

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202514Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review of NDA 202514 Review #2

Date	January 31, 2012
From	William M. Boyd, M.D.
Subject	Medical Officer Review
NDA #	202514
Applicant	Merck Sharp & Dohme Corp.
Date of Submissions	January 13, 2012
PDUFA Goal Date	March 13, 2012
Type of Application	505(b)(1)
Name	Zioptan (tafluprost ophthalmic solution) 0.0015%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction

NDA 202514 for Zioptan (tafluprost ophthalmic solution) 0.0015% received a Complete Response Letter dated November 7, 2011, which cited the following deficiency:

Your NDA does not provide assurance of the sterility of the final drug product. While you have revised your (b)(4) processing validation protocol in your submission of October 27, 2011, (b)(4) (b)(4) filling procedures using this revised validation protocol. In the absence (b)(4) we cannot determine that the product is sterile and safe for use.

To address this deficiency, provide a report describing three consecutive successful (b)(4) processing simulations (b)(4) that you will use for manufacturing the product using the inspection and accounting procedures provided in the revised (b)(4) processing validation protocol submitted in the October 27, 2011 amendment.

Merck submitted an amendment on January 13, 2012, which constituted a Complete Response.

2. Sterility Assurance

From the Product Quality Microbiology Review finalized 1/18/2012:

On 13 January 2011 the applicant filed a Class 1 resubmission with the requested data from 3 consecutive (b)(4) processing simulations (b)(4) using the revised validation protocol submitted to the agency on 27 October 2011. (b)(4) batches 10019, 10020, and 10021 were manufactured separately and batch 10019 had a sterile (b)(4)

(b) (4). A summary of the three (b) (4) is provided in Table 1 below.

Table 1- Summary results from (b) (4) processing simulation studies (Sponsor Table 3.2.P.3.5-2452-ophsln:11)

Batch Number	Mfg. Date	(b) (4)	# of Units Positive for Growth
10019	20Nov2011	(b) (4)	0
10020	22Nov2011		0
10021	24Nov2011		0

The revised (b) (4) procedures were summarized in Module 3.5.5.2 and were consistent with data reviewed for the Product Quality Microbiology Reviews #1 and #2. Briefly, (b) (4) ampules were filled (b) (4)

(b) (4) Growth promotion studies are conducted for each batch and must be acceptable.

This application is recommended for approval on the basis of product quality microbiology.

3. Safety Update

Per Merck, the safety data presented in the Safety Update in the January 13, 2012, resubmission, are consistent with those submitted to the original NDA and the Safety Update in May 2011. Therefore, Merck is not proposing any changes to the proposed package insert and proposed patient package insert previously submitted to the FDA.

Currently, there are no ongoing clinical studies for tafluprost that are sponsored by Merck in the US or in any ex-US country. However, there are **two** ongoing ex-US/non- IND, post-marketing surveillance studies for tafluprost that are being sponsored by Merck's development partner, Santen, in some of the countries where they hold the Marketing Authorization.

(b) (4)
(b) (4)
There were no non-clinical studies that were either ongoing or completed during the reporting period for this Safety Update. The eight ongoing ex-US clinical studies mentioned above are discussed in this Safety Update Report. (b) (4)
(b) (4)

Five of these ongoing (b) (4) studies are double masked. The sixth study is an open labeled long term safety study for the (b) (4) in Japan that has approximately 42 patients exposed to tafluprost monotherapy during the four week open label randomization phase. The remaining two ongoing studies are post-marketing safety surveillance studies for tafluprost in Japan and Korea. In addition to these eight ongoing studies, the final Clinical Study Report of one completed study (b) (4) study) is being submitted in this Safety Update.

Table 2.7.4: 1

Ongoing Studies to be Included in the Safety Update Report for Tafluprost

Protocol	Study Name	Duration	Treatment Arms and Randomization or Enrollment Ratio	Randomized or Entered N	Status
ONGOING STUDIES					
(b) (4) EU Superiority study (b) (4)	Phase III, randomized, double-masked study to compare efficacy and safety of the PF (b) (4) to tafluprost 0.0015% and timolol 0.5% eye drops given as individual monotherapies	6 months –primary evaluation of efficacy at 3 months; data beyond 3 months used to investigate long-term safety of the (b) (4)	Approximately 600 patients will be enrolled to this study: 220 patients (110/group) for the comparison of timolol (b) (4) (stratum 1) and 380 patients (190/group) for the comparison of tafluprost (b) (4) (stratum 2).	247 currently enrolled	Treatment Phase ongoing
(b) (4) EU Non-inferiority study (b) (4)	Phase III, randomized, double-masked study to compare efficacy and safety of the PF (b) (4) to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly	6 months treatment (up to 4 week washout, 6 months treatment, 1-3 week post-study follow-up).	Approximately 380 patients will be enrolled to this study in 1:1 (b) (4) vs concomitant taf and tim	401 currently enrolled	Treatment Phase ongoing
(b) (4) EU PK study (b) (4)	Ph I, single center, double-masked, 3-period crossover for PK, safety, and tolerability of (b) (4) vs PF taf and PF tim monotherapy	Duration of the first, second and third treatment period are 7 days each (Day 1 to Day 7); 4 weeks between the treatment Periods; post-study follow-up period of 1-3 weeks.	15 healthy volunteers will be randomized to ensure that at least 12 healthy volunteers randomized	15 Final Enrollment	Treatment Phase ongoing

Ongoing Studies to be Included in the Safety Update Report for Tafluprost (Cont.)

Protocol	Study Name	Duration	Treatment Arms and Randomization or Enrollment Ratio	Randomized or Entered N	Status
(b) (4) Japan (b) (4)- Taf-Taf/Tim	Phase III Double-masked comparative study (b) (4) compared to Taf monotherapy and Taf/Tim given concomitantly	4 week observation with Taf and 4 week double-masked treatment period	Approx 480 subjects.160 subjects per group in 1:1:1 randomization to (b) (4) or Taf/Tim concomitant administration	374 currently enrolled	Treatment Phase ongoing
(b) (4) Japan (b) (4)Tim	Phase III Double-masked comparative study (b) (4) compared to Timolol monotherapy in patients	4 week observation with tim and 4 week double-masked treatment period	Approx 140 subjects (70 subjects per group) in 1:1 randomization to Tim or (b) (4)	138 currently enrolled	Treatment Phase ongoing
(b) (4) Japan Long Term Safety Study- (b) (4)	Phase III Long term Open Label study of (b) (4)	4 week open randomization; 52 week open label treatment period	Approx 126 subjects (42 subjects per group for each observation period ophthalmic solution); 4 week open label period of pts randomized to Taf, Tim, or Taf/Tim concomitant administration; 52 wk treatment period of patients (b) (4)	136 currently enrolled	Treatment Phase ongoing
Post-approval regulatory commitment, open label study in Japan	TAPROS ophthalmic solution 0.0015% Special Drug Use-results Survey (Investigation on Long-term Use)	Followed for 2, 12 and 24 months, follow-up of 6 months if discontinued TAPROS due to AE	All patients enrolled to tafluprost PC by centralized registration system (TAPROS is the marketed tafluprost in Japan).	4502 tafluprost PC	Treatment Phase ongoing
Post-approval regulatory commitment, open label study in Korea	Post Marketing Surveillance on Safety and Efficacy of Tafluprost PC Eye Drops in Korean Patients in Accordance with "Regulation for Re-Examination of New Drugs, Etc."	Visit for assessment at Week 4; total study duration 6 years after product release.	3000 or more Korean pts.	550 tafluprost PC	Treatment Phase ongoing
(b) (4)					
Taf= PF tafluprost 0.0015% (or PC tafluprost 0.0015% for Japan Studies) Tim = PF timolol 0.5% (or PC timolol 0.5% for Japan Studies)					

Study 77553 (b) (4)

Study 77553, the Phase 3 open label (b) (4) study with 185 patients, was completed and summarized in the original Safety Update (May 2011). The study was performed to assess changes in ocular symptoms and signs in patients with ocular hypertension or primary open-angle glaucoma who were switched from preserved latanoprost 0.005% eye drops to preservative-free tafluprost 0.0015% eye drops. The most frequent non-serious AEs were eye irritation N= 6 (3%), eye pain N= 5 (3%), and eye pruritus N= 5 (3%). Drug related ocular AEs were reported for 20 (10.9%) patients. The systemic AE of headache was reported most frequently (3%). There were no systemic AEs related to study drug, as determined by the investigators. There was one serious adverse event reported in this study for a patient with unstable angina. The patient was not discontinued from the study, the AE was not related to study drug (as determined by the investigator), and the patient recovered from the SAE. These AEs are consistent with the safety profile of tafluprost.

Study (b) (4) **(EU PK Study)**

A phase 1, randomized, double-masked, 3-period cross-over clinical study to compare the pharmacokinetics, safety and tolerability of (b) (4) tafluprost 0.0015% and timolol 0.5% eye drops to those of preservative free tafluprost 0.0015% and timolol 0.5% eye drops in healthy volunteers

As of the cut-off date of November 7, 2011, there have been no patient discontinuations and no serious adverse events reported for this PK study 201150.

Study (b) (4) **(EU Superiority Study)**

A phase 3, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative-free (b) (4) tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given as individual monotherapies in patients with open angle glaucoma or ocular hypertension

Study data remain masked since the study is ongoing, however preliminary review indicates of 247 randomized patients, 12 patients have discontinued, 2 of which were due to AEs. Adverse events necessitating discontinuation from the study for 2 patients were: 1) non-serious AEs of ocular burning, facial redness, tingling of lips, dulling sensorium; all of which were considered as related to study medication by the investigator and the patient recovered. Study medication assignment remained masked. 2) a serious adverse event of vertiginous syndrome, considered as not related to study medication and the patient recovered. Study medication assignment remained masked.

There were 5 SAEs reported for this study in the reporting timeframe: vertiginous syndrome; high IOP; TIA and Raynaud's syndrome; adenolymphoma, and anorectal /hemorrhoidal pain; all were judged to be not related to study medication.

(b) (4) **(EU Non-Inferiority Study)**

A phase 3, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative-free (b) (4) tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly in patients with open angle glaucoma or ocular hypertension.

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Study data remain masked since the study is ongoing; of 401 randomized patients, 20 have discontinued, 9 of which were due to AEs. One patient who discontinued experienced 2 SAEs: a hiatal hernia and a cerebral infarction. There were 7 patients who discontinued due to ocular AEs.

There were 10 SAEs reported for this study during the reporting timeframe: gastrointestinal ulcer bleeding, esophageal hemorrhage, parotid swelling, cerebral infarction, renal colic, gastric neoplasm, mechanical ileus, colonic polyp, arm fracture, tachycardia; all were judged to be not related to study medication.

Appendix 2.7.4: 2

Randomized Patients Who Discontinued Study (b) (4) (EU Non-inferiority)
 as of 11Nov2011* (Ongoing)

Country	Site Number	Patient Number	Age (b) (4)	Gender	Status Change Reason	Reason for Discontinuation
				Female	AE	Photosensitive, Conjunctivitis
				Female	AE	Irritating of the eye, dry eye, sensitivity to light, foreign body sensation in the eye, puffy eyelids, redness of the eyelids
				Female	AE	According to patient's complaint of moderate eye pain, redness of the eye, discomfort and irritation in the eye, patient has stopped IP installation
				Female	AE	Exacerbation of ocular allergy
				Male	AE	Conjunctival redness
				Female	AE	Dyspnoea
				Female	AE	Hypersensitivity to drug
				Female	AE	Allergic conjunctivitis
				Female	AE	Two SAEs: cerebral infarction, Hiatal hernia
				Female	DISC	Voluntary withdraw - patient request
				Male	DISC	Voluntary withdraw - patient request
				Male	DISC	Voluntary withdraw - patient request
				Male	DISC	Voluntary withdraw - patient request
				Male	DOSE	Patient unable/unwilling to follow dosing
				Female	DOSE	Patient unable/unwilling to follow dosing
				Male	DOSE	Patient unable/unwilling to follow dosing
				Female	DOSE	Patient unable/unwilling to follow dosing
				Male	IE	Improper Entry
				Female	IOP	IOP uncontrolled as judged by the investigator,
				Male	OTHER/ Misrandomi- zation (screen failure)	Note: no CRF data entered
* Listing as of 07Nov2011 is not available						

Study (b) (4) (Japan (b) (4) Compared to Tafluprost Monotherapy and Tafluprost/Timolol Given Concomitantly Study)

A double-masked study of DE-111 ophthalmic solution versus tafluprost ophthalmic solution 0.0015% alone and concomitant use of tafluprost ophthalmic solution 0.0015% plus timolol ophthalmic solution 0.5% in patients with primary open angle glaucoma or ocular hypertension

Of the 374 patients who are randomized in this study, only 1 patient has discontinued due to a non-serious ocular AE; the AE was punctate keratitis. There were no SAEs reported in this study at the time of the November 7, 2011, cut-off date.

Study (b) (4) (Japan (b) (4) Compared to Timolol Monotherapy Study)

A double-masked study of (b) (4) ophthalmic solution versus timolol ophthalmic solution 0.5% in patients with primary open angle glaucoma or ocular hypertension

Of the 138 patients who are randomized in this study, 3 patients have discontinued due to 6 non-serious ocular AEs including ocular hyperemia, eye irritation, eyelid edema, and adenoviral conjunctivitis. There was 1 SAE of large intestine carcinoma reported in this study at the time of the November 7, 2011, cut-off date.

Appendix 2.7.4: 4

Randomized Patients who Discontinued from
 Japan Study (b) (4) as of 07Nov2011 (Ongoing)

Protocol No.	Subject ID	Country	Sex	Age	Discontinued date	MedDRA-PT
(b) (4)	(b) (4)	Japan	Female	(b) (4)	(b) (4)	Ocular hyperaemia
	(b) (4)	Japan	Female			Eye irritation
	(b) (4)	Japan	Female			Eyelid oedema
	(b) (4)	Japan	Female			Ocular hyperaemia
	(b) (4)	Japan	Female			Adenoviral conjunctivitis
	(b) (4)	Japan	Female			Ocular hyperaemia
	(b) (4)	Japan	Female			Improper Entry

Study (b) (4) (Japan (b) (4) Long Term Study)

A Phase 3 long-term open-label study of (b) (4) ophthalmic solution in patients with open angle glaucoma or ocular hypertension

Of the 126 patients who are randomized in this study, one patient discontinued due to a non-serious non-ocular AE of generalized rash.

There were 2 patients with reported unrelated SAEs of cellulitis and uterine leiomyoma at the time of the November 7, 2011, cut-off date; these 2 patients were both in the run-in period of the study on either timolol or tafluprost and were not on the (b) (4)

Post Approval Studies (Japan and Korea)

The two remaining studies (post-approval regulatory commitment studies), are long-term open-label post-marketing surveillance studies ongoing in Japan (TAPROS) and Korea.

Worldwide Adverse Experience (WAES) Database

The Worldwide Adverse Experience (WAES) database was searched for spontaneous reports from healthcare providers for tafluprost received from 02-Mar-2011 through 07-Nov-2011.

Table 2.7.4: 10

Tafluprost: 02-Mar-2011 to 07-Nov-2011
 Summary Tabulation of Spontaneous Events Received from HCPs

System Organ Class	Preferred Term	Serious events	Non-serious events
Cardiac disorders	Palpitations	0	1
	Tachycardia	0	1
Ear and labyrinth disorders	Deafness	0	1
Eye disorders	Abnormal sensation in eye	0	2
	Age-related macular degeneration	0	1
	Blepharal pigmentation	0	3
	Blepharitis	0	3
	Conjunctival oedema	0	1
	Conjunctivitis allergic	0	2
	Corneal disorder	0	1
	Cystoid macular oedema	1	1
	Dry eye	0	3
	Eye allergy	0	1
	Eye irritation	0	6
	Eye pain	0	7
	Eyelash discolouration	0	1
	Eyelid erosion	0	1
	Eyelid oedema	0	1
	Eyelids pruritus	0	1
	Eyes sunken	0	3
	Ocular hyperaemia	0	13
	Photalgia	0	1
	Photophobia	0	1
	Punctuate keratitis	0	1
	Scleritis	0	1
	Vision blurred	0	4
Visual acuity reduced	1	0	
Gastrointestinal disorders	Gingivitis	0	1
	Rectal haemorrhage	0	1
	Tongue discolouration	0	1
General disorders and administration site conditions	Adverse event	0	1
	Application site haematoma	0	1
	Application site mass	0	1
	Incorrect product storage	0	1
	No adverse event	0	1
	Oedema peripheral	0	1
	Sensation of foreign body	0	2
Sense of oppression	0	1	

Tafluprost: 02-Mar-2011 to 07-Nov-2011
Summary Tabulation of Spontaneous Events Received from HCPs (Cont.)

System Organ Class	Preferred Term	Serious events	Non-serious events
Immune system disorders	Hypersensitivity	0	2
Infections and infestations	Rhinitis	0	1
Injury, poisoning and procedural complications	Incorrect dose administered	0	1
	Medication error	0	1
Investigations	Blood pressure increased	0	1
	Electrophoresis protein abnormal	0	1
	Intraocular pressure fluctuation	0	1
	Intraocular pressure increased	0	2
	Transaminases abnormal	0	1
Musculoskeletal and connective tissue disorders	Back pain	0	1
	Muscle spasms	0	1
	Myalgia	0	1
Nervous system disorders	Dizziness	0	1
	Dysgeusia	0	1
	Headache	0	4
	Hypoaesthesia	0	1
	Motor dysfunction	0	1
Psychiatric disorders	Confusional state	1	0
	Depressed mood	0	1
	Restlessness	0	1
Respiratory, thoracic and mediastinal disorders	Bronchospasm	0	1
	Cough	0	2
	Dyspnoea	0	1
	Epistaxis	0	1
	Oropharyngeal discomfort	0	1
	Oropharyngeal pain	0	1
	Throat irritation	0	1
Skin and subcutaneous tissue disorders	Alopecia	0	1
	Dermatitis allergic	0	1
	Dermatitis contact	0	1
	Erythema	0	1
	Hypertrichosis	0	3
Social circumstances	Mental disability	0	1
Vascular disorder	Vein pain	0	1
TOTAL NUMBER OF EVENTS		118	
DISTINCT NUMBER OF REPORTS		66	

Summary Statement

The safety results included in this Safety Update Report are consistent with those submitted in the original NDA submission and subsequent initial Safety Update. As a result, no changes have been made to the proposed package insert and the proposed patient package insert. The currently proposed labeling adequately represents the safety profile of tafluprost.

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William M. Boyd, M.D.
NDA 202514
Zioptan (tafluprost ophthalmic solution) 0.0015%

4. Labeling

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the labeling found in this review.

The revised package insert and revised patient package insert submitted on 1/23/2012 are acceptable.

The carton and container labeling submitted on 11/4/2011 are acceptable.

The package insert, patient package insert, carton and container labeling are located in the Appendix at the end of this review.

5. Recommendations

RECOMMENDED REGULATORY ACTION:

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse reactions.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WILLIAM M BOYD
01/31/2012

WILEY A CHAMBERS
02/01/2012

NDA 202514 Zioptan™ (tafluprost ophthalmic solution) 0.0015%

Proposed indication: reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products ¹
Subject	Division Director Summary Review
NDA Number	NDA 202514
Related IND	IND 62,690 (MK-2452)
Applicant Name	Merck Sharpe & Dohme Corp. (Merck)
Application Type	505(b)(1)
Date of Original Submission	January 7, 2011 (standard review)
PDUFA Goal Date	November 7, 2011
Proprietary Name / Established (USAN) Name	Zioptan™ Tafluprost ophthalmic solution
Dosage Form	Sterile ophthalmic solution
Dosage Strength	0.0015% (15 micrograms/mL)
Preservative	Preservative free
Route of Administration	Topical
Dose	One drop in affected eye or eyes once daily in the evening
Proposed Indication(s)	reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
How Supplied	Foil pouch containing strip of 10 single-use LDPE ampoule, containing 0.3 mL clear solution
Action for Application	<i>Complete Response</i>

¹ The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

NDA 202514 Zioptan™ (tafluprost ophthalmic solution) 0.0015%

Proposed indication: reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Lucious Lim, Bill Boyd, Wiley Chambers 9/28/2011
CDTL Review	Bill Boyd 11/7/2011
Deputy Director	Wiley Chambers 11/7/2011
Statistical Review	Yunfan Deng, Yan Wang 7/20/2011
Carcinogenicity Assessment Committee (CAC)	David Jacobson-Kram 5/6/2011
Pharmacology/Toxicology Review	James Wild, Wendelyn Schmidt 7/20/2011 Abby Jacobs 7/25/2011
CMC – ONDQA, Division II, Branch V Review	Maotang Zhou, Rapti Madurawe 8/26/1011, 10/24/2011, Terrance Ocheltree 11/7/2011
Product Quality Microbiology Review	Jessica Cole, Stephen Langille 9/30/2011, 11/4/2011 David Hussong 11/4/2011
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo 7/20/2011
OSI/DGCPC	Kassa Ayalew, Susan Thompson, Jean Mulinde 6/27/2011
OSE/DMEPA Proprietary Name	Denise Baugh, Todd Bridges, Carol Holquist 4/15/2011 (Saflutan denied) Denise Baugh, Todd Bridges, Carol Holquist 8/31/2011 (Zioptan acceptable)
OSE/DMEPA Labeling Review PI and carton/container	Denise Baugh, Todd Bridges, Carol Holquist 8/24/2011
OMP/Patient Package Labeling	Sharon Williams, Melissa Hulett and LaShawn Griffiths 11/3/2011
OPDP/DPP (formerly DDMAC)	Package insert: Christine Corser, 10/19/2011 Patient Package insert: Adora Ndu 11/3/2011

CDTL=Cross-Discipline Team Leader

OND=Office of New Drugs

OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Promotion, (formerly DDMAC=Division of Drug Marketing, Advertising and Communication)

PMHT=Pediatric and Maternal Health Staff

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DDRE= Division of Drug Risk Evaluation

DRISK=Division of Risk Management

ONDQA=Office of New Drug Quality Assessment

OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI))

OMP = Office of Medical Policy

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1. Summary and Recommendations

Based on the reviews of NDA 202514, I concur that the application should be issued a *Complete Response* at this time because of outstanding Product Quality Microbiology Sterility deficiencies as summarized in 1.1 below. Other reviewers have found the application acceptable for approval from the clinical, statistical, clinical pharmacology, toxicology (including carcinogenicity), and manufacturing perspective. The Office of Compliance has recommended that the manufacturing sites for the drug product are acceptable on October 13, 2011 and the Office of Scientific Investigations has recommended that clinical data are acceptable to support the application. Labeling recommendations have been received from OSE/DMEPA for the carton and containers, and from DDMAC for product labeling; their recommendations have been incorporated. The Office of Medical Policy (OMP) and DDMAC have reviewed the patient package insert and their recommendations incorporated.

Carton and container labeling has been finalized. Both the package insert and patient package insert are considered final by the review team, to the extent that they can be included with the action letter.

Zioptan (tafluprost ophthalmic solution)² 0.0015% is a prostaglandin F_{2α} analogue indicated for reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension in adult patients. The dosing regimen is 1 drop of tafluprost solution in the conjunctival sac given once daily in the evening in the affected eye or eyes. The product to-be-marketed is a preservative free (PF), sterile, clear solution supplied in single-dose ampules. Phase 3 clinical trials included both the PF and preservative-containing (PC) formulations; the preservative is benzalkonium chloride. The efficacy of this new molecular entity was demonstrated in two Phase 3 clinical trials (Study 15-003 and 001) conducted in US and Europe comparing tafluprost to timolol, along with a bridging trial (Study 77550). Other Phase 1, 2 and 3 studies conducted during development were also included in the application.

1.1 Product Quality Microbiology Sterility Deficiencies:

According to Dr Jessica Cole, the Product Quality Microbiology Reviewers, there are microbiology deficiencies that need to be addressed before approval. Specifically, her review recommends that

- (1) the (b)(4) procedures are not adequate because existing procedures allow additional inspection of positive vials after incubation has begun and as such are not adequate to insure sufficient sterility assurance for this (b)(4) processed sterile drug product. She notes that the (b)(4)

(b)(4) She recommends the applicant

² The established name for ophthalmic products includes the active ingredient and the formulation as shown here. The concentration of the formulation is listed outside the parentheses and is not part of the established name.

- (a) remove from the (b) (4) procedure or provide an adequate scientific justification for the additional inspection/scrutiny of (b) (4) ampules compared to product-filled ampules.
 - (b) provide any relevant (b) (4) data (i.e., positive samples or failures, etc.), if applicable, regarding the filling line proposed for tafluprost
 - (c) confirm that a single filling line is proposed for tafluprost
- (2) the submitted documentation does not include a full accounting and description of units from (b) (4) processing validation studies. (b) (4)

(b) (4) She recommends the applicant

- (a) provide the number of units filled, rejected, incubated, inspected, and positive for growth for all (b) (4) conducted on each filling line proposed for tafluprost.

Following internal discussion and teleconferences with Merck, the question was raised whether the (b) (4) runs could be performed and submitted as a post-marketing commitment by the end of the first quarter in 2012. Merck agreed to such an approach.

However, Dr. David Hussong, Associate Director for Quality Microbiology notes that “This would mean that approval of the application could permit marketing of product prior to a complete demonstration of sterile manufacturing capability. We wanted to allow the applicant the opportunity to complete the validation and begin drug manufacture as promptly as possible, and proposed that the approval would be conditioned upon a commitment to withhold shipment of product until the validation was complete. However, that condition cannot be enforced in a post-approval commitment. If the applicant chose to market the product and subsequently (b) (4) failed (in March or April), the following outcomes may occur and would need to be addressed.

1. All marketed product could be recalled for lack of sterility assurance.
2. Patients might be exposed to contaminated products. Bacteria capable of growing in the solution would have time to reach great populations.
3. The Quality Assurance department may exercise its authority to investigate the cause of the failure and conclude there is no risk. Their conclusion may be subject to bias.

Two of these outcomes are undesirable from a regulatory and safety perspective.

Based on these considerations and the applicant’s lack of willingness to perform these studies in a more timely fashion, I conclude that the application should not be approved until three consecutive (b) (4) are completed successfully and reported to the application file.”

To address the outstanding deficiency,

Merck should provide a report describing three consecutive successful (b) (4) processing simulations on the filling line that will be used for manufacturing the product using the inspection and accounting procedures provided in the revised (b) (4) processing validation protocol submitted in the October 27, 2011 amendment.

1.2 Post-Marketing Studies:

None at this time

1.3 Other Issues

None at this time

2. Background

Tafluprost is a fluorinated analogue of prostaglandin F_{2α} (PGF_{2α}) developed for the reduction of elevated intraocular pressure (IOP) due to open-angle glaucoma and ocular hypertension. This NME is currently marketed in over 30 countries in Europe and Asia in preservative-containing (PC) and preservative-free formulations. Tafluprost was developed by Santen Inc starting in 2001, submitted under IND 62,690 and licensed by Merck Sharpe and Dohme, Corp (Merck) in 2009.

In the US there are multiple products approved for treatment of IOP including beta-adrenergic antagonists (beta-blockers), alpha- adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors and prostaglandin (PG) analogs. Currently approved PG products include Xalatan (latanoprost) 0.005%, Travatan and Travatan Z (travoprost) 0.004% Lumigen (bimatoprost) 0.01% and 0.03%. Bimatoprost 0.03% is also marketed under the trade name Latisse for hypotrichosis to increase the length, thickness and darkness of eyelashes. Travatan Z is a preservative free formulation (without benzalkonium chloride). Rescula (unoprostone isopropyl) 0.15% is approved for use in patients who have not responded to or cannot tolerate other IOP lowering products. Most of the currently-marketed PG analogues contain the preservative benzalkonium chloride (BAK); the applicant states that BAK may contribute to the risk for developing of symptoms of dry eye and some patients may exhibit delayed-type hypersensitivity and plans on marketing the single-use PF formulation of tafluprost.

PG products have associated class adverse reactions which include increased pigmentation of the iris and the periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. Increased iris pigmentation may be permanent.

The following Regulatory Meetings were held during drug development:

- IND meeting with Santen Incorporated, October 12, 2005 - to discuss a possible NDA for tafluprost.
- EOP2 meeting with Santen and Merck, August 24, 2009 – the preservative free formulation was discussed. A bridging study comparing the PC and PF formulation was being conducted; duration of treatment would need to be at least 12 weeks. (b) (4)

Regarding pediatric development, the Division stated that a waiver would be anticipated because there are currently available therapies for IOP in children and the safety of a PG analogue [tafluprost] in

pediatric patients was a concern – the Division noted that an adequate pediatric study for tafluprost would be expected to have a duration of at least 20 years to satisfactorily answer questions on safety due to long term increased in iris pigmentation in this population. (b) (4)

... NDA (b) (4) were discussed. The Division responded that Agency routinely conducts an Advisory Committee Meeting for all new molecular entities.

3. CMC/Product Quality Microbiology

Dr Maotang Zhou from ONDQA notes that the information in the application is enough to assure the identify, strength, purity, and quality of the drug product, adding that the NDA provided sufficient information on raw material controls, manufacturing process and process controls, adequate specifications, and stability data. On October 13, 2011, manufacturing facilities were recommended as acceptable by the Office of Compliance.

The application was granted a categorical exclusion from environmental assessment; the basis of this exclusion is the fact that the estimated concentration of the active ingredient at the point of entry into the aquatic environment will be less than 1 ppb from all products using this material as the active ingredient.

The drug substance is manufactured in Japan and has intrinsic antimicrobial activity. The composition is provided in the table below:

Table 1- Composition of the drug product (Sponsor Table 3.2.P.1-2452-ophsln:1)

Drug substance	Reference	Percent (w/v)	Quantity (mg/mL)	Function
Tafluprost	In-house [†]	0.0015	0.015	Drug substance
Excipients				(b) (4)
Glycerol	PhEur/USP			
Sodium dihydrogen phosphate dihydrate	PhEur/USP			
Disodium edetate	PhEur/USP			
Polysorbate 80	PhEur			
Sodium hydroxide [†] and/or hydrochloric acid, concentrated [†]	PhEur/USP	q.s.	q.s. [§]	pH adjuster
Water for injection	PhEur	q.s.	q.s. [§]	pH adjuster
	PhEur			(b) (4)
				(b) (4)

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As stated by Dr Zhou: “The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains the drug substance tafluprost and the excipients, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid, and water for injection. Glycerol is used (b) (4) of the drug product. Sodium hydroxide and hydrochloric acid are used to adjust the solution pH to 5.5 – 6.7. All the excipients are of compendial grade (USP/NF).”

“The drug product solution is manufactured, (b) (4) by Laboratoire Unither, France. The drug product manufacturing process (b) (4)

(b) (4) Each single-use ampoule is filled with 0.3 mL of the sterile solution containing 4.5 µg [0.0045 mg] of tafluprost and affixed with a label. The labeled ampoules are packed (b) (4) pouches, 10 ampoules per pouch. The pouches are then packed in carton boxes. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).” They are packaged in the (b) (4) pouch (b) (4).

The stability data provided support the proposed 36-month shelf life when stored at 2-8°C protected from moisture.

Dr Jessica Cole, the Product Quality Microbiology Reviewer, further notes that the preservative-free tafluprost 0.0015% solution is sterile-(b) (4) filled into single-use ampoules using (b) (4) fill-seal technology. The container closure system is a low density polyethylene (LDPE) single-dose ampoule (b) (4) Each single-use vial contains 30 mL, and droplets are (b) (4) each. The containers are manufactured in strips (b) (4) and packed in to (b) (4) pouches (10 per pouch) (b) (4) from solution.

