Study TNB-TO-01, analytical runs contained two QC concentrations (10 and 100 ng/mL) that were repeated six (6) times.

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

## 4. APPENDICES

### 4.1. Individual Study Reviews

#### 4.1.1. Study SNJ-TO-02

**TITLE:**

SNJ-1773 Phase 1 Clinical Study (Repeated Instillation Study)

Study Initiation: 22NOV2002

Study Completion: 14JAN2003

Investigator/Site: (b) (4)

**OBJECTIVES:**

To investigate the safety of 1.0% and 1.5% SNJ-1773 ophthalmic solutions instilled four times daily as repeated doses for seven days in healthy male volunteers

**STUDY DESIGN:**

This was a Phase 1 open-label study in 12 healthy adult male volunteers aged 20 to 35 years. Subjects were instilled one drop of 1.0% (six subjects) or 1.5% (six subjects) SNJ-1773 ophthalmic solution to both eyes four times daily as repeated doses for seven days in sequential fashion. On Day 7, the investigational product was instilled only once in the morning. The investigator medically assessed the feasibility of proceeding to the higher dose based on adverse event data and results from observation and examinations up to the end of observation at 24 hours post-instillation of the 1.0% concentration on Day 7.

**FORMULATIONS:**

The following formulations were administered in Study SNJ-TO-02:

- 1) 1.0% SNJ-1773 ophthalmic solution containing 10 mg/mL bepotastine besilate
- 2) 1.5% SNJ-1773 ophthalmic solution containing 15 mg/mL bepotastine besilate

The lot number for both products is 02M62 and the expiration date is June 2003.

**PHARMACOKINETIC ASSESSMENTS:**

Venous blood samples for determination of plasma concentrations of bepotastine were collected at the following time points: prior to the 1<sup>st</sup> instillation on Day 1, 1 hour before the 4<sup>th</sup> instillation on Day 6, and prior to and 1, 2, 4, 8, 12, and 24 hours post-instillation on Day 7.

**BIOANALYTICAL METHODOLOGY**

Plasma concentrations of bepotastine were determined via a high performance liquid chromatography (HPLC) method. This method used (b) (4) as an internal reference standard and had a linear quantitation range of 2 to 300 ng/mL bepotastine, with 92.5% to 109.3% recovery.

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

Bepotastine concentrations were summarized by descriptive statistics.

## RESULTS:

### **Study Population and Demographics**

Six (6) subjects receiving investigational product in each dose group were included in the pharmacokinetic (PK) analysis (e.g. no subjects were excluded from analysis). A summary of demographic and baseline characteristics for the study population is presented in Table 1. There were no relevant differences in demographic characteristics between the study groups.

Table 1. Demographics and Baseline Characteristics – Study SNJ-TO-02

Treatment	N	Age* (yr)	Height (cm)	Weight (kg)
1.0% SNJ-1773	20	23.3 (22 – 25)	170.88 ± 5.03	59.05 ± 5.51
1.5% SNJ-1773	10	22.8 (20 – 24)	173.65 ± 6.67	61.57 ± 4.97

\*Data presented as mean (range); otherwise presented as mean ± SD.

