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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-516**

**Medical Review(s)**

**Medical Officer's Review of NDA 21-516**  
Review #2

**NDA 21-516**  
Medical Officer's Review #2

**Submission Date:** May 6, 2004  
May 11, 2004

**Review Completed:** May 19, 2004

**Trademark:**

Istalol

**Generic Name:**

timolol maleate ophthalmic solution 0.5%

**Sponsor:**

Senju Pharmaceutical Co., Ltd.  
5-8 Hiranomachi 2-chrome  
Chuo-ku  
Osaka 541-0046  
Japan

**Authorized U.S. Agent:**

Marvin Garret  
Vice-President  
ISTA Pharmaceuticals, Inc.  
15279 Alton Parkway, Suite 100  
Irvine, CA 92618

Telephone 949-788-5303  
Facsimile 949-727-0833

**Pharmacologic Category:**

beta-blocker

**Reviewer's Comments:**

*Revised labeling based on previous review, discussion with the applicant, revised container and carton labeling, and a corrected package insert transmitted by the applicant on May 11, 2004.*

*The sponsor has accepted all changes to the labeling as requested by the Division. This labeling is acceptable.*

12 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**Recommendations:**

The application supports the safety and effectiveness of Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Per the Pediatric Research Equity Act ("PREA") enacted on December 3, 2003, the sponsor should provide information on the use of timolol maleate ophthalmic solution in pediatric patients under 6 years of age.

It is recommended that NDA 21-516 be approved with the labeling submitted.

William M. Boyd, M.D.  
Medical Officer

**cc:**

HFD-550/Div Files  
HFD-550/MO/Boyd  
HFD-550/Dep Div Dir/Chambers  
HFD-550/Chem/Khorshidi  
HFD-550/Chem TL/Ng  
HFD-550/PharmTox/ChenZ  
HFD-550/PharmTox TL/Yang  
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HFD-550/PM/Puglisi

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Medical Officer's Review of NDA 21-516  
Original

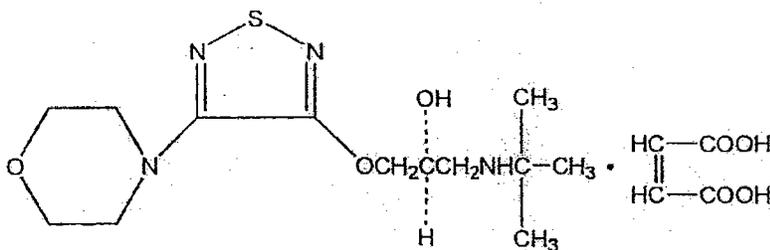
NDA 21-516  
Medical Officer's Review

Submission Date: September 27, 2002  
Review Completed: July 7, 2003

Trademark: Istalol

Generic Name: timolol maleate ophthalmic solution 0.5%

Chemical Name:



Mol Wt 432.49  
timolol maleate  $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

(-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt)

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Irvine, CA 92618

Telephone 949-788-5303  
Facsimile 949-727-0833

Pharmacologic Category: beta-blocker

Related IND: IND 59,046

Referenced NDA: NDA 18-086

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## **Executive Summary**

### **1 Recommendations**

#### **1.1 Recommendation on Approvability**

NDA 21-516 is recommended for approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma after outstanding Chemistry/Manufacturing issues and labeling issues have been resolved.

#### **1.2 Recommendation on Phase 4 Studies**

No Phase 4 studies are recommended.

### **2 Summary of Clinical Findings**

#### **2.1 Brief Overview of Clinical Program**

Senju Pharmaceutical Co., Ltd. has submitted a 505(b)(2) New Drug Application for Istalol (timolol maleate ophthalmic solution) 0.5%.

This 505(b)(2) NDA relies, in part, on the FDA's findings of safety and efficacy for timolol maleate ophthalmic solution for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. All patents and periods of exclusivity for the original product [Merck's NDA 18-086 for Timoptic (timolol maleate ophthalmic solution) 0.5%] in the United States have expired.

Senju selected the 505(b)(2) filing because:

- changes to the labeling from the innovator product are desired
- support comes from clinical studies
- a PDUFA user fee has been submitted.

In this NDA submission, Senju proposes a new formulation of timolol maleate ophthalmic solution with potassium sorbate (0.47%) in order to purportedly enhance the ocular bioavailability of the timolol instilled.

With the exception of the potassium sorbate, the formulations of Istalol and timolol maleate ophthalmic solution are essentially the same. Potassium sorbate is a well-known, well-studied ophthalmic drug product component.

The primary clinical support for this NDA submitted by the Sponsor consists of one Phase 3 clinical study conducted under IND 59,046 comparing Istalol (timolol maleate ophthalmic solution) 0.5% administered QD to timolol maleate ophthalmic solution (manufactured by [redacted]) administered BID. **Note:** In this trial, Istalol (timolol maleate ophthalmic solution) 0.5% was referred to as Timolol-LA 0.5% (TLA) and timolol maleate ophthalmic solution (manufactured by [redacted]) was referred to as TIM.

The sponsor conducted a 12-month, multi-center, randomized, double-masked, parallel-group clinical trial that compared the safety and efficacy of Istalol (timolol maleate ophthalmic solution) 0.5% administered QD (q AM) to timolol maleate ophthalmic solution (manufactured by [redacted]) administered BID. 3-month data was submitted on September 27, 2002, and a safety update with 12-month data was submitted on January 22, 2003.

## 2.2 Efficacy

The submitted study in NDA 21-516 is sufficient to establish efficacy for Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Once-daily dosed Istalol (timolol maleate ophthalmic solution) 0.5% lowers intraocular pressure between 5 and 7 mmHg from baseline.

## 2.3 Safety

The safety data contained in this submission is generally comparable to that reported for Merck's NDA 18-086 for Timoptic (timolol maleate ophthalmic solution) 0.5%. There are some differences in the adverse event profile as noted in the package insert labeling.

## 2.4 Dosing

Timoptic (timolol maleate ophthalmic solution) 0.5% is labeled for once or twice daily administration. Timoptic-XE (timolol maleate gel forming solution) 0.5% is labeled for once daily (AM) administration.

Senju Pharmaceutical Co., Ltd has proposed Istalol (timolol maleate ophthalmic solution) 0.5% be administered once daily.

## 2.5 Special Populations

No additional data on special populations was obtained.

## Clinical Review

### 1 Introduction and Background

- 1.1 Trademark:** Istalol 0.5%
- Generic Name:** timolol maleate ophthalmic solution
- NDA Drug Classification:** 3S
- Proposed Indication:** treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
- Dosage Form and Route of Administration:** ophthalmic solution for topical ocular administration
- Age Groups:** Adults 18 years of age and older

**1.2** There are numerous topical products currently available for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma either as first line or second line therapies. These products include topical beta-blockers, topical carbonic anhydrase inhibitors, topical alpha-2 agonists, and topical prostaglandin analogues.

**1.3** There were no important milestones in the development of this product.

**1.4** The WARNINGS Section of the labeling for topical beta-blockers includes the following statement:

**The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).**

### 2 Significant Findings from Chemistry, Animal Pharmacology and Toxicology

Agree with Chemistry recommendations. See Chemistry Review for detailed comments.

Agree with Pharmacology/Toxicology recommendations. See Pharmacology/Toxicology Review for detailed comments.

### 3 Human Pharmacokinetics and Pharmacodynamics

#### 3.1 Pharmacokinetics

Agree with Clinical Pharmacology and Biopharmaceutics recommendations. See Clinical Pharmacology and Biopharmaceutics Review for detailed comments.

#### 3.2 Pharmacodynamics

See above (3.1).