During her review, Dr. Cole noted that the (b) (4) processing validation studies (b) (4) are not sufficient to provide adequate sterility assurance for this drug product, due to a moderate risk for the release of non-sterile drug product. To address this concern, Merck agreed to provide data on 3 (b) (4) runs by the first quarter of 2012, however, when this plan was reviewed by the Quality Microbiology staff, they determined that the results of these 3 (b) (4) would need to be submitted to the application and reviewed before the application could be approved.

During the course of the review, Dr. Cole and Dr. Maotang Zhou sent multiple requests for addition information and clarification to the applicant on various aspects related to the manufacture of the drug substance and drug product, including sterilization procedure and validation, process validation reports, production parameters, media challenge results, temperature monitoring, endotoxin specifications, test methods, leachables, freeze-dry cycles, control or residual solvents, secondary packaging, English translation; these responses were received and reviewed during the present (first) review cycle.

Comment:

The application is not recommended for approval from the Product Quality Microbiology perspective, until Merck submits “a report of studies that include the results of three consecutive successful (b) (4) processing simulations of the Zioptan manufacturing process on filling line (b) (4) using the revised inspection and accounting procedures.” (See Section 1.1) For this reason, the final recommendation from ONDQA remains a Complete Response. Manufacturing facility inspections were recommended as acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr James Wild, the Pharmacology/Toxicology Reviewer, summarized that there was no systemic toxicity observed in several repeat-dose topical ocular studies in monkeys at 100-fold higher than anticipated in man. In repeat-dose intravenous studies up to 26 weeks in rats, systemic toxicity involving bone, bone marrow, liver and kidney was seen. In dogs studies lasting up to 39 weeks, dogs showed less systemic toxicity, had symptoms of salivation, emesis, miosis; one animal had hepatic failure others had reversible ALT elevations. In dogs, cardiovascular effects including minor increase blood pressure, heart rate and QTc changes were seen with repeat IV administration of tafluprost.

In rabbits both preservative free and preservative containing (0.01% benzalkonium chloride) tafluprost penetrated cornea and aqueous humor similarly. Topical administration in animals resulted in ocular distribution (cornea, aqueous humor, iris/ciliary body, sclera, conjunctiva, retina, choroid, vitreous humor and lens). Tafluprost penetrated placenta in pregnant rats and was present in milk in lactating rats. Like PGF₂α, it causes uterine contractions in animal studies.

Systemic distribution was rapid but much lower than eye, and suggested that the tafluprost may have drained into the oral cavity through the lacrimal duct with subsequent elimination via liver and kidney. Tafluprost (AFP-168) was metabolized by rabbit carboxyesterase to tafluprost acid (AFP-172), the active moiety.

Ocular changes including iridial darkening, sunken eyelids, and blue-gray discoloration of the lower eyelid were seen in repeated-ocular dose toxicology studies of up to one year duration in monkeys. These changes are consistent with ocular changes observed in this prostaglandin analogue class. Dr. Wild writes that these effects along with the other ocular effect associated with the PGF₂ α analogues, eyelash darkening and thickening, are considered to be mainly cosmetic, not associated with loss of function, and not toxicologically significant.

Tafluprost is considered a Pregnancy Category C. Teratogenic effects were assessed in rats and rabbits: In embryo-fetal development studies, tafluprost administered intravenously was teratogenic. Tafluprost caused increases in post-implantation losses in rats and rabbits and reductions in fetal body weights in rats, increased the incidence of vertebral skeletal abnormalities in rats and the incidence of skull, brain and spine malformations in rabbits. In a pre- and postnatal development study in rats, increased mortality of newborns, decreased body weights and delayed pinna unfolding were observed in offspring. The labeling will reflect these studies and the relative doses at which they were observed.

Despite the inadequate design of the mouse carcinogenicity study, the Carcinogenicity Assessment Committee (CAC) concurred that sufficient carcinogenicity testing had been conducted for tafluprost administered in the clinical setting by the topical ocular route at the maximum recommended human dose (MRHD). Factors influencing this decision were the very low systemic exposure associated with the expected MRHD, negative genetic toxicology findings, and the lack of neoplasm findings in carcinogenicity studies for other drugs in the same pharmacological class. Labeling will note that: Tafluprost was not carcinogenic when administered subcutaneously daily for 24 months at doses up to 30 μ g/kg/day in (b) (4) (over 1600- times, the maximum clinical exposure based on plasma AUC).

Tafluprost was not mutagenic or clastogenic in a battery of genetic toxicology studies, including an *in vitro* microbial mutagenesis assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, and an *in vivo* mouse micronucleus assay in bone marrow.

In rats, no adverse effects on mating performance or fertility were observed with intravenous dosing of tafluprost at a dose of 100 μ g/kg/day (at least 1600 times higher than human exposure).

Comment: The application is recommended for approved from a pharmacology/toxicology standpoint.

5. Clinical Pharmacology/Biopharmaceutics

Dr Yongheng Zhang, the Clinical Pharmacology Reviewer, notes that tafluprost (AFP-168, MK-2452) is an ester pro-drug of a new synthetic prostaglandin F₂ α (PGF₂ α) analogue, selective for the FP prostanoid receptor. Tafluprost acid is believed to reduce intraocular pressure by increasing uveoscleral outflow. Further activity may be mediated by tafluprost-induced relaxation of the ciliary muscle and changes in ciliary muscle extracellular matrix thus facilitating increased outflow from aqueous humor. The exact mechanism of action is

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unknown. Reduction of the intraocular pressure starts approximately 2 to 4 hours after the first administration with the maximum effect reached after 12 hours and maintained for more than 24 hours after instillation.

Following instillation, tafluprost is absorbed through the cornea and is hydrolyzed to the biologically active acid metabolite, tafluprost acid (AFP-172). Following instillation of one drop of the 0.0015% solution once daily into each eye of healthy volunteers, the concentrations of tafluprost acid peaked at a median time of 10 minutes on both Days 1 and 8. The mean plasma C_{max} of tafluprost acid was 26 pg/mL on Day 1 and 27 pg/mL on Day 8. The mean plasma AUC estimates of tafluprost acid were 394 pg*min/mL and 432 pg*min/mL on Day 1 and 8, respectively.

Tafluprost, an ester prodrug, is hydrolyzed to its biologically active acid metabolite in the eye. The acid metabolite is further metabolized via fatty acid β -oxidation and phase II conjugation.

Mean plasma tafluprost acid concentrations were below the limit of quantification of the bioanalytical assay (10 pg/mL) at 30 minutes following topical ocular administration of tafluprost 0.0015% ophthalmic solution.

No interactions are anticipated in humans because systemic concentrations of tafluprost acid were low following instillation.

COMMENT

The clinical pharmacology review recommends that the studies support approval and labeling changes have been finalized.

6. Clinical Microbiology/Immunology

Not applicable.

7. Clinical/Statistical-Efficacy

The clinical development program for tafluprost included various Phase 1, 2 and 3 studies; those discussed in this document are outlined in **Appendix A**.

- Phase 2 Study 15-001 and Study 15-002 evaluated six doses of tafluprost ranging from 0.0003% to 0.005% for 4 weeks and Study 74457 compared tafluprost 0.0015% to latanoprost, in a study lasting 6 weeks.
- Two Phase 3 trials compared tafluprost 0.0015% to timolol maleate ophthalmic solution, 0.5%. Study 15-003 evaluated treatment for 12 months and tested the PC formulation; Study 001 evaluated treatment for 12 weeks and tested the PF formulation. These trials were double-masked, non-inferiority trials, and the NI margin 1.5 mmHg. Both studies met their predefined non-inferiority margin.
- A bridging study, Study 77550 compared the tafluprost PF and PC formulations in a cross-over design and again the results showed the two formulations to perform comparably; therefore, the results of both Phase 3 studies are appropriate to support approval of this application.

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- A third Phase 3 trial compared tafluprost PC to latanoprost 0.005% (Study 74458 for 24 months), however this trial failed to meet the pre-specified NI margin. The results of this trial were known at the time of the end-of-phase 2 meeting.
- It is noted in the statistical review that open-label Study 77552 compared ocular signs and symptoms when patients were switched from PC latanoprost to PF tafluprost.

The details of the protocol design and inclusion and exclusion criteria are located in Dr. Lim's Medical Officer Review. These trials had similar designs and the endpoint of IOP was measured at protocol-specified visits (approximately 4-6 daily visits per year, with 1-3 measurements per day to assess diurnal variation). The patients in these studies did not have newly-diagnosed IOP or glaucoma but part of the design included a washout period to establish a baseline. The primary endpoint in both Study 15-003 and 74458 were IOP at 6 months, although the studies lasted 12 and 24 months, respectively to evaluate long term outcome. Dr Lim noted that tolerance did not develop over this time course. Study 001 was only 12 weeks in length, as agreed in the EOP2 August 24, 2009 meeting.

A brief summary of the Phase 3 studies is excerpted from Dr. Deng's Statistical Review:

“**Study 15-003** was a randomized, double-masked, parallel group, multicenter, 12-month trial comparing the efficacy and safety of PC tafluprost 0.0015% with PC timolol 0.5%. A total of 458 patients were randomized. At the start of the study, 267 were randomized to tafluprost, out of which 250 completed the first 6 months of treatment, and 240 completed 12 months of treatment. Of the 191 patients randomized to timolol, 168 completed the first 6 months, and 162 completed 12 months of treatment. IOP was measured at 8AM, 10AM, and 16PM at baseline visit, Week 2, Week 6, Month 3, Month 6, and Month 12 visits; and at 8AM, and 10AM at Month 9 visit.

[In Table 9 of Dr Deng's review, approximately 54% of patients had primary open-angle glaucoma, 45% had ocular hypertension, and a few patients had pigmentary glaucoma or pseudo exfoliative glaucoma.]

“For both studies 15-003 and 74458, the primary efficacy analysis for U.S. regulatory purposes examined the two-sided 95% confidence interval for the difference in IOP in the study eye between treatments at each time point at each visit through Month 6. Tafluprost was considered equivalent (non-inferior) to timolol/latanoprost if the upper limit of the confidence interval for the difference did not exceed 1.5 mmHg at all time points and did not exceed 1.0 mmHg at a majority of time points.” [page 20 Dr Deng's review]

“**Study 001** was a randomized, multi-center, active comparator-controlled, 12-week, double-masked clinical trial to compare the efficacy and safety of preservative-free (PF) tafluprost (0.0015%) and PF timolol 0.5%. A total of 643 patients were randomized, among which 320 patients were randomized to tafluprost treatment and 306 completed the study. Of 323 patients randomized to timolol, 312 completed the study. IOP was measured at 8AM, 10AM, and 16PM at baseline visit, Week 2, Week 6, and Month 3 visits.

[In Table 12 of Dr Deng's review, approximately 60% of patients had primary open-angle glaucoma, 40% had ocular hypertension.]

“Non-inferiority of tafluprost to timolol was established if the upper bound of the two-sided 95% confidence interval (CI) of the between-treatment difference in mean IOP change from baseline (PF tafluprost minus PF timolol maleate) was no higher than 1.5 mmHg at all 9 time points during the study (0800 hrs, 1000 hrs and 1600 hrs at Weeks 2, 6 and 12).” [page 20 Dr Deng's review]

“**Study 77550** was a randomized, investigator-masked, multicenter, cross-over phase III study on two formulations (preserved and unpreserved) of tafluprost 0.0015% eye drops in patients with open-angle glaucoma or ocular hypertension. The study consisted of two treatment periods: preserved followed by unpreserved formulation or unpreserved followed by preserved formulation of study medication tafluprost 0.0015% once daily. Duration of both treatment periods was four weeks, separated by a washout period of at least four weeks. A total of 43 patients were randomized in the study. IOP was measured at 8AM, 12PM, 16PM, and 20PM at baseline visit, Week 1, and Week 4 visits of each treatment period.

“Equivalence for the two formulations was defined in this protocol if the 95% confidence interval for the difference in IOP reduction between groups (PF minus PC) was within the equivalence range of -1.5 mmHg and 1.5 mmHg.” [page 11 Dr Deng's review].

“**Study 74458** was a randomized, double-masked, active-controlled, parallel-group, 24-month, multinational, and multicenter trial comparing efficacy and safety of PC tafluprost 0.0015% comparing with PC latanoprost 0.005%. A total of 533 patients were randomized. At the start of the study 269 patients were randomized to tafluprost treatment, out of which 246 completed the first 6 months of treatment, 229 completed 12 months of treatment, and 185 completed 24 months of treatment. Of the 264 patients randomized to latanoprost, 252 completing the first 6 months, 247 completing 12 months, and 217 completed 24 months of treatment. IOP was measured at 8AM, 12PM, 16PM, and 20PM at baseline visit, Month 3, Month 6, Month 12, Month 18, and Month 24 visits; and at 8AM on Week 2, Week 6, Month 9 and Month 15 visit.”

[In Table 18 of Dr Deng's review, approximately 56% had primary open-angle glaucoma, 37% had ocular hypertension, and the remaining patients had capsular glaucoma, pigmentary glaucoma or were normal.

7.1 Efficacy Results:

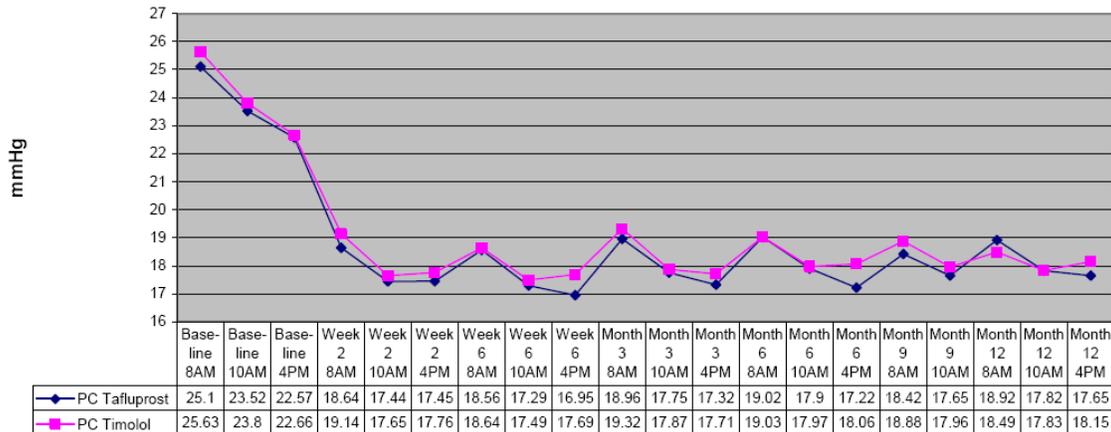
(A) **Study 15-003** – baseline IOPs were comparable and the results as shown below met the prespecified 1.5 mmHg NI margin, and most of the values were within 1 mmHg (see Statistical Review). The table and graph below are from Dr. Lim’s review:

Table 8: Study 15-003 Baseline IOPs (in worst eye)

	Timepoint	Mean ± SD mmHg
PC Tafluprost	8:00	25.61 ± 3.06
	10:00	23.52 ± 3.61
	16:00	22.57 ± 3.70
PC Timolol	8:00	25.63 ± 3.18
	12:00	23.80 ± 3.84
	16:00	22.66 ± 4.03

Source: Table 14.2.1.1 of Study 15-003 Report

Mean IOP per Visit and Time



Reviewer’s Comments: Baseline mean IOP of the two treatment arms is similar. The mean IOP for PC tafluprost 0.0015% and PC timolol 0.5% is similar at all time points measured.

Comment:

Results for Study 15-003 of the ITT Population (figure from Dr Lim’s review) comparing PC tafluprost to PC timolol. Both the Medical Officer (MO) and Statistical review concluded that non-inferiority was demonstrated in 15-003. This is the PC formulation of tafluprost but is linked to the to-be-marketed formulation of tafluprost based on Study 77550.

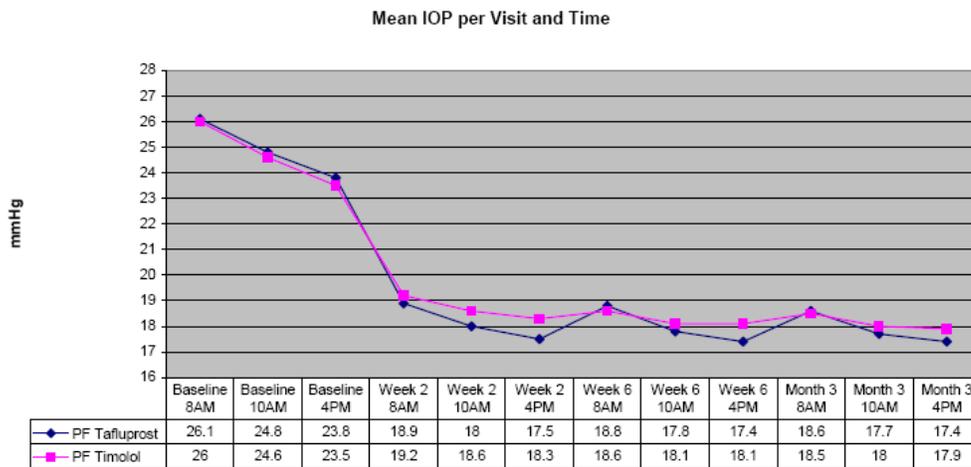
(B) Study 001 – compared PF tafluprost to PF timolol and both products showed IOP-lowering effect throughout the 12 weeks of treatment. The IOP-lowering effect of PF tafluprost was within the 1.5 mmHg non-inferiority margin compared to PF timolol at all visits and time points. The table and graph below are from Dr. Lim’s review:

Table 13: Study 001 Baseline IOPs (in worst eye)

	Timepoint	Mean ± SD mmHg
PF Tafluprost	8:00	26.1 ± 2.75
	10:00	24.8 ± 3.26
	16:00	23.8 ± 3.38
PF Timolol	8:00	26.0 ± 2.50
	12:00	24.6 ± 2.85
	16:00	23.5 ± 3.16

Source: Table 14.2.1.1 of Study 15-003 Report

Study 001 FAS Population



Reviewer’s Comments: Baseline mean IOP of the two treatment arms is similar. The mean IOP for PF tafluprost 0.0015% and PF timolol 0.5% is similar at all time points measured.

Comment:

Study 001 lasted only 12 weeks, but the tafluprost met the NI margin at all time points, and for many of these points the values were within 1 mmHg.

(C) Study 77550 – Dr. Deng notes that Study 77550 investigated the pharmacodynamics (as expressed in IOP) of the preserved and unpreserved formulation of tafluprost 0.0015% eye drops and that similar and clear IOP-lowering effect was seen at week 1 and week 4, meeting the 1.5 mmHg margin, as shown in the table below and in the graph provided by Dr. Lim.

Table 2: IOP Change from Baseline for Study 77550 (FAS, LOCF, RM ANCOVA)

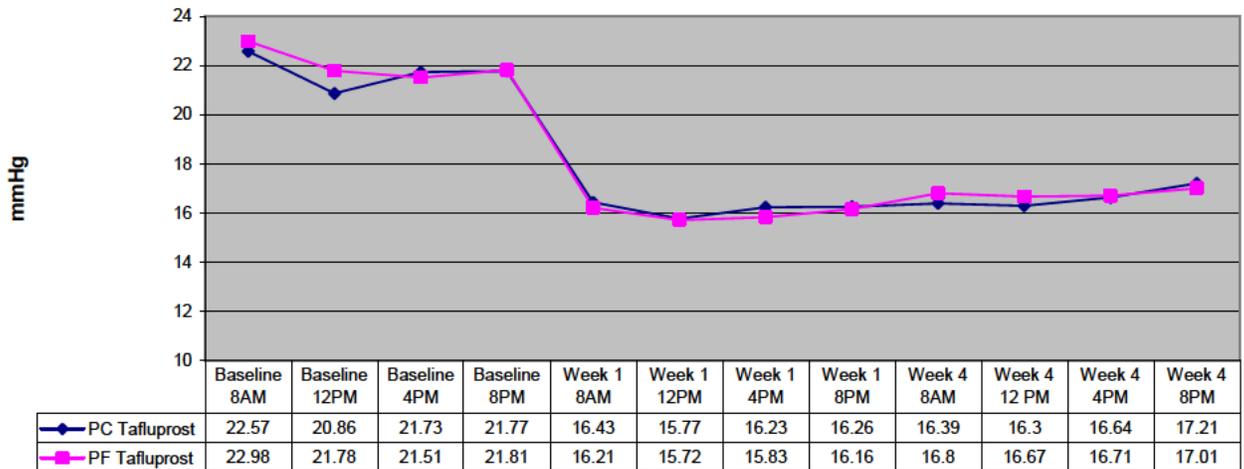
Study 77550			
Visit / Time	PF Tafluprost 0.0015% (N=43) Mean (mmHg)	PC Tafluprost 0.0015% (N=42) Mean (mmHg)	Difference (95% CI) ¹ (mmHg)
Week 1			
8:00	-6.77	-6.14	-0.32 (-0.96, 0.32)
12:00	-6.06	-5.08	-0.25 (-0.89, 0.40)
16:00	-5.69	-5.50	-0.39 (-1.03, 0.26)
20:00	-5.65	-5.51	-0.13 (-0.77, 0.52)
Week 4			
8:00	-6.17	-6.18	0.24 (-0.51, 0.98)
12:00	-5.10	-4.56	0.11 (-0.64, 0.86)
16:00	-4.80	-5.08	0.00 (-0.74, 0.75)
20:00	-4.80	-4.56	-0.30 (-1.04, 0.45)

¹ Based on RM ANCOVA with terms for baseline IOP, sequence, period, treatment, time, sequence by time, period by time, and treatment by time.

Source: Table 14.2.1.2 and Table 14.2.3.1 of Study 77550 Report.

Study 77550: FAS population

Mean IOP per Visit and Time



Comment:

Study 77550 provided evidence of comparability of PC and PF formulations on efficacy and serves as a bridging study, therefore Study 15-003 of the PC formulation can serve as one of two studies to support NDA approval; the other is Study 001.

(D) Study 74458 – baseline IOPs were comparable but the results as shown below failed to meet the prespecified 1.5 mmHg NI margin, in most (18/24) time point measurements (See table from Statistical Review page 37). Based on the table only 6 of 24 time points met the 1.5 mmHg margin: 8:00AM at Week 2, 8:00AM at Week 6, 16:00PM and 20:00PM at Month 3, 20:00PM at Month 12, and 20:00PM at Month 18), and the lower limit for all measurements excludes zero.

Study 74458			
Visit / Time	PC Tafluprost 0.0015% (N=264) LSMean ² (mmHg)	PC Latanoprost 0.5% (N=264) LSMean ² (mmHg)	Difference (95% CI) ¹ (mmHg)
Week 2			
8:00	-7.99	-8.69	0.70 (0.21, 1.19)
Week 6			
8:00	-7.85	-8.80	0.95 (0.44, 1.46)
Month 3			
8:00	-7.95	-9.07	1.11 (0.57, 1.66)
12:00	-7.27	-8.46	1.19 (0.71, 1.67)
16:00	-6.73	-7.38	0.65 (0.18, 1.12)
20:00	-6.19	-7.05	0.86 (0.43, 1.30)
Month 6			
8:00	-7.74	-9.08	1.33 (0.75, 1.91)
12:00	-7.03	-8.55	1.52 (1.00, 2.03)
16:00	-6.46	-7.66	1.19 (0.71, 1.68)
20:00	-6.18	-7.15	0.97 (0.52, 1.43)
Month 9			
8:00	-7.41	-8.80	1.39 (0.80, 1.99)
Month 12			
8:00	-7.17	-8.85	1.68 (1.05, 2.31)
12:00	-6.89	-8.31	1.42 (0.87, 1.96)
16:00	-6.02	-7.45	1.43 (0.90, 1.95)
20:00	-5.62	-6.88	1.26 (0.72, 1.80)
Month 15			
8:00	-7.43	-9.14	1.72 (1.09, 2.34)
Month 18			
8:00	-7.49	-9.06	1.57 (0.92, 2.22)
12:00	-7.09	-8.22	1.13 (0.58, 1.69)
16:00	-6.23	-7.45	1.21 (0.67, 1.75)
20:00	-5.84	-6.94	1.10 (0.54, 1.10)
Month 24			
8:00	-7.21	-8.84	1.63 (0.97, 2.28)
12:00	-6.91	-8.24	1.34 (0.76, 1.92)
16:00	-6.04	-7.19	1.15 (0.59, 1.70)
20:00	-5.74	-6.84	1.10 (0.53, 1.67)

¹Based on ANCOVA with terms for treatment and baseline IOP.

Table 17: Study 74458 Baseline IOPs (in worst eye)

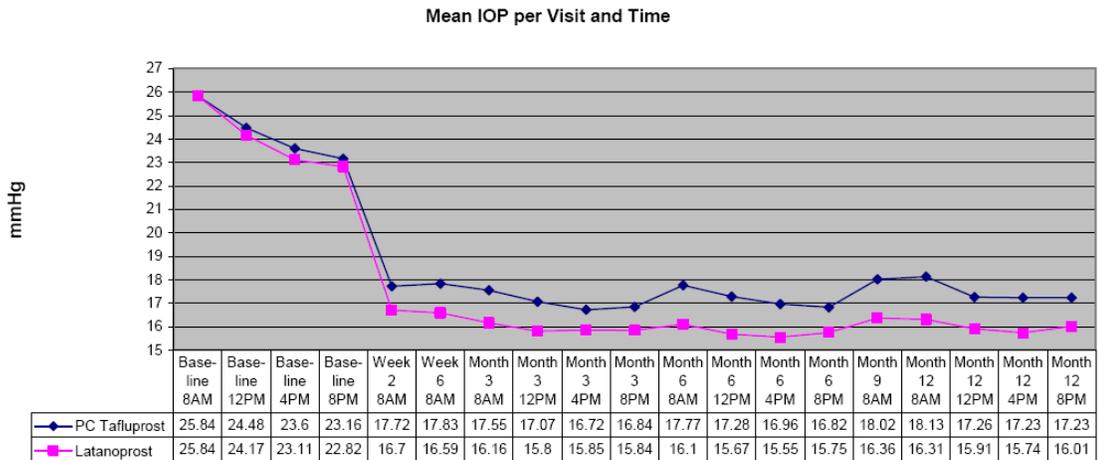
	Timepoint	Mean ± SD (mmHg)
PC Tafluprost	8:00	25.84 ± 2.94
	12:00	24.48 ± 3.41
	16:00	23.60 ± 3.67
	20:00	23.16 ± 3.66
PC Latanoprost	8:00	25.26 ± 2.86
	12:00	24.17 ± 3.02
	16:00	23.11 ± 3.45
	20:00	22.82 ± 3.63

Source: Table 14.2.1.1 of Study 74458 Report.

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Study 74458 ITT Population



Reviewer's Comments: Baseline mean IOP of the two treatment arms is similar. The mean IOP for PC tafluprost 0.0015% and latanoprost 0.05% is similar at baseline. The mean IOP of latanoprost 0.05% is consistently lowered than PC tafluprost 0.0015% by approximately 1-2 (0.87-1.82) mmHg at all time points measured.

Comment:

Study 74458 failed to show tafluprost is noninferior to latanoprost; the latter product has numerically greater reduction in IOP, as seen in the table below.

Summary Comments on Efficacy:

The results of Phase 3 Studies 15-003 and 001 show that tafluprost are effective in lowering IOP. Both clinical trials met the pre-specified NI margin of 1.5 mmHg and most 95% CI limits were within a 1 mmHg margin. In these studies tafluprost was compared to timolol. However, the third Phase 3 Study 74458 failed to show that tafluprost was non-inferior to latanoprost, with the latter showing a numerically greater reduction in IOP. Mean IOP with tafluprost was between 17 to 19 mmHg in the timolol controlled-studies and 17 to 18 in the latanoprost-controlled study. Study 15-003 evaluated the PC formulation and Study 001 evaluated the PF formulation, a bridging study 77550 showed that the two formulations were non-inferior based on the predefined NI margin.

In summary, tafluprost ophthalmic solution 0.0015% is effective in reducing IOP.

Adjunctive therapy

Study 74460 - a randomized, placebo-controlled, Phase 3 study to investigate the efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy to timolol 0.5% eye drops in open-angle glaucoma or ocular hypertension patients who are only partially controlled with timolol. A total of 185 patients were randomized; 96 to tafluprost and 89 to vehicle treatment. Prostaglandin naïve patients aged 18 years or older with primary open-angle glaucoma, capsular glaucoma, pigmentary glaucoma or ocular hypertension were enrolled. IOP had to be 22 to 30 mmHg in at least one eye in at least one measurement of the diurnal IOP (08:00,

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10:00, 16:00) at the baseline visit, during treatment with timolol 0.5% twice daily in a 4-week open-label run-in period. A 6-week randomized treatment period (timolol + tafluprost/vehicle) was followed by a 6-week extension period (timolol + tafluprost; vehicle switched to tafluprost). The primary efficacy variable comprised the change from baseline in diurnal IOP at 6 weeks. The extension period efficacy variables comprised the change from baseline in diurnal IOP at 12 weeks. Compared to baseline values (measured after a 4-week run in on timolol), the timolol-tafluprost group showed an IOP reduction of 5.5 to 5.8 mmHg (minimum and maximum range for the 6-week time point: primary endpoint for the study) and timolol-vehicle group showed an IOP reduction of 4.0 to 4.2 mmHg.

7.2 Proposed Labeling Regarding Efficacy:

The applicant's proposed labeling for the results of controlled phase 3 clinical trials appears consistent with the findings from these studies, as summarized below:



(b) (4)

To make the CLINICAL STUDIES section consistent with other IOP products, the following simplified text will be included:

In clinical studies up to 24 months in duration, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 23 - 26 mm Hg who were treated with ZIOPTAN dosed once daily in the evening demonstrated reductions in intraocular pressure at 3 and 6 months of 6 – 8 mmHg and 5 – 8 mmHg, respectively.

(b) (4)

7.3 Noninferiority Margin:

The non-inferiority limit for the Phase 3 studies was 1.5 mmHg based on the upper limit of the 95% CI for the difference between groups (tafluprost - control). For this analysis (Studies 15-003 and 74458), non-inferiority was defined as the upper limit of the 95% CI being ≤ 1.5 mmHg at all time points and ≤ 1.0 mmHg at a majority of time points. (page 11, Dr Deng's review) The Division notified the applicant that this margin needed to be met for each measurement of IOP, and that the applicant's initial proposal to determine a mean daily IOP was not acceptable.

As summarized in Appendix A of Dr Deng's review: Based on study 77550, tafluprost PC and PF have similar IOP lowering effect, and based on Table 36 (Studies 15-003 and 001) timolol PC and PF have similar IOP lowering effect. In Study 15-001, the applicant included a placebo arm which was used to estimate the change from baseline for placebo. Because none of the studies submitted in this NDA have any direct comparison between timolol and placebo,

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to treatment effect of timolol over placebo and further derive the NI margin the following assumptions were made by Dr Deng:

- If the IOP lowering effect of timolol is lower than that of tafluprost, using tafluprost as the substitute to derive the NI margin is not necessary because if tafluprost can beat placebo, there is no need of NI study or NI margin.
- If the IOP lowering effect of timolol is similar or better than that of tafluprost, using the treatment effect of tafluprost as substitute for the treatment effect of timolol will not over estimate the treatment effect of timolol.

The statistical reviewer pooled the three tafluprost arms in 15-001 (including 0.001%, 0.0025% and 0.005%) and compared them to the placebo IOP change.