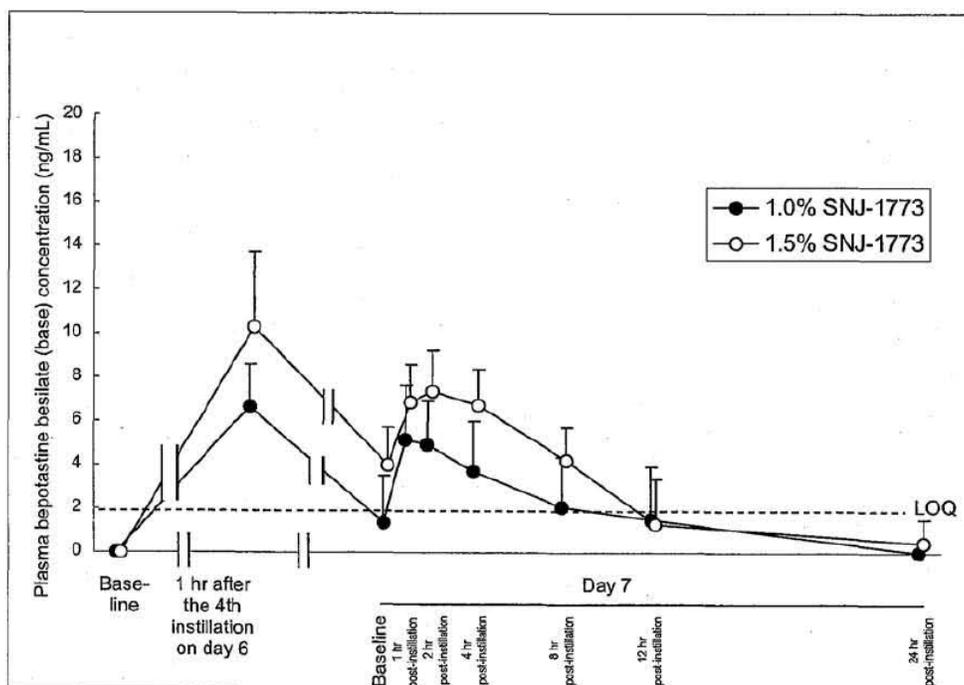
Source: SNJ-TO-02 Study Report, Section 11.2

### **Bepotastine Plasma Pharmacokinetics**

Plasma concentration-time profiles for bepotastine following ophthalmic administration of SNJ-1773 bilaterally four times daily for seven days in healthy male subjects are presented in Figure 1. A summary of plasma concentrations of bepotastine following ophthalmic administration of SNJ-1773 bilaterally four times daily for seven days in healthy male subjects is presented in Table 2.

Following ophthalmic administration of SNJ-1773 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; C<sub>max</sub> values for 1.0% and 1.5% SNJ-1773 following four times daily bilateral ophthalmic administration for 7 days 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.

Figure 1. Mean Plasma Concentration-Time Profiles for Bepotastine Besilate Following Ophthalmic Administration of SNJ-1773 Bilaterally Four Times Daily for Seven Days in Healthy Male Subjects



Source: SNJ-TO-02 Study Report, Section 11.4.1

Table 2. Summary of Bepotastine Besilate Plasma Concentrations Following Ophthalmic Administration of SNJ-1773 Bilaterally Four Times Daily for Seven Days in Healthy Male Subjects

	Day 1	Day 6	Day 7						
0 hr	0 hr	1 hr	0 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr
<b>1.0% SNJ-1773</b>									
N	6	6	6	6	6	6	6	6	6
Mean	0	6.630	1.383	5.138	5.130	3.747	2.080	1.507 <sup>†</sup>	0
SD	0	1.936	2.149	2.503	1.959	2.249	2.282	2.409	0
Minimum	0	4.14	0	2.20	2.33	0	0	0	0
Maximum	0	8.59	4.40	9.15	8.10	6.09	4.36	5.46	0
<b>1.5% SNJ-1773</b>									
N	6	6	6	6	6	6	6	6	6
Mean	0	10.267	4.000	6.872	7.335	6.685	4.233	1.260 <sup>†</sup>	0.430 <sup>†</sup>
SD	0	3.470	1.696	1.711	1.876	1.677	1.459	2.079	1.053
Minimum	0	4.33	2.15	4.55	4.80	3.80	2.06	0	0
Maximum	0	15.10	6.47	9.63	10.26	8.69	5.91	4.91	2.58

<sup>†</sup> Note, the reported mean concentrations are below the limit of quantitation, suggesting BLQ values were assigned a value of zero (0).

Source: SNJ-TO-02 Study Report, Section 11.4.1

**SPONSOR'S CONCLUSIONS:**

In the Phase 1 study of oral bepotastine besilate, the plasma concentration of bepotastine besilate after a single administration at a usual dose of 10 mg was  $101.3 \pm 3.5$  ng/mL. This was approximately 10 times that of repeated instillation of one drop of 1.5% SNJ-1773 ophthalmic solution to both eyes four times daily. Thus, the potential for systemic effects is minimal.