### 4 Description of Clinical Data and Sources

4.1 Included in this medical officer's review is an evaluation of a single clinical trial conducted in the United States.

4.2 See Table 1 for a descriptive summary of the clinical trial.

**Table 1 – Description of Data Sources**

<b>Protocol Number</b>	TIMLA-301
<b>Study Design</b>	Multi-Center, Randomized, Double-Masked, Parallel-Group
<b>Treatment Duration</b>	12 months
<b>Patient Population</b>	18 years of age or greater with ocular hypertension or open angle glaucoma
<b>Treatment Groups</b>	<ul style="list-style-type: none"> <li>• TLA<sup>1</sup></li> <li>• TIM</li> </ul>
<b>Dosing</b>	<ul style="list-style-type: none"> <li>• TLA qAM; TLA vehicle qPM</li> <li>• TIM qAM and qPM</li> </ul>
<b>No. Sites</b>	21
<b>No. Subjects Enrolled/Randomized</b>	332
<b>Status</b>	Original Submission – 3-month data; January 22, 2003, submission, final (12-month) report

4.3 No new safety information from post-marketing experience was presented in this submission.

4.4 There are no data in the published literature pertinent to the review of this submission.

### 5 Clinical Review Methods

<sup>1</sup> TLA corresponds to Istalol (timolol maleate ophthalmic solution) 0.5%; TLA vehicle corresponds to the Istalol vehicle; TIM corresponds to timolol maleate ophthalmic solution (manufactured by .E 3

These abbreviations are utilized throughout the review of Protocol TIMLA-301.

- 5.1 Included in this medical officer's review is the evaluation of one clinical trial conducted at 21 clinical centers located in the United States.
- 5.2 The submission is provided in paper format. Electronic data sets are provided. Both paper and electronic formats were utilized in the review of this application.
- 5.3 There is no evidence to indicate that the trial was not conducted in accordance with accepted ethical standards.
- 5.4 A financial disclosure statement is submitted. None of the investigators in this clinical study have reported financial interests as defined by 21CFR Part 54.

## 6 Integrated Review of Efficacy

- 6.1 The submitted study in NDA 21-516 is sufficient to establish efficacy for Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.
- 6.2 The efficacy database consisted of a single clinical trial conducted at 21 centers in the United States in support of the safety and efficacy of Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.
- 6.3 **Protocol TIMLA-301**

Title: A Double-masked, Randomized, Parallel Study of the Safety and Efficacy of Timolol-LA in Patients with Ocular Hypertension or Open-angle Glaucoma

Test Drug Schedule: 1 drop from "AM" bottle between 0800 and 1000 hours and 1 drop from "PM" bottle between 2000 and 2200 hours

**Table 2 – List and Description of Investigators**

<b>Principal Investigators</b>	<b>ID Number</b>	<b>No. of Subjects Randomized</b>
Thomas Mundorf, M.D. Mundorf Eye Center 1718 East 4 <sup>th</sup> St., Suite 703 Charlotte, NC 28204 Phone: 704-334-3222 Fax: 704-334-1532	101	19
Walter Atlas, M.D. Charlotte Eye, Ear, Nose and Throat Assoc., P.A. 1600 East Third Street Charlotte, NC 28204 Phone: 704-945-4112 Fax: 704-944-4895	102	19
Gregg Berdy, M.D. Ophthalmology Associates 456 North New Ballas Road, Suite 386 Creve Coeur, MO 63141 Phone: 314-993-5000 Fax: 314-993-5558	103	9
Arash Mansouri, M.D. Access Eye Center 110 Cambridge Street Fredericksburg, VA 22405 Phone: 540-371-2020 Fax: 540-373-0141	104	24
Moiz Mohammed Carim, M.D. Carim Eye & Retina Center 1981 State Hill Road Wyomissing, PA 19610 Phone: 610-376-1981 Fax: 610-376-3153	105	8
Andrew Cottingham, M.D. South Texas Eye Institute of San Antonio 2424 Babcock, Ste. 101 San Antonio, TX 78229 Phone: 210-692-1388 Fax: 210-692-1629	106	16

**Table 2 – List and Description of Investigators – Continued**

<b>Principal Investigators</b>	<b>ID Number</b>	<b>No. of Subjects Randomized</b>
Randy Craven, M.D. Glaucoma Consultants Of Colorado, P.C. 8381 South Park Lane Littleton, CO 80120 Phone: 303-797-1900 Fax: 303-347-1341	107	13
Mark Gorovoy, M.D. Eye Associates of Fort Myers 4225 Evans Ave. Fort Myers, FL 33901 Phone: 941-936-8655 941-939-1444 Fax: 941-936-8683	108	14
Marvin Greenberg, M.D. University Physicians Pavilion 7421 N. University Dr., Ste. 109 Tamarac, FL 33321 Phone: 954-726-2080 Fax: 954-726-2105	109	8
James Hart, M.D. Hart Ophthalmology Assoc., PSC 300 South 8 <sup>th</sup> St., Ste. 284 W Murray, KY 42071 Phone: 270-753-3131 Fax: 270-753-3169	110	21
Joseph Krug, M.D. Horizon Eye Care 135 South Sharon Amity, Suite 100 Charlotte, NC 28211 Phone: 704-365-0555 Fax: 704-367-8120	111	8

**Table 2 – List and Description of Investigators – Continued**

<b>Principal Investigators</b>	<b>ID Number</b>	<b>No. of Subjects Randomized</b>
Stephen Lane, M.D. Associated Eye Care 232 North Main St. Stillwater, MN 55082 Phone: 651-439-8500 Fax: 651-439-5106	112	11
Kenneth Olander, M.D. Maryville Eye Center 622 Smithview Dr. Maryville, TN 37803 Phone: 865-982-3520 Fax: 865-982-9746	113	17
Kenneth Sall, M.D. Sall Eye Surgery Medical Center 9604 E. Artesia Blvd., Suite 203 Bellflower, CA 90706 Phone: 562-804-1974 562-804-7672 Fax: 562-804-4350	114	20
Howard Schenker, M.D. Rochester Ophthalmological Group, PC 2100 Clinton Avenue S. Rochester, NY 14618 Phone: 716-244-6011 Fax: 716-244-0236	115	20
Samuel Solish, M.D. Eyecare Medical Group 53 Sewall Street Portland, ME 04102 Phone: 207-773-4723 Fax: 207-773-7034 207-773-1077	116	10

**Table 2 – List and Description of Investigators – Continued**

<b>Principal Investigators</b>	<b>ID Number</b>	<b>No. of Subjects Randomized</b>
Dara Stevenson, M.D. Stevenson Medical/Surgical Eye Center 3535 Bienville St., Suite 325 E. New Orleans, LA 70119 Phone: 504-486-1001 Fax: 504-483-9051	117	16
Richard Sturm, M.D. Ophthalmic Consultants of Long Island 200 Hempstead Ave. Lynbrook, NY 11563 Phone: 516-593-7709 Fax: 516-593-7548	118	21
Jeffrey Whitsett, M.D. 1237 Campbell Road Houston, TX 77055 Phone: 713-365-9099 Fax: 713-365-9356	119	12
Robert D. Williams, M.D. Taustine Eye Center 1169 Eastern Parkway Suite 3334 Louisville, KY 40217 Phone: 502-458-9004 Fax: 502-458-9842	120	18
Brandon Wool, M.D. 315 Metairie Rd., Ste. 302 Metairie, LA 70005 Phone: 504-835-2197 Fax: 504-835-2631	121	28

**Reviewer's Comments:**

*It is preferable to have at least 10 patients per arm per center.*

*For the three sites inspected by the Division of Scientific Investigations (102, 110, 121), no major deficiencies were noted that would be expected to compromise the integrity of the data.*

## Study Design

In this double-masked, parallel study, each patient was randomized to receive TLA QD (AM) or TIM BID, O.U. for twelve months. Masking was maintained through the use of a vehicle solution. Patients were instructed to apply the study medications between 0800 and 1000 hours (trough) and between 2000 and 2200 (peak) hours. Patients returned for regular visits for efficacy and safety measures.