Dr Deng concludes a 1.5 mmHg non-inferiority margin for a non-inferiority study using timolol as the active comparator seems reasonable based on the following observations:

- Studies 15-002, 15-003, and 001 showed that the IOP lowering effect of timolol is consistent across different studies; and is also consistent from treatment Day 7 for up to Month 12 and does not diminish over the treatment course. Moreover, the treatment effect at the same time point (8:00, 10:00, etc) is similar whether it is on treatment Day 7 or on Month 12.
- Study 15-001 showed that the IOP lowering effect of placebo is consistent from treatment Day 7 for up to Day 28 and does not increase over the treatment course. Thus, it is reasonable to assume that the treatment effect of placebo will be similar (if not worse) if the treatment continues for a longer period of time.
- Study 15-001 showed that the mean IOP change from baseline was similar in all three tafluprost treatment groups, and the 0.005% tafluprost group had a slightly lower treatment effect compared with the other two tafluprost groups (0.001% and 0.0025%).
- The final concentration of tafluprost the applicant selected for registration purpose is 0.0015%, which falls in between 0.001% and 0.0025%. Based on the results of Studies 15-001, 15-002, 15-003, and 001, the treatment effect of 0.0015% group seems similar to that of 0.001%, and 0.0025% groups, and slightly better than that of 0.005% group.
- The treatment effect of tafluprost can be used to estimate the treatment effect of timolol.
- Study 15-001 showed that the point estimates of the treatment difference between combined tafluprost group (0.001% + 0.0025% + 0.005%) and placebo were all below -3.00 mmHg for every time point; in addition, the upper bound of 95% CI of the treatment difference were all below -1.5 mmHg for every time point.

Comment:

The clinical reviewers and statistical reviewers recommend approval of the application.

8. Safety

Per Dr. Lim's review, data from all controlled, double-masked trials that evaluated the 0.0015% tafluprost were evaluated and this included Studies 15-002, 74457, 15-003, 74458, 001 as summarized in the table below, thus 905 patients received tafluprost 0.0015% PC or PF, 543 received timolol 0.05% PC or PF and 311 were treated with latanoprost 0.005%.

Overview of Exposure to Study Drug by Protocol

Protocol #	Safety N	PC or PF tafluprost 0.0015%	PC or PF Timolol 0.05%	Latanoprost 0.005%
15-002	144	30	29	28
74457	38	19		19
15-003	450	267	191	
74458	533	269		264
001	643	320	323	
Total	1808	905	543	311

Supportive information was gathered from Study 15-001, 74460, 77550, 77552 and five Japanese studies.

Routine clinical testing for topical ophthalmic drug (biomicroscopy, visual acuity, etc) was conducted. Clinical and laboratory safety evaluations were specific in the protocols.

RESULTS of SAFETY ASSESSMENT:

Three tafluprost and three latanoprost patients died in Study 74458 of various causes. No patient deaths were reported from 15-003 and 001. A broad range of serious adverse events, 4 involving the eye and others involving most of the SOC were reported generally in one patient each and no pattern or signal was discerned from these individual serious adverse events. Regarding discontinuation, a somewhat higher number of patients discontinued due to lack of efficacy on tafluprost 23 (2.5%) vs. 9 (1.7%) timolol vs. 3 (1%) for latanoprost, as presented in the table below from Dr Lim's review, page 65:

7.3.3 Dropouts and/or Discontinuations

Patient Dropouts
Studies 15-002, 74457, 74458, 15-003 and 001

Patients	Tafluprost 0.0015% n (%)	Timolol Maleate 0.5% n (%)	Latanoprost 0.005% n (%)
Total randomized	905 (100)	543 (100)	311 (100)
Completed Study	811 (89.6)	502 (92.4)	286 (92.0)
Discontinued Study:	94 (10.4)	41 (7.6)	25 (8.0)
Adverse event	24 (2.7)	13 (2.4)	8 (2.6)
Concomitant medication	2 (0.2)	0 (0.0)	0 (0.0)
Lack of efficacy	23 (2.5)	9 (1.7)	3 (1.0)
Non-compliance	5 (0.6)	4 (0.7)	2 (0.6)
Improper entry	1 (0.1)	2 (0.4)	1 (0.3)
Patient request	27 (3.0)	9 (1.7)	9 (2.9)
Lost to follow-up	11 (1.2)	3 (0.6)	2 (0.6)
Physician decision	1 (0.1)	1 (0.2)	0 (0.0)

Comment:

Although it does not impact approval or labeling, it would be interesting to understand whether the reported discontinuation due to lack of efficacy were seen more in Study 74458 (Europe) where the product was compared to latanoprost, given that the efficacy in the timolol-controlled trial showed similar IOP control and both 15-003 and 001 met their NI margin.

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Ocular adverse reactions reported at an incidence of $\geq 2\%$ in these clinical studies included ocular hyperemia (10%) ocular stinging/irritation (7%), ocular pruritis including conjunctivitis (5%), dry eye (3%), ocular pain (3%), eyelash darkening (2%), growth of eyelashes (2%) and blurred vision (2%). Non-ocular adverse reactions reported at an incidence of 2 – 6% in these clinical studies in patients treated with tafluprost 0.0015% were headache (6%), common cold (4%), cough (3%) and urinary tract infection (2%).

7.4.1 Common Adverse Events

**Number (%) of Patients with Adverse Events Reported by $\geq 2\%$ of Patients
Studies 15-002, 74457, 74458, 15-003, and 001 Pooled**

Adverse Event	Tafluprost 0.0015% N=905 n (%)	Timolol Maleate 0.5% N=543 n (%)	Latanoprost 0.005% N=311 n (%)
OCULAR			
Eye Disorders	349 (38.6)	118 (21.7)	115 (40.0)
Blepharitis	9 (1.0)	3 (0.6)	7 (2.3)
Cataract aggravated	9 (1.0)	0 (0.0)	13 (4.2)
Conjunctival hyperemia	97 (10.7)	23 (4.2)	22 (7.1)
Dry eye	27 (3.0)	11 (2.0)	9 (2.9)
Eyelash darkening	15 (1.7)	0 (0.0)	9 (2.9)
Growth of eyelashes	21 (2.3)	0 (0.0)	11 (3.5)
Ocular pain	31 (3.4)	15 (2.8)	6 (1.9)
Ocular stinging/irritation	65 (7.2)	38 (7.0)	22 (7.1)
Ocular pruritus	44 (4.9)	11 (2.0)	5 (1.6)
Vision blurred	19 (2.1)	15 (2.8)	2 (0.6)

Visual field constriction	12 (1.3)	2 (0.4)	9 (2.9)
NONOCULAR			
Cardiac Disorders	21 (2.3)	7 (1.3)	14 (4.5)
Gastrointestinal Disorders	65 (7.2)	24 (4.4)	14 (4.5)
General Disorders and Administration Site Conditions	49 (5.4)	27 (5.0)	8 (2.6)
Infections and Infestations	136 (15.0)	79 (14.5)	48 (15.4)
Common cold	36 (4.0)	13 (2.4)	8 (2.6)
Flu	16 (1.8)	5 (0.9)	12 (3.9)
Sinusitis	9 (1.0)	3 (0.6)	8 (2.6)
Urinary tract infection	18 (2.0)	6 (1.1)	2 (0.6)
Injury, Poisoning and Procedural Complications	40 (4.4)	18 (3.3)	9 (2.9)
Investigations	35 (3.9)	9 (1.7)	28 (9.0)
Low density lipoprotein cholesterol abnormal NOS	4 (0.4)	0 (0.0)	7 (2.3)
Metabolism and Nutrition Disorders	29 (3.2)	17 (3.1)	7 (2.3)
Musculoskeletal and Connective Tissue Disorders	81 (9.0)	28 (5.2)	32 (10.3)
Nervous System Disorders	86 (9.5)	45 (8.3)	26 (8.4)
Headache	51 (5.6)	15 (2.8)	15 (4.8)
Respiratory, Thoracic and Mediastinal Disorders	60 (6.6)	22 (4.1)	15 (4.8)
Cough	27 (3.0)	9 (1.7)	7 (2.3)
Skin and Subcutaneous Tissue Disorders	36 (4.0)	10 (1.8)	13 (4.2)
Surgical and Medical Procedures	23 (2.5)	7 (1.3)	10 (3.2)
Vascular Disorders	38 (4.2)	19 (3.5)	7 (2.3)
Hypertension arterial	7 (0.8)	0 (0.0)	7 (2.3)

The following observations from individual studies are excerpted from Dr Deng's review:

For **Study 15-003**, the most prevalent ocular adverse event was ocular hyperemia, which was reported by 44 out of the 458 patients (9.6%). The largest difference was seen in ocular hyperemia: 34 (12.7%) patients for PC tafluprost and 10 (5.2%) patients for PC timolol ($p=0.007$), and eye pruritus: 19 (7.1%) patients for PC tafluprost and 5 (2.6%) patients for PC timolol ($p=0.039$). The most prominent related ocular adverse events were ocular hyperemia, eye irritation, eye pain, and eye pruritus.

For **Study 001**, the adverse events of conjunctival and ocular hyperemia (2.8% and 1.6%, respectively) were reported more frequently in the PF tafluprost group than in the PF timolol group in which no conjunctival hyperemia and 0.6% ocular hyperemia were reported. Photophobia was reported with an incidence of 1.3% in the PF tafluprost group compared with the PF timolol group, which had none. Eye pruritus was reported in 6 (1.9%) patients and 3 (0.9%) patients in the tafluprost and timolol group, respectively.

For **Study 77550**, there were somewhat more ocular adverse events for the unpreserved formulation than for the preserved formulation. A total of 20 ocular adverse events were reported by 11 (25.6%) patients for the unpreserved formulation, whereas 7 ocular adverse events were reported by 6 (14.3%) patients for the preserved formulation. Conjunctival hyperemia was the most common adverse event in this study, 2 patients for the preserved formulation and 6 patients for the unpreserved formulation reported conjunctival hyperemia. Most of the ocular adverse events were of mild severity and none were severe.

For **Study 74458**, there were slightly more ocular adverse events in the PC tafluprost group than in the PC latanoprost group. The most prevalent ocular adverse event was eye irritation, which was reported by 20 out of the 528 patients (3.8%). The most prominent related ocular adverse events were redness (ocular hyperemia and conjunctival hyperemia), eye irritation, growth of eyelashes and eye pain. The largest difference was seen in related eye pain (13 for tafluprost and 4 for latanoprost).

Per Dr Lim's review, clinical laboratory (hematology, blood chemistry and urinalysis) evaluations were analyzed in five phase 1 studies (74450, 74451, 74452, 74453, and 15-005) and two phase 3 studies (74458 and 15-003). No clinically significant observations were seen. Cardiovascular parameters (systolic blood pressure, diastolic blood pressure and heart rate) were measured in studies 15-002, 74457, 74458, 15-003 and 001. No clinically relevant changes in cardiovascular parameters were observed. Twelve-lead ECGs were performed on all subjects in early phase 1 studies. There were no clinically significant effects reported.

8.1 Adverse events of special interest

Pigmentation:

The labeling will reflect that tafluprost ophthalmic solution has been reported to cause increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes which is expected to increase as long as tafluprost is administered. The pigmentation change is due to increased

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melanin content in the melanocytes rather than to an increase in the number of melanocytes. Iris pigmentation may develop slowly and is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes may be reversible in some patients. The long term effects of increased pigmentation are not known. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment.

Eyelash Changes:

Tafluprost may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, color, thickness, shape and number of lashes.

Other Warnings:

PGF2a analogues may result in macular edema (including cystoid macular edema) mainly in aphakic patients and those with other risk factors. They should not be used in patients with active intraocular inflammation. There is no experience with tafluprost in neovascular, acute-closure, narrow-angle, or congenital glaucoma, minimal experience with pigmentary and pseudoexfoliative glaucoma and in aphakic patients.

Comment:

The adverse events reported in the tafluprost studies are consistent with events reported with this drug class, and are summarized in labeling.

9. Advisory Committee Meeting

The application was not presented before an Advisory Committee. There are currently four PG analogues approved: Xalatan, Travatan, Lumigan, Rescula.

10. Pediatrics

Pediatric studies for this product were waived because necessary studies are not feasible because there are too few subjects, too geographically dispersed, to properly conduct necessary studies. (b) (4)

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection

Manufacturing facilities are acceptable.

11.2 Office of Scientific Investigation (OSI) Audits

Inspections of two investigators were completed. One from Study 15-003 was considered NAI. Another from 15-001 was considered VAI due to minor transcription and reporting errors, which were corrected. The overall recommendation from OSI was that the studies appear to have been conducted adequately and data may be used to support the application.

11.3 Debarment certification

Merck Sharpe & Dohme Corp certified that they had not used services of any debarred individual [as required under FD&C Act Section 306(a) or (b)].

11.4 Financial Disclosure

Dr. Lim states that there is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

11.5 Other Regulatory Issues

None

12. Labeling

The package insert, patient package insert, and carton and container labeling were reviewed as applicable by the Division, DMEPA, DDMAC and the patient labeling group (now part of the Office of Medical Policy)

- **Package insert (PI):** The PI is written in PLR format and has been reviewed by all groups, and includes the recommendations made by these groups. DMEPA recommended deleting language that the single-use ampoule is sufficient to treat both eyes to avoid inappropriate use and saving the opened ampoule for future doses and risking bacterial contamination. A statement “discard unused portion” is recommended for this product containing no preservative. Additional comments regarding formatting and font size, bolding, color, and graphics were made. DDMAC’s comments were also incorporated.
- **Patient package Insert (PPI):** The PI is submitted with the original application was revised to remove promotional, incorrect and misleading language, reviewed by OMP patient package labeling group and DDMAC.
- **Carton and Container Labels:** The labels were reviewed by CMC and DMEPA.
- **Proprietary Name:** The applicant’s initial proposed proprietary name of Saflutan was unacceptable because of its similarity to Xalatan and the applicant was sent a letter on April 15, 2011. The subsequent proposed proprietary name Zioptan was reviewed and found acceptable from the safety and promotional perspective by DMEPA on August 31, 2011 and a letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on October 31, 2011. If applicable, the name will be re-reviewed within 90 days of the application’s approval.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The deficiencies identified in Product Quality Microbiology Review regarding (b) (4) were discussed, including the potential that they could be addressed as post-marketing commitments. However, Product Quality Microbiology recommends that results of 3

consecutive (b) (4) runs must be reviewed before the application can be approved. Therefore, a *Complete Response* letter should be issued and should include the following text:

Your NDA does not provide assurance of the sterility of the final drug product. While you have revised your (b) (4) processing validation protocol in your submission of October 27, 2011, you have not conducted (b) (4) to evaluate your (b) (4) filling procedures using this revised validation protocol. In the absence of the (b) (4), we cannot determine that the product is sterile and safe for use.

To address this deficiency, provide a report describing three consecutive successful (b) (4) processing simulations on the filling line that you will use for manufacturing the product using the inspection and accounting procedures provided in the revised (b) (4) processing validation protocol submitted in the October 27, 2011 amendment.

13.2 Risk Benefit Assessment

Two Phase 3 studies demonstrated that Zioptan is safe and effective in the reduction of IOP in patients with open-angle glaucoma and ocular hypertension, by meeting their prespecified NI margin, and a bridging study demonstrated that the PC and PF formulations had similar efficacy.

The safety profile of tafluoprost is consistent with the adverse events previously identified for this class including pigmentary changes and some ocular irritation and toxicity; these findings are addressed in labeling and are similar to other products in the class.

The product is preservative free, however, no specific benefits were included as endpoints in the study, nor were any particular compliance, efficacy, or safety differences in terms of advantages noted for the PF versus the PC product. Because there is not preservative included, the instructions will state that the product is for single use and any unused portion should be discarded.

The patient package insert provides information on the product and its use in easy to understand language and includes pictorial directions on how the product should be used.

13.3 Recommendation for Postmarketing Requirements (PMR) and Commitments (PMC)

None at this time

APPENDIX A: CLINICAL TRIAL SUMMARIES

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Proposed indication: reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
15-001 dose-response study	Parallel-group, multi-center, randomized, dose-response, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost ophth soln (0.001%, 0.0025%, 0.005%) Placebo Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop BID OU 1 drop QPM OU	28 days	152 subjects in a ratio of 1:1:1:1:1
15-002 dose-response study	Parallel-group, multi-center, randomized, dose-response, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost ophth soln (0.0003%, 0.0015%, 0.0025%) Timolol 0.5% ophth soln Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop BID OU 1 drop QPM OU	28 days	144 subjects in a ratio of 1:1:1:1:1
74457 Pilot safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln. Latanoprost	1 drop QPM OU 1 drop	6 weeks	38 subjects in a ratio of 1:1 (19 in the tafluprost group and 19 in the latanoprost group)

Table 3: Summary of Key Design Elements for Studies 15-003, 001, and 74458

Protocol	Study Design	Duration	Treatment Arms	Endpoints (as defined in the protocol)	Endpoints (as requested by FDA)
15-003	Randomized, Active-controlled, Double-masked, parallel-group, multicenter, 12-month trial	12 months	PC Tafluprost 0.0015% q.d. PC Timolol 0.5% b.i.d. Randomization Ratio: 3:2	Change from baseline in diurnal IOP reduction at month 6 for the study eye	IOP at each time point at each visit through month 6
001	Randomized, Active-controlled, Double-masked, parallel-group, multicenter, 12-week trial	12 weeks	PF Tafluprost 0.0015% q.d. PF Timolol 0.5% b.i.d. Randomization Ratio: 1:1	Mean change from baseline in IOP at all 9 time points during the study (0800, 1000, 1600 hrs at Weeks 2, 6, and 12) for the study eye	Mean change from baseline in IOP at all 9 time points during the study (0800, 1000, 1600 hrs at Weeks 2, 6, and 12)
74458	Randomized, Active-controlled, Double-masked, parallel-group, multicenter, 24-month trial	24 months	PC Tafluprost 0.0015% q.d. Latanoprost 0.005% q.d. Randomization Ratio: 1:1	Change from baseline in diurnal IOP at 6 months for the study eye	IOP at each time point at each visit through month 6

Source: Studies 15-003, 001, and 74458 Protocols.

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Table 4: Summary of Key Design Elements for Studies 74460, 77550, and 77552

Protocol	Study Design	Duration	Treatment Arms	Endpoints (as defined in the protocol)
77550	A Crossover Comparison Between the Preservative-Containing and Preservative-Free Formulation	8 week (4 weeks per treatment period)	PF Tafluprost 0.0015% q.d. vs. PC Tafluprost 0.0015% q.d. Randomization Ratio: 1:1	Mean change from baseline in IOP at all 9 timepoints during the study (0800, 1000, 1600 hrs at Weeks 2, 6, and 12)
74460	Randomized, Double-masked, Placebo-controlled, parallel-group, multicenter	6 weeks double masked, 6 to 12 weeks open-label	PF Tafluprost 0.0015% q.d. + Timolol b.i.d VS. PF Tafluprost 0.0015% q.d. + Placebo b.i.d Randomization Ratio: 1:1	Change from baseline in diurnal IOP reduction at week 6
77552	A Phase IIIb Study on the Changes in Ocular Signs, Symptoms and Conjunctival Inflammatory Markers in Patients with Ocular Hypertension or Open-Angle Glaucoma Switched from Preservative-Containing Latanoprost 0.005% Eye Drops to Preservative Free Tafluprost 0.0015% Eye Drops.	12 weeks	PF Tafluprost 0.0015% q.d. vs. PC Latanoprost 0.005% q.d. Randomization Ratio: 1:1	Changes in ocular signs, symptoms, and conjunctival inflammatory markers occur when patients are switched from latanoprost 0.005% eye drops with preservative to tafluprost 0.0015% eye drops without preservative

Source: Studies 77550, 74460, and 77552 Protocols.

Renata Albrecht, MD
Director, DTOP

Edward Cox, MD, MPH
Director, OAP

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

/s/

RENATA ALBRECHT
11/07/2011

EDWARD M COX
11/07/2011

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 202514
Supplement #	
Applicant Name	Merck Sharpe & Dohme Corp.
Date of Submission	January 7, 2011
PDUFA Goal Date	November 7, 2011
Proprietary Name / Established (USAN) Name	Zioptan tafluprost ophthalmic solution
Dosage Forms / Strength	ophthalmic solution, sterile / 0.0015%
Proposed Indication(s)	Reduction in intraocular pressure in open-angle glaucoma or ocular hypertension
Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Lucious Lim
Statistical Review	Yunfan Deng, Yan Wang
Pharmacology Toxicology Review	James Wild, Wendelyn Schmidt
CMC Review/OBP Review	Maotang Zhou, Rapti Madurawe
Product Quality Microbiology Review	Jessica Cole, Stephen Langille
Supervisory Product Quality Microbiology Review	David Hussong
Clinical Pharmacology Review	Yongheng Zhang, Phil Colangelo
DSI	Kassa Ayalew, Susan Thompson, Jean Mulinde
CDTL Review	William Boyd
Deputy Division Director's Review	Wiley Chambers
Division Director's Review	Renata Albrecht
OSE/DMEPA	Denise Baugh, Todd Bridges, Carol Holquist

OND=Office of New Drugs
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Tafluprost is an analog of prostaglandin F_{2α} developed for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Other members of this class (prostaglandin F_{2α} analogs) have been previously approved for this indication. Tafluprost 0.0015% has been approved in a number of other countries outside of the US in preservative-free or preservative containing formulations. The formulation that the applicant is seeking approval of in NDA 202514 is a preservative free formulation.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of tafluprost. For a detailed discussion of NDA 202514, the reader is referred to the individual discipline specific reviews. In addition Dr. Boyd's Cross-Discipline Team Leader Memorandum and Dr. Chambers' Deputy Division Director's Review and Dr. Albrecht's Division Director Review also summarize key issues in the NDA submission. This memorandum will focus on the Product Quality Microbiology deficiency issue.

The Product Quality Microbiology Reviewer and the Supervisory Product Quality Microbiology Reviewer both recommend a Complete Response action because of inadequate information to support the quality of the product, specifically assurance of sterility. To address this deficiency the applicant should perform and submit for review the results of three consecutive successful (b) (4) processing simulations on the filling line that will be used to manufacture the product using the revised inspection and accounting procedures. This issue is further discussed below.

The chemistry manufacturing and controls, pharmacology and toxicology, and clinical pharmacology, reviewers recommend approval. The facilities have been found to be in compliance with cGMPs. The results of the rat and mouse carcinogenicity studies have been reviewed by the Executive Carcinogenicity Assessment Committee; they found the rat carcinogenicity study to be an adequate study, no tafluprost-related neoplasms were found, and that no additional carcinogenicity testing was needed.

Regarding Product Quality Microbiology, the applicant performed a number of (b) (4), but review of the results found that the accounting for the containers in the initial three (b) (4) was lacking. Two additional (b) (4) were performed that did include complete accounting; in one of these two (b) (4), two containers from one of the (b) (4) were non-sterile. However, the applicant's procedure led them to re-inspect the containers and disregard positive findings of any container observed to have a breach in container integrity. According to the procedures, containers are to be inspected twice prior to the (b) (4) (and the same would be true for shipment), however the third inspection where containers to disregard are identified, after growth has occurred, is not consistent with FDA's Guidance for Industry, (b) (4) — Current Good Manufacturing Practice (b) (4). The applicant has now amended their procedures, but to date has not performed three consecutive (b) (4) using the amended procedures.

An essential part of assessing the assurance of sterility for a product manufactured by (b) (4) processing are the results of (b) (4) performed by adequate methods. Although (b) (4) (b) (4) testing has not been performed using the amended method. In the absence of the (b) (4), we cannot determine that the product is sterile and safe for use.

The recommendation from the Product Quality Microbiology Reviewer, Team Leader, and Supervisor is that the information provided on the revised testing procedure and the lack of having performed three consecutive (b) (4) using that procedure provides inadequate information of the assurance of the quality of the product, specifically its sterility. Therefore

the recommendation from the Product Quality Microbiology Review team is that in the absence of the (b) (4), we cannot determine that the product is sterile and safe for use. Therefore this issue is a deficiency that needs to be addressed prior to approval. The Division Director concurs with this recommendation; the Deputy Division Director and Cross-Discipline Team Leader do not concur with this recommendation. I have met with Product Quality Microbiology Reviewer, Team Leader, and Supervisor, the Division Director, and Deputy Division Director to discuss this issue. I concur with the recommendation of the Product Quality Microbiology Reviewer, Team Leader, and Supervisor, and the Division Director on this issue of inadequate information to assure the quality of the product, specifically its sterility, and that additional information will be needed prior to approval to address this deficiency. The additional needed information is three consecutive successful (b) (4) using the amended procedure of October 27, 2011.

The results of the clinical trials support the clinical safety and efficacy of tafluprost for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Two trials found non-inferiority of tafluprost to timolol; one trial utilized tafluprost with a preservative, the other trial tested preservative free tafluprost. A trial comparing preservative containing and preservative free tafluprost found comparable levels of IOP lowering. There are also results of a trial comparing tafluprost to latanoprost; in this trial tafluprost did not make its non-inferiority margin. The safety database included over 900 patients exposed to tafluprost. The most frequent ocular adverse reaction was conjunctival hyperemia. Other adverse reactions reported included ocular pruritis, ocular stinging/irritation, cataract, dry eye, ocular pain, eyelash darkening, growth of eyelashes, and blurred vision. Prostaglandin F2 α analogs have also been associated with increased pigmentation of the iris, periorbital tissue, and eyelashes, and deepening of the eyelid sulcus. For additional details on the efficacy and safety findings from the clinical trials the reader is referred to the clinical and statistical reviews.

The application for Zioptan (tafluprost ophthalmic solution) was not presented to the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC). Other members of the prostaglandin F2 α class have been approved for treatment of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. In addition, the data from the clinical trials did not reveal any complex issues with regards to safety and efficacy for the product.

In summary, the application should be issued a Complete Response letter noting the deficiency regarding incomplete information to assure the sterility of the product. The Complete Response letter will also provide a means to address the deficiency by providing results from three consecutive successful (b) (4) processing simulations on the filling line that will be used to manufacture the product using the revised inspection and accounting procedures of October 27, 2011.

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/s/

EDWARD M COX
11/07/2011

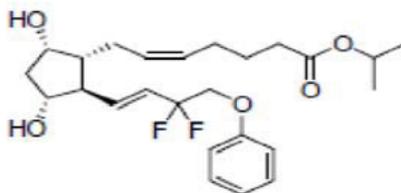
Deputy Division Director Review of NDA 202-514

Date	November 5, 2011
From	Wiley A. Chambers, M.D.
NDA #	202514
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	January 7, 2011
Type of Application	505(b)(1)
Name	Zioptan (tafluprost ophthalmic solution) 0.0015%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction/Background

Tafluprost (AFP-168, MK-2452) is a new chemical entity drug product proposed for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. It is an ester prodrug of a synthetic prostaglandin F2 α (PGF2 α) analog that is converted *in vivo* into the pharmacologically active tafluprost acid. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) have been approved for reducing of elevated IOP in open angle glaucoma and ocular hypertension in a number of countries including Austria, Germany, Czech Rep, Denmark, Finland, Norway, Poland, Sweden, Iceland, Italy, Spain, Portugal, the Netherlands, Romania, Bulgaria, Estonia, Latvia, Lithuania, Slovak Rep, United Kingdom, Russia, Ukraine, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Uzbekistan, Japan, Korea, Hong Kong, and Indonesia. Tafluprost is not marketed in the United States.

2. CMC



The drug substance, tafluprost, is a colorless to light yellow viscous liquid, with a molecular formula of C₂₅H₃₄F₂O₅ and a molecular weight of 453.53 Daltons. Tafluprost is manufactured, packaged, and stability-tested at (b) (4). The information on manufacturing processes and controls for tafluprost is described in (b) (4) DMF (b) (4). All chemistry issues have been resolved.

The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains tafluprost, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid to adjust to pH 5.5-6.7, and water for injection. Glycerol is used (b) (4) of the drug product. The drug product solution is manufactured,

(b) (4) by Laboratoire Unither, France. (b) (4)

The ampoules are packed (b) (4) pouches, 10 ampoules per pouch. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).

COMPOSITION OF THE DRUG PRODUCT (mg per mL)

Tafluprost	0.0015
Glycerol	(b) (4)
Sodium dihydrogen phosphate dehydrate	(b) (4)
Disodium edentate	(b) (4)
Polysorbate 80	(b) (4)
NaOH/HCl	Adjust pH
Water for injection	q.s.

Regulatory Specifications:

Appearance	Clear, colorless solution. (b) (4)
Tafluprost identification/HPLC, UV	Match reference standard
pH	5.5-6.7
Osmolality	260-300 mOsm/kg
Impurities	(b) (4)
Tafluprost Assay	(b) (4)
Sterility	(b) (4)
Endotoxin	(b) (4)
Particulate Matter (light obscuration/microscopy)	(b) (4)

Ophthalmic drug product specifications normally include a limit on unspecified impurities at (b) (4). The exceptions in recent years have been with products in which the concentration of the active ingredient is less than (b) (4). These exception products have had specifications for unspecified impurities listed as (b) (4) instead of a percent of the active ingredient. While it would have been preferable to list this specification (b) (4), the current proposed specification is acceptable because the concentration of the active ingredient is less than (b) (4).

(b) (4)

While it would be preferable to use the entire specification, the failure to include the full specification is not a sufficient reason by itself to not approve the product.

FACILITIES INSPECTIONS:

The overall recommendation from the Office of Compliance is “Acceptable” in EES.

3. Nonclinical Pharmacology/Toxicology

The active metabolite, tafluprost acid (AFP-172) is the pharmacologically active agent. In primary pharmacology studies, tafluprost acid (AFP-172) was shown to bind to the FP prostanoid receptor with subnanomolar affinity, and binding was shown to be substantially selective for this receptor.

The primary safety signals in safety pharmacology studies were a low incidence of central nervous effects in mice and a dose-dependent increase in blood pressure, heart rate, and Qtc intervals in anesthetized dogs. However, the cardiovascular effects occurred only minimally in repeated-intravenous dose toxicology studies in dogs, and did not occur in repeated-ocular dose studies in monkeys. Because clinical exposures are expected to be on the order of 100 fold lower than the exposures associated with the high ocular doses in the monkey studies, cardiovascular toxicity is not expected to be a clinical concern.

Ocular changes included iridial darkening, sunken eyelids, and blue-gray discoloration of the lower eyelid. However, all of the tafluprost-related ocular changes are consistent with ocular changes observed with other marketed PGF2 α analogs. These effects are considered to be mainly cosmetic, not associated with loss of function, and not toxicologically significant. Other, more serious ocular toxicities including pronounced inflammation or alterations in electroretinography were not observed with topical ocular administration of tafluprost at any of the administered doses.

Topical ocular administration of 3H-tafluprost in rats and monkeys resulted in widespread ocular distribution. Repeated dosing produced a similar ocular distribution pattern, and accumulation did not occur in any tissue other than the lens where concentrations increased approximately 50% after 21 days of dosing.

Tafluprost acid was >90% bound to serum albumin from rat, rabbit, dog and humans. Tafluprost demonstrated extensive tissue distribution consistent with renal and hepatobiliary excretion and limited CNS distribution. Tissue distribution following repeated ocular dosing was similar to that following a single dose indicating an absence of systemic tissue accumulation. Tafluprost administered topically to the eye or intravenously was excreted primarily in urine and through hepatobiliary excretion with final deposition in feces.

3H-Tafluprost or its metabolites transferred into milk in lactating rats, and crossed the placental barrier in pregnant rats. Milk Cmax radioactivity levels were similar to those in plasma, and fetal exposure was approximately two thirds that of plasma exposure.