**REVIEWER ASSESSMENT:**

Results from Study SNJ-TO-02 adequately described the systemic exposure of bepotastine following multiple ophthalmic administration of SNJ-1773 bilaterally four times daily for seven days in healthy male subjects. The Applicant's pharmacokinetic conclusions based on these findings are acceptable from a Clinical Pharmacology perspective.

The estimated maximum total daily dose of bepotastine besilate administered in Study SNJ-TO-02 is approximately 4 mg for the 1.0% solution and 6 mg for the 1.5% solution. The proposed DOSAGE AND ADMINISTRATION of Bepreve™ (bepotastine besilate ophthalmic solution, 1.5%) is to instill one drop into the affected eye(s) twice a day (BID). The estimated maximum total daily dose for this proposed regimen is approximately 3 mg. Thus, the anticipated systemic exposure with the proposed regimen is expected to be less than that observed in the current study.

#### 4.1.2. Study TNB-TO-01

**TITLE:**

Phase 1 Study of TAU-284: Single Oral Administration in Healthy Male Volunteers

Study Initiation: October 1991

Study Completion: November 1991

Site: (b) (4)

**OBJECTIVES:**

To investigate the safety and pharmacokinetics of single oral doses of TAU-284 in healthy male volunteers

**STUDY DESIGN:**

In this Phase 1 study, 16 healthy male subjects were divided into panels I and II, each consisting of 8 subjects. TAU-284 tablets were administered to six of eight subjects and placebo tablets were administered to two subjects in each panel. The doses were 2.5, 5, 10, 20, and 40 mg (20 mg × 2), and the administration period for each dose was defined as steps I, II, III, IV, and V, respectively. In panel I, subjects assigned to TAU-284 received 2.5 mg as a single oral dose the first week (step I), 10 mg the third week (step III), and 40 mg (2 × 20 mg) the fifth week (step V). Subjects assigned to receive TAU-284 in panel II received 5 mg the second week (step II) and 20 mg the fourth week (step IV). The drugs were given by a simple blind method. The drug was administered under fasting conditions, and dosing was started from the lowest dose of 2.5 mg and increased, with confirmation of safety, to 40 mg. Following the final step, the effect of food intake on the pharmacokinetics of TAU-284 was investigated. Panel II subjects ingested a light breakfast and received 20 mg TAU-284 30 minutes after breakfast.

*Reviewer Comment: For purposes of ophthalmic NDA 22-288, only the fasted pharmacokinetic information was reviewed.*

**FORMULATIONS:**

For the test drugs, tablets containing 2.5, 5, 10, and 20 mg of TAU-284 and placebo tablets corresponding to each dose (indistinguishable by appearance) were used.

*Reviewer Comment: No batch/lot information was provided.*

**PHARMACOKINETIC ASSESSMENTS:**

Blood samples were collected before administration and 0.5, 1, 2, 3, 4, 6, 10, and 24 hours after administration. Urine was collected before administration and in the following intervals up to 24 hours after administration: 0–2, 2–4, 4–6, 6–10, and 10–24 hours.

**BIOANALYTICAL METHODOLOGY**

Plasma and urine concentrations of bepotastine were determined via a high performance liquid chromatography (HPLC) method. The quantification limit was 2 ng/ml in plasma and 50 ng/ml in urine. This method used (b) (4) as an internal reference standard. The plasma method had a linear quantitation range of 2 to 1000 ng/mL bepotastine, with 96.8% to 98.5% recovery. This method also displayed a high within-run precision as reflected in coefficient of variation (CV) values of 3.7% at 10 ng/mL bepotastine and 1.8% at 100 ng/mL bepotastine for repeated injections.