The maximum treatment concentration and frequency for timolol in any ocular form was 0.5%, BID. This was the only concentration to be selected for this study. As the intended dosing regimen for TLA for chronic use in patients will be once-daily, this was the dosing regimen selected for this study. In contrast, TIM is typically used BID, and thus was the dosing regimen selected for this positive control agent in this study. The treatment period selected for this study was one year; the duration required by most major regulatory agencies for chronic safety and efficacy studies. A planned, interim analysis at three months allowed for initial filing of ocular hypotensive efficacy data.

Randomization occurred during Visit 1. Patients who met all entry criteria were randomized in strict numerical order as they qualified. Treatment assignment, based on numerical order of entry into the study, was generated by a list of random numbers supplied by the statistician at the time of drug labeling. "Study eye" was defined as the eye with the higher IOP on Day 1 based on the mean of the 0730-0930 and 1000-1200 hour measurements. In the event of the IOPs being equal, the left eye was designated as the study eye for patients with an even randomization number and the right eye was so designated if the number was odd.

## Inclusion Criteria

To be included in the study, the 300 patients were required to be:

- 1) 18 years of age or greater.
- 2) Diagnosis of open angle glaucoma (OAG) or ocular hypertension (OHT) in the study eye(s). Pseudoexfoliation or pigment dispersion component is acceptable. Previous laser surgery (including laser trabeculoplasty but excluding refractive procedures) or intraocular surgery (including cataract extraction or glaucoma filtering procedures) is acceptable. Iridectomy is acceptable, as long as the reason for the procedure was NOT angle closure.
- 3) Unmedicated IOP  $\geq$  22 mm Hg in one or both eyes, with no more than 5 mm Hg inter-eye difference at 0730-0930 and 1000-1200 hours at unmedicated Visit 1.
- 4) Corrected visual acuity by ETDRS in each eye of +1.0 logMAR or better (equivalent to 20/200).
- 5) Able and willing to give signed informed consent.
- 6) Able and willing to follow study instructions.

## **Exclusion Criteria**

Excluded from the study were individuals with characteristics as follows:

### **OPHTHALMIC**

- 1) Known hypersensitivity to any component of the formulation or to topical anesthetics, (e.g., timolol or other  $\beta$ -adrenoceptor antagonists, benzalkonium chloride, sorbic acid, etc.).
- 2) Known lack of ocular hypotensive response to topical ophthalmic, non-cardioselective  $\beta$ -adrenoceptor antagonists (in the opinion of the investigator).
- 3) Refractive surgery in study eye(s) (e.g., radial keratotomy, PRK, LASIK, etc.).
- 4) Chronic angle closure glaucoma or a history of acute angle closure treated with a peripheral iridotomy.
- 5) Ocular trauma within the past three months.
- 6) Ocular surgery or laser treatment within the past six months.
- 7) History or evidence of ocular infection, inflammation, clinically significant blepharitis or conjunctivitis within 2 months, or of herpes simplex keratitis.
- 8) Contact lens wear within 15 minutes of instillation of study medication.
- 9) Other than ocular hypotensive medications which must be washed out according to the provided schedule, ocular medication of any kind (with the exception of lubricating drops for dry eye) within 30 days of Visit 0.
- 10) Clinically significant ocular disease (e.g. corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for one month is not judged safe.
- 11) Any abnormality preventing reliable applanation tonometry of either eye.

### **GENERAL/SYSTEMIC**

- 12) Contraindications to  $\beta$ -adrenergic antagonists including but not limited to bronchial asthma (past or present), severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.
- 13) Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, hepatic, renal, cardiovascular or endocrine disorders) which might interfere with the study.
- 14) Participation in any study involving an IND investigational drug within the past 30 days.
- 15) Changes in systemic medication within 30 days prior to screening that could have a substantial effect on IOP, or anticipated changes during the study.
- 16) Excluded were women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study.

## Study Medications

The product was supplied as a colorless clear aqueous solution, 5 mL filled in white polyethylene containers (10 mL in capacity) with caps and eye dropper tips. The product was labeled with investigational labels with the study number, patient number, and period number and other relevant information, including a statement: "Caution: New Drug – Limited by Federal Law to Investigational Use". The labels were removed and adhered to the patient's case report form. At the conclusion of each treatment period, all bottles and kits were collected. Masking was maintained through the use of an "AM" and a "PM" bottle. For patients randomized to TLA, the "AM" bottle contained active, and the "PM" bottle contained vehicle. For patients randomized to TIM, both the "AM" and "PM" bottle contained active.

### Identity of Investigational Product(s)

- i. Timolol-LA ophthalmic solution (Lot number 21660) was a sterile, isotonic, buffered, aqueous solution of timolol maleate (0.5%) containing timolol maleate (equivalent to 0.5% timolol), sodium chloride, 0.47% potassium sorbate, monobasic sodium phosphate monohydrate, sodium hydroxide, and water for injection. This product was preserved with 0.005% benzalkonium chloride.
- ii. Timolol-LA vehicle solution (Lot number 91079, 31251) was a sterile, isotonic, buffered aqueous solution containing sodium chloride, 0.47% potassium sorbate, monobasic sodium phosphate monohydrate, sodium hydroxide, and water for injection. This product was preserved with 0.005% benzalkonium chloride.
- iii. Timolol maleate ophthalmic solution (Lot number 81420; [redacted]) was a sterile, isotonic, buffered, aqueous solution of timolol maleate (0.5%) containing timolol maleate (equivalent to 0.5% timolol), monobasic and dibasic sodium phosphate monohydrate, sodium hydroxide to adjust pH, and water for injection. This product was preserved with 0.010% benzalkonium chloride.

Individuals requiring or planning use of any form of ocular hypotensive medications (prescription or over-the-counter) were not to be enrolled in the study. Disallowed ocular medications included miotics, epinephrine-related compounds, carbonic anhydrase inhibitors,  $\alpha$ -adrenergic agonists,  $\beta$ -adrenergic blockers, and prostaglandin-type drugs. Intermittent use of over-the-counter artificial tear lubricant products and lid scrubs was acceptable. However, topical ocular allergy medications (OTC or prescription) were not allowed. Systemic therapy with agents that could have had a substantial effect on IOP was to be consistent in dose, regimen, and agent within the thirty (30) days prior to screening and throughout the study.

## Efficacy and Safety Variables

The primary measure of efficacy was intraocular pressure (mean intraocular pressure at each visit at each time point, peak and trough). Secondary measures of efficacy were change from baseline in Mean defect (MD) score on perimetry and cup-to-disc ratio.

The primary analysis for this study was efficacy after all patients completed three months of treatment. Patients continued in the trial until receiving 12 months of treatment, at which time an additional efficacy and safety analysis was performed. Ocular hypotensive efficacy may be answered after three months of treatment; however for certain regulatory filings, a full 12 months of treatment is required for safety reporting. The 12 month analysis was a masked extension of the 3 month trial; no probability adjustment was planned. The trial statistician conducted the interim analysis, and the results were communicated to the Sponsor. The monitors, site personnel, and patients remained masked to the treatment assignment.

Safety was assessed using: ocular signs and symptoms; ETDRS Corrected Visual Acuity; biomicroscopy of anterior segment including evaluation of corneal epithelium conjunctiva and lens; and ophthalmoscopy.