Tafluprost was shown to be negative for genotoxicity in an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosome aberration assay in Chinese Hamster lung cells, and an *in vivo* mouse bone marrow micronucleus assay.

In both a 24-month rat carcinogenicity study and a 78-week mouse carcinogenicity study where tafluprost was administered subcutaneously, no unusual tumors or significantly increased tumor incidence suggestive of tafluprost-related carcinogenicity was observed.

4. Clinical Pharmacology/Biopharmaceutics

In four Phase 1 dose-escalation studies (74450, 74451, 74452, and 74453), neither tafluprost nor tafluprost acid could be detected when using a bioanalytical method (HPLC/MS/MS) with LLOQ at 0.2 ng/mL (tafluprost) and 0.1 ng/mL (tafluprost acid). One confounding factor is that the plasma samples may have not been stored properly in some of these studies to ensure adequate sample stability. In a subsequent Study 15005, systemic exposure following topical ocular administration of 0.0015% tafluprost ophthalmic solution was successfully assessed using an improved analytical method (HPLC/MS/MS) with LLOQ at 10 pg/mL (tafluprost acid). Furthermore, Study 77551 was conducted to verify if the systemic bioavailability of tafluprost in humans after topical ocular q.d. administration of either tafluprost (0.0015%) PF or PC ophthalmic solution is similar.

5. Sterility Assurance

This is a non-preserved aqueous solution that is sterile filtered and (b) (4) filled into single-use containers using (b) (4) technology.

Endotoxin testing will occur according to USP<85> gel clot, kinetic turbidimetric, or kinetic chromogenic methods. (b) (4)

Reference is made to Ph.Eur. (b) (4) for the sterility test method using (b) (4) filtration. Validation studies were conducted with three lots (MTD0866, MTD0868, and MTD0900) which the Product Quality Microbiology Reviewer assumes are the preserved formulation. Ten bottles of a 2.5 mL formulation were filtered for a total sample size (b) (4)

The results were comparable to control samples and are sufficient to validate the sterility test method for the non-preserved formulation.

The initial review of the application considered the (b) (4) procedures to be inadequate. The (b) (4) procedures allowed additional inspection of positive vials after incubation had begun and as such were not adequate to insure sufficient sterility assurance for this (b) (4) processed sterile drug product. (b) (4)

The applicant revised the (b) (4) procedure to include a full accounting of units from (b) (4) processing validation studies. Module 3.2.P.3.5.5.2.2 Process Validation and /or Evaluation requires documentation of the number of units filled, rejected (pre-incubation), incubated, and positive for growth in the batch record. The Microbiology reviewer concluded that the applicant had submitted revised methods which addressed all concerns from the first review. However, there was only a single (b) (4) (10014) which supported the proposed (b) (4) processing procedure. The applicant committed to conduct three consecutive (b) (4) processing validation studies by 31 March 2011. The reviewer has asked that the applicant provide the results of three consecutive successful (b) (4) processing simulations on filling line (b) (4) using the revised inspection and accounting procedures before approval.

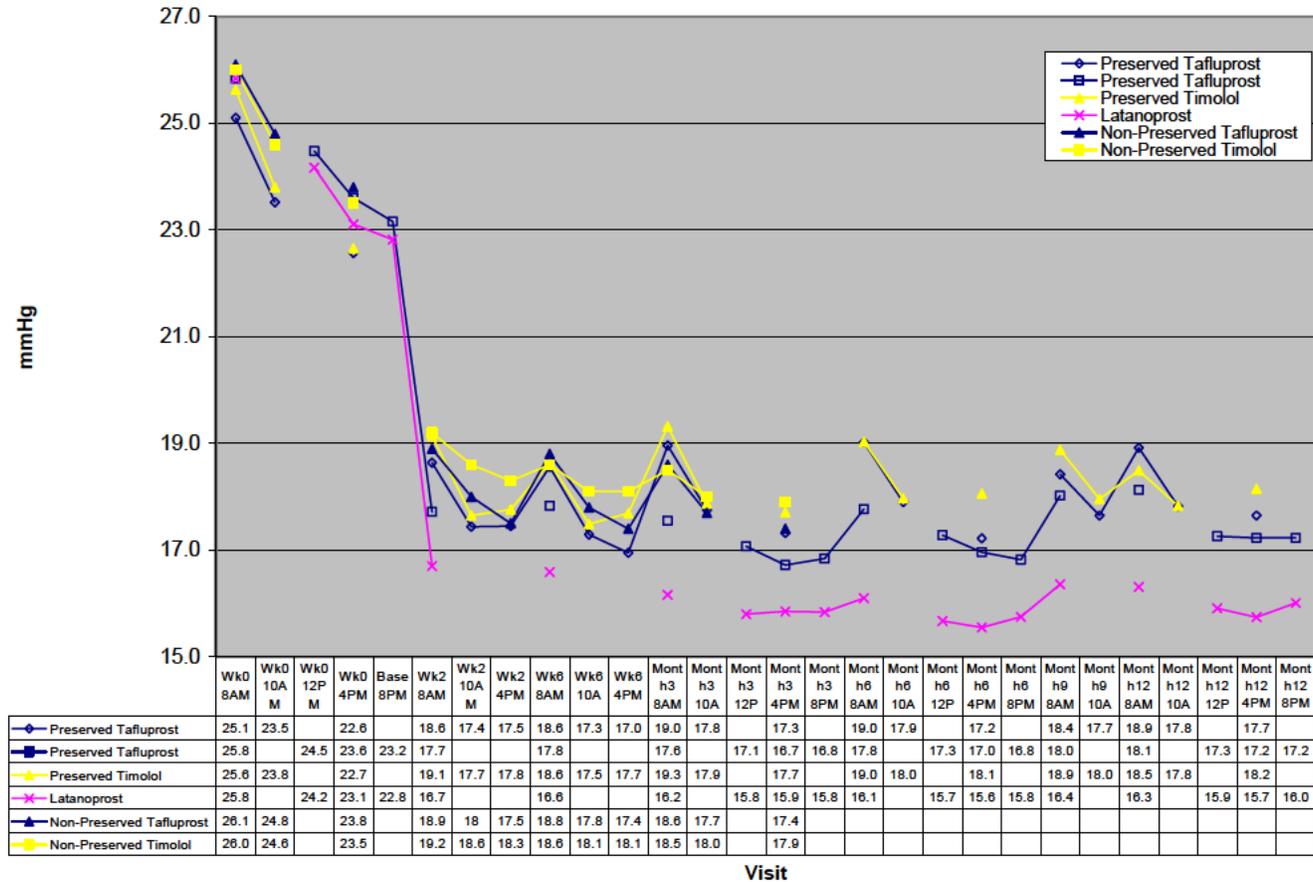
I disagree with requirement to conduct three additional (b) (4) prior to approval because it does not appear to be one of the reasons to not approve an application listed in 21 CFR 314.125. The applicant has amended their procedures to provide an acceptable procedure. The three additional (b) (4) are considered a validation procedure, and methods validation is often conducted after approval, not as a condition of approval.

6. Clinical/Statistical - Efficacy

Analyses of Endpoints

The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

Mean IOP (Studies 001,15-003 and 74458)



As noted in the graph above, tafluprost ophthalmic solution (preserved and non-preserved) is equivalent to timolol ophthalmic solution (preserved and non-preserved) in its ability to lower intraocular pressure. The 95% confidence intervals for IOP reduction is within the equivalence margins of 1.5mmHg at all timepoints and within 1 mmHg for the majority of timepoints. Tafluprost ophthalmic solution was not demonstrated to be equivalent to latanoprost ophthalmic solution. The data support Zioptan (tafluprost ophthalmic solution) 0.0015% administered once daily in the evening for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

7. Safety

Five studies are used to support the safety and efficacy of tafluprost. The patient exposure and safety assessments were adequate.

Exposure to Study Drug by Protocol

Protocol #	Number of Patients	Tafluprost	Timolol	Latanoprost
15-002	144	87	29	28
74457	38	19		19
15-003	458	267	191	
74458	533	269		264
001	643	320	323	
Total	1816	962	543	311

Serious Adverse Events occurring in more than 1 patient (Studies 001, 15-002, 15-003, 74457, 74458)

Adverse Event	Tafluprost (n=905)	Timolol (n=543)	Latanoprost (n=311)
Retinal vein occlusion	-	2	-
Coronary artery disease	4	-	-
Chest pain	2	-	2
Death	3	-	3
Back pain	2	-	-
Syncope	-	2	-
Dyspnea	2	-	-
Hypertension aggravated	2	-	-

The most common ocular adverse events (pooled) were conjunctival hyperemia (10.7%) and ocular stinging/irritation (7.2%). The most common nonocular adverse event was headache (5.6%).

Adverse Events reported by $\geq 2\%$ of patients from Studies 001, 15-002, 15-003, 74457, and 74458

Adverse Event	Tafluprost (n=905)	Timolol (n=543)	Latanoprost (n=311)
Conjunctival hyperemia	97 (11%)	23 (4%)	22 (7%)
Ocular stinging/irritation	65 (7%)	38 (7%)	22 (7%)
Headache	51 (6%)	15 (3%)	15 (5%)
Ocular pruritis	44 (5%)	11 (2%)	5 (2%)
Cold	36 (4%)	13 (2%)	8 (3%)
Ocular pain	31 (3%)	15 (3%)	6 (2%)
Dry eye	27 (3%)	11 (2%)	9 (3%)
Cough	27 (3%)	9 (2%)	7 (2%)
Growth of eyelashes	21 (2%)	-	11 (3%)
Vision blurred	19 (2%)	15 (3%)	2 (1%)
Urinary tract infection	18 (2%)	6 (1%)	2 (1%)
Flu	16 (2%)	5 (1%)	12 (4%)
Eyelash darkening	15 (2%)	-	9 (3%)
Visual field constriction	12 (1%)	2 (<1%)	9 (3%)
Blepharitis	9 (1%)	3 (<1%)	7 (2%)
Cataract increased	9 (1%)	-	13 (4%)
Sinusitis	9 (1%)	3 (<1%)	8 (3%)
Hypertension	7 (1%)	0	7 (2%)
Low density lipoprotein cholesterol abnormal	4 (<1%)	0	7 (2%)

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Zioptan (tafluprost ophthalmic solution) 0.0015%, dosed once each evening, is safe for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The most common ocular adverse events (pooled) were conjunctival hyperemia (11%) and ocular stinging/irritation (7%). The most common nonocular adverse event was headache (6%).

8. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because it is a member of the class of ophthalmic prostaglandin analogs with similar potential risks and benefits as other members in this class. The benefits and risks of using prostaglandin analogs to treat elevated intraocular pressure have been previously discussed at a meeting of the Dermatologic and Ophthalmologic Advisory Committee on December 8, 1995, and the safety profile of tafluprost did not raise any new significant safety

issues. The clinical design including endpoints of the adequate and well-controlled studies was similar to other approved drugs in this class and we are not aware of any controversial issues that would benefit from further advisory committee discussion.

9. Pediatrics

Tafluprost has not been studied in the pediatric population. The product qualifies for a waiver because of the small pediatric patient population with ocular hypertension or glaucoma. While the use in pediatric patients below the age of 16 years is not recommended because the treatment of pediatric ocular hypertension is usually a surgical treatment and there is the potential safety concern related to long term increased pigmentation following chronic use. The short term (five year use) has been studied with other prostaglandin analogs. The five year use demonstrated that increased pigmentation continues throughout the period, but at five years there were no adverse consequences.

10. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. Per the DSI review finalized 6/27/2011:

Two clinical sites were inspected in support of this application. In general, inspection of Dr. Douglas Day's site revealed that he adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations and the final classification for this inspection is No Action Indicated (NAI).

Inspection of Dr. David Wirta's site documented regulatory violations and the preliminary classification for this inspection is Voluntary Action Indicated (VAI) for errors in recordkeeping of adverse events, which were isolated and relatively minor. Incorrect causality of adverse events was corrected and later reported to the sponsor.

The studies at these sites appear to have been conducted adequately, and the data generated may be used in support of the application.

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment considered originally proposed proprietary name, Saflutan. In an April 15, 2011, letter to

the applicant DMEPA found this proprietary name unacceptable since it is orthographically similar to, and shares overlapping product characteristics with, Xalatan.

In an August 31, 2011, letter to the applicant, DMEPA found the proprietary name Zioptan to be acceptable.

DMEPA was invited to all internal labeling meeting and provided recommendations on the packaging configuration and the package insert labeling.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)/DIVISION OF PROFESSIONAL PROMOTION (DPP)

OPDP provided labeling comments based on the substantially complete version of the labeling titled, "N202514_Label1.doc" which was sent via email from Constantine Markos on October 17, 2011.

The warning against use of contact lenses with the use of other prostaglandin analogs is not applicable to tafluprost since it does not contain a preservative which can be absorbed into the contact lenses and remain in contact with the eye.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 7/31/09:

In this submission, the Applicant seeks approval of preservative-free (PF) tafluprost 0.0015% ophthalmic solution administered once daily for the treatment of elevated intraocular pressure (IOP). The Applicant submitted three non-inferiority efficacy studies (two timolol non-inferiority studies [15-003 and 001] and one Latanoprost Non-Inferiority Study [74458]), and a study comparing the PC formulation and PF formulation (Study 77550).

For study 15-003 comparing preservative-containing (PC) tafluprost with PC timolol, both PC tafluprost and the active comparator PC timolol showed IOP-lowering effect throughout the 12-month study period. Tafluprost reached the predetermined criteria for non-inferiority (1.5 mmHg) at each visit and time point using timolol as the active comparator.

For study 001 comparing PF tafluprost versus PF timolol, both PF tafluprost and the active comparator (PF timolol) showed IOP-lowering effect throughout the 12 weeks of treatment. The IOP-lowering effect of PF tafluprost was within the 1.5 mmHg non-inferiority margin compared to PF timolol at all visits and time points.

Study 77550 investigated the pharmacodynamics (as expressed in IOP) of the preserved and unpreserved formulation of tafluprost 0.0015% eye drops in patients with open-angle glaucoma or ocular hypertension. For both the preservative-containing and preserve-free formulation, a similar and clear IOP-lowering effect was seen already at week 1 and the IOP-lowering effect was sustained and similar for both formulations at week 4.

For study 74458, both PC tafluprost and PC latanoprost reduced IOP throughout the 24 months treatment period. However, tafluprost did not reach the predetermined criterion for noninferiority (1.5

mmHg) versus latanoprost. Using the non-inferiority margin of 1.5 mmHg, both studies 15-003 and 001 demonstrated noninferiority of tafluprost 0.0015% to timolol 0.5% in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in both preservative-containing and preservative-free formulation. Study 77550 demonstrated that the IOP lowering effects for the PC formulation and the PF formulation were similar.

Based on the totality of the evidence provided by these pivotal studies, we recommend the approval of PF tafluprost 0.0015% dosed once daily for the treatment of elevated intraocular pressure in patients with open glaucoma or ocular hypertension.

11. Labeling

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the labeling below.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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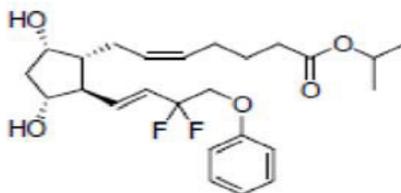
WILEY A CHAMBERS
11/07/2011

Cross-Discipline Team Leader Review of NDA 202-514

Date	November 4, 2011
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202514
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	January 7, 2011
PDUFA Goal Date	November 6, 2011
Type of Application	505(b)(1)
Name	Zioptan (tafluprost ophthalmic solution) 0.0015%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction

Chemical Structure of Tafluprost



Tafluprost (AFP-168, MK-2452) is a new chemical entity drug product developed for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. It is an ester prodrug of a synthetic prostaglandin F₂α (PGF₂α) analogue, relatively selective for the FP prostanoid receptor and converted *in vivo* into the pharmacologically active tafluprost acid (AFP-172).

The proposed product, tafluprost ophthalmic solution 0.0015% (one eye drop once daily), does not contain any antimicrobial preservative agents, such as benzalkonium chloride, which is commonly used in the currently approved prostaglandin analogues. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) have been approved for reducing of elevated IOP in open angle glaucoma and ocular hypertension in many countries other than the United States including Austria, Germany, Czech Rep, Denmark, Finland, Norway, Poland, Sweden, Iceland, Italy, Spain, Portugal, the Netherlands, Romania, Bulgaria, Estonia, Latvia, Lithuania, Slovak Rep, United Kingdom, Russia, Ukraine, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Uzbekistan, Japan, Korea, Hong Kong, and Indonesia. Tafluprost is not marketed in the United States.

2. Background

There are currently numerous topical treatments for lowering intraocular pressure in patients with open angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors and prostaglandin analogs.

Studies 15-001, 15-002, 15-003, 74458 and 001 were used in the efficacy analysis. Studies 15-002, 74457, 15003, 74458 and 001 were used in the safety analysis.

An End-of-Phase 2 meeting was held on August 24, 2009, with Merck to discuss the clinical development plan for a preservative-free ophthalmic formulation of tafluprost. Merck proposed to conduct Study 001, a three-month study of preservative-free (PF) tafluprost compared to PF timolol, to support the approval of preservative free tafluprost. A Pre-NDA meeting was held on August 13, 2010, to discuss the content and the format of the proposed NDA.

The class effects for prostaglandin analogs, including tafluprost ophthalmic solution 0.0015% have been reported to include changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and the periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. Increased iris pigmentation may be permanent.

3. CMC

From the two CMC Reviews finalized 8/26/2011 and 10/24/2011:

The drug substance, tafluprost, is a colorless to light yellow viscous liquid, with a molecular formula of $C_{25}H_{34}F_2O_5$ and a molecular weight of 453.53 Daltons. Tafluprost is a new molecular entity (NME) and it has not been previously marketed in the United States. Tafluprost is manufactured, controlled, packaged, and stability-tested at (b) (4). The information on manufacturing processes and controls for tafluprost is described in (b) (4) DMF (b) (4). A letter of authorization to refer to DMF (b) (4) was provided on behalf of (b) (4). DMF (b) (4) has been reviewed and all chemistry issues have been resolved. As revised, the DMF is adequate to support the current NDA.

The drug product, tafluprost 0.0015% ophthalmic solution is a sterile aqueous isotonic solution that contains the drug substance tafluprost and the excipients, sodium dihydrogen phosphate dihydrate, polysorbate 80, disodium edetate, glycerol, sodium hydroxide and/or hydrochloric acid, and water for injection. Glycerol is used (b) (4) of the drug product. Sodium hydroxide and hydrochloric acid are used to adjust the solution pH to 5.5 – 6.7. All the excipients are of compendial grade (USP/NF). The drug product solution is manufactured, (b) (4) by Laboratoire Unither, France. The drug product manufacturing process (b) (4)

(b) (4) Each single-use ampoule is filled with 0.3 mL of the sterile solution containing 4.5 µg of tafluprost and affixed with a label. The labeled ampoules are packed in (b) (4) pouches, 10 ampoules per pouch. The pouches are then packed in carton boxes. Commercial cartons are either 30-count (3 pouches) or 90-count (9 pouches) and sample cartons are 10-count (1 pouch).

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Table 3.2.P.1-2452-ophsln: 1

Composition of Tafluprost 15 microg/mL Eye Drops in Single-Dose Container.

Drug substance	Reference	Percent (w/v)	Quantity (mg/mL)	Function
Tafluprost	In-house ¹	0.0015	0.015	Drug substance
Excipients			(b) (4)	(b) (4)
Glycerol	PhEur/USP	(b) (4)	(b) (4)	(b) (4)
Sodium dihydrogen phosphate dihydrate	PhEur/USP			
Disodium edetate	PhEur/USP			
Polysorbate 80	PhEur			
Sodium hydroxide ¹ and/or hydrochloric acid, (b) (4)	PhEur/USP PhEur			
Water for injection	PhEur			
				pH adjuster
				pH adjuster
				(b) (4)
				(b) (4)

PROPOSED REGULATORY SPECIFICATIONS:

Drug Product Specification (as revised in the 7/11/2011 amendments)		
Test	Method	Acceptance Criteria
Appearance	Ph. Eur. 2.2.1 and 2.2.2	Clear, colorless solution. Practically free from visible particles.
Identification/HPLC, UV/Tafluprost	In-house HPLC	UV spectrum is similar to the result of reference standard; retention time is within ± 5% of reference standard
pH	Ph. Eur. 2.2.3	5.5 – 6.7
Osmolality	Ph. Eur. 2.2.35	260 – 300 mOsm/kg
Impurities/Degradantes/HPLC/ Tafluprost		(b) (4)
Assay/ HPLC/ Tafluprost		
Sterility		
Endotoxin test		
Particulate Matter (light Obscuration/Microscopy)		

From the CMC Review finalized 10/24/2011:

FACILITIES INSPECTIONS:

The overall recommendation from the Office of Compliance is “Acceptable” in EES.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 7/20/2011:

Tafluprost (AFP-168) is a PGF₂α analogue intended for topical ocular administration. The active metabolite, tafluprost acid (AFP-172) is the pharmacologically active agent. In primary pharmacology studies, tafluprost acid (AFP-172) was shown to bind to the FP prostanoid receptor with subnanomolar affinity, and binding was shown to be substantially selective for this receptor.

The primary safety signals in safety pharmacology studies were a low incidence of central nervous effects in mice and a dose-dependent increase in blood pressure, heart rate, and Qtc intervals in anesthetized dogs. However, the cardiovascular effects occurred only minimally in repeated-intravenous dose toxicology studies in dogs, and did not occur in repeated-ocular dose studies in monkeys. Because clinical exposures are expected to be on the order of 100 fold lower than the exposures associated with the high ocular doses in the monkey studies, cardiovascular toxicity is not expected to be a clinical concern.

Ocular changes included iridial darkening, sunken eyelids, and blue-gray discoloration of the lower eyelid. However, all of the tafluprost-related ocular changes are consistent with ocular changes observed with other marketed PGF₂α analogues. These effects are considered to be mainly cosmetic, not associated with loss of function, and not toxicologically significant. Other, more serious ocular toxicities including pronounced inflammation or alterations in electroretinography were not observed with topical ocular administration of tafluprost at any of the administered doses.

Topical ocular administration of 3H-tafluprost in rats and monkeys resulted in widespread ocular distribution. Repeated dosing produced a similar ocular distribution pattern, and accumulation did not occur in any tissue other than the lens where concentrations increased approximately 50% after 21 days of dosing.

Tafluprost acid was >90% bound to serum albumin from rat, rabbit, dog and humans. Tafluprost demonstrated extensive tissue distribution consistent with renal and hepatobiliary excretion and limited CNS distribution. Tissue distribution following repeated ocular dosing was similar to that following a single dose indicating an absence of systemic tissue accumulation. Tafluprost administered topically to the eye or intravenously was excreted primarily in urine and through hepatobiliary excretion with final deposition in feces.

3H-Tafluprost or its metabolites transferred into milk in lactating rats, and crossed the placental barrier in pregnant rats. Milk C_{max} radioactivity levels were similar to those in plasma, and fetal exposure was approximately two thirds that of plasma exposure.

Tafluprost was shown to be negative for genotoxicity in an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosome aberration assay in Chinese Hamster lung cells, and an *in vivo* mouse bone marrow micronucleus assay. In both a 24-month rat carcinogenicity study and a 78-week mouse carcinogenicity study where tafluprost was administered subcutaneously, no unusual tumors or significantly increased tumor incidence suggestive of tafluprost-related carcinogenicity was observed.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 7/20/2011:

In four Phase 1 dose-escalation studies (74450, 74451, 74452, and 74453), neither tafluprost nor tafluprost acid could be detected when using a bioanalytical method (HPLC/MS/MS) with LLOQ at 0.2 ng/mL (tafluprost) and 0.1 ng/mL (tafluprost acid). One confounding factor is that the plasma samples may have not been stored properly in some of these studies to ensure adequate sample stability. In a subsequent Study 15005, systemic exposure following topical ocular administration of 0.0015% tafluprost ophthalmic solution was successfully assessed using an improved analytical method (HPLC/MS/MS) with LLOQ at 10 pg/mL (tafluprost acid). Furthermore, Study 77551 was conducted to verify if the systemic bioavailability of tafluprost in humans after topical ocular q.d. administration of either tafluprost (0.0015%) PF or PC ophthalmic solution is similar.

Two Phase 2 dose-ranging studies in glaucoma patients were conducted to inform dose selection for Phase 3. In Study P15001, 0.001%, 0.0025%, and 0.005% concentrations of tafluprost were tested. One group of patients received placebo and another received latanoprost (positive control). The IOP reduction- time profiles suggested that the optimal dose of tafluprost is between 0.001% and 0.0025%. In the second Study P15002, the tafluprost concentration was tested at 0.0003%, 0.0015%, and 0.0025%. The study showed that 0.0015% of tafluprost offered the best balance between efficacy (IOP reduction) and tolerability (measured by eye comfort, conjunctival hyperemia, et al).

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 9/30/2011:

This is a non-preserved aqueous solution that is sterile filtered and (b) (4) filled into single-use containers using (b) (4) technology.

Endotoxin testing will occur according to USP<85> gel clot, kinetic turbidimetric, or kinetic chromogenic methods. (b) (4)

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Reference is made to Ph.Eur. (b)(4) for the sterility test method using (b)(4) filtration. Validation studies were conducted with three lots (MTD0866, MTD0868, and MTD0900) which the Product Quality Microbiology Reviewer assumes are the preserved formulation. Ten bottles of a 2.5 mL formulation were filtered for a total sample size (b)(4)

The results were comparable to control samples and are sufficient to validate the sterility test method for the non-preserved formulation.

In a submission dated November 2, 2011, Merck committed to provide the FDA with data from 3 consecutive (b)(4) runs under their new SOP, by March 31, 2012.

From the Product Quality review dated November 4, 2011:

The applicant has submitted revised methods which address all concerns from the first review. Currently, there is only a single (b)(4) (10014) which supports the proposed (b)(4) processing procedure. The applicant committed to conduct three consecutive (b)(4) processing validation studies by 31 March 2011 [sic].

As a deficiency, this Product Quality review states:

Provide the results of three consecutive successful (b)(4) processing simulations on filling line (b)(4) using the revised inspection and accounting procedures.

In this Medical Officer's opinion, the November 2, 2011, submission by Merck adequately addresses these deficiencies. As noted in the sterility assurance review, the revised methods are acceptable. The item lacking is the completion of three additional (b)(4) processing validation studies. It is not uncommon to accept methods validation after approval. The failure to complete validation studies with a (b)(4) do not appear to be a reason to turn down an application as described in 21 CFR 314.125. These issue related to (b)(4) validation studies may therefore be reasonably addressed post-approval. There is a (b)(4) (10014) which supports the proposed (b)(4) processing procedure.

7. Clinical/Statistical - Efficacy

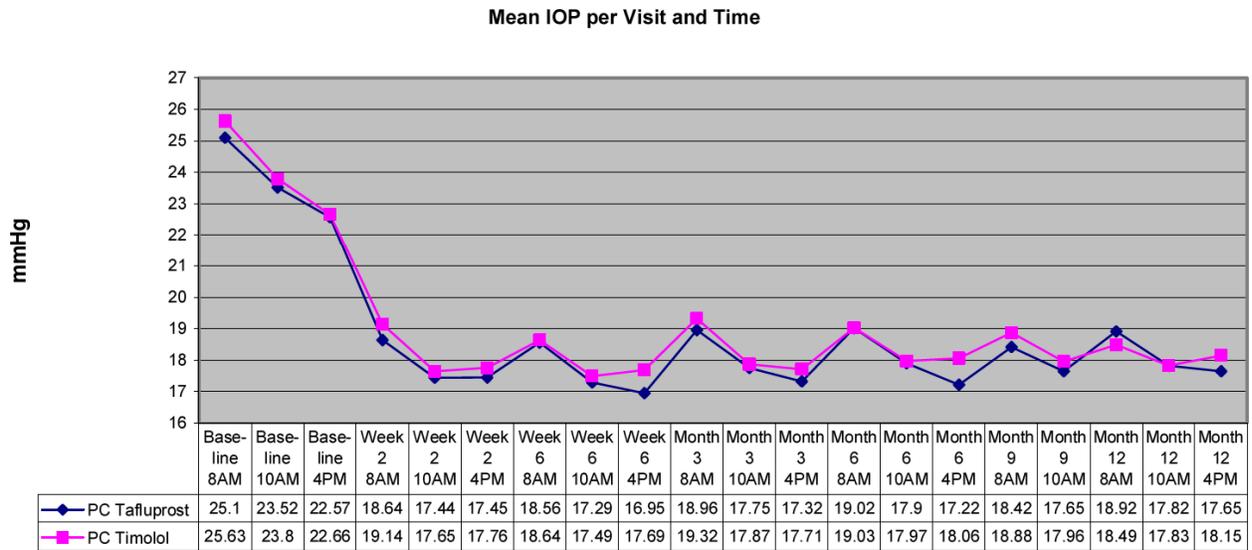
From the original Medical Officer Review dated 9/28/2011:

Analyses of Endpoints

The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

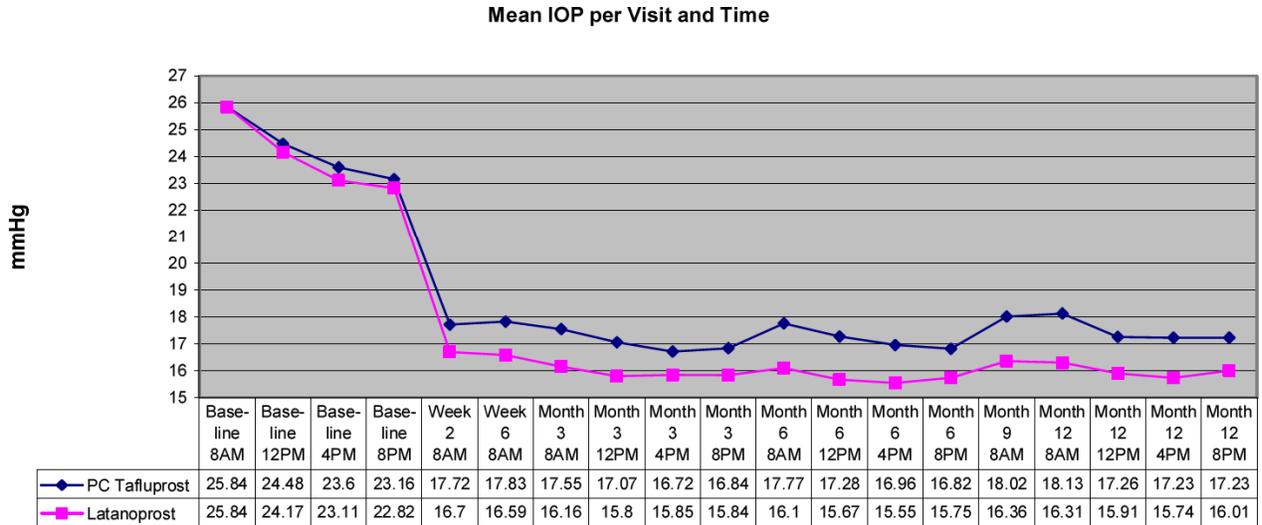
Phase 3 Trials

Study 15-003 ITT Population



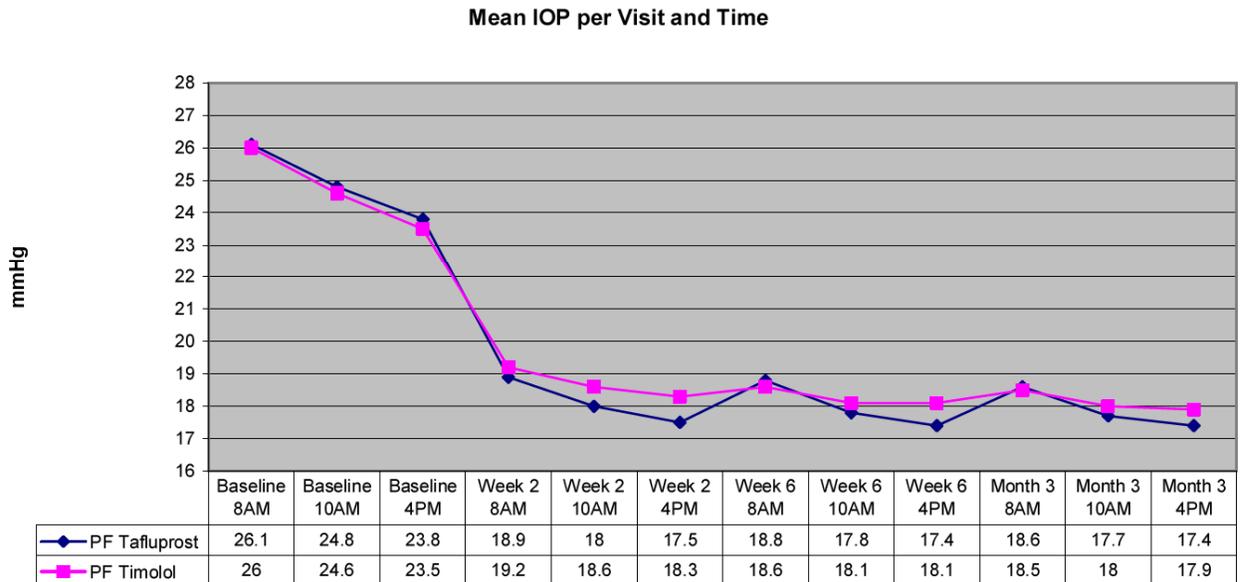
Baseline mean IOP of the two treatment arms is similar. The mean IOP for PC tafluprost 0.0015% and PC timolol 0.5% is similar at all time points measured.