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

The maximum plasma concentration of the drug ( $C_{max}$ ) and the time ( $T_{max}$ ) at which it occurred were measured. The elimination half life ( $T_{1/2}$ ) was calculated from the elimination rate constant obtained by linear regression of the logarithm of the plasma levels in the elimination phase. The area under the plasma concentration–time curve ( $AUC_{24}$ ) until the final blood sampling time point was calculated from the measured values by the trapezoid method. The area under the curve for infinite time ( $AUC_{\infty}$ ) was obtained by adding the  $AUC_{24}$  value to a value (final measured value/elimination rate constant) obtained by extrapolation of the elimination rate constant.

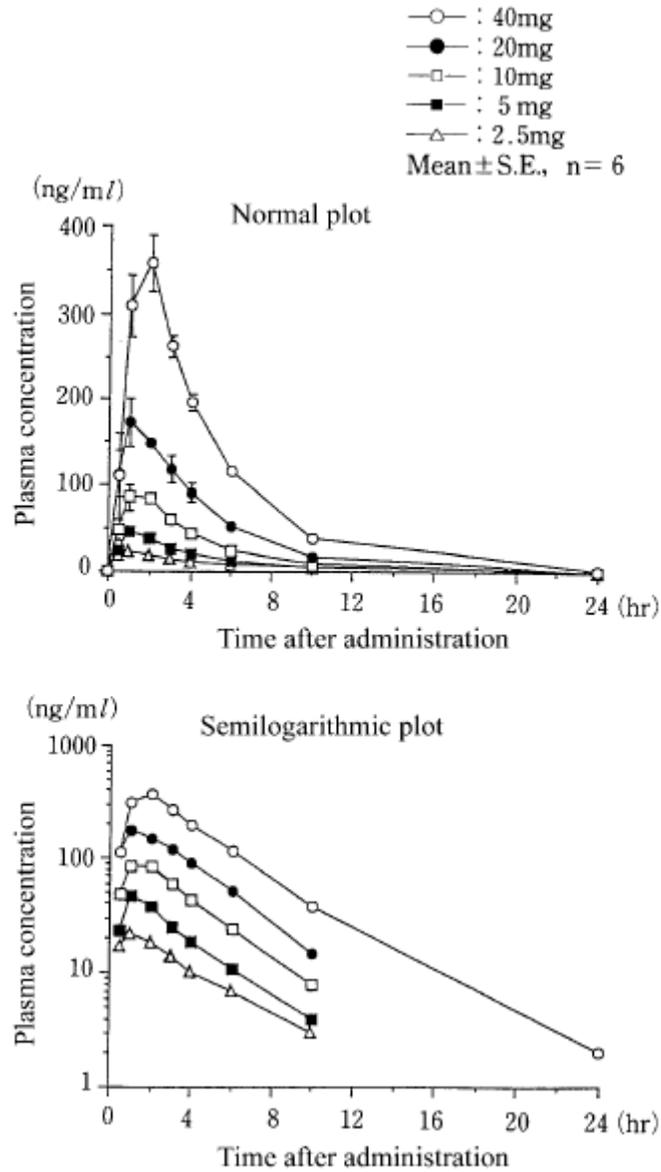
**RESULTS:**

Plasma concentration-time profiles for unchanged TAU-284 following single oral administration in the fasted state in healthy male subjects are presented in Figure 1. A summary of TAU-284 pharmacokinetic parameters following single oral administration in the fasted state in healthy male subjects is presented in Table 2.

Maximum plasma concentrations of bepotastine were achieved within 2 hours for all dose groups studied. Elimination of bepotastine from the plasma followed a monophasic decline with a half-life of approximately 3 hours (mean half life range: 2.3–3.3 hours). The decline in concentrations reached values below the detection limit 24 hours after administration with all doses except the highest dose studied (40 mg).  $C_{max}$  and AUC of unchanged bepotastine increased in a dose-dependent manner. No metabolites were observed following single oral administration of TAU-284 at any dose.

Approximately 76 to 88% of the TAU-284 dose was excreted in urine by 24 hours following TAU-284 administration across all dose groups studied. Metabolites in which the  $N-(CH_2)_3COOH$  group of TAU-284 was changed to  $N-CH_2COOH$  and to  $N-H$  were detected, accounting for about 0.3% and 1% of the original dose, respectively with TAU-284 doses of 20 mg or higher. In addition, a trace amount of a peak that may have been a metabolite was detected in some urine samples at high doses.