**Table 3 – Schedule of Visits and Measurements**

Visit	Day/Week	Procedures										
		Consent/ History	Pregnan- cy test <sup>1</sup>	HR/BP	VA	Symp	IOP	Bio	Oph	VF	Study Meds	Exit
0	Pre-study	X	X	X	X	X <sup>2</sup>	X	X	X	X <sup>3</sup>		
Washout												
1	Day 1			X	X	X	X	X				
	+2.5 hours			X			X					
	+3.0 hours											X <sup>4</sup>
	+3.25 hours			X		X						
2	Week 1			X	X	X	X	X				X
3	Week 2			X	X	X	X	X				X
	+2.5 hours			X		X	X					
4	Week 6			X	X	X	X	X				X
	+ 2.5 hours			X		X	X					
5	Week 12			X	X	X	X	X		X		X
	+ 2.5 hours			X		X	X		X			
6	Month 6			X	X	X	X	X		X		X
	+ 2.5 hours			X		X	X		X			
7	Month 9			X	X	X	X	X	X			X
	+ 2.5 hours			X		X	X					
8	Month 12		X	X	X	X	X	X		X		X
	+ 2.5 hours			X		X	X		X			X

HR/BP = heart rate/blood pressure; Symp = Symptoms questionnaire; VA = visual acuity; Bio = biomicroscopy; Oph = ophthalmoscopy (Visits 0 and 5, 6, 7 and 8 only; dilated at Visit 0, 5, 6, and 8, or patient final visit); VF = automated threshold visual fields.

Dilated ophthalmoscopy was to occur AFTER the +2.5 hour IOP measurement for Visits 5, 6 and 8.

At each visit, patients were questioned regarding their ocular and systemic symptoms.

## Subject Disposition and Demographics

**Table 4 – Subject Disposition at 12 Weeks**

Status	Treatment	
	TLA N (%)	TIM N (%)
Entered	166	166
Completed	154 (93)	155 (93)
Not completed	12 (7)	11 (7)
Terminated	8 (5)	6 (4)
Discontinued	4 (2)	5 (3)

**Table 5 – Subject Disposition at 12 Months**

Status	Treatment	
	TLA N (%)	TIM N (%)
Entered	166	166
Completed	145 (87)	145 (87)
Not completed	21 (13)	21 (13)
Terminated	11 (7)	9 (6)
Discontinued	10 (6)	12 (7)

### **Reviewer's Comments:**

*There were 332 patients enrolled in the study: 166 patients randomized to TLA and 166 patients randomized to TIM.*

*The intent to treat population (last observation carried forward) consisted of 332 subjects; the per protocol (observed cases) population consisted of 327 subjects.*

*The most frequent reason for discontinuation in the study prior to Week 12 was adverse events (4% overall, 12/309). Two patients, one in each treatment group, discontinued prior to Month 3 due to lack of treatment effect (1%, 2/309).*

*The most frequent reason for discontinuation in the study prior to Month 12 was adverse events (6% overall, 17/290). These 17/290 include the 12 subjects discontinued prior to Week 12.*

**Table 6 – Discontinued Patients and Reasons  
Listing of Patients not Completing through Week 12 (Visit 5)**

Invest.#	Pt#	Tx	Reason	Comment	Exit Day
115	216	TLA	Treatment failure		84
115	319	TIM	Treatment failure		43
101	003	TLA	Adverse event	Patient had headaches	70
102	079	TLA	Adverse event	Superficial punctate keratitis	35
104	265	TLA	Adverse event	Severe anemia	10
105	147	TLA	Adverse event	Ocular allergy	45
110	349	TLA	Adverse event	Complaints of nervousness and fatigue	14
115	214	TLA	Adverse event	Dizziness, fatigue	12
121	283	TLA	Adverse event	Traumatic hyphema OD	13
101	007	TIM	Adverse event	Patient withdrew due to difficulty making visits after discharged from hospital (retroperitoneal bleeding)	158
102	083	TIM	Adverse event	Decrease in visual acuity; subsequent YAG capsulotomy	91
104	098	TIM	Adverse event	Allergic dermatitis on eyelids OU and conjunctivitis OU	26
112	119	TIM	Adverse event	Blur OS, lightheaded and tightness in arm and leg	49
121	141	TIM	Adverse event	Lid irritation – itching OU	1
104	107	TLA	Protocol violation	Emphysema	8
104	103	TIM	Protocol violation	Chronic angle closure glaucoma	10
108	314	TIM	Protocol violation	Unable to complete reliable visual field	85
111	091	TLA	Patient withdrew consent		69
110	179	TLA	Other	Patient treated only one eye; sponsor requested dropping	140
118	273	TLA	Other	After randomization, discovered patient had hx of asthma and was using anti-asthma meds; dropped after discussion with CRO	9
104	268	TIM	Other	Relocating	42
119	024	TIM	Other	Patient withdrew consent	82
121	286	TIM	Other	Transportation issues	28

**Reviewer’s Comments:**

*Twenty-three subjects did not complete Week 12. The case report forms for subjects 101-007 (TIM) and 110-179 (TLA) are not included in the original submission or in any subsequent amendment. It is unclear why these subjects are considered discontinued patients not completing through Week 12.*

**Table 7 – Summary of Demographics  
(Safety Population)**

Measure	TLA	TIM
<b>N</b>	166	166
<b>Age (y)</b>		
Mean $\pm$ s.e.m. <sup>2</sup>	64.3 $\pm$ 12.4	64.9 $\pm$ 11.1
Range	29-92	32-85
<b>Gender</b>		
Female	102 (61%)	101 (61%)
Male	64 (39%)	65 (39%)
<b>Race</b>		
Caucasian	135 (81%)	132 (80%)
Asian	2 (1%)	2 (1%)
Black	21 (13%)	21 (13%)
Hispanic	7 (4%)	11(7%)
Other	1 (1%)	0
<b>Iris Color</b>		
Brown	79 (48%)	88 (53%)
Hazel	23 (14%)	23 (14%)
Blue	53 (32%)	44 (27%)
Gray	5 (3%)	3 (2%)
Other	6 (4%)	8 (5%)
<b>Glaucoma Dx</b>		
OAG	116 (70%)	114 (69%)
OHT	50 (30%)	51 (31%)