Study 74458 ITT Population



Baseline mean IOP of the two treatment arms is similar. The mean IOP for PC tafluprost 0.0015% and latanoprost 0.05% is similar at baseline. The mean IOP of latanoprost 0.05% is consistently lowered than PC tafluprost 0.0015% by approximately 1-2 (0.87-1.82) mmHg at all time points measured.

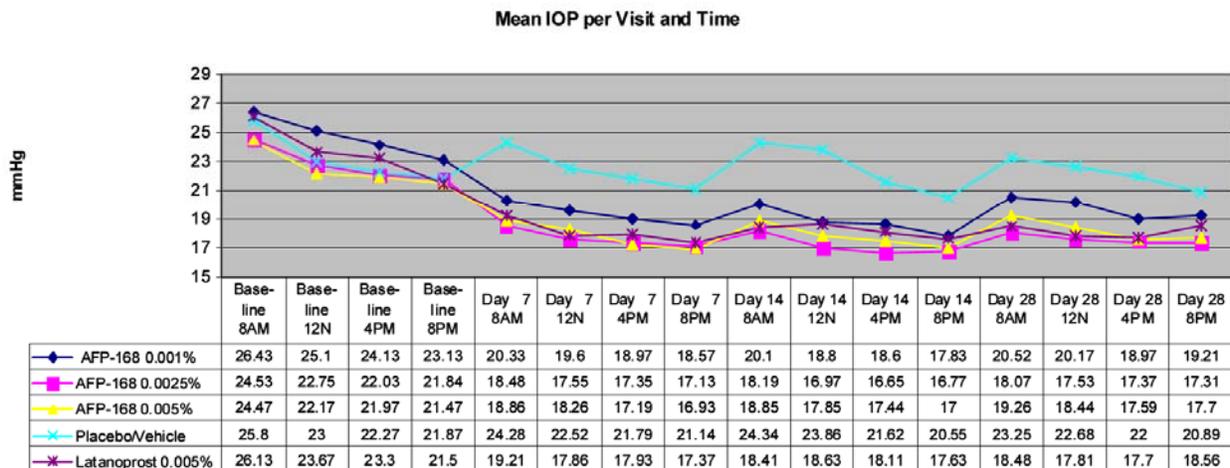
Study 001 FAS Population



Baseline mean IOP of the two treatment arms is similar. The mean IOP for PF tafluprost 0.0015% and PF timolol 0.5% is similar at all time points measured.

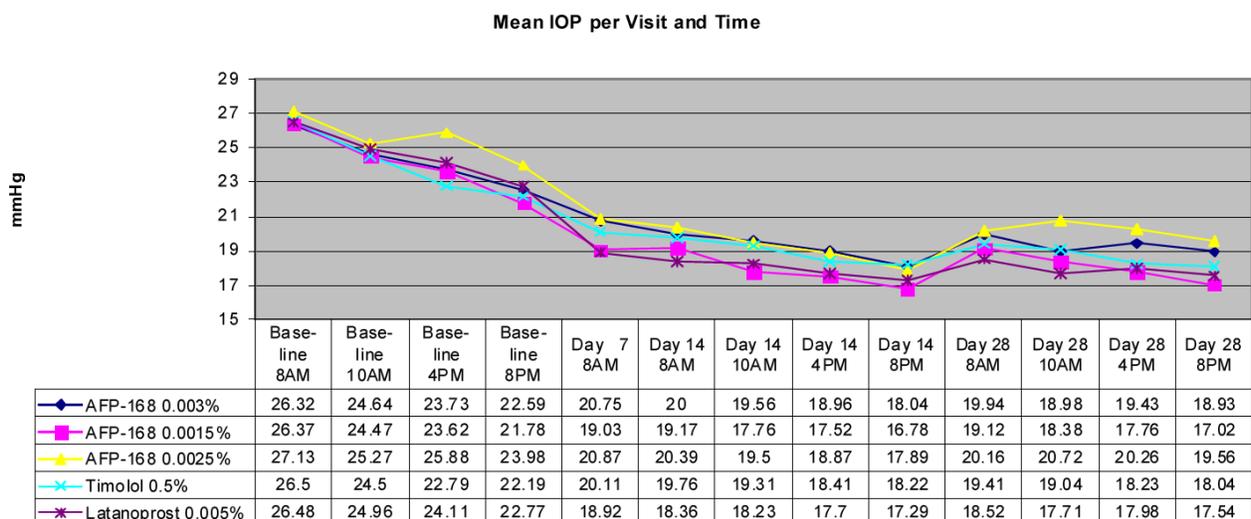
Dose Response Trials

Study 15-001 Per Protocol Population



The mean IOP for all three concentrations of tafluprost (AFP-168) and latanoprost are consistently lower than placebo/vehicle at all time points measured. The mean IOP of all three concentrations of tafluprost are similar over visit days and time. The numerically largest mean IOP reduction between Baseline and Day 28 was observed with tafluprost 0.0025%. A definitive dose-response was not demonstrated.

Study 15-002 Per Protocol Population



The mean IOP of all three concentrations of tafluprost (AFP-168) are similar over visit days and time. The numerically largest mean IOP reduction between Baseline and Day 28 was observed with tafluprost 0.0015%. A definitive dose response was not demonstrated.

Efficacy Summary Statement

From the results of study 15-003 and 001, based on the Full Analysis Set (FAS) analysis with LOCF method, the average IOP was reduced at all the post baseline time point in both treatment groups. For the comparison between tafluprost and timolol, at all post baseline time points in both studies, the upper limit of the 95% CI for the between-treatment difference was within the 1.50 mmHg margin and the majority of timepoints were within 1 mmHg. Both studies demonstrated that tafluprost was non-inferior to timolol in both preservative-containing and preservative-free formulations.

From the results of study 74458, based on the FAS analysis with LOCF method, the average IOP was reduced at all the post baseline time point in both treatment groups. For the comparison between tafluprost and latanoprost, at only 5/10 time points (8:00AM at Week 2 and 6, 16:00PM and 20:00PM at Month 6, and 20:00PM at Month 12), the upper limit of the 95% CI for the between-treatment difference was within the 1.50 mmHg margin.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Zioptan (tafluprost ophthalmic solution) 0.0015% experienced a statistically and clinically significant decrease in intraocular pressure.

The data support Zioptan (tafluprost ophthalmic solution) 0.0015% administered once daily in the evening for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

8. Safety

From the original Medical Officer Review dated 9/28/2011:

Five studies are used to support the safety and efficacy of tafluprost. The patient exposure and safety assessments were adequate.

Exposure to Study Drug by Protocol

Protocol #	Number of Patients	Tafluprost	Timolol	Latanoprost
15-002	144	87	29	28
74457	38	19		19
15-003	458	267	191	
74458	533	269		264
001	643	320	323	
Total	1816	962	543	311

Eight deaths were reported during the clinical development of tafluprost. One subject in study 74460 died of stroke and arterial hypertension 11 days after completion of a 12-week course of tafluprost.

The number of deaths is consistent with the population being studied and the studies' time frame. Narrative summaries of the deaths were submitted and are consistent with the causes of death listed.

Deaths in the Safety Population

Study #	Patient #	Age (yrs)	Treatment	Time on treatment	Cause of death/Event
74460	2203	77	tafluprost	3 months	Cerebrovascular accident
74458	3101	46	tafluprost	10 months	Bronchial carcinoma
74458	4103	77	tafluprost	12 months	Circulatory system insufficiency
74458	4153	51	tafluprost	11 months	Pulmonary embolus
74458	0351	82	latanoprost	18 months	Myocardial infarction
74458	7153	64	latanoprost	5 months	Unknown
74458	9153	76	latanoprost	24 months	Flu and multi-organ Insufficiencies
(b) (4)	L-032-08	71	latanoprost	12 months	Hepatic tumor

Patient Dropouts Studies 15-002, 74457, 74458, 15-003 and 001

Patients	Tafluprost 0.0015% n (%)	Timolol Maleate 0.5% n (%)	Latanoprost 0.005% n (%)
Total randomized	905 (100)	543 (100)	311 (100)
Completed Study	811 (89.6)	502 (92.4)	286 (92.0)
Discontinued Study:	94 (10.4)	41 (7.6)	25 (8.0)
Adverse event	24 (2.7)	13 (2.4)	8 (2.6)
Concomitant medication	2 (0.2)	0 (0.0)	0 (0.0)
Lack of efficacy	23 (2.5)	9 (1.7)	3 (1.0)
Non-compliance	5 (0.6)	4 (0.7)	2 (0.6)
Improper entry	1 (0.1)	2 (0.4)	1 (0.3)
Patient request	27 (3.0)	9 (1.7)	9 (2.9)
Lost to follow-up	11 (1.2)	3 (0.6)	2 (0.6)
Physician decision	1 (0.1)	1 (0.2)	0 (0.0)

There were a total of 110 serious adverse events, inclusive of deaths, across all treatment groups in all masked phase 2 and phase 3 studies (Studies 15-002, 74457, 74458, 15-002 and 001) during the clinical development of tafluprost; 62 of these patients were treated with tafluprost.

Serious Adverse Events
Studies 15-002, 74457, 74458, 15-003 and 001
Incidence >0% in at Least One Treatment Group

Adverse Event	Tafluprost 0.0015% (N=905) n (%)	Timolol Maleate 0.5% (N=543) n (%)	Latanoprost 0.0005% (N=311) n (%)
OCULAR			
Eye Disorders	4 (0.4)	4 (0.7)	2 (0.6)
Cataract	1 (0.1)	0 (0.0)	0 (0.0)
Cataract aggravated	0 (0.0)	0 (0.0)	1 (0.3)
Conjunctival bleb	0 (0.0)	0 (0.0)	1 (0.3)
Intraocular pressure increased	1 (0.1)	0 (0.0)	0 (0.0)
Macular edema	0 (0.0)	1 (0.2)	0 (0.0)
Retinal detachment	1 (0.1)	1 (0.2)	0 (0.0)
Retinal vein branch occlusion	1 (0.1)	0 (0.0)	0 (0.0)
Retinal vein occlusion	0 (0.0)	2 (0.4)	0 (0.0)
NONOCULAR			
Cardiac Disorders	8 (0.9)	4 (0.7)	2 (0.6)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.3)
Angina unstable	1 (0.1)	0 (0.0)	0 (0.0)
Asystole	0 (0.0)	1 (0.2)	0 (0.0)
Atrial fibrillation	1 (0.1)	1 (0.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac failure congestive	1 (0.1)	0 (0.0)	0 (0.0)
Coronary artery disease	4 (0.40)	0 (0.0)	0 (0.0)
Inferior myocardial infarction	0 (0.0)	1 (0.2)	0 (0.0)
Long QT syndrome	0 (0.0)	1 (0.2)	0 (0.0)
Myocardial infarction	1 (0.1)	0 (0.0)	0 (0.0)
Ear and Labyrinth Disorders	1 (0.1)	0 (0.0)	0 (0.0)
Vertigo	1 (0.1)	0 (0.0)	0 (0.0)
Endocrine Disorders	1 (0.1)	0 (0.0)	0 (0.0)
Goiter	1 (0.1)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	5 (0.6)	1 (0.2)	3 (1.0)
Abdominal pain	1 (0.1)	0 (0.0)	1 (0.3)
Colitis	0 (0.0)	1 (0.2)	0 (0.0)
Diverticulosis	1 (0.1)	0 (0.0)	0 (0.0)
Gastritis	1 (0.1)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.1)	0 (0.0)	0 (0.0)
Esophageal stricture	0 (0.0)	0 (0.0)	1 (0.3)
Pancreatitis chronic	1 (0.1)	0 (0.0)	0 (0.0)
Rectal polyp	0 (0.0)	0 (0.0)	1 (0.3)
General Disorders and Administration Site Conditions	7 (0.8)	2 (0.4)	5 (1.6)
Adverse drug reaction	0 (0.0)	1 (0.2)	0 (0.0)
Chest pain	2 (0.2)	0 (0.0)	2 (0.6)
Death	3 (0.3)	0 (0.0)	3 (1.0)
Fever	1 (0.1)	0 (0.0)	0 (0.0)
Hernia	0 (0.0)	1 (0.2)	0 (0.0)
Nonspecific chest pain	1 (0.1)	0 (0.0)	0 (0.0)
Hepatobiliary Disorders	3 (0.3)	1 (0.2)	0 (0.0)
Bile duct stone	1 (0.1)	0 (0.0)	0 (0.0)
Cholecystitis	1 (0.1)	1 (0.2)	0 (0.0)
Gallbladder disorder	1 (0.1)	0 (0.0)	0 (0.0)
Infections and Infestations	3 (0.3)	0 (0.0)	4 (1.3)
Chronic Sinusitis	0 (0.0)	0 (0.0)	1 (0.3)
Gastroenteritis	1 (0.1)	0 (0.0)	0 (0.0)
Gastrointestinal fungal infection	1 (0.1)	0 (0.0)	0 (0.0)
Maxillary sinusitis	0 (0.0)	0 (0.0)	1 (0.3)
Shigella infection	1 (0.1)	0 (0.0)	0 (0.0)
Urospepsis	0 (0.0)	0 (0.0)	1 (0.3)
Viral infection	0 (0.0)	0 (0.0)	1 (0.3)
Injury, Poisoning and Procedural Complications	5 (0.6)	3 (0.6)	5 (1.6)
Compression fracture	0 (0.0)	0 (0.0)	1 (0.3)
Fracture	0 (0.0)	1 (0.2)	0 (0.0)
Fracture bone	1 (0.1)	0 (0.0)	0 (0.0)
Heat exhaustion	1 (0.1)	0 (0.0)	0 (0.0)
Injury to shoulder NOS	0 (0.0)	0 (0.0)	1 (0.3)
Joint dislocation	0 (0.0)	1 (0.2)	0 (0.0)
Knee injury	1 (0.1)	0 (0.0)	0 (0.0)
Lumbar vertebral fracture	1 (0.1)	0 (0.0)	0 (0.0)
Meniscus lesion	0 (0.0)	0 (0.0)	1 (0.3)
Pelvic fracture	1 (0.1)	0 (0.0)	0 (0.0)
Scapula fracture	0 (0.0)	0 (0.0)	1 (0.3)
Tendon rupture	0 (0.0)	1 (0.2)	1 (0.3)
Investigations	1 (0.1)	0 (0.0)	0 (0.0)
Catheterisation cardiac	1 (0.1)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders	0 (0.0)	1 (0.2)	1 (0.3)
Hypoglycemia	0 (0.0)	0 (0.0)	1 (0.3)
Morbid obesity	0 (0.0)	1 (0.2)	0 (0.0)

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Musculoskeletal and Connective Tissue Disorders	7 (0.8)	1 (0.2)	2 (0.6)
Arthrosis	1 (0.1)	0 (0.0)	0 (0.0)
Back pain	2 (0.2)	0 (0.0)	0 (0.0)
Back pain aggravated	0 (0.0)	0 (0.0)	1 (0.3)
Cervical spine degeneration	1 (0.1)	0 (0.0)	0 (0.0)
Chronic back pain	0 (0.0)	1 (0.2)	0 (0.0)
Hips osteoarthritis	1 (0.1)	0 (0.0)	0 (0.0)
Intervertebral disc prolapse	1 (0.1)	0 (0.0)	0 (0.0)
Knee osteoarthritis	1 (0.1)	0 (0.0)	0 (0.0)
Spondylosis deformans	0 (0.0)	0 (0.0)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	6 (0.7)	0 (0.0)	5 (1.6)
Breast carcinoma	0 (0.0)	0 (0.0)	1 (0.3)
Cancer	1 (0.1)	0 (0.0)	0 (0.0)
Carcinoma bronchiogenic	1 (0.1)	0 (0.0)	0 (0.0)
Colorectal cancer	0 (0.0)	0 (0.0)	1 (0.3)
Metastases to liver	1 (0.1)	0 (0.0)	1 (0.3)
Ovarian cystadenoma	1 (0.1)	0 (0.0)	0 (0.0)
Ovarian low malignant potential tumor	0 (0.0)	0 (0.0)	1 (0.3)
Prostate cancer	1 (0.1)	0 (0.0)	0 (0.0)
Rectal adenoma	0 (0.0)	0 (0.0)	1 (0.3)
Renal cell carcinoma	1 (0.1)	0 (0.0)	0 (0.0)
Nervous System Disorders	3 (0.3)	4 (0.7)	2 (0.6)
Depressed level of consciousness	0 (0.0)	0 (0.0)	1 (0.3)
Headache	1 (0.1)	0 (0.0)	0 (0.0)
Loss of consciousness	0 (0.0)	0 (0.0)	1 (0.3)
Stroke	1 (0.1)	1 (0.2)	0 (0.0)
Syncope	1 (0.1)	2 (0.4)	0 (0.0)
Unconsciousness	0 (0.0)	1 (0.1)	0 (0.0)
Pregnancy, Puerperium and Prenatal Conditions	1 (0.1)	0 (0.0)	0 (0.0)
Pregnancy	1 (0.1)	0 (0.0)	0 (0.0)
Psychiatric Disorders	0 (0.0)	0 (0.0)	1 (0.3)
Schizophrenia, residual type	0 (0.0)	0 (0.0)	1 (0.3)
Renal and Urinary Disorders	5 (0.6)	0 (0.0)	0 (0.0)
Bleeding urogenital	1 (0.1)	0 (0.0)	0 (0.0)
Hematuria	1 (0.1)	0 (0.0)	0 (0.0)
Incontinence	1 (0.1)	0 (0.0)	0 (0.0)
Renal failure acute	1 (0.1)	0 (0.0)	0 (0.0)
Ureteric stenosis	1 (0.1)	0 (0.0)	0 (0.0)
Reproductive System and Breast Disorders	3 (0.3)	0 (0.0)	1 (0.3)
Endometrial hypertrophy	1 (0.1)	0 (0.0)	0 (0.0)
Genital cyst	1 (0.1)	0 (0.0)	0 (0.0)
Gynecomastia	0 (0.0)	0 (0.0)	1 (0.3)
Vaginal prolapse	1 (0.1)	0 (0.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	6 (0.7)	2 (0.4)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	1 (0.2)	0 (0.0)
Dyspnea	2 (0.2)	0 (0.0)	0 (0.0)
Epistaxis	1 (0.1)	0 (0.0)	0 (0.0)
Pharyngeal hemorrhage	1 (0.1)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.1)	1 (0.2)	0 (0.0)
Pulmonary fibrosis	1 (0.1)	0 (0.0)	0 (0.0)
Skin and Medical Procedures	1 (0.1)	0 (0.0)	1 (0.3)
Skin cancer	1 (0.1)	0 (0.0)	0 (0.0)
Skin lesion	0 (0.0)	0 (0.0)	1 (0.3)
Surgical and Medical Procedures	6 (0.7)	2 (0.4)	2 (0.6)
Basal cell carcinoma excision	0 (0.0)	0 (0.0)	1 (0.3)
Benign tumor excision	0 (0.0)	1 (0.2)	0 (0.0)
Breast reduction	0 (0.0)	0 (0.0)	1 (0.3)
Chemotherapy	1 (0.1)	0 (0.0)	0 (0.0)
Cholecystectomy	1 (0.1)	0 (0.0)	0 (0.0)
Colectomy partial	0 (0.0)	1 (0.2)	0 (0.0)
Coronary stent placement	1 (0.1)	0 (0.0)	0 (0.0)
Gallbladder operation	1 (0.1)	0 (0.0)	0 (0.0)
Gastric bypass	0 (0.0)	1 (0.2)	0 (0.0)
Knee operation	1 (0.1)	0 (0.0)	0 (0.0)
Penile operation	0 (0.0)	1 (0.2)	0 (0.0)
Renal transplant	1 (0.1)	0 (0.0)	0 (0.0)
Vascular Disorders	2 (0.2)	2 (0.4)	1 (0.3)
Carotid artery stenosis	0 (0.0)	1 (0.2)	0 (0.0)
Hypertension aggravated	2 (0.2)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (0.3)
Varicose veins of lower extremities	0 (0.0)	1 (0.2)	0 (0.0)

The most common ocular adverse events (pooled) were conjunctival hyperemia (10.7%) and ocular stinging/irritation (7.2%). The most common nonocular adverse event was headache (5.6%).

Number (%) of Patients with Adverse Events Reported by ≥ 2 % of Patients
Studies 15-002, 74457, 74458, 15-003, and 001 Pooled

Adverse Event	Tafluprost 0.0015% N=905 n (%)	Timolol Maleate 0.5% N=543 n (%)	Latanoprost 0.005% N=311 n (%)
OCULAR			
Eye Disorders	349 (38.6)	118 (21.7)	115 (40.0)
Blepharitis	9 (1.0)	3 (0.6)	7 (2.3)
Cataract aggravated	9 (1.0)	0 (0.0)	13 (4.2)
Conjunctival hyperemia	97 (10.7)	23 (4.2)	22 (7.1)
Dry eye	27 (3.0)	11 (2.0)	9 (2.9)
Eyelash darkening	15 (1.7)	0 (0.0)	9 (2.9)
Growth of eyelashes	21 (2.3)	0 (0.0)	11 (3.5)
Ocular pain	31 (3.4)	15 (2.8)	6 (1.9)
Ocular stinging/irritation	65 (7.2)	38 (7.0)	22 (7.1)
Ocular pruritus	44 (4.9)	11 (2.0)	5 (1.6)
Vision blurred	19 (2.1)	15 (2.8)	2 (0.6)
Visual field constriction	12 (1.3)	2 (0.4)	9 (2.9)
NONOCULAR			
Cardiac Disorders	21 (2.3)	7 (1.3)	14 (4.5)
Gastrointestinal Disorders	65 (7.2)	24 (4.4)	14 (4.5)
General Disorders and Administration Site Conditions	49 (5.4)	27 (5.0)	8 (2.6)
Infections and Infestations	136 (15.0)	79 (14.5)	48 (15.4)
Common cold	36 (4.0)	13 (2.4)	8 (2.6)
Flu	16 (1.8)	5 (0.9)	12 (3.9)
Sinusitis	9 (1.0)	3 (0.6)	8 (2.6)
Urinary tract infection	18 (2.0)	6 (1.1)	2 (0.6)
Injury, Poisoning and Procedural Complications	40 (4.4)	18 (3.3)	9 (2.9)
Investigations	35 (3.9)	9 (1.7)	28 (9.0)
Low density lipoprotein cholesterol abnormal NOS	4 (0.4)	0 (0.0)	7 (2.3)
Metabolism and Nutrition Disorders	29 (3.2)	17 (3.1)	7 (2.3)
Musculoskeletal and Connective Tissue Disorders	81 (9.0)	28 (5.2)	32 (10.3)
Nervous System Disorders	86 (9.5)	45 (8.3)	26 (8.4)
Headache	51 (5.6)	15 (2.8)	15 (4.8)
Respiratory, Thoracic and Mediastinal Disorders	60 (6.6)	22 (4.1)	15 (4.8)
Cough	27 (3.0)	9 (1.7)	7 (2.3)
Skin and Subcutaneous Tissue Disorders	36 (4.0)	10 (1.8)	13 (4.2)
Surgical and Medical Procedures	23 (2.5)	7 (1.3)	10 (3.2)
Vascular Disorders	38 (4.2)	19 (3.5)	7 (2.3)
Hypertension arterial	7 (0.8)	0 (0.0)	7 (2.3)

Safety Summary Statement

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Zioptan (tafluprost ophthalmic solution) 0.0015%, dosed once each evening, is safe for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The most common ocular adverse events (pooled) were conjunctival hyperemia (11%) and ocular stinging/irritation (7%). The most common nonocular adverse event was headache (6%).

9. Advisory Committee Meeting

No Advisory Committee Meeting has been scheduled. There are no outstanding clinical issues which are believed to benefit from an advisory committee discussion at this time.

10. Pediatrics

Tafluprost has not been studied in the pediatric population. Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. Per the DSI review finalized 6/27/2011:

Two clinical sites were inspected in support of this application. In general, inspection of Dr. Douglas Day's site revealed that he adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations and the final classification for this inspection is No Action Indicated (NAI).

Inspection of Dr. David Wirta's site documented regulatory violations and the preliminary classification for this inspection is Voluntary Action Indicated (VAI) for errors in recordkeeping of adverse events, which were isolated and relatively minor. Incorrect causality of adverse events was corrected and later reported to the sponsor.

The studies at these sites appear to have been conducted adequately, and the data generated may be used in support of the application.

CDTL Review
William M. Boyd, M.D.
NDA 202514
Zioptan (tafluprost ophthalmic solution) 0.0015%

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment considered originally proposed proprietary name, Saflutan. In an April 15, 2011, letter to the applicant DMEPA found this proprietary name unacceptable since it is orthographically similar to, and shares overlapping product characteristics with, Xalatan.

In an August 31, 2011, letter to the applicant, DMEPA found the proprietary name Zioptan to be acceptable.

DMEPA was invited to all internal labeling meeting and provided recommendations on the packaging configuration and the package insert labeling.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)/DIVISION OF PROFESSIONAL PROMOTION (DPP)

OPDP provided labeling comments based on the substantially complete version of the labeling titled, "N202514_Label1.doc" which was sent via email from Constantine Markos on October 17, 2011.

The warning against use of contact lenses with the use of other prostaglandin analogues is not applicable to tafluprost since it does not contain a preservative which can be absorbed into the contact lenses and remain in contact with the eye.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 7/31/09:

In this submission, the Applicant seeks approval of preservative-free (PF) tafluprost 0.0015% ophthalmic solution administered once daily for the treatment of elevated intraocular pressure (IOP). The Applicant submitted three non-inferiority efficacy studies (two timolol non-inferiority studies [15-003 and 001] and one Latanoprost Non-Inferiority Study [74458]), and a study comparing the PC formulation and PF formulation (Study 77550).

For study 15-003 comparing preservative-containing (PC) tafluprost with PC timolol, both PC tafluprost and the active comparator PC timolol showed IOP-lowering effect throughout the 12-month study period. Tafluprost reached the predetermined criteria for non-inferiority (1.5 mmHg) at each visit and time point using timolol as the active comparator.

For study 001 comparing PF tafluprost versus PF timolol, both PF tafluprost and the active comparator (PF timolol) showed IOP-lowering effect throughout the 12 weeks of treatment. The IOP-lowering

effect of PF tafluprost was within the 1.5 mmHg non-inferiority margin compared to PF timolol at all visits and time points.

Study 77550 investigated the pharmacodynamics (as expressed in IOP) of the preserved and unpreserved formulation of tafluprost 0.0015% eye drops in patients with open-angle glaucoma or ocular hypertension. For both the preservative-containing and preserve-free formulation, a similar and clear IOP-lowering effect was seen already at week 1 and the IOP-lowering effect was sustained and similar for both formulations at week 4.

For study 74458, both PC tafluprost and PC latanoprost reduced IOP throughout the 24 months treatment period. However, tafluprost did not reach the predetermined criterion for noninferiority (1.5 mmHg) versus latanoprost. Using the non-inferiority margin of 1.5 mmHg, both studies 15-003 and 001 demonstrated noninferiority of tafluprost 0.0015% to timolol 0.5% in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in both preservative-containing and preservative-free formulation. Study 77550 demonstrated that the IOP lowering effects for the PC formulation and the PF formulation were similar.

Based on the totality of the evidence provided by these pivotal studies, we recommend the approval of PF tafluprost 0.0015% dosed once daily for the treatment of elevated intraocular pressure in patients with open glaucoma or ocular hypertension.

12. Labeling

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the labeling found in this review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 202514, Zioptan (tafluprost ophthalmic solution) 0.0015% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. There is substantial evidence of safety and effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Zioptan (tafluprost ophthalmic solution) 0.0015% experienced a statistically and clinically significant reduction in intraocular pressure. The data support Zioptan (tafluprost ophthalmic solution) 0.0015% administered once daily in the evening for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The most common ocular adverse events (pooled) were conjunctival hyperemia (10.7%) and ocular stinging/irritation (7.2%). The most common nonocular adverse event was headache (5.6%).

CDTL Review
William M. Boyd, M.D.
NDA 202514
Zioptan (tafluprost ophthalmic solution) 0.0015%

RISK BENEFIT ASSESSMENT:

Studies 15-003 and 001 demonstrate that the IOP lowering ability of tafluprost 0.0015% is not inferior to timolol 0.5%. Study 74458 had unequal baselines and is difficult to interpret. The safety profile of tafluprost 0.0015% is similar to other marketed topical prostaglandin analogues.

The benefit of tafluprost 0.0015% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The risk for using this drug is consistent with the currently marketed prostaglandin analogues.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, and Clinical Pharmacology have recommended approval for this application. Product Quality does not recommend approval.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

Merck commits to provide the FDA with data from 3 consecutive media fill runs under the new SOP, by March 31, 2012.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM M BOYD
11/07/2011

WILEY A CHAMBERS
11/07/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 202514
Priority or Standard	Standard
Submit Date(s)	January 7, 2011
Received Date(s)	January 7, 2011
PDUFA Goal Date	November 6, 2011
Division / Office	DAIOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	July 15, 2011
Established Name	tafluprost ophthalmic solution 0.0015%
(Proposed) Trade Name	Zioptan
Therapeutic Class	prostaglandin
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	Ophthalmic solution
Dosing Regimen	One (1) drop in the affected eye(s) once daily in the evening
Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Intended Population(s)	Patients ages 18 years and older with open-angle glaucoma or ocular hypertension

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 202514 is recommended for approval with the labeling revisions found in this review.