Figure 1. Mean Plasma Concentration-Time Profiles for Unchanged TAU-284 Following Single Oral Administration of TAU-284 in the Fasted State in Healthy Male Subjects



Source: TNB-TO-1 Study Report

Table 2. Summary of TAU-284 Pharmacokinetic Parameters Following Single Oral Administration of TAU-284 in the Fasted State in Healthy Male Subjects

Dose (mg)	Cmax (ng/mL)	Tmax (hr)	AUC <sub>24</sub> (ng·hr/mL)	AUC <sub>∞</sub> (ng·hr/mL)	T1/2 (hr)	Urinary Excretion (%)
2.5	22.4 (2.1)	0.8 (0.1)	113.7 (7.0)	113.7 (7.0)	3.3 (0.3)	77.9 (1.4)
5	46.2 (4.0)	1.2 (0.2)	203.6 (6.7)	203.6 (6.7)	2.5 (0.1)	76.4 (3.5)
10	101.3 (3.5)	1.2 (0.2)	438.6 (29.1)	438.6 (29.1)	2.4 (0.1)	84.4 (1.4)
20	199.5 (13.1)	1.5 (0.3)	879.7 (60.6)	879.7 (60.6)	2.3 (0.1)	84.0 (3.5)
40	393.6 (23.7)	1.6 (0.3)	1909.4 (80.9)	1916.4 (81.1)	2.9 (0.2)	87.9 (3.0)

Data reported as mean (SE).

Source: TNB-TO-1 Study Report

**SPONSOR'S CONCLUSIONS:**

TAU-284 displayed linear pharmacokinetic characteristics within a dose range 2.5 to 40 mg. Based on the results of the urinary excretion, 75–90% of the dose was excreted as the unchanged form of the drug by 24 hours after administration, showing that the bioavailability of the drug is high and that renal excretion is the major elimination pathway. TAU-284 is not metabolized to a great extent; a trace amount (~ 1%) of metabolites was detected only in urine at a dose of 20 mg or higher.

**REVIEWER ASSESSMENT:**

Results from the single dose escalation study Study TNB-TO-1 adequately described the pharmacokinetics of bepotastine following single oral administration of TAU-284 in the fasted state in healthy male subjects. The Applicant's pharmacokinetic conclusions based on these findings are acceptable from a Clinical Pharmacology perspective.

The report submitted for Study TNB-TO-1 was only a summary of study results; no individual plasma or urine concentration and pharmacokinetic parameter listings were included in the submission. Therefore, individual pharmacokinetic data could not be reviewed.

#### 4.1.3. Study TNB-HE-07

**TITLE:**

Metabolism of Bepotastine Besilate (TAU-284) in Human Liver Microsomes and the Main Effects on P450 Activity

**OBJECTIVES:**

To compare the metabolic interactions of TAU-284 and terfenadine in human liver microsomes

**METHODS:**

For the reactions in human liver microsomes, a reaction mixture was prepared in which human microsomes (final concentration 0.5 mg protein/mL), D-G-6P (final concentration 5 mM), D-G-6PDH (final concentration 2 units/mL), NADP (final concentration 3 mM) and MgCl<sub>2</sub> (final concentration 6 mM) were contained within a 1/15M phosphate buffer solution (PB) (pH 7.4). The degradation experiments were performed with the microsome reaction mixture at 37°C with incremental sampling for 5 to 30 minutes. The concentrations of TAU-284, the various substrates, and internal standards were analyzed using a validated HPLC method with UV detection.

**TEST MATERIALS:**

The TAU-284 (Lot No. 13), terfenadine (Lot No. 3), and UR-02025 (Lot No. 1; used as the internal standard [IS] for terfenadine) was obtained from Ube Industries Ltd (b) (4), the internal standard for TAU-284 (Lot No. A001, (b) (4)) was used. The following probes were used for each specified CYP: CYP3A, testosterone and 6P-hydroxytestosterone with 11 $\alpha$ -hydroxyprogesterone and ketoconazole as IS; CYP2C9, tolbutamide and hydroxytolbutamide with chlorpropamide and sulfaphenazole as IS; CYP2C19, S-(+)-mephenytoin and (+)-4'-hydroxyl-mephenytoin with pentobarbital and omeprazole as IS.