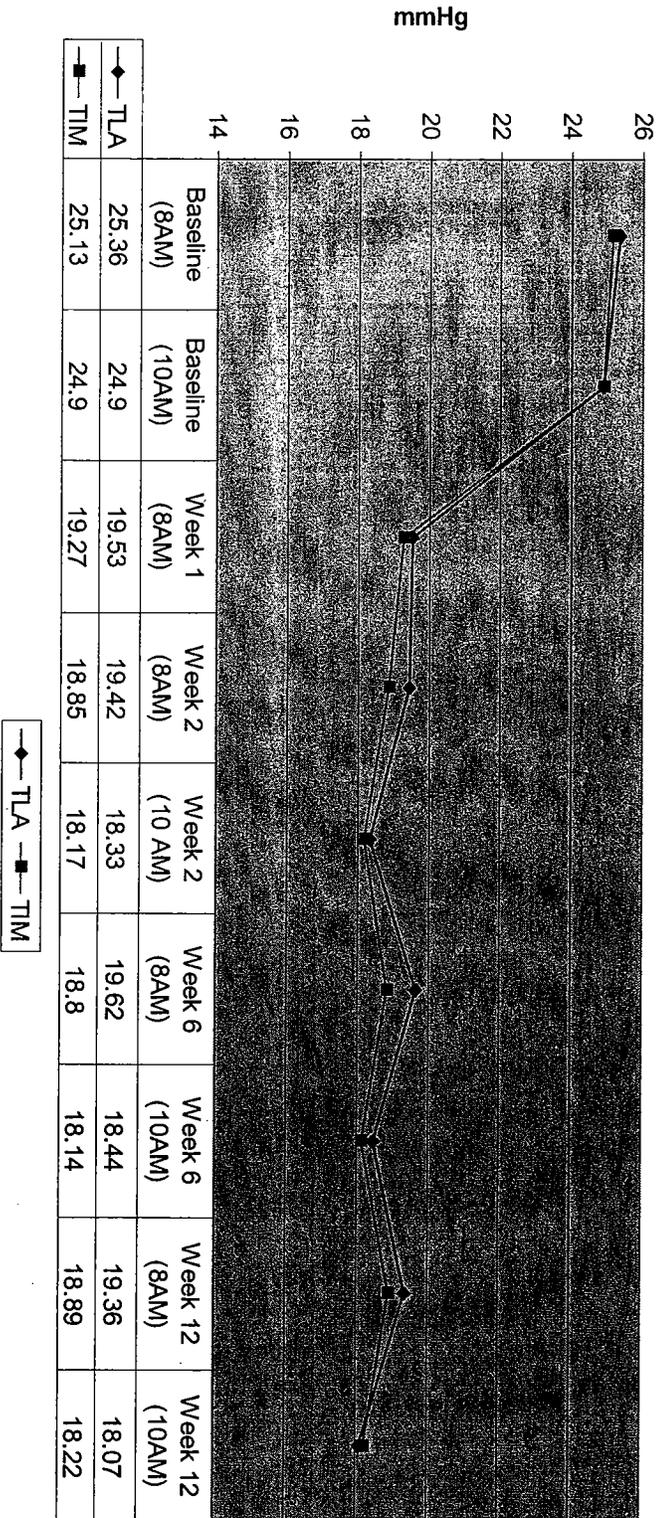
**Reviewer's Comments:**

*For the safety population, there were no statistically significant differences between the 2 treatment groups for any of the demographic characteristics.*

<sup>2</sup> s.e.m. = Standard Error of the Mean

Efficacy – Protocol TIMLA-301 – Primary Efficacy Variable at 12 Weeks – Intent-to-Treat Population (LOCF)

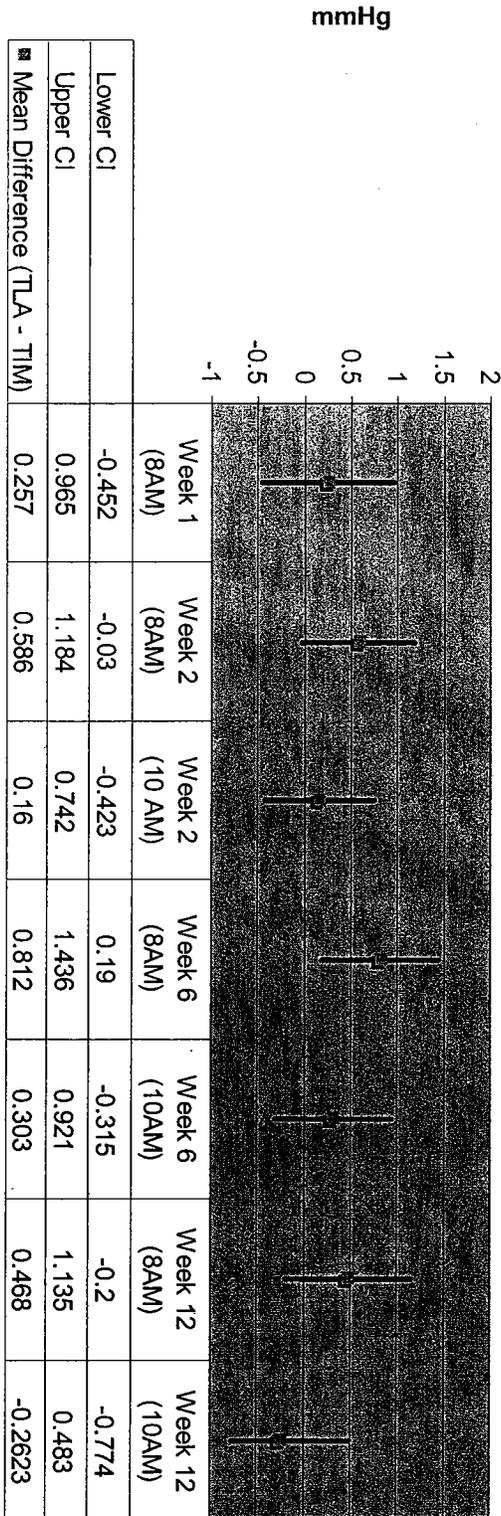
Mean IOP per Visit and Time



Reviewer’s Comments:

Once daily-dosed TLA [Istalol (timolol maleate ophthalmic solution) 0.5%] demonstrates equivalence in the ability to lower IOP compared to twice-daily-dosed TIM (timolol maleate ophthalmic solution) dosed over 12 weeks. Once daily-dosed TLA [Istalol (timolol maleate ophthalmic solution) 0.5%] lowers IOP between 6 and 7 mmHg from baseline. TIM (timolol maleate ophthalmic solution) lowers IOP between 6 and 7 mmHg from baseline.

Mean Difference (TLA - TIM) with 95% Confidence Intervals

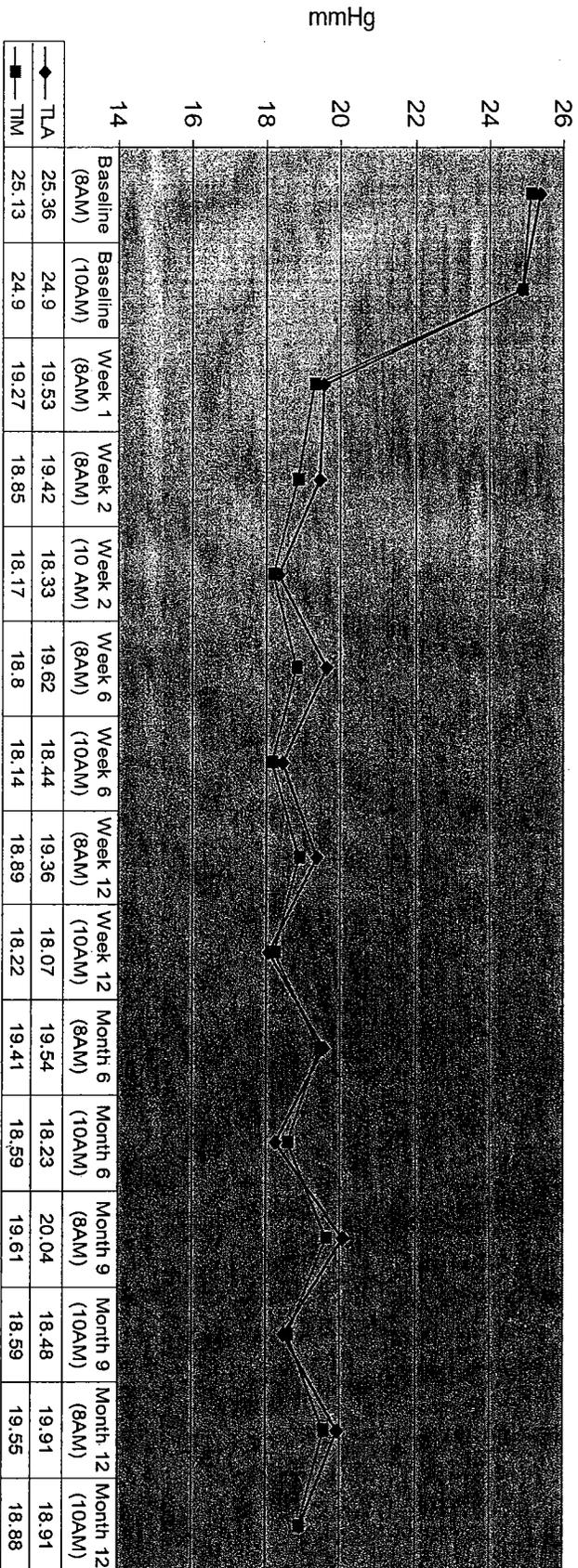


**Reviewer's Comments:**

*At none of the visits did the 95% confidence intervals for between-treatment comparisons exceed 1.5 mmHg. At most of these visits, these intervals did not exceed 1.0 mm Hg.*