The application supports the safety and effectiveness of tafluprost ophthalmic solution 0.0015% for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

1.2 Risk Benefit Assessment

The data contained in this submission establishes the efficacy of tafluprost 0.0015% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

Studies 15-003 and 001 demonstrate that the IOP lowering ability of tafluprost 0.0015% is not inferior to timolol 0.5% and do not differ from timolol by a clinically significant amount. Study 74458 had unequal baselines and is difficult to interpret.

The safety profile of tafluprost 0.0015% is similar to other marketed topical prostaglandin analogues. The most common ocular adverse events were conjunctival hyperemia (11%) and ocular stinging/irritation (7%).

The benefit of tafluprost 0.0015% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The risk for using this drug is consistent with the currently marketed prostaglandin analogues.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarket Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name:	tafluprost ophthalmic solution 0.0015%
Proposed Trade Name:	Zioptan
Chemical Class:	new molecular entity
Pharmacological Class:	prostaglandin F _{2α} analog
Proposed Indication:	reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

Dosing Regimen:	one drop in the affected eye(s) once daily in the evening
Age Groups:	patients 18 years or older

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently numerous topical treatments for lowering intraocular pressure in patients with open angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors and prostaglandin analogs.

2.3 Availability of Proposed Active Ingredient in the United States

Tafluprost is not marketed in the United States. See Section 2.6 of this review.

2.4 Important Safety Issues With Consideration to Related Drugs

The class effects for prostaglandin analogs, including tafluprost ophthalmic solution 0.0015% have been reported to include changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and the periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. Increased iris pigmentation may be permanent.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An End-of-Phase 2 meeting was held on August 24, 2009, with Merck to discuss the clinical development plan for a preservative-free ophthalmic formulation of tafluprost. Merck proposed to conduct Study 001, a three-month study of preservative-free (PF) tafluprost compared to PF timolol, to demonstrate the equivalence of PF tafluprost to preservative-containing (PC) tafluprost. A Pre-NDA meeting was held on August 13, 2010, to discuss the content and the format of the proposed NDA.

2.6 Other Relevant Background Information

PC and PF tafluprost 0.0015% have been approved in over 30 countries including Austria, Germany, Czech Rep, Denmark, Finland, Norway, Poland, Sweden, Iceland, Italy, Spain, Portugal, the Netherlands, Romania, Bulgaria, Estonia, Latvia, Lithuania, Slovak Rep, United Kingdom, Russia, Ukraine, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Uzbekistan, Japan, Korea, Hong Kong, and Indonesia for the reduction of elevated intraocular pressure in open-angle glaucoma and ocular hypertension.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application conformed with Good Clinical Practices.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Tafluprost is a sterile, isotonic ophthalmic solution containing 0.015 mg tafluprost, filled (b) (4) into single-dose containers. The solution is clear and colorless.

Clinical Review

Lucious Lim, M.D., M.P.H.

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Zioptan (tafluprost ophthalmic solution) 0.0015%

Composition of Tafluprost 15 microg/mL Eye Drops in Single-Dose Container.

Drug substance	Reference	Percent (w/v)	Quantity (mg/mL)	Function
Tafluprost	In-house†	0.0015	0.015	Drug substance
Excipients			(b) (4)	(b) (4)
Glycerol	PhEur/USP			
Sodium dihydrogen phosphate dihydrate	PhEur/USP			
Disodium edetate	PhEur/USP			
Polysorbate 80	PhEur			
Sodium hydroxide [‡] and/or hydrochloric acid, concentrated [‡]	PhEur/USP			pH adjuster
Water for injection	PhEur			pH adjuster
				(b) (4)
				(b) (4)
				(b) (4)

The formulation of tafluprost that was used in Clinical Study 001 is the same as the one intended for marketing. This formulation is preservative free.

4.2 Clinical Microbiology

There are no clinical microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

No systemic toxicity was observed in several repeated-dose topical ocular studies in monkeys.

Specific ocular toxicity was apparent with ocular administration of tafluprost in repeated-ocular dose toxicology studies of up to one year duration in monkeys. Ocular changes included iridial darkening, sunken eyelids, and blue-gray discoloration of the lower eyelid. These changes are consistent with ocular changes observed in this drug class, prostaglandin analogues.

See original Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tafluprost acid, a prostaglandin analog is a relatively selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

4.4.2 Pharmacodynamics

See original Biopharmaceutics review.

4.4.3 Pharmacokinetics

See original Biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
15-001 dose-response study	Parallel-group, multi-center, randomized, dose-response, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost ophth soln (0.001%, 0.0025%, 0.005%) Placebo Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop BID OU 1 drop QPM OU	28 days	152 subjects in a ratio of 1:1:1:1
15-002 dose-response study	Parallel-group, multi-center, randomized, dose-response, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost ophth soln (0.0003%, 0.0015%, 0.0025%) Timolol 0.5% ophth soln Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop BID OU 1 drop QPM OU	28 days	144 subjects in a ratio of 1:1:1:1:1
74457 Pilot safety/efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln. Latanoprost	1 drop QPM OU 1 drop	6 weeks	38 subjects in a ratio of 1:1 (19 in the tafluprost group and 19 in the latanoprost group)

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
			0.005% ophth soln	QPM OU		
15-003 safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln PC timolol maleate 0.5% ophth soln	1 drop QPM OU 1 drop BID OU	12 months	450 subjects in a ratio of 3:2 (267 in the tafluprost group and 191 in the timolol group)
74458 safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln. Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop QPM OU	24 months	533 subjects in a ratio of 1:1 (269 in the tafluprost group and 264 in the latanoprost group)
001 safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PF tafluprost 0.0015% ophth soln PF timolol maleate 0.5% ophth soln	1 drop QPM OU 1 drop BID OU	12 weeks	643 subjects in a ratio 1:1 (320 in the tafluprost group and 323 in the timolol group)

5.2 Review Strategy

The submitted clinical study report and protocol for the studies identified in section 5.1 above were reviewed and formed the primary basis of safety and efficacy for this application. Studies 15-001, 15-002, 15-003, 74458 and 001 were used in the efficacy analysis. Studies 15-002, 74457, 15003, 74458 and 001 were used in the safety analysis.

The entire application was submitted in electronic format.

5.3 Discussion of Individual Studies/Clinical Trials

Study 15-001 - Dose Response Study

Title: A randomized, double-masked, parallel-group, multicenter, dose-response trial of tafluprost ophthalmic solution in patients with open-angle glaucoma or ocular hypertension (United States)

Clinical Review

Lucious Lim, M.D., M.P.H.

NDA 202514

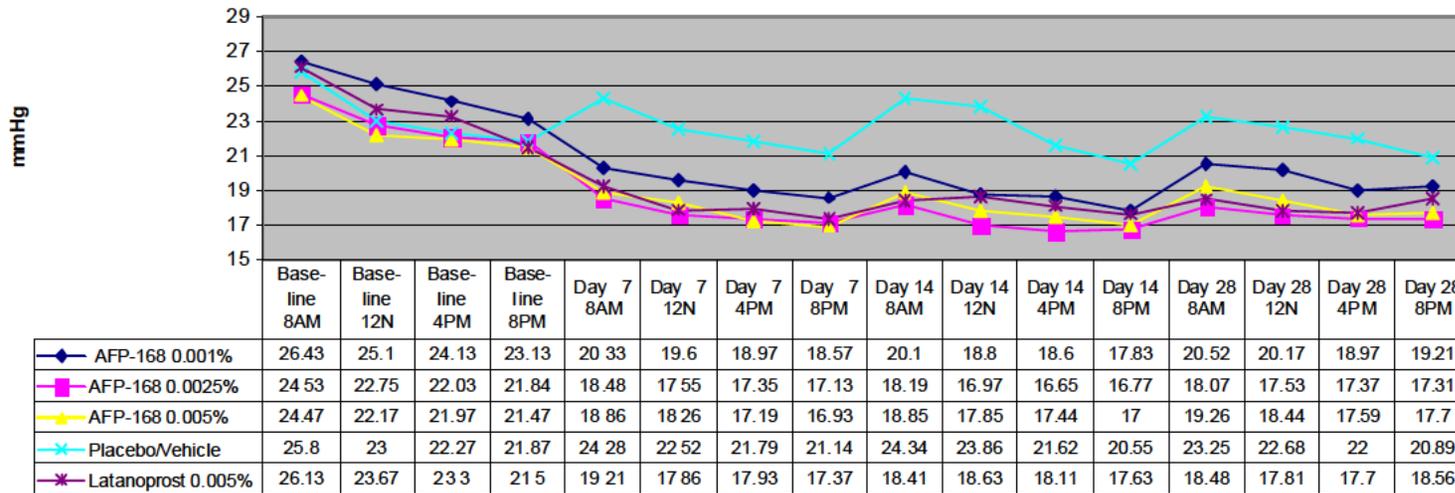
Zioptan (tafluprost ophthalmic solution) 0.0015%

Study Design

This study was a prospective, multi-center, double-masked, parallel group, randomized, dose-ranging trial designed to investigate the dose-response relationship of PC tafluprost in patients with open-angle glaucoma or ocular hypertension and to compare the safety and efficacy of three concentrations of PC tafluprost (0.001%, 0.0025%, 0.005%) with placebo (vehicle) and latanoprost 0.005%. A total of 152 patients were enrolled and 142 completed the study. Patients received masked study medication for 28 days. In addition to the baseline visit, there were visits at Day 7, 14 and 28. IOP measurements were taken at 8 AM, 12 PM, 4 PM and 8 PM at Day 0 (baseline), 7, 14 and 28.

Study 15-001 Per Protocol Population

Mean IOP per Visit and Time



Reviewer's Comments: *The mean IOP for all three concentrations of tafluprost (AFP-168) and latanoprost are consistently lower than placebo/vehicle at all time points measured. The mean IOP of all three concentrations of tafluprost are similar over visit days and time. The numerically largest mean IOP reduction between Baseline and Day 28 was observed with tafluprost 0.0025%. A definitive dose-response was not demonstrated.*

Study 15-002

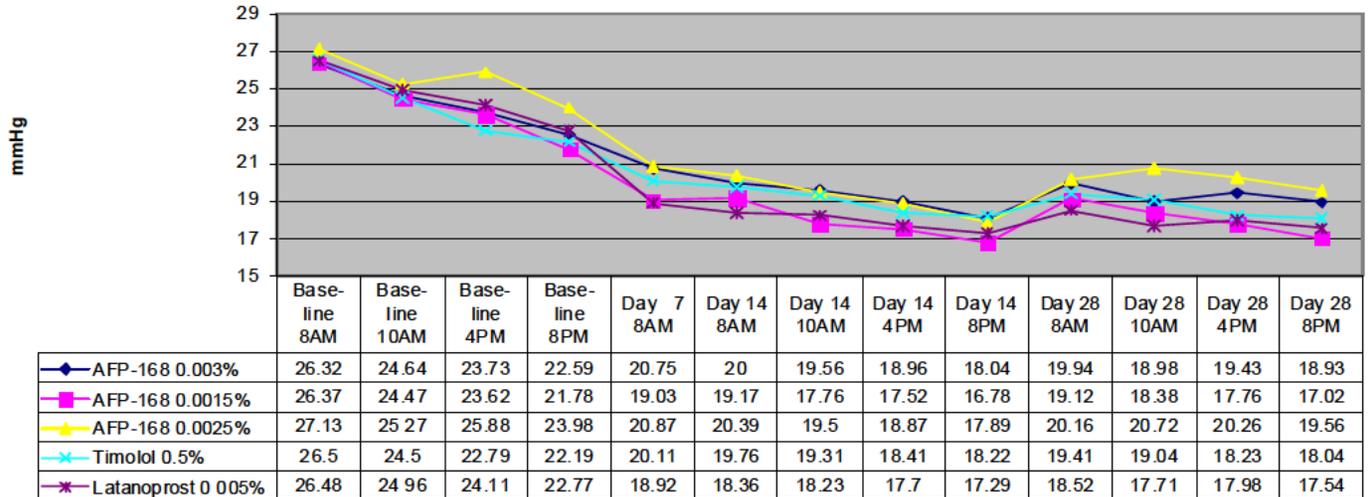
Title: A randomized, double-masked, parallel-group, multicenter, dose-response trial comparing the safety and efficacy of tafluprost ophthalmic solution with 0.5% timolol maleate and 0.005% latanoprost in patients with open-angle glaucoma or ocular hypertension (United States)

Study Design

This study was a prospective, multi-center, double-masked, parallel group, randomized, dose-ranging trial designed to investigate the dose-response relationship of PC tafluprost in patients with open-angle glaucoma or ocular hypertension and to compare the safety and efficacy of three concentrations of PC tafluprost (0.0003%, 0.0015%, 0.0025%) with timolol 0.05% and latanoprost 0.005%. A total of 144 patients were enrolled and 139 completed the study. Patients received masked study medication for 28 days. In addition to the baseline visit, there were visits at Day 7, 14 and 28. IOP measurements were taken at 8 AM, 10 PM, 4 PM and 8 PM at Day 0 (baseline), 14 and 28 and in addition at 8AM on Day7.

Study 15-002 Per Protocol Population

Mean IOP per Visit and Time



Reviewer’s Comments: *The mean IOP of all three concentrations of tafluprost (AFP-168) are similar over visit days and time. The numerically largest mean IOP reduction between Baseline and Day 28 was observed with tafluprost 0.0015%. A definitive dose-response was not demonstrated.*

Study 15-003

Title: A randomized, double-masked, parallel group, multi-center, 12-month trial comparing the efficacy and safety of tafluprost 0.0015% with timolol 0.5% in subjects with open-angle glaucoma or ocular hypertension (United States)

Study Design

This study was a prospective, multi-center (26 sites), double-masked, parallel group, randomized, active-controlled trial designed to evaluate the efficacy and safety of tafluprost 0.0015% ophthalmic solution compared to timolol maleate 0.5% ophthalmic solution in subjects with open-angle glaucoma or ocular hypertension. Approximately 450 patients were planned for enrollment in a ratio of 3:2 (tafluprost:timolol). Subjects received treatment for 12 months.

Schedule of Visits and Assessments

	Screening Period			Treatment Period							
	Visit 1 Screening	Washout/ Waiting Period	Visit 2 Day 0 < 8:00- 16:00	Visit 3 Week 2 (14 d ± 3) < 8:00- 16:00	Visit 4 Week 6 (42 d ± 3) < 8:00- 16:00	Visit 5 Month 3 (91 d ± 7) < 8:00- 16:00	Visit 6 Month 6 (182 d ± 14) < 8:00- 16:00	Visit 7 Month 9 (274 d ± 14) < 8:00- 10:00	Visit 8 Month 12 (365 d ± 14) < 8:00- 16:00		
Informed Consent	X										
Medical History/Update	X		X								
Pregnancy Test ¹	X										
Review Entry Criteria	X		X								
Update Concomitant Meds			X		X						
Review Subject Compliance			X		X						
Adverse Events				X		X					
Blood Pressure & Heart Rate	X		X	X	X	X	X	X	X	X	
Visual Acuity	X		X	X	X	X	X	X	X	X	
Overall Drop Discomfort				X	X	X	X	X	X	X	
Conjunctival Hyperemia	X		X	X	X	X	X	X	X	X	
Biomicroscopy	X		X	X	X	X	X	X	X	X	
IOP	X		X ²	X ³	X ³	X ³	X ³	X ⁴	X ³	X ³	
Pauchymetry & Gonioscopy	X										
Iris & Eyelash Photos			X			X					
Visual Field Test	X ⁵						X				
Ophthalmoscopy	X									X ⁶	
Blood & Urine Samples	X ⁷									X	
Endothelial Cell Assessment ⁸			X				X			X	
Dispense Study Meds						X				X	
Instill Morning Study Med ⁹				X		X				X	
Collect Study Meds						X				X	
Exit										X	

¹ A urine pregnancy test must be conducted for all women of childbearing potential.
² After the Visit 2 IOP measurement at 8:00, IOP will be measured at 10:00 and 16:00. IOP measurements should be performed within ± 30 mins of the required time.
³ IOP must be measured at 8:00 and after the morning dose (T₀) at T₀ + 2 hours (10:00) and T₀ + 8 hours (16:00). IOP measurements should be performed within ± 30 minutes of the specified time.
⁴ IOP must be measured at 8:00 and after the morning dose (T₀) at T₀ + 2 hours (10:00).
⁵ A Visual Field Test must be performed at Visit 1 or before Visit 2 if one has not been done within 3 months prior to Visit 1.
⁶ Ophthalmoscopy performed after the 16:00 IOP measurement.
⁷ Fasting blood and urine samples must be obtained so that the results are available by Visit 2.
⁸ At selected centers only.
⁹ In-office instillation of morning study medication must occur immediately (i.e., within 10 minutes) after the 8:00 IOP measurement.

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Inclusion Criteria

Patients of any race meeting all of the following criteria at screening were considered eligible for this study:

1. Provided signed, written informed consent
2. Male or female 18 years of age or older
3. Diagnosed with open-angle glaucoma (primary open-angle glaucoma, pseudoexfoliative glaucoma, or pigmentary glaucoma) or ocular hypertension
4. Best-corrected ETDRS visual acuity score of +0.6 logMAR (Snellen equivalent of 20/80) or better in each eye
5. Able to follow instructions and make all required study visits
6. If patient is a female of child bearing potential¹, she had a negative urine pregnancy test result at Visit 1 and will be using reliable method of contraception throughout the study²

In addition, patients had to meet all of the following criteria at Visit 2 (Baseline, Day 0):

1. Patient had completed the required washout/waiting period
2. IOP of 22-34 mmHg in at least one eye at the 8:00 morning measurement on Day 0
3. Patient's blood and urine laboratory values were acceptable

¹A woman is considered of childbearing potential unless she is post-menopausal (at least 2 years since last menses occurred), is without a uterus or both ovaries, or has had a bilateral tubal ligation.

²Reliable methods of contraception include: spermicide with barrier, chemical contraceptive, or intrauterine device (IUD).

Exclusion Criteria

Patients with any of the following conditions were not eligible to participate in the study:

1. Females who were pregnant, nursing or planning a pregnancy, or females of childbearing potential who were not using a reliable method of contraception
2. Previous participation in any clinical trial in which tafluprost (AFP-168) was an investigational drug
3. Any uncontrolled systemic disease (e.g., hypertension, diabetes)
4. Cardiovascular, respiratory, or ocular (including ocular laser procedures) surgery within 6 months prior to Visit 1 in the treated eye(s)
5. History of any glaucoma filtration surgery
6. Clinically relevant low or high heart rate or blood pressure for age, or contraindications to beta-blocker therapy such as chronic obstructive pulmonary disease, bronchial asthma, greater than first degree heart block, and uncontrolled congestive heart failure

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Zioptan (tafluprost ophthalmic solution) 0.0015%

7. Change of an existing chronic therapy that could substantially effect IOP or the study outcomes within 30 days prior to Visit 1, or anticipated change in such therapy during the study³
8. Current alcohol or drug abuse
9. Known allergy or hypersensitivity to the study medications or their components, including benzalkonium chloride (BAK)
10. Patients who could not safely discontinue use of ocular hypotensive medications during the washout period
11. Use of any ocular medications other than anti-glaucoma medications within 1 week prior to Visit 1 or the planned use of any ocular medications during the study period (intermittent use of artificial tears was allowed)
12. Use of contact lenses at Visit 1 or during the study
13. History of any refractive surgery, (including RK, PRK, LASIK, and LASEK)
14. History of retinal detachment, proliferative diabetic retinopathy, or any retinal disease that may progressive during the study
15. Any active external ocular disease, inflammation, or infection of the eye and/or eyelids within the last 3 months (mild chronic blepharitis was allowed)
16. Any corneal abnormality or other condition interfering with or preventing reliable Goldmann applanation tonometry
17. Anterior chamber angle less than Grade 2 (Schaffer classification) as measured by gonioscopy
18. Advanced visual field defect or evidence of progressive visual field loss within the last year
19. Any ocular disease or condition that in the opinion of the investigator could put the patient at significant risk, could confound the study results, or could interfere significantly with the patient's participation in the study
20. Current participation in another clinical trial involving an investigational drug/device, or participation in such a trial within the last 30 days

In addition, patients with the following condition at Visit 2 were excluded from participation:

1. IOP of >34 mmHg in any eye at any time point on Day 0

The investigator or the Santen Medical Monitor could also declare any patient ineligible for any sound medical reason.

³Therapies that could substantially affect IOP or the study outcomes include, but are not limited to, alpha-adrenergic agents, beta-adrenergic blockers, calcium channel blockers, carbonic anhydrase inhibitors (CAIs), angiotensin-converting enzyme inhibitors, oral corticosteroids, and hypertensive medications.

Primary Efficacy Variable

The primary efficacy variable was change from baseline in the overall diurnal IOP at the end of 6 months. IOP measurements were done at 8:00, 10:00, and 16:00 at Baseline (Visit 2), Week 2 (Visit 3), Week 6 (Visit 4), Month 3 (Visit 5), Month 6 (Visit 6), and Month 12 (Visit 8). IOP measurements were also done at 8:00 and 10:00 at Month 9 (Visit 7).

Reviewer's comments:

The Review Team disagrees with using a single overall diurnal IOP at month 6 to evaluate efficacy. The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

Secondary Efficacy Variables

The secondary efficacy variables were change from baseline in the overall diurnal IOP at the end of 3 months, change from baseline in time-wise IOPs (at 8:00, 10:00 and 16:00) at 3 and 6 months and proportion of responders at 6 months.

Investigators

Investigator	Investigator #	# of Patients Enrolled
Stacey Ackerman, M.D. Philadelphia Eye Associates Philadelphia, PA 19148	114	1
John Alpar, M.D. St. Luke's Eye Institute Amarillo, TX 79106	147	15
Yue-Kong Au, M.D. Bossier City, LA 71111	161	4
Jason Bacharach, M.D. North Bay Eye Petaluma, CA 94954	160	30
John Bokosky, M.D. Eye Care of San Diego San Diego, CA 92103	023	10
Moiz Carim, M.D. Carim Eye & Retina Center Wyomissing, PA 19610	149	5
Jerome Crampton, M.D. Andover Eye Associates Andover, MA 01845	017	7
Douglas Day, M.D.	128	40

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Investigator	Investigator #	# of Patients Enrolled
Omni Eye Service Atlanta, GA 30342		
Richard Evans, M.D. San Antonio, TX 78240	092	28
Alan Jackson, M.D. Physicians Research Options, LLC Sandy, UT 84070	163	0
Elizabeth Mitchell, M.D. Total Eye Care Memphis, TN 38119	152	34
Thomas Mundorf, M.D. Mundorf Eye Center Charlotte, NC 28204	011	17
Kenneth Olander, M.D. University Eye Surgeons Maryville, TN 37805	154	17
Juan Orellana, M.D. Orellana Retina Associates, PLLC Raleigh, NC 27612	155	1
Bernard Perez, M.D. International Eye Center Tampa, FL 33603	156	19
Eugene Protzko, M.D. Seidenberg Protzko Eye Associates Bel Air, MD 21014	117	35
Kenneth Sall, M.D. Sall Eye Research center Artesia, CA 16066	045	40
Gail Schwartz, M.D. Glaucoma Consultants Towson, MD 21204	162	4
Elizabeth Sharpe, M.D. Glaucoma Consultants & Center For Eye Research Mt. Pleasant, SC 29464	129	31
Joseph Sokol, M.D. Opticare Eye Health Center Waterbury, CT 06708	157	5
Alfred Solish, M.D. Southern California Glaucoma Consultants	164	12

Investigator	Investigator #	# of Patients Enrolled
Pasadena, CA 91105		
Samuel Solish, M.D. Eye Care Medical Group Portland, ME 04102	091	5
Onex Stevenson, M.D. Stevenson Medical Surgical Eye Center New Orleans, LA 70119	159	10
Michael Tepedino, M.D. Cornerstone Healthcare High Point, NC 27262	118	19
Thomas Walters, M.D. Texan Eye Care Austin, TX 78746	063	22
Stephen Whiteside, M.D. Eye Center of Central Texas Temple, TX 76502	021	21
Robert Williams, M.D. Taustine Eye Center Louisville, KY 40217	094	26

See Section 6 for efficacy results and Section 7 for safety.

Study 74458

Title: Efficacy and Safety of Tafluprost 0.0015% Eye Drops as Compared to Latanoprost 0.005% Eye Drops. A Phase III Study in Patients with Open-Angle Glaucoma or Ocular Hypertension.

Study Design

This study was a prospective, multi-center (49 sites), multi-national (8 countries), double-masked, parallel group, randomized, active-controlled trial designed to evaluate the efficacy and safety of tafluprost 0.0015% ophthalmic solution compared to latanoprost 0.005% ophthalmic solution in subjects with open-angle glaucoma or ocular hypertension. Approximately 480 patients were planned for enrollment in a ratio of 1:1 (tafluprost:latanoprost). Subjects received treatment for 24 months.

Schedule of Visits and Assessments

Procedure	Screening	Baseline	Week 2	Week 6	Month 3	Month 6	Month 9	Month 12	Week 2-4 (V8+ 2-4 wk)	Month 15	Month 18	Month 21	Month 24	Follow up period (V12+ 2-4 wk)
	V1	V2 Day 0	V3 (±3 days)	V4 (±3 days)	V5 (±7 days)	V6 (±14 days)	V7 (±14 days)	V8 (±14 days)	V9	V10 (±14 days)	V11 (±14 days)	V12 (±14 days)	V12 (±14 days)	V13 Post study
WASH-OUT														
Informed consent	X	X ¹												
Inclusion & exclusion criteria	X													
Corneal thickness	X													
Medical history	X													
Baseline symptoms and	X													
Prior medication	X													
Pregnancy test	X ¹													
Gonioscopy	X													
Changes to prior and concomitant medication	X													
Aes														
Vital signs (BP and HR)	X													
Visual acuity	X													
Biometrics	X													
Conjunctival redness	X													
IOP	X													
Ophthalmoscopy	X													
Iris color/cyelash/lid photographs	X													
Safety laboratory samples	X													
Visual field test	X													
Laser flare meter*														
Endothelial cell density*														
Overall drop discomfort														
Patient compliance														

X¹ IOP after washout of 22-34 mmHg in at least one eye at the 8:00 measurement;
 X² IOP diurnal curve (IOP at 8:00, 12:00, 16:00 and 20:00);
 * At selected centers only;
 X² for females of childbearing potential only
 X³ Single IOP measurement at 8:00
 ** Informed consent for the extension period up to 2 years

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Inclusion Criteria

Patients of any race and either sex meeting all of the following criteria were considered eligible for this study:

- Aged 18 years or more
- A diagnosis of open-angle glaucoma (either primary open-angle glaucoma, pigmentary glaucoma or capsular glaucoma) or ocular hypertension
- An untreated (after washout) IOP of 22-34 mmHg in at least one eye at the 8:00 measurement at baseline (Visit 2)
- A best-corrected ETDRS visual acuity score of +0.6 logMAR (Snellen equivalent of 20/80) or better in each eye
- Patient on prior glaucoma medication must have a minimum wash-out as shown below:
 1. ≥ 4 weeks for β -adrenergic antagonists (β -blockers)
 2. ≥ 4 weeks for prostamides or prostaglandin analogs
 3. ≥ 3 weeks for α -adrenergic agonists (α -agonists)
 4. ≥ 7 days for carbonic anhydrase inhibitors (CAIs)
 5. ≥ 5 days for miotics
- Are willing to follow instructions
- Have provided a written informed consent

Exclusion Criteria

- Females who are pregnant, nursing or planning a pregnancy, or females of childbearing potential who are not using a reliable method of contraception
- Previous participation in any clinical trial in which tafluprost was an investigational drug
- Any uncontrolled systemic disease (e.g. hypertension, diabetes)
- Filtration surgery without time limit or any other ocular (including ocular laser procedures) surgery within 6 months prior to Visit 1 in the treated eye(s)
- IOP greater than 34 mmHg at any time point in either eye at Visit 2 (baseline)
- Change of an existing chronic therapy that could substantially effect IOP or the study outcomes within 30 days prior to Visit 1 (screening), or anticipated change in such therapy during the study¹
- Known allergy or hypersensitivity to the study medications or their components, including benzalkonium chloride (BAK)
- Use of contact lenses at Visit 1 (screening) or during the study
- Any active external ocular disease, inflammation, or infection of the eye and/or eyelids within 3 months from the study start
- Any ocular disease/condition that in the opinion of the investigator may put the patient at significant risk or may confound the study results or may interfere significantly with the patient's participation in the study

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Zioptan (tafluprost ophthalmic solution) 0.0015%

- Any corneal abnormality or other condition preventing reliable applanation tonometry
- Anterior chamber angle less than grade 2 according to Schaffer classification as measured by gonioscopy
- Advanced visual defect
- Patients who cannot safely discontinue use of ocular hypotensive medications during the washout period
- Use of any other antiglaucoma medications than the study medications during the study
- Current alcohol or drug abuse
- Current participation in another clinical trial involving an investigational drg/device, or participation in such a trial within the last 30 days

Primary Efficacy Variable

The primary efficacy variable was change from baseline in the overall diurnal IOP at month 6. IOP measurements were done at 8:00, 12:00, 16:00, and 20:00 at Baseline (Visit 2), Month 3 (Visit 5), Month 6 (Visit 6), Month 12 (Visit 8), Month 18 (Visit 11), and Month 24 (Visit 12). IOP measurements were also done at 8:00 at week 2 (Visit 3), month 9 (Visit 7), and month 15 (Visit 10).

Reviewer’s comments:

The Review Team disagrees with using a single overall diurnal IOP at month 6 to evaluate efficacy. The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

Secondary Efficacy Variables

The secondary efficacy variables were:

1. Change from baseline in the overall diurnal IOP at month 3
2. Change from baseline in the time-wise IOPs at months 3 and 6
3. Proportion of responders at month 6

A responder was defined as a patient with a certain reduction of IOP (e.g. 15% with increasing steps of 5%) as compared to baseline or with a certain target IOP value (e.g. 20 mmHg with decreasing steps of 1 mmHg).