**RESULTS:**

The metabolism of TAU-284 by human liver microsomes is presented in Figure 1. Metabolism of TAU-284 was minimal; the residual amount of unchanged TAU-284 remaining after 120 min of incubation was 95.5 to 99.1% . The effects of TAU-284 and control chemical inhibitors on cytochrome P450-dependent activities in human liver microsomes are summarized in Table 1. Based on this kinetic data with TAU-284 concentrations ranging from 2 to 200  $\mu$ M, it is likely that TAU-284 will have no effects on the metabolism of concomitant drugs involving CYP3A4, 2C9, and 2C19.

Figure 1 Metabolism of TAU-284 by Human Liver Microsomes

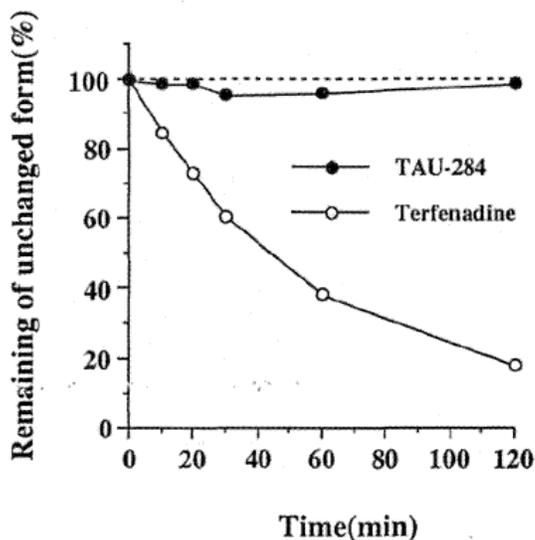


Table 1 Effects of TAU-284 and Various Inhibitors (Positive Controls) on Cytochrome P450-Dependent Activities in Human Liver Microsomes

Inhibitor	Concentration (μM)	Remaining Activity (%)
<i>CYP3A4 (Testosterone 6β-hydroxylation)</i>		
TAU-284	2	100.0 ± 1.8
	20	100.9 ± 1.1
	200	98.4 ± 2.0
Ketoconazole	2	4.9 ± 1.0
<i>CYP2C9 (Tolbutamide hydroxylation)</i>		
TAU-284	2	98.8 ± 3.4
	20	98.9 ± 4.5
	200	99.4 ± 2.0
Sulfaphenazole	2	10.6 ± 0.4
<i>CYP2C19 (S-Mephenytoin 4'-hydroxylation)</i>		
TAU-284	2	99.8 ± 1.6
	20	102.3 ± 3.0
	200	97.9 ± 5.5
Omeprazole	2	17.0 ± 2.3

Each value represents the mean ± SD of three experiments.

Source: TNB-HE-07 Study Report

**SPONSOR'S CONCLUSIONS:**

Based on the findings from Study TNB-HE-07, the potential for metabolic drug interactions with TAU-284 is low.

**REVIEWER ASSESSMENT:**

The Applicant's conclusions based on the findings from Study TNB-HE-07 are acceptable from a Clinical Pharmacology perspective. Although certain cytochrome P450 enzymes were not studied (CYP1A2, CYP2C8, CYP2D6), systemic concentrations following ophthalmic

administration are expected to be low, such that metabolic drug interactions are not expected with the ophthalmic product.