Safety Update – Protocol TIMLA-301 – Primary Efficacy Variable at 12 Month – Intent-to-Treat Population (LOCF)

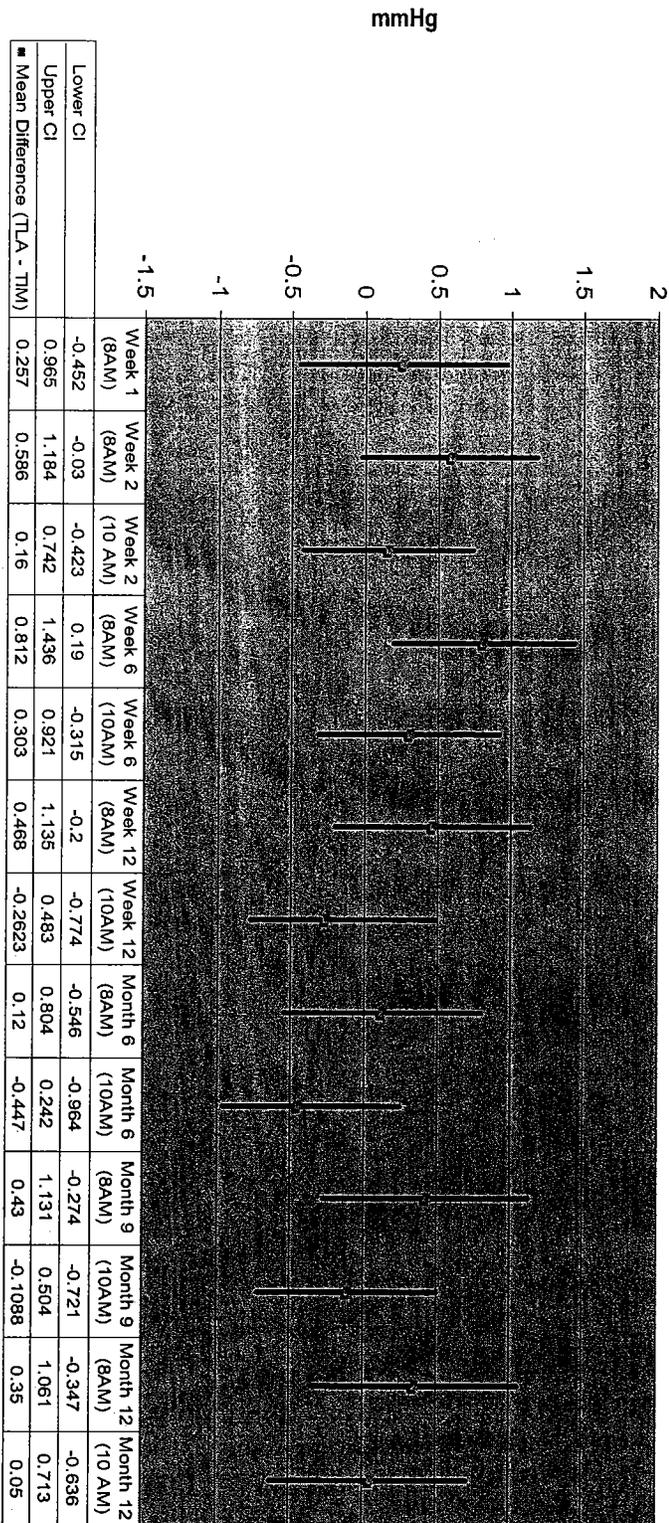
Mean IOP per Visit and Time (12 Month Data)



Reviewer’s Comments:

Once daily-dosed TLA [Istalol (timolol maleate ophthalmic solution) 0.5%] demonstrates equivalence in the ability to lower IOP compared to twice-daily-dosed TIM (timolol maleate ophthalmic solution) dosed over 12 months. Once daily-dosed TLA [Istalol (timolol maleate ophthalmic solution) 0.5%] lowers IOP between 5 and 7 mmHg from baseline. TIM (timolol maleate ophthalmic solution) lowers IOP between 5 and 7 mmHg from baseline.

Mean Difference (TLA - TIM) with 95% Confidence Intervals (12 Month Data)



Reviewer's Comments:

At none of the visits did the 95% confidence intervals for between-treatment comparisons exceed 1.5 mmHg. At most of these visits, these intervals did not exceed 1.0 mm Hg.

Lower CI Upper CI Mean Difference (TLA - TIM)

## 6.4 Efficacy Conclusions

The submitted study in NDA 21-516 (TIMLA-301) is sufficient to establish efficacy for Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Once-daily dosed Istalol (timolol maleate ophthalmic solution) 0.5% lowers intraocular pressure between 5 and 7 mmHg from baseline.

Results from the intent to treat and per protocol population analyses were similar and demonstrate the equivalence of once-daily dosed Istalol (timolol maleate ophthalmic solution) 0.5% to timolol maleate ophthalmic solution dosed twice-daily.

There were no statistically significant differences between the two treatment groups for any of the demographic characteristics. No overall differences in efficacy were observed between elderly and younger patients, between males and females, or between Caucasian and non-Caucasian patients in the 12 month analysis.

## 7 Integrated Review of Safety

- 7.1 The submitted study in NDA 21-516 is sufficient to establish the relative safety of Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

The safety data contained in this submission is generally comparable to that reported for Merck's NDA 18-086 for Timoptic (timolol maleate ophthalmic solution) 0.5%.

- 7.2 The safety database consists of safety data from one clinical trial, Protocol TIMLA-301, conducted at 21 centers in the United States.

### 7.3 Protocol TIMLA-301

For safety variables, the safety population included all enrolled patients who received treatment (with patients analyzed by their actual treatment group).

Table 8 – Listing of Serious Adverse Events at 12 Months

Inv. No.	Subject No.	Treatment	Adverse Event	Outcome
101	7	TIM	Shock secondary to retroperitoneal bleed L. kidney	Recovered w/o sequelae
	9	TIM	Right lower extremity pain	Recovered w/o sequelae
	10	TLA	Congestive heart failure	Recovered w/o sequelae
102	74	TIM	Hip replacement	Recovered w/o sequelae
		TIM	Dislocation of R. total hip arthroplasty	Recovered w/o sequelae
	78	TIM	Squamous cell carcinoma – upper nose	Recovered w/o sequelae
		TIM	Basal cell carcinoma – mid upper back	Recovered w/o sequelae
		TIM	Basal cell carcinoma – posterior ear	Recovered w/o sequelae
		TIM	Basal cell carcinoma – L. chin	Recovered w/o sequelae
		TIM	Basal cell carcinoma – R. forehead	Recovered w/o sequelae
84	TLA	Skin cancer – L. upper back R. temple R. neck	Recovered w/o sequelae	
	333	TIM	R. knee arthroplasty	Recovered w/o sequelae
		TIM	L. knee arthroplasty	Recovered w/o sequelae
	334	TIM	Transient vision loss (eye unknown)	Recovered w/o sequelae
		TIM	Herniated disc surgery	Recovered w/o sequelae
104	263	TIM	Diagnosed with bladder cancer	Condition unchanged
	264	TLA	Diagnosed with terminal lung cancer	Death
	265	TLA	Anemia	Recovered w/o sequelae
		TLA	Pulmonary Cancer	Condition unchanged
	107	197	TLA	Blocked R. coronary artery
108	48	TIM	Approx. 14" large intestine removed for benign growth	Recovered w/o sequelae
109	25	TLA	Enlarged thyroid	Recovered w/o sequelae
		TIM	Pneumonia	Recovered w/o sequelae
	312	TIM	Dysuria.	Recovered w/o sequelae
110	327	TLA	Pyuria	Condition improving
			Increased abdominal girth	Recovered w/o sequelae
			Unstable angina	Recovered w/o sequelae
			Transient ischemic attack	Recovered w/o sequelae
			Hysterectomy	Recovered w/o sequelae
			Cerebral microvascular ischemia	Recovered w/o sequelae