Investigators

Investigator	Investigator #	# of Patients Enrolled
Professor Uusitalo Kuopio, Kuopio University, Finland	01	20

Investigator	Investigator #	# of Patients Enrolled
Docent Puska Helsinki, University Hospital, Finland	02	3
Prof. Airaksinen Oulu, University Hospital, Finland	03	17
Dr. Makinen Tampere, Mehilainen Oy, Finland	04	11
Dr. Bergstrom Lund, Universitetssjukhuset, Sweden	11	18
Dr. Fristrom Linkoping, Universitetssjukhuset, Sweden	12	12
Dr. Eriksson Jonkoping, Ryhovs Lanssjukhus, Sweden	13	11
Dr. Jenssen Bergen, Haukeland University Hospital, Norway	21	8
Prof. Baudouin Paris, Hopital des Quinze-Vingts, France	31	5
Prof. Malecaze Toulouse, Hopital Purpan, France	32	4
Prof. Pisella Tours, Hopital Bretonneau, France	33	1
Prof. Villain Montpellier, Hopital Gui de Chauliac, France	34	1
Prof. Cochereau Angers, CHU d'Angers, France	35	12
Prof. Nordmann Paris, Hopital des Quinze-Vingts, France	36	1
Prof. Rouland Lille, Hopital Claude Huriez, France	37	3
Prof. Denis Lyon, Hopital Edouard Herriot, France	38	6
Prof. Bron Dijon, Hopital General, CHU de Dijon, France	39	10

Investigator	Investigator #	# of Patients Enrolled
Dr. Malet Bordeaux, Hopital Pellegrin, France	71	3
Dr. Duong Paris, Fondation Rothschild, France	72	3
Dr. Benchaboune Saint Etienne, Hopital Bellevue, France	73	5
Dr. Lachkar Paris, Hopital Saint Joseph, France	74	0
Prof. Romanet Grenoble, Hopital Nord, France	75	8
Prof. Zagorski Lublin, Katedra I Klinika Okulistyki Akademii Medycznej, Poland	41	14
Dr. Cwirko Wroclaw, Spektrum Sp.z o.o., Poland	42	0
Prof. Czechowicz-Janicka Warszawa, Centrum Leczenia Jaskry I Chorob Oka, Poland	43	7
Prof. Iwaskiewicz-Bilikiewicz Gdansk, Klinika Chorob Oczu Akademii Medycznej, Poland	44	15
Prof. Karczewicz Szczecin, Klinika Okulistyki Pomorskiej Akademii Medycznej, Poland	45	10
Dr. Mariak Bialystok, Katedra Klinika Okulistyki Akademii Medycznej, Poland	46	21
Prof. Nizankowska Wroclaw, Klinika I Keatedra Okulistyki Akademii Medycznej, Poland	47	11
Prof. Pecold Poznan, Katedra Okulistyki I Klinika Okulistyczna Akademii Medycznej, Poland	48	20
Prof. Szaflik Warszawa, Samodzielny Publiczny	49	9

Investigator	Investigator #	# of Patients Enrolled
Kliniczny Szpital Okulistyczny, Poland		
Dr. Wylegala Katowice, Okregowy Szpital Kolejowy Oddzial Okulistyczny, Poland	81	16
Prof. Pillunat Dresdan LKP, Universitätsaugenklinik, Germany	51	0
Prof. Pfeiffer Mainz, Augenklinik der Joh.- Gutenberg-Universität, Germany San Antonio, TX 78229	52	9
Dr. Vorwerk Magdeburg, Otto-von Guericke Universität, Germany	53	1
Dr. Hoffmann Schweinfurt, Praxis, Germany	54	6
Dr. Riedel Dresden, Praxis, Germany	55	19
Prof. Michelson Erlangen, Universitäts-Augenklinik, Germany	56	9
Prof. Kampik München, Augenklinik der Universität, Germany	57	6
Dr. Hamacher Starnberg, Praxis, Germany	58	32
Prof. Mester Sulzbach Saarland, Bundesknappschaftskrankenhaus, Germany	59	5
Dr. Braun Zwickau, Praxis, Germany	61	14
Dr. Bayer Weilheim, Augenarztpraxis, Germany	62	32
Dr. Petzold Kulmbach, Praxis, Germany	63	21
Dr. Richter Regensburg, Praxis, Germany	64	16

Investigator	Investigator #	# of Patients Enrolled
Dr. Henjes Torgau, Praxis, Germany	65	5
Dipl. Med. Oehmig Chemnitz, Praxis, Germany	66	12
Dr. Kurtz Tel Aviv, Sourasky Medical Center, Israel	91	14
Prof. Geyer Haifa, Carmel Medical Center, Israel	92	15
Dr. Zalish Rehovot, Kaplan Medical Center, Israel	93	7
Dr. Neshet Kfar Saba, Meir Medical Center, Israel	94	11
Prof. Traverso Genova, hospital San Martino, Italy	99	14

See Section 6 for efficacy results and Section 7 for safety.

Study 001

Title: A Phase III, Randomized, Active Comparator-Controlled, Twelve-Week, Double-Masked Clinical Trial to Compare the Efficacy and Safety of Preservative-Free MK-2452 (0.0015%) and Preservative-Free Timolol maleate (0.5%) in Patients with Open-Angle Glaucoma and Ocular hypertension

Study Design

This study was a prospective, multi-center (50 sites), multi-national (3 countries), double-masked, parallel group, randomized, active-controlled trial designed to evaluate the efficacy and safety of preservative free tafluprost 0.0015% (MK-2452) ophthalmic solution compared to preservative-free timolol maleate 0.5% ophthalmic solution in subjects with open-angle glaucoma or ocular hypertension. Approximately 620 patients were planned for enrollment in a ratio of 1:1 (tafluprost:timolol). Subjects received treatment for 12 weeks.

Schedule of Visits and Assessments

	Pre-Study Period		Treatment Period				Post-Study Period
	Screening/Washout Day -28 to -2	Baseline Day -1	Week 2	Week 6	Week 8	Week 12	+14 Days Telephone Contact
Visits	Visit 1 ¹	Visit 2 -1	Visit 3 ¹⁴ 14	Visit 4 ¹⁴ 42	Visit 5 56	Visit 6 ^{14,15} 84	98
Target Day		-1	14	42	56	84	98
Permissible Visit Window ² (Relative to Target Day)		±2 days	±3 days	±5 days	±5 days	±5 days	±2 days
Procedures to be performed in the following order. Right eye measurements should be followed by left eye measurements for all exams.							
Obtain informed consent ³	X						
Assign baseline number	X						
Collect demographics	X						
Review inclusion/exclusion criteria	X	X					
Urine pregnancy/dipstick test (for women of childbearing age) ⁴	X	X		X			
Collect medical / ocular history	X						
Review prior/concomitant medications	X						
Review adverse events	X						
Collect vital signs ⁵	X	X	X	X	X	X	X
Perform Visual Acuity Test (including refraction ⁶)	X	X	X	X	X	X	X
Automated perimetry (Humphrey or Octopus)	X	X ¹⁰	X	X	X	X	X
External and adnexa ocular examination	X	X ¹¹	X	X	X	X	X
Hypertension assessment	X	X ¹¹	X	X	X	X	X
Ocular surface examination using fluorescein staining	X	X ¹⁰	X	X	X	X	X
Slit lamp biomicroscopy	X	X ¹⁰	X	X	X	X	X
Intraocular pressure measurement (Goldmann) ⁷	X ^{11,8}	X ¹⁰	X	X	X	X	X
Gonioscopy	X						
Dilated fundus examination ¹⁰	X						

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Schedule of Visits and Assessments

Compound No. MKC-3452 Protocol No. 001-00	Pre-Study Period		Treatment Period				Post-Study Period
	Screening/Washout Day -28 to -2	Baseline Day -1	Week 2	Week 6	Week 8	Week 12	+ 14 Days
Visits	Visit 1 ¹	Visit 2	Visit 3 ¹⁴	Visit 4 ¹⁴	Visit 5	Visit 6 ^{14, 15}	Telephone Contact
Target Day		-1	14	42	56	84	98
Permissible Visit Window ² (Relative to Target Day)		±2 days	±3 days	±5 days	±5 days	±5 days	±2 days
Procedures to be performed in the following order. Right eye measurements should be followed by left eye measurements for all exams.							
Discontinue glaucoma medications ¹¹	X						
Assign allocation number via IVRS		X		X	X		
Dispense study medication via IVRS		X		X	X	X	
Infill morning study medication by site personnel ¹²			X	X	X	X	
Dispense medication dosing diary		X		X	X	X	
Collect study medication dose packs for compliance accounting			X	X	X	X	
Monitor medication compliance via medication diary			X	X	X	X	
¹ Eligible treatment-naïve patients (those who have never used or who have not used ocular hypotensive medication for at least 4 weeks prior to the Screening Visit (Visit 1) may be randomized at the Screening Visit only if IOP measurements can be performed at all prescribed time points (0800 hrs, 1000 hrs, and 1600 hrs), and all Screening and Baseline visit procedures can be completed. Treatment naïve patients who do not have the proper IOP assessment at Screening may return for the Baseline Visit (Visit 2) 1 to 3 days following the Screening Visit. ² Deviation from visit windows permitted per protocol requires consultation between the Investigator and the Sponsor and written documentation of the collaborative decision on patient management. Exposure to drug must be at least 12 weeks. ³ A patient consent form must be signed prior to any study-specific procedures. ⁴ Women of childbearing potential will have a urine pregnancy test at each office visit. A positive urine pregnancy test at Visit 1 (Screening) requires immediate exclusion from the study. At Visit 2 (Baseline) and subsequent visits, a positive urine pregnancy test requires immediate interruption of study medication until serum β-hCG can be locally performed and found to be negative. Patient must be permanently discontinued and followed per Section 3.4.4 if pregnancy is confirmed by a positive serum pregnancy test. ⁵ Obtain the mean of 2 separate measurements for pulse and BP; patient is seated for BP measurements after 5 minutes of rest. ⁶ Refraction does not need to be performed at each visit. Determine initial best corrected visual acuity. Thereafter, refraction should be repeated only as needed. ⁷ At Visit 1 (Screening), automated perimetry may be performed before gonioscopy and before dilation on the day of the visit. Alternatively, this procedure may be performed either the day before or the day after the visit. Note: All procedures must be performed within 2 days of the initial visit. At the Final Visit, automated perimetry may be performed the day before the visit, or the day of the visit before gonioscopy and before dilation.							

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Schedule of Visits and Assessments

⁸ To be performed in both eyes. IOP measures will be taken at 0800 hrs, 1000 hrs, and 1600 hrs on Day -1 (Visit 2- Baseline) and at Weeks 2, 6, and 12. Entry criteria IOP measures at each time point (0800 hrs, 1000 hrs, and 1600 hrs) will be the average of 2 consecutive measurements if these differ by ≤ 2 mmHg. The 2 measurements should be recorded, and the Sponsor will determine the mean. However, if the 2 consecutive measurements differ by >2 mmHg, then a third measurement will be performed and the median of the three measurements must meet the entry criteria (the median is the middle measurement after sorting the measurements from low to high). All 3 measurements should be recorded, and the Sponsor will determine the median.

⁹ Eligible treatment-naïve patients with a Screening/Baseline visit must have IOP measurements at 0800 hrs, 1000 hrs, and 1600 hrs.

¹⁰ Perform the dilated fundus exam after the 1600 hrs IOP measurement at the Screening Visit (Visit 1) for treatment naïve patients who qualify for randomization at Visit 1, and at Week 12 (Visit 6). Note: For non-treatment naïve patients, there is no specified time for the dilated fundus exam, except it should be after all other ophthalmic procedures have been performed. Additional details for Screening and Final Visits fundus examination can be found in Sections 3.2.3.5.1 and 3.2.3.5.7.

¹¹ Patients cannot discontinue their previous glaucoma medications and begin the washout prior to signing consent.

¹² Patients do not dose the morning of a scheduled office visit; in-office instillation of morning study medication must occur immediately (i.e., within 10 minutes) after the 0800 hrs IOP measurement.

¹³ This procedure does not need to be repeated for treatment-naïve patients returning for the Baseline Visit (Visit 2) 1 to 3 days after the Screening Visit (Visit 1).

¹⁴ Site personnel should contact each patient the day before scheduled visits in the treatment period to remind the patient to take their evening dose within the dosing window (1900 hrs to 2100 hrs). Patients should also be instructed that if they miss their evening dose before a scheduled visit they should contact the site and reschedule the study visit within the visit window. If, however, a patient cannot return within the visit window, then the visit should occur as scheduled.

¹⁵ In the event a patient discontinues from the study, all procedures from Visit 6 should be performed and recorded in an unscheduled visit.

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Inclusion Criteria

Ocular Inclusion Criteria

Note: Both eyes should be treated with study medication regardless of whether one or both meet the IOP criteria unless, in the judgment of the Investigator, the non-qualifying eye should not be treated. See Inclusion Criteria 6 and 7.

At Visit 1 (Screening)

1. Patient has been diagnosed with primary open-angle glaucoma, pigmentary glaucoma, capsular glaucoma/pseudoexfoliation, or ocular hypertension.
2. Patient is currently prescribed ocular hypotensive medication with a stable treatment regimen that began at least 30 days prior to the Screening Visit, or patient is treatment-naïve (those who have never used or who have not used ocular hypotensive medication for at least 4 weeks prior to the Screening Visit (Visit 1)).
3. Patient must be able to safely discontinue the use of all topical and/or systemic ocular hypotensive medication during the washout period (up to 4-weeks pre-study), as determined by the Investigator. Rescue medication (dorzolamide, 2%) may be used if required, and the Investigator must determine that no significant vision loss will occur.

Note: See Table 2-1 in Section 2.4.1.1.1 for list of medications and washout schedule.

4. Patient has a best corrected ETDRS visual acuity score of $+0.6$ logMAR (Snellen equivalent of 20/80) or better in each eye.
5. Patient is willing and able to avoid wearing contact lenses from 4 weeks prior to dosing with study medication through 24 hours after final dosing.

At Visit 2 (Baseline)

All previous criteria must continue to be met, including:

6. Patient has a mean (or median) IOP of ≥ 23 and ≤ 36 mmHg in at least one eye at the 0800 hrs time point at the Baseline Visit (Visit 2).
7. Patient has < 5 mmHg difference in mean (or median) IOP between eyes at each time point (0800 hrs, 1000 hrs, and 1600 hrs) at Baseline (Visit 2).

General Inclusion Criteria

At Visit 1 (Screening)

8. Patient is a male or female ≥ 18 years of age on the day of signing the informed consent.
9. Patient is willing and able to self-administer (or has an able person available on a daily basis to assist with administration of) study medications.
10. Patient is able to read, understand and complete diaries, understands the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent.

11. Patient is

Of reproductive potential and agrees to remain abstinent* or use (or have their partner use) one of the following highly effective methods of birth control within the projected duration of the study: hormonal contraceptives, intrauterine device (IUD), diaphragm, condoms, and vasectomy. The use of a barrier contraceptive device should always be supplemented with the use of a spermicide.

OR

A female who is **not** of reproductive potential is defined as one who has either (1) reached natural menopause (≥ 46 years of age plus 12 months of spontaneous amenorrhea), (2) 6 weeks post surgical bilateral oophorectomy, (3) hysterectomy, or (4) bilateral tubal ligation.

* If abstinence is not a locally acceptable method of contraception, then a highly effective birth control method must be used.

Exclusion Criteria

Ocular Exclusion Criteria

At Visit 1 (Screening)

1. Patient has a mean (or median) IOP > 36 mmHg in either eye at the Screening Visit (Visit 1).
2. Patient has a history of or current abnormal corneal sensation or any abnormality in either eye preventing reliable Goldmann applanation tonometry.
3. Patient has narrow anterior chamber angles in either eye judged potentially occludable if pupillary dilatation were to occur, evidence or history of acute or chronic angle closure, or is at risk for angle closure as evidenced by anterior chamber angle less than grade 2 according to Schaeffer classification, as measured by gonioscopy.

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4. Patient has a pupil in either eye that will not dilate sufficiently for adequate evaluation of the retina.
5. Patient has an ocular opacity in either eye preventing posterior segment examination.
6. Patient is unable to use study medication in the affected eye(s).
7. Patient has a history in either eye of any inflammatory ocular surface disease involving bulbar conjunctiva, cornea, sclera and lid margin (e.g., herpes simplex keratitis or corneal ulcers), or a history of anterior or posterior uveitis in either eye within 6 months prior to the Screening Visit (Visit 1).
8. Patient has a history of retinal detachment, proliferative diabetic retinopathy, or any retinal disease in either eye that may be progressive during the study.
9. Patient experienced a significant visual field loss or showed evidence of progressive visual field loss within the last year (as defined by >1 dB/yr average loss or vision threatening new defect). Patients with severe central field loss in either eye defined as a sensitivity ≤ 10 dB in at least 2 of the 4 visual field test points closest to the point of fixation.
10. Patient has a history or evidence of acute ocular injection, embedded corneal foreign body, or clinically significant ocular inflammation or infection in either eye within 3 months of the Screening Visit (Visit 1).
11. Patient has significant ocular symptoms or signs such as photophobia, flashes or streaks of light, metamorphopsia, diplopia, or transient loss of vision in either eye.
12. Patient has had intraocular surgery (e.g., cataract extraction) in either eye within 4 months prior to Visit 1.
13. Patient has a history of any glaucoma surgery, such as laser trabeculoplasty, trabeculotomy, or other filtration surgery in either eye.
14. Patient has a history of any refractive surgery (including RK, PRK, LASIK, and LASEK) in either eye.
15. Patient used ocular medications (other than anti-glaucoma medications and topical ocular lubricants) within 1 week prior to the Screening Visit (Visit 1).
16. Patient is planning to use ocular medications during the study period (intermittent use of preservative-free topical ocular lubricants is allowed).
17. Patient has persistent allergic conjunctivitis or allergic conjunctivitis that is likely to be manifest during the study and likely to confound results.
18. Patient is currently on two or more anti-glaucoma medications (except Cosopt™ or its generic formulation).

At Visit 2 (Baseline)

19. Patient has a mean (or median) IOP >36 mmHg in either eye at any time point (0800 hrs, 1000 hrs, and 1600 hrs) of the Baseline Visit (Visit 2).

General Exclusion Criteria

At Visit 1 (Screening)

20. Patient had a change in dose or initiation of systemic therapies (including herbal medications, vitamins, and nutrient supplements [e.g., fish oil, and zinc]) that can substantially affect IOP or the study outcome, such as (but not limited to) alpha-adrenergic agents, beta-adrenergic blockers, calcium channel blockers, carbonic anhydrase inhibitors (CAIs), angiotensin-converting enzyme inhibitors or other anti-hypertensive medications within 30 days prior to the Screening Visit (Visit 1), or anticipates a change in such therapy during the study.
21. Patient has a history of hypersensitivity to more than two chemical classes of drugs, including prescriptions and over-the-counter medications.
22. Patient has, in the opinion of the investigator, confounding pain syndromes (i.e., chronic pain requiring daily treatment other than acetaminophen or NSAID), psychiatric conditions, such as psychotic disease or uncontrolled major depression based on criteria such as DSM-IV, dementia, or significant neurological disorders other than migraine.
23. Patient is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.
24. Patient is currently participating or has participated in a study with an investigational compound or device within 4 weeks of signing the informed consent.
25. Patient has previously been clinically treated with tafluprost.
26. Patient is, at the time of signing the informed consent, a user of recreational or illicit drugs (including marijuana) or has had a recent history (within the last year) of drug or alcohol abuse or dependence.
27. Patient is pregnant or breastfeeding, or expecting to conceive within the projected duration of the study.
28. Patient has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might confound the results of the study, or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate.
29. Patient has a screening systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg or a pulse rate >100 beats/min.

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30. Patient has a history within 6 months prior to the Screening Visit (Visit 1) or current evidence of a clinically significant cardiovascular disorder, including, but not limited to:
- acute coronary syndrome
 - unstable angina
 - congestive heart failure (e.g. EF \leq 40%)
 - heart block with more severe than first degree
 - cardiomyopathy
 - sinus bradycardia (HR $<$ 50)
 - any symptomatic arrhythmia requiring medical intervention
31. Patient has any history of bronchial asthma, wheezing, pneumonia, chronic obstructive pulmonary disease (COPD), other pulmonary disease, or abnormal chest x-ray.
32. Patient has a history of any major systemic disorder that is unstable or undergoing change in therapy within the past 6 months prior to screening.
33. Patient has malignancy diagnosed \leq 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer.
34. Patient has donated blood products or has had phlebotomy of $>$ 300 mL within 8 weeks of signing informed consent, or intends to donate or receive blood products within the projected duration of the study.

Primary Efficacy Variable

The primary efficacy variable was mean IOP change from baseline at all 9 time points during the study (8:00, 10:00, and 16:00 at Weeks 2, 6, and 12).

Reviewer’s comments:

The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

Secondary Efficacy Variable

The secondary efficacy variable was proportion of patients with a favorable IOP response defined as \geq 25% reduction in IOP from baseline to Week 12.

Investigators

Investigator	Investigator #	# of Patients Enrolled
Stanley J. Berke, M.D. Ophthalmic Consultants of Long	0007	22

Investigator	Investigator #	# of Patients Enrolled
Island Lynbrook, NY 11563		
Michael Berlin, M.D. Glaucoma Institute of Beverly Hills Los Angeles, CA 90048	0008	1
Loius B. Cantor, M.D. IU EYE at Carmel Indianapolis, IN 46202	0009	11
Mark, DiSclafani, M.D. Eye Associates of Manatee, LLC Bradenton, FL 34209	0013	8
Catherine Fitzmorris, M.D. Gulf South Eye Associates Metairie, LA 70006	0015	20
Ronald Frenkel, M.D. East Florida Eye Institute Stuart, FL 34994	0016	11
Joshua Ki Hu, M.D. Suncoast Clinical Research New Port Richey, FL 34652	0018	3
Mahmoud A. Khaimi, M.D. Dean A. McGee Eye Institute Oklahoma City, OK 73104	020	2
Richard Kleinert, M.D. Fallon Clinic, Inc. Worcester, MA 01606	021	6
Donald McCormack, M.D. Boulder Medical Center Boulder, CO 80304	0025	22
Felipe Medeiros, M.D. University of California La Jolla, CA 92093	0026	21
Eydie Miller-Ellis, M.D. University of Pennsylvania Philadelphia, PA 19104	0027	9
George F. Nardin, M.D. Windward Eye Physicians and Surgeons Kailua, HI 96734	0028	0
Robert J. Noecker, M.D. UPMC Eye Center	0029	0

Investigator	Investigator #	# of Patients Enrolled
Pittsburg, PA 15213		
Jose L. Perez-Becerra, M.D. Belle Vue Eye Center San Antonio, TX 78221	0031	3
Eugene Protzko, M.D. Seidenberg Protzko Eye Associates Bel Air, MD 21014	0032	28
Alan L. Robin, M.D. Baltimore, MD 21014	0033	6
Mark S. Rubin, M.D. International Eye Associates P.A. Ormond Beach, FL 32174	0034	15
Joseph L. Sokol, M.D. Connecticut Eye Specialists Shelton, CT 06484	0036	2
James C. Tsai, M.D. Yale University New Haven, CT 06510	0037	3
Fiaz Zaman, M.D. Houston Eye Associates Houston, TX 77025	0040	21
Andre Mermoud, Dr. Med Clinique de Montchoisi Lausanne, Switzerland	0052	4
Eamon Sharkawi, Dr. Med Jules Goning Hospital Lausanne, Switzerland	0053	15
Tarek Shaarawy, Dr. Med Hospitaux Universitaires de Geneve Geneva, Switzerland	0054	7
Jens Funk, Dr. Med Universitaetsspital Zuerich Zurich, Switzerland	0055	7
Stacey L. Ackerman, M.D. Philadelphia Eye Associates Philadelphia, PA 19148	0056	6
Jason Bacharach, M.D. North Bay Eye Associates Petaluma, CA 94954	0057	8
Howard S. Barnebey, M.D. Specialty Eyecare Centre	0058	9

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Investigator	Investigator #	# of Patients Enrolled
1920 116th Ave., NE Bellevue, WA 98004		
Marshall N. Cyrlin, M.D. Associated Vision Consultants Southfield, MI 91205	0059	6
Harvey B. Dubiner, M.D. Clayton Eye Center Morrow, GA 30260	0060	25
Richard M. Evans, M.D. Medical Center Ophthalmology Associates San Antonio, TX 78240	0061	9
Norman S. Levy, M.D. Florida Ophthalmic Institute Gainesville, FL 32605	0062	2
Eugene B. McLaurin, M.D. Total Eye Care, P.A. Memphis, TN 38119	0063	49
James H. Peace, M.D. United Medical Research Institute Inglewood, CA 90301	0064	14
Michael H. Rotberg, M.D. Charlotte Eye, Ear, Nose and Throat Charlotte, NC 28210	0065	10
Howard I. Schenker, M.D. Rochester Ophthalmological Group Rochester, NY 14618	0066	25
Elizabeth D. Sharpe, M.D. Glaucoma Consultants and Center for Eye Research, PA Mount Pleasant, SC 29464	0067	23
George C. Thorne Jr., M.D. Eye Physicians of Austin Austin, TX 78756	0068	19
Robert D. Williams, M.D. Taustine Eye Center Louisville, KY 40217	0069	17
David Wirta, M.D. Newport Beach, CA 92663	0070	67
Luis P. Julvez, M.D. Hospital Universitario Miguel Servet	0077	17

Investigator	Investigator #	# of Patients Enrolled
Zaragoza, Spain		
Julian Garcia-Feijoo, M.D. Hoapital Clinico San Carlos Madrid, Spain	0078	19
Alfonso Anton-Lopez, M.D. Institute Catala de Retina Barcelona, Spain	0079	6
Francisco Munoz-Negrete, M.D. Hospital Ramon y Cajal Madrid, Spain	0080	17
Maria Isabel Canut-Jordana, M.D. Clinica Barraquer Centralita Barcelona, Spain	0081	12
Javier Moreno-Montanes, M.D. Clinica Universitaria de la Universidad de Navarra Pamplona, Spain	0082	13
Eugene Protzko, M.D. Seidenberg Protzko Eye Associates Bel Air, MD 21014	0083	9
George F. Nardin, M.D. Windward Eye Physicians and Surgeons Kaneohe, HI 96744	0096	3
Stacey L. Ackerman, M.D. Philadelphia Eye Associates Philadelphia, PA 19148	0097	4
Stacey L. Ackerman, M.D. Philadelphia Eye Associates Philadelphia, PA 19148	0098	2
Howard S. Barnebey, M.D. Specialty Eyecare Centre 901 Boren Ave. Bellevue, WA 98004	100	5

Reviewer's Comments:

Four investigators (Ackerman SL, Barnebey HS, Nardin GF, and Protzko E) were identified as the investigator for multiple study sites. The total number of patients that Drs. Ackerman, Barnebey, Nardin and Protzko enrolled was 12 (1.9%), 14(2.2%), 3 (0.5%), and 37(5.8%),

respectively. The Applicant was asked to clarify the reason for multiple site numbers assigned to the same investigator.

Applicant Response: The reason Drs Ackerman, Barnebey, Nardin, and Protzko are listed more than once as part of the investigator list is because of Merck’s Standard Operating Procedure for creating site numbers in the Clinical Trial Management System, Electronic Data Capture system and Clinical Portal and Collaboration system. Merck’s procedure is to create a unique site number when an investigator is overseeing multiple locations with unique patient populations. The Clinical Research Associates confirm that these investigators need more than one site number when completing the site validation visit at each site.

Reviewer’s comments: Based on the locations of the multiple sites, it is unlikely that they represent unique patient populations.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the reduction of intraocular pressure in male or female patients, 18 years old or more, with open angle glaucoma or ocular hypertension.

6.1.1 Methods

Description of the clinical trial design is contained in Section 5.3.

6.1.2 Demographics

Patient Demographics

		Study	
		15-003	
Treatment Group		tafluprost	timolol
Total enrollment in study		267	191
Race	White	167 (62.5%)	123 (64.4%)
	Black or African American	64 (24.0%)	47(24.6%)
	Asian	0	1 (0.5%)
	Hispanic or Latino	36 (13.5%)	19 (9.9%)
	Other	0	1 (0.5%)
	N	267	191
	Mean	61.3 yrs	61.5 yrs

Age	Min	21 yrs	21 yrs
	Median	61 yrs	62 yrs
	Max	88 yrs	84 yrs
Gender	Male	104 (39.0%)	83 (43.5%)
	Female	163 (61.0%)	108 (56.5%)
Iris color	Blue	58 (21.7%)	48 (25.1%)
	Gray	1 (0.4%)	0
	Blue-brown	19 (7.1%)	14 (7.3%)
	Gray-brown	1 (0.4%)	2 (1.0%)
	Green	9 (3.4%)	6 (3.1%)
	Green-brown	14 (5.2%)	3 (1.6%)
	Brown	155 (58.1%)	109 (57.1%)
	Yellow-brown	0	1 (0.5%)
Other	10 (3.7%)	8 (4.2%)	

		Study	
		74458	
Treatment Group		tafluprost	latanoprost
Total enrollment in study		269	264
Race	Caucasian	268 (99.6%)	123 (64.4%)
	Black	0	2 (0.8%)
	Asian	1 (0.4%)	0
Age	N	269	264
	Mean	62.5 yrs	62.4 yrs
	Min	23	18
	Median	64	64
	Max	86	88
Gender	Male	109 (40.5%)	112 (42.4%)
	Female	160 (59.5%)	152 (57.6%)
Iris color	Blue/Gray	204 (37.9%)	210 (39.8%)
	Blue/Gray-brown	88 (16.4%)	94 (17.8%)
	Green	14 (2.6%)	16 (3.0%)
	Green-brown	56 (10.4%)	48 (9.1%)
	Brown	158 (29.4%)	140 (26.5%)
	Yellow-brown	4 (0.7%)	8 (1.5%)
	Other	14 (2.6%)	12 (2.3%)

		Study	
		001	
Treatment Group		tafluprost	timolol
Total enrollment in study		320	323
	White	236 (73.8%)	244 (75.5%)

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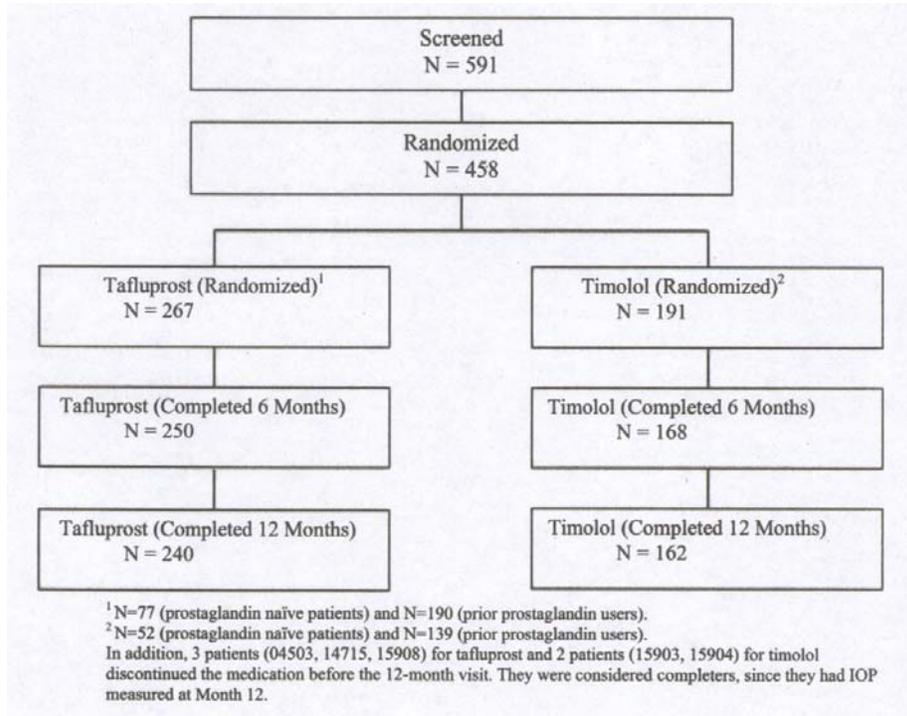
Zioptan (tafluprost ophthalmic solution) 0.0015%

Race	Black or African American	64 (23.4%)	71 (22.0%)
	Asian	6 (1.9)	5 (1.5%)
	American Indian or Alaska Native	1 (0.3%)	3 (0.9%)
	Native Hawaiian or Other Pacific Islander	1 (0.3%)	0
	Multi-Racial	1 (0.3%)	0
Age	N	320	323
	Mean	63.3 yrs	63.3 yrs
	Min	25	21
	Median	64	64
	Max	91	94
Gender	Male	137 (42.8%)	131 (40.6%)
	Female	183 (57.2%)	192 (59.4%)

Reviewer's Comments: *Iris color data was not collected for Study 001. The Agency was informed of this at the pre-NDA meeting on June 30, 2010. The Agency strongly recommends that this information be collected in any future trials.*

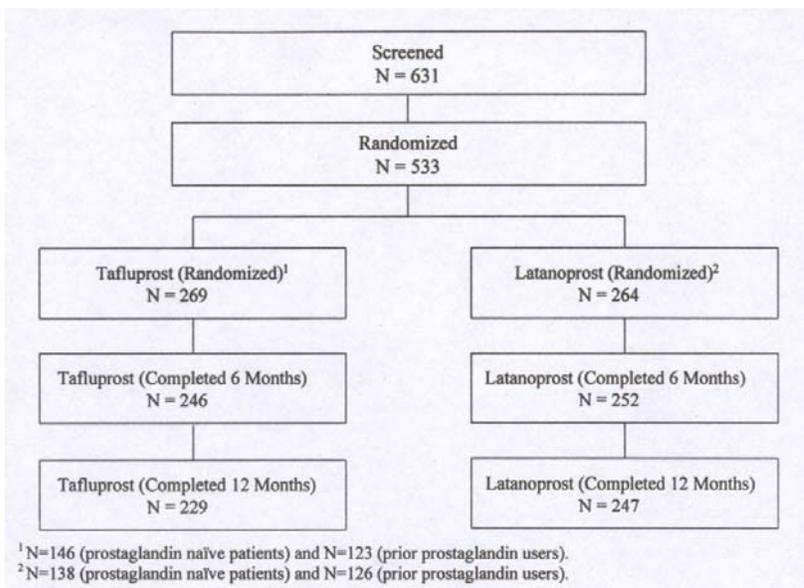
6.1.3 Subject Disposition

Study 15-003



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Study 74458



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Study 001

	Tafluprost 0.0015%		Timolol Maleate 0.5%		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					158	
Patients in population	320		323		643	
Study Disposition						
COMPLETED	306	(95.6)	312	(96.6)	618	(96.1)
DISCONTINUED	14	(4.4)	11	(3.4)	25	(3.9)
ADVERSE EVENT	4	(1.3)	3	(0.9)	7	(1.1)
LOST TO FOLLOW-UP	2	(0.6)	0	(0.0)	2	(0.3)
PHYSICIAN DECISION	1	(0.3)	1	(0.3)	2	(0.3)
PROTOCOL VIOLATION	0	(0.0)	2	(0.6)	2	(0.3)
WITHDRAWAL BY SUBJECT	7	(2.2)	5	(1.5)	12	(1.9)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for Study 15-003 was change from baseline in the overall diurnal IOP at the end of 6 months. IOP measurements were done at 8:00, 10:00, and 16:00 at Baseline (Visit 2), Week 2 (Visit 3), Week 6 (Visit 4), Month 3 (Visit 5), Month 6 (Visit 6), and Month 12 (Visit 8). IOP measurements were also done at 8:00 and 10:00 at Month 9 (Visit 7).