#### 4.1.4. Study TNB-TO-4

##### **TITLE:**

Determination of Protein Binding in the Phase 1 Clinical Trial of the Antiallergic Agent TAU-284 (Bepotastine Besilate) – Bioequivalence Trials Among Drug Products

##### **OBJECTIVES:**

To determine the protein binding of TAU-284 in healthy adult males

##### **METHODS:**

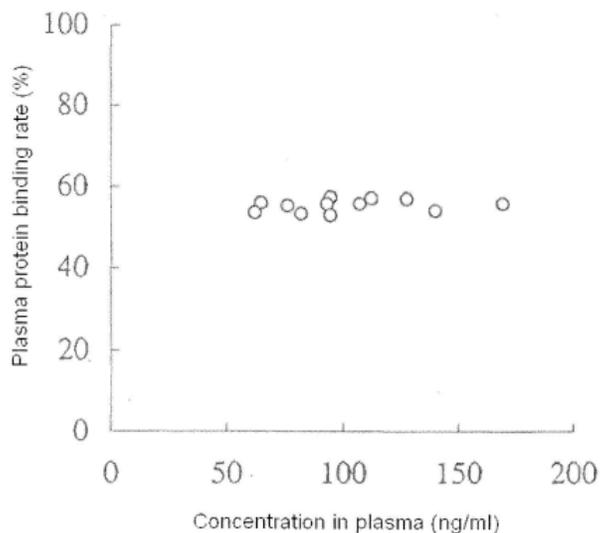
Blood samples for determination of TAU-284 protein binding were drawn from six (6) healthy adult male volunteers enrolled in Study TNB-TO-4, a Phase 1, randomized, crossover bioequivalence study. Subjects were allocated to receive two 5 mg tablets of TAU-284 and one 10 mg tablet of TAU-284. In vivo protein binding was measured in the first phase of the trial (Phase I) in the six individuals randomized to receive one 10 mg tablet. Blood samples were collected at 1 and 2 hours post-dose, and the separated plasma (1 ml) was added to an (b)(4). The concentrations of betotastine in the plasma and the filtrate were measured by HPLC. The lower limit of quantitation of the assay was 2 ng/mL. The equation below was used for determination of protein binding:

$$\text{Plasma protein binding rate (\%)} = \{1 - (\text{concentration in filtrate}/\text{concentration in plasma})\} \times 100$$

##### **RESULTS:**

The relationship between plasma protein binding of TAU-284 expressed as a percent and total concentrations of TAU-284 in plasma is presented in Figure 1. Mean plasma protein binding of betotastine 1 and 2 hours after administration was 55.4%. Protein binding was independent of TAU-284 concentration over the range of concentrations observed in this study (60 to 170ng/mL).

Table 1 Percent Protein Binding Versus Total Concentrations of TAU-284



**SPONSOR'S CONCLUSIONS:**

Based on the findings from Study TNB-HE-07, the protein binding rate in vivo for TAU-284 was 55.4% and was virtually independent of the concentration in plasma.

**REVIEWER ASSESSMENT:**

The Applicant's conclusions based on the protein binding results from Study TNB-TO-4 are acceptable from a Clinical Pharmacology perspective.

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Charles Bonapace  
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BIOPHARMACEUTICS

## CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 22-288  
 Drug Name: Bepotastine besilate ophthalmic solution 1.5%  
 Applicant: Ista Pharmaceuticals  
 Submission Date: 12NOV2008  
 Filing Date: 15DEC2008  
 PDUFA Date: 12SEP2008  
 OCP Primary Reviewer: Kimberly L. Bergman, PharmD  
 OCP Team Leader: Charles Bonapace, PharmD

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<b><i>Fileability:</i></b> <b><i>Is the Clinical Pharmacology section of the application fileable?</i></b> <b><i>(if 'NO', please comment as to why it is not fileable)</i></b>	<b><i>X</i></b>			
<i>Fileability Review Components</i>				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Appendices for Study SNJ-TO-02 were not submitted in translated form. These include Appendix 16.2.6, Individual PK Data.

\_\_\_\_\_  
OCP Primary Reviewer

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Date

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OCP Team Leader

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Date

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

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Kimberly Bergman  
12/15/2008 02:36:25 PM  
BIOPHARMACEUTICS

Charles Bonapace  
12/16/2008 06:26:20 AM  
BIOPHARMACEUTICS