Original NDA 21-516

Istalol (timolol maleate ophthalmic solution) 0.5%

Table 8 – Listing of Serious Adverse Events 12 Months 12 Months – continued

Inv. No.	Subject No.	Treatment	Adverse Event	Outcome
111	89	TIM	Retinal detachment	Condition unchanged
	231	TIM	High grade R. carotid artery stenosis	Recovered w/o sequelae
113	233	TIM	Renal failure	Recovered w/o sequelae
	236	TIM	Chronic lung disease with interstitial fibrosis	Condition improving
	237	TIM	Cervical spondylitis w/ radiculopathy	Recovered w/o sequelae
	239	TLA	Heart attack	Recovered w/o sequelae
114	55	TLA	Gastrointestinal bleed	Recovered w/o sequelae
			Stomach ulcers	Recovered w/o sequelae
			Chest pain	Condition unchanged
			Coronary artery disease	Condition unchanged
			Atrial fibrillation	Condition unchanged
115	319	TIM	Coronary artery blockage	Recovered w/o sequelae
	342	TIM	R. rotator cuff torn requiring surgery	Recovered w/o sequelae
116	241	TIM	Hip replacement	Recovered w/o sequelae
	250	TLA	Breast cancer	Condition improving
117	126	TIM	Shortness of breath	Recovered w/o sequelae
118	192	TLA	Pericarditis	Recovered w/o sequelae
	274	TIM	Food allergy anaphylaxis	Recovered w/o sequelae
	278	TIM	Angina	Recovered w/o sequelae
	163	TLA	Blocked coronary artery	Recovered w/o sequelae
120	139	TIM	Myocardial infarction	Recovered w/o sequelae
	283	TLA	Traumatic hyphema	Recovered w/o sequelae

**Reviewer Comments:**

The sponsor should provide the duration of treatment (i.e. number of study days until advent of adverse event) for each subject with a serious adverse event through Month 12.

**Deaths:** Patient 104-264 (TLA) expired due to lung cancer on [ ]  
 1 received her first dose of study medication on [ ] and was diagnosed with terminal lung cancer on [ ]  
 1 The subject entered the study on [ ]  
 1 The study drug was discontinued, and she exited the study.

Original NDA 21-516

Istalol (timolol maleate ophthalmic solution) 0.5%

**Table 9 – Most Frequent Adverse Events at Week 12  
Number of Patients Reporting<sup>3</sup>**

Event	TLA N= 166		TIM N= 166	
	N	%	N	%
Burn/sting, eye, on instillation	63	38	37	22.3
Injection	10	6	10	6
Hypertension	9	5.4	7	4.2
Itching, eye	8	4.8	5	3
Allergic reaction	5	3	3	1.8
Asthenia	5	3	0	0
Headache	5	3	4	2.4
Infection	5	3	2	1.2
Ocular discomfort	5	3	5	3

**Table 10 – Most Frequent Adverse Events at Month 12  
Number of Patients Reporting<sup>4</sup>**

Event	TLA N= 166		TIM N= 166	
	N	%	N	%
Burn/sting, eye, on instillation	69	41.6	38	22.9
Injection	17	10.2	12	7.2
Hypertension	14	8.4	18	10.8
Infection	10	6.0	5	3.0
Headache	9	5.4	6	3.6
Eye/vision, blurred	9	5.4	6	3.6
Accidental injury	8	4.8	6	3.6
Itching, eye	8	4.8	5	3.0
Cataract nos	7	4.2	1	0.6
Visual acuity decreased	7	4.2	6	3.6
Cold, common	6	3.6	5	3.0
Depression	6	3.6	4	2.4
Rhinitis	6	3.6	4	2.4
Discomfort, eye	6	3.6	6	3.6
Dry eyes	6	3.6	5	3.0
Asthenia	5	3.0	1	0.6
Infection, respiratory nos	5	3.0	6	3.6
Conjunctivitis	5	3.0	3	1.8
Corneal lesion	5	3.0	2	1.2
Keratitis	5	3.0	4	2.4
Visual field defect	5	3.0	1	0.6
Vitreous disorder	5	3.0	2	1.2

**Reviewer's Comments:**

*Burning/stinging upon instillation, conjunctival injection, and hypertension remain the most frequent adverse events seen with TLA [Istalol (timolol maleate ophthalmic solution) 0.5%] at 12 months.*

<sup>3</sup> Five or more patients per group reporting.

<sup>4</sup> Five or more patients per group reporting.

## Visual Fields/Cup to Disc Ratio

**Table 11 – Visual Fields: Mean MD (dB) at Week 12**

Visit	Treatment	N	Mean	Std	Min	Max
Baseline	TLA	166	-1.91	3.23	-22.62	2.90
	TIM	166	-2.06	2.51	-9.98	3.00
Week 12	TLA	150	-1.63	2.85	-15.96	8.99
	TIM	154	-2.34	3.09	-13.55	7.56
Change	TLA	150	0.14	1.86	-7.45	6.49
	TIM	154	-0.27	2.21	-9.70	4.71

**Table 12 – Cup/Disc Ratio (Study Eye) at Week 12**

Visit	Treatment	N	Mean	Std	Min	Max
Baseline	TLA	165	0.45	0.19	0.10	0.90
	TIM	166	0.47	0.20	0.10	0.85
Week 12	TLA	149	0.45	0.18	0.10	0.90
	TIM	155	0.48	0.20	0.10	0.90
Change	TLA	148	0.00	0.00	-0.10	0.10
	TIM	155	0.00	0.00	-0.20	0.20

### Reviewers Comments:

*There are no clinically significant differences between treatment groups after 12 weeks in mean MD (db) or in cup to disc ratio. 12 month data are similar.*

*One subject (106-066, TIM) was noted to have a worsening of the cup to disc ratio of 0.3 units over a 12 month period.*

### Visual Acuity

**Table 13 – Mean Change from Baseline (logMar score)**

Visit	Treatment	N	Mean	Std	Min	Max
Baseline	TLA	166	0.000	0.00	0.00	0.00
	TIM	166	0.000	0.00	0.00	0.00
Week 1	TLA	154	-0.004	0.09	-0.18	0.30
	TIM	158	-0.002	0.08	-0.30	0.32
Week 2	TLA	149	-0.006	0.10	-0.32	0.36
	TIM	149	0.005	0.09	-0.24	0.38
Week 6	TLA	159	-0.006	0.10	-0.32	0.44
	TIM	163	0.003	0.10	-0.22	0.38
Week 12	TLA	151	0.011	0.12	-0.30	0.64
	TIM	155	0.012	0.10	-0.24	0.40

**Reviewer's Comments:**

*There are no clinically significant differences between treatment groups after 12 weeks in mean change from Baseline logMar score. 12 month data are similar.*

*A preferable method of capturing visual acuity changes between groups is to utilize a table which compares visual acuity between treatment groups tabulated by changes in line number (on the ETDRS or a comparable chart) comparing patient's final evaluation to Baseline (Number and Percent of Patients).*

**Mean Heart Rate****Table 14 – Mean Heart Rate (bpm)**

Time	Visit	Tx	N	Mean	S.D.	Min	Max
<b>Trough</b>							
	Baseline	TLA	166	73.25	8.74	54	100
		TIM	166	73.09	8.42	43	100
	Week 1	TLA	155	72.57	8.60	54	100
		TIM	158	70.56	8.40	51	92
	Week 2	TLA	149	73.23	9.52	52	102
		TIM	149	70.09	8.68	49	90
	Week 6	TLA	159	71.93	8.75	53	98
		TIM	163	70.82	7.77	52	88
	Week 12	TLA	151	71.32	9.56	42	100
		TIM	155	69.68	8.64	46	96
<b>Peak</b>							
	Baseline	TLA	166	73.39	9.02	48	104
		TIM	166	72.44	9.12	50	104
	Week 2	TLA	142	70.66	8.25	52	100
		TIM	146	68.64	8.04	46	88
	Week 6	TLA	156	69.83	9.12	42	100
		TIM	159	68.65	8.22	50	88
	Week 12	TLA	149	69.62	8.74	45	98
		TIM	154	68.81	8.22	47	95

**Reviewer's Comments:**

*As expected, dosing with timolol decreases heart rate in each group.*

*There are no clinically significant differences between treatment groups after 12 weeks in mean heart rate (bpm). 12 month data are similar.*

**8 Dosing, Regimen, and Administration Issues**

Senju Pharmaceutical Co., Ltd has proposed Istalol (timolol maleate ophthalmic solution) 0.5% be administered once daily. Once-daily dosed Istalol (timolol maleate ophthalmic solution) 0.5% lowers intraocular pressure between 5 and 7 mmHg from baseline.

## **9 Use in Special Populations**

- 9.1** Applicant's analyses on the effects of gender, age, and ethnicity on efficacy and safety are adequate.
- 9.2** Senju Pharmaceutical Co., Ltd requested a deferral of pediatric studies for this drug product in a request dated May 22, 2002. The deferral was granted, and pediatric studies were deferred until September, 1, 2005.
- 9.3** No additional data in other special populations are needed.

## **10 Conclusions, Recommendations, and Labeling**

- 10.1** The submitted study in NDA 21-516 is sufficient to establish efficacy for Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Once-daily dosed Istalol (timolol maleate ophthalmic solution) 0.5% lowers intraocular pressure between 5 and 7 mmHg from baseline.

The submitted study in NDA 21-516 is sufficient to establish the relative safety of Istalol (timolol maleate ophthalmic solution) 0.5% for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

The safety data contained in this submission is generally comparable to that reported for Merck's NDA 18-086 for Timoptic (timolol maleate ophthalmic solution) 0.5%.

- 10.2** NDA 21-516 is recommended for approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma after outstanding Chemistry/Manufacturing issues and labeling issues have been resolved.

The sponsor should provide the duration of treatment (i.e. number of study days until advent of adverse event) for each subject with a serious adverse event through Month 12.

### 10.3 Labeling Review

On November 11, 2002, the Sponsor formally submitted the brand name Istalol for consideration.

A consult was sent to the Division of Medication Errors and Technical Support (DMETS HFD-420) on December 2, 2002, requesting feedback on the proposed brand name.

Per the DMETS completed consultation dated June 24, 2003:

- DMETS does not recommend the use of the proprietary name "Istalol." Istalol has the potential to sound and/or look-like the currently marketed products, Stadol, Esmolol, and Sotalol.
- Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proprietary name, "Istalol", acceptable from a promotional perspective.

Stadol contains butorphanol tartrate and is indicated for the management of pain (including postoperative analgesia), preoperative or pre-anesthetic medication, relief of pain during labor, and to supplement balanced anesthesia. The nasal spray has been shown in clinical trials to be effective in the treatment of migraine headache pain.

Both drug products [*Stadol and Istalol*] are in liquid form; however, they differ in dosage form (injection and nasal spray vs. ophthalmic drops), route of administration (parenteral and nasal vs. eye), strength (1 mg/mL, 2 mg/mL, and 10 mg/mL vs. 0.5 %), and directions of use (every three to four hours, before surgery/labor, or when in pain (nasal) vs. once a day).

#### Reviewer's Comments:

*Respectfully disagree with the DMETS conclusion regarding the use of the brand name Istalol.*

*Disagree that the handwritten prescription (page 5 of DMETS review) appropriately represents the prescription ordering process for an ophthalmic product.*

*Stadol and Istalol differ in dosage form, route of administration, strength, and directions of use.*

Esmolol hydrochloride is the established name for Brevibloc. It is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in preoperative, postoperative, or other emergent circumstances where short-term control of ventricular rate with a short-acting agent is desirable.

These two drug products [*Esmolol and Istalol*] are available as a solution, but they differ in dosage form (injection vs. ophthalmic drops), strength as well as the number of strengths (10 mg/mL and 250 mg/mL vs. 0.5%), route of administration (parenteral vs. ophthalmic), and the directions of use (loading dose of 500 mcg/kg/min for one minute followed by a maintenance dose of 50 mcg/kg/min vs. one drop into affected eye once a day).

**Reviewer's Comments:**

*Respectfully disagree with the DMETS conclusion regarding the use of the brand name Istalol.*

*Esmolol and Istalol differ in dosage form, route of administration, strength, and directions of use.*

Sotalol (a beta-adrenergic blocking agent) is the established name for Betapace and Betapace AF. Betapace is indicated for ventricular arrhythmias and the initial recommended dose is 80 mg twice a day.

However, they [*Sotalol and Istalol*] differ in dosage form (tablets vs. ophthalmic drops), route of administration (oral vs. ophthalmic), and strength as well as the number of strengths (80 mg, 120 mg, 160 mg, and 240 mg vs. 0.5%).

**Reviewer's Comments:**

*Respectfully disagree with the DMETS conclusion regarding the use of the brand name Istalol.*

*Sotalol and Istalol differ in dosage form, route of administration, strength, and directions of use.*

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On Original**

19 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

NDA 21-516 is recommended for approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma after outstanding Chemistry/Manufacturing issues and labeling issues have been resolved.

The sponsor should provide the duration of treatment (i.e. number of study days until advent of adverse event) for each subject with a serious adverse event through Month 12.

William Boyd, M.D.  
Clinical Team Leader

cc:

HFD-550/Div Files  
HFD-550/MO/Boyd  
HFD-550/Dep Div Dir/Chambers  
HFD-550/Stat/Rahman  
HFD-550/Stat/Lin  
HFD-550/Chem/Khorshidi  
HFD-550/Chem TL/Ng  
HFD-550/PharmTox/ChenZ  
HFD-550/PharmTox TL/Yang  
HFD-550/BioPharm/Kim  
HFD-550/Biopharm TL/Bashaw  
HFD 420/DMETS/Fan  
HFD-420/DMETS TL/Toyer  
HFD-47/DSI/Shibuya  
HFD-46/47/DSI Assoc Dir/ El-Hage  
HFD-550/PM/Puglisi

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William Boyd  
7/16/03 02:08:46 PM  
MEDICAL OFFICER

Wiley Chambers  
7/17/03 12:56:22 PM  
MEDICAL OFFICER