The primary efficacy endpoint for Study 74458 was change from baseline in the overall diurnal IOP at month 6. IOP measurements were done at 8:00, 12:00, 16:00, and 20:00 at Baseline (Visit 2), Month 3 (Visit 5), Month 6 (Visit 6), Month 12 (Visit 8), Month 18 (Visit 11), and Month 24 (Visit 12). IOP measurements were also done at 8:00 at week 2 (Visit 3), month 9 (Visit 7), and month 15 (Visit 10).

The primary efficacy endpoint for Study 001 was mean IOP change from baseline at all 9 time points during the study (8:00, 10:00, and 16:00 at Weeks 2, 6, and 12).

Reviewer's comments:

The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

Analysis Populations:

Safety: All randomized patients who received at least one dose of study drug and had a subsequent safety measurement.

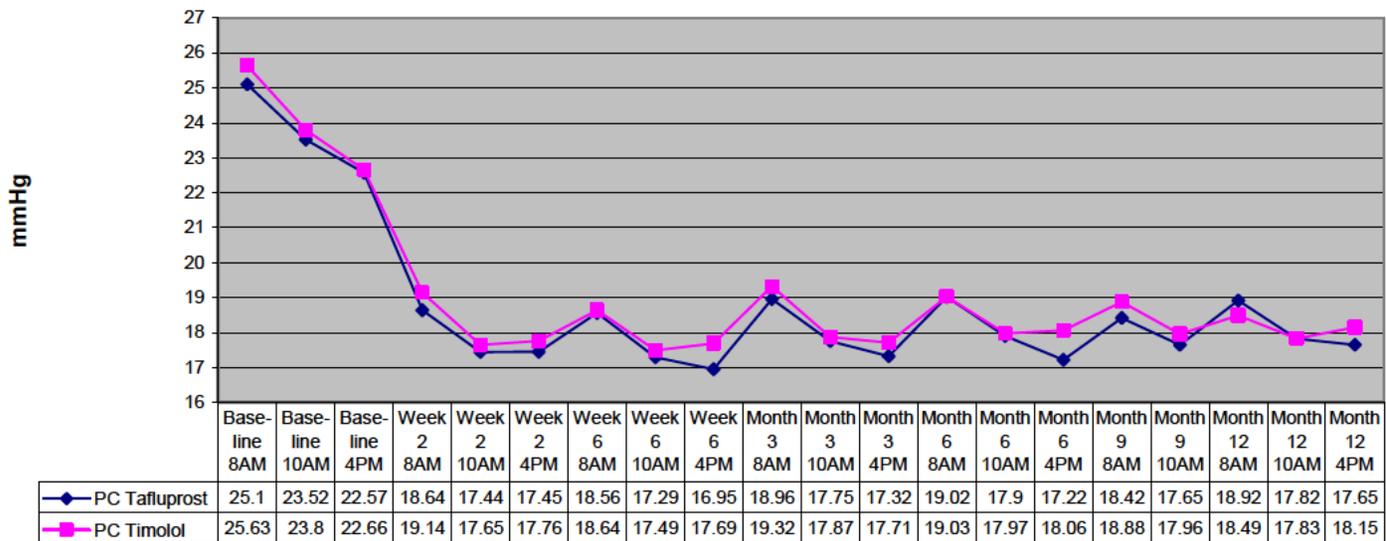
Intent-to-Treat (ITT): All randomized patients who received at least one dose of study drug and had at least one efficacy measurement. This was the primary analysis for the efficacy endpoint.

Full Analysis Set (FAS): All randomized patients who received at least one dose of study drug and had at least one efficacy measurement available for the analysis endpoint.

Per-Protocol (PP): All randomized patients who received at least one dose of study drug and had at least one efficacy measurement, excluding those patients or measures for a given patient with a major protocol violation expected to alter the outcome to treatment.

Study 15-003 ITT Population

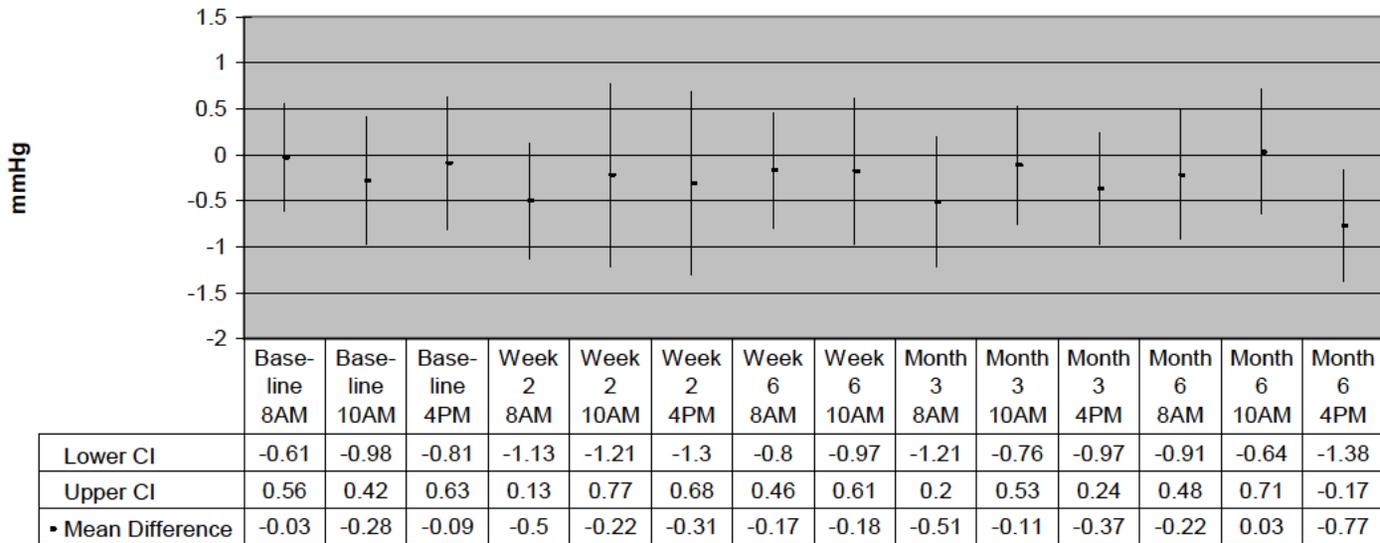
Mean IOP per Visit and Time



Reviewer's Comments: Baseline mean IOP of the two treatment arms is similar. The mean IOP for PC tafluprost 0.0015% and PC timolol 0.5% is similar at all time points measured.

Study 15-003 FAS Population

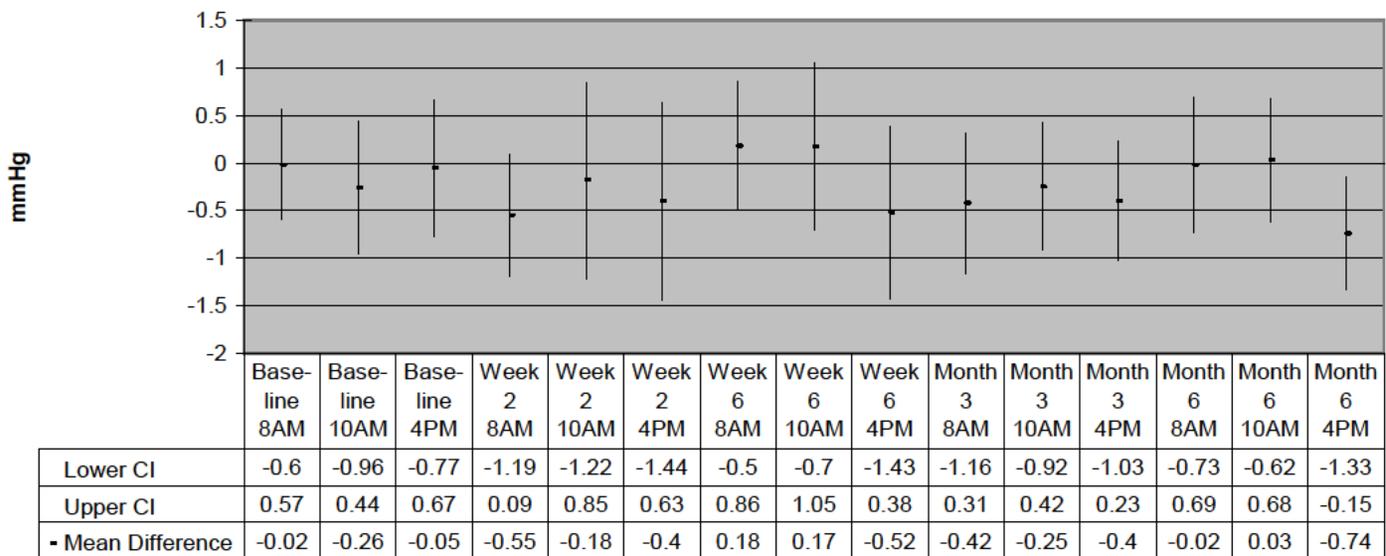
Mean Difference (PC Tafluprost 0.0015% - PC Timolol 0.5%) with 95% Confidence Intervals



Reviewer’s Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean IOP values (PC tafluprost 0.0015% QD minus PC timolol 0.5% BID) and confidence intervals are within 1 mmHg at a majority of the time points and within 1.5 mmHg at all time points.*

Study 15-003 PP Population

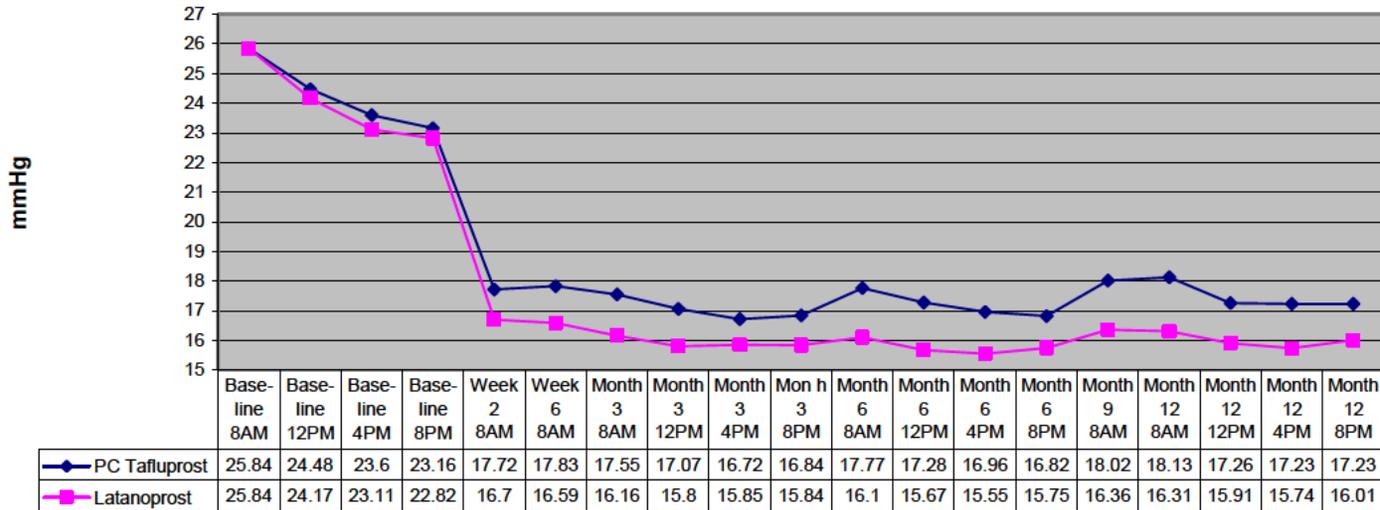
Mean Difference (PC Tafluprost 0.0015% - PC Timolol 0.5%) with 95% Confidence Intervals



Reviewer’s Comments: *The analysis for the PP population is similar to that of the FAS population analysis. The 95% confidence intervals of the difference is less than 1.5 mmHg at all time points.*

Study 74458 ITT Population

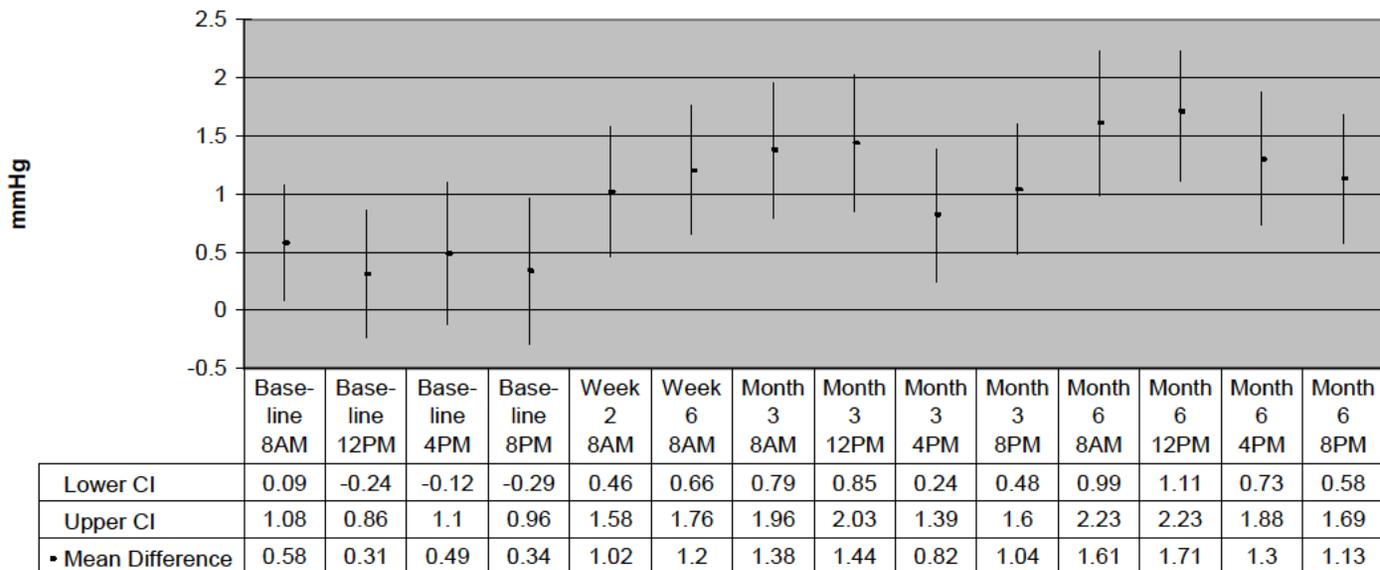
Mean IOP per Visit and Time



Reviewer’s Comments: Baseline mean IOP of the two treatment arms is similar. The mean IOP for PC tafluprost 0.0015% and latanoprost 0.05% is similar at baseline. The mean IOP of latanoprost 0.05% is consistently lowered than PC tafluprost 0.0015% by approximately 1-2 (0.87-1.82) mmHg at all time points measured.

Study 74458 FAS Population

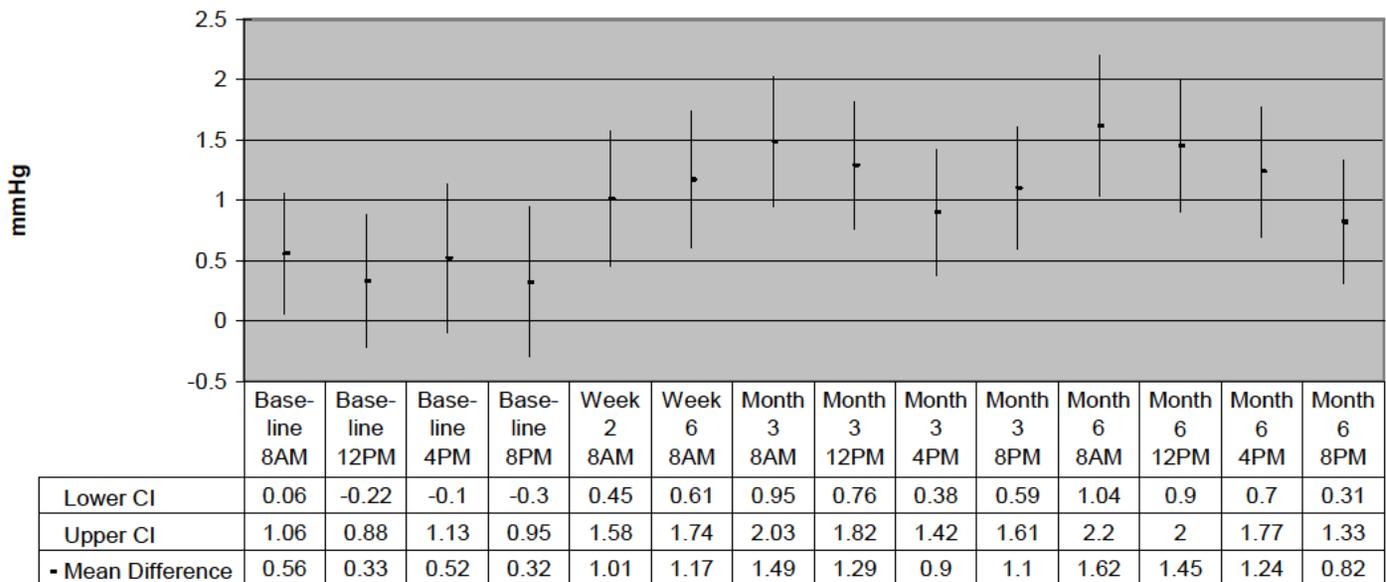
Mean Difference (PC Tafluprost 0.0015% - PC Latanoprost 0.005%) with 95% Confidence Intervals



Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is statistically different at the 8AM time point. The mean difference between the mean IOP of tafluprost 0.0015% and latanoprost 0.005% is statistically significant at all time points (i.e., all confidence intervals do not cross 0).*

Study 74458 PP Population

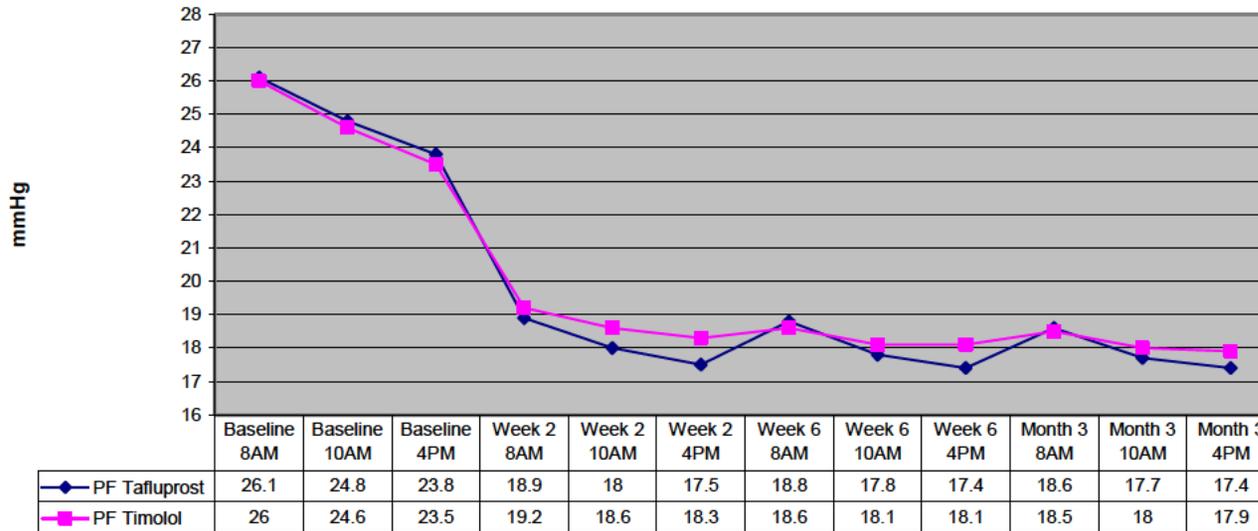
Mean Difference (PC Tafluprost 0.0015% - PC Latanoprost 0.005%) with 95% Confidence Intervals



Reviewer's Comments: *The analysis for the PP population is similar to that of the FAS population analysis.*

Study 001 FAS Population

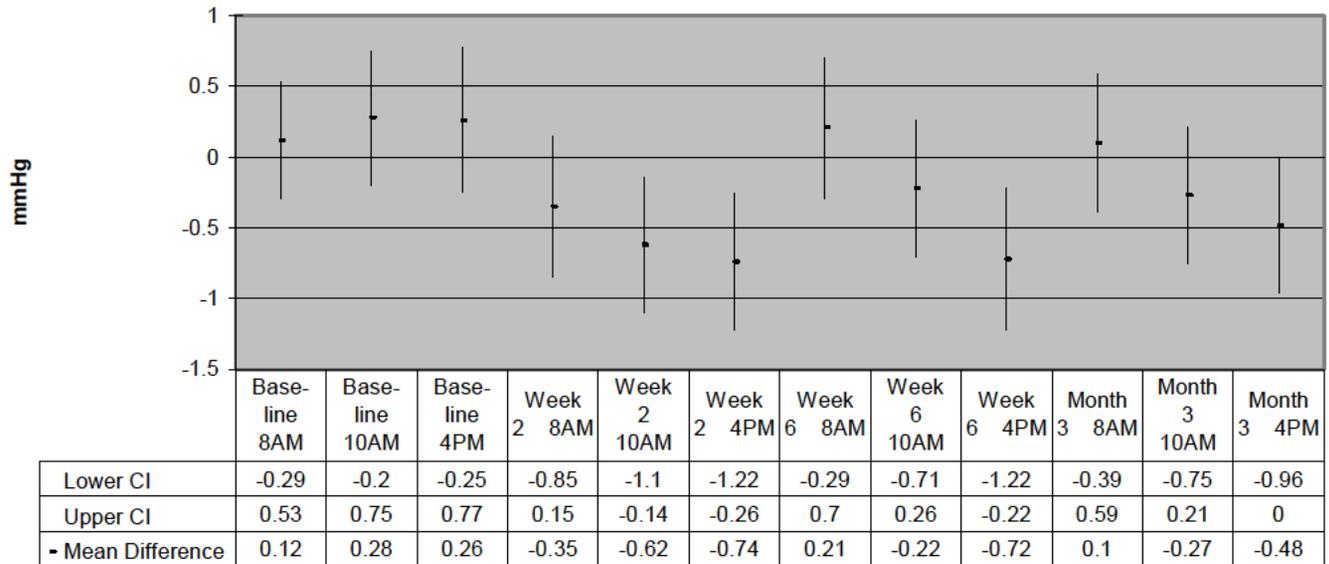
Mean IOP per Visit and Time



Reviewer's Comments: Baseline mean IOP of the two treatment arms is similar. The mean IOP for PF tafluprost 0.0015% and PF timolol 0.5% is similar at all time points measured.

Study 001 FAS Population

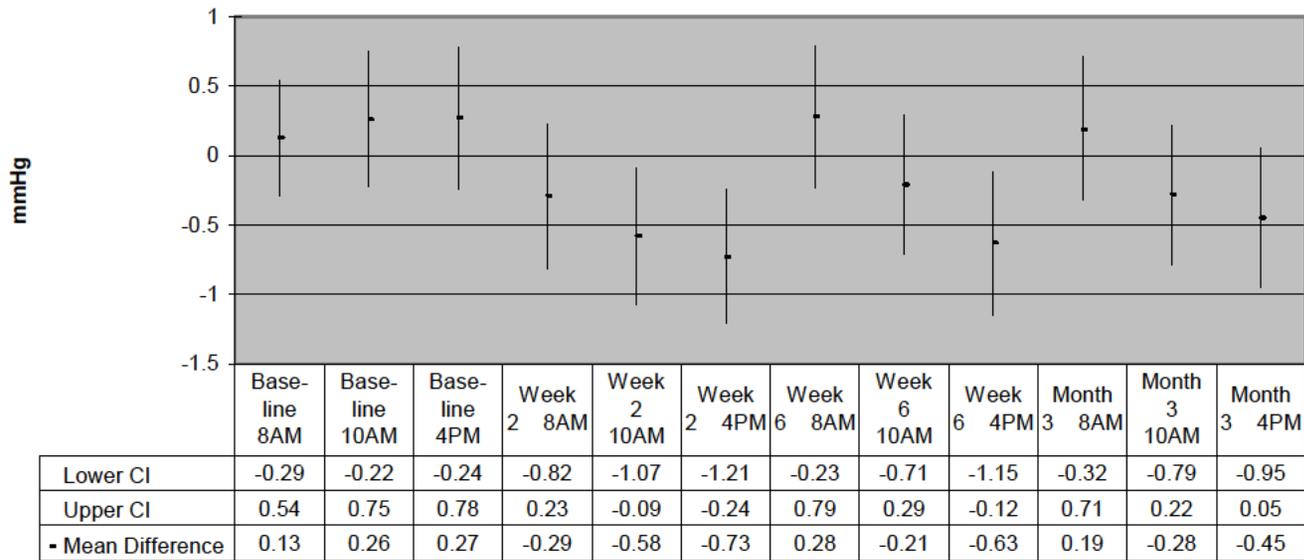
Mean Difference (PF Tafluprost 0.0015% - PF Timolol 0.5%) with 95% Confidence Interval



Reviewer’s Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The confidence interval of the mean difference between the mean IOP of PF tafluprost 0.0015% and PF timolol 0.5% is within 1.0 mmHg at a majority of the time points measured and is within 1.5 mmHg at all time points.*

Study 001 PP Population

Mean Difference (PF Tafluprost 0.0015% - PF Timolol 0.5%) with 95% Confidence Interval



Reviewer’s Comments: *The analysis for the PP population is similar to that of the FAS population analysis.*

6.1.5 Subpopulations

For Studies 15-003, 74458 and 001, the effects of age, gender, race, prior prostaglandin use, baseline IOP on the IOP-reducing effect of tafluprost were investigated.

For Studies 15-003 and 74458, the effects of central corneal thickness and iris color were investigated.

Reviewer's Comments:

No clinically significant effects were identified. Central corneal thickness and iris color data were not collected for Study 001.

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

The optimal dosing regimen for this class of drug, prostaglandin analogues has been previously investigated with latanoprost. Once daily administration in the evening has been shown to be superior to twice daily administration for this drug class and to administration in the AM.

6.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study 15-003 and Study 74458, subjects received treatment for 12 months and 24 months respectively. No evidence of tolerance was detected.

6.1.8 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7 Review of Safety

7.1 Methods

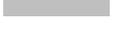
Primary Data Used to Evaluate safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
15-002 Dose-response study	Parallel-group, multi-center, randomized, dose-response, double-masked,	Patients 18 years or more with open-angle glaucoma or ocular	PC tafluprost ophth soln (0.003%, 0.0015%, 0.0025%)	1 drop QPM OU	28 days	144 subjects in a ratio of 1:1:1:1:1

		hypertension	Timolol maleate 0.5% ophth soln Latanoprost 0.005% ophth soln	1 drop BID OU 1 drop QPM OU		
74457 Pilot safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop QPM OU	6 weeks	38 subjects in a ratio of 1:1
15-003 Safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln PC timolol maleate 0.05% ophth soln	1 drop BID OU 1 drop BID OU	12 months	450 subjects in a ratio of 3:2 (267 in the tafluprost group and 191 in the timolol group)
74458 Safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop QPM OU	24 months	533 subjects in a ratio of 1:1 (269 in the tafluprost group and 264 in the latanoprost group)
001 Safety/ efficacy study	Parallel-group, multi-center, randomized, active-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PF tafluprost 0.0015% ophth soln PF timolol maleate 0.05% ophth soln	1 drop BID OU 1 drop BID OU	12 weeks	643 subjects in a ratio of 1:1 (320 in the tafluprost group and 323 in the timolol group)

Supportive Data Used to Evaluate Safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
15-001 Dose-	Parallel-group, multi-	Patients 18 years or more	PC tafluprost ophth soln	1 drop QPM OU	28 days	152 subjects in a ratio of 1:1:1:1:1

response study	center, randomized, dose-response, double-masked,	with open-angle glaucoma or ocular hypertension	(0.001%, 0.0025%, 0.005%) Placebo Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop QPM OU		
74460 Adjunctive therapy to timolol study	Parallel-group, multi-national, multi-center, randomized, placebo-controlled, double-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln Timolol maleate 0.005% ophth soln Vehicle	1 drop QPM OU 1 drop BID OU 1 drop QPM OU	12 weeks (6 weeks treatment period (timolol + tafluprost or timolol + vehicle) followed by 6 week extension period (vehicle switched to tafluprost))	185 subjects in a ratio of 1:1 (96 in the tafluprost group and 89 in the vehicle group)
77550 PF/PC formulation comparison Crossover study	Multi-center, randomized, cross-over, investigator-masked	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln PFtafluprost 0.0015% ophth soln	1 drop QPM OU 1 drop QPM OU	8 weeks (4 weeks/ treatment period)	43 subjects
77552 Latanoprost to PF tafluprost switch open-label study	Open-label, multi-national, multi-center	Patients 18 years or more with open-angle glaucoma or ocular hypertension	PC tafluprost 0.0015% ophth soln Latanoprost 0.005% ophth soln	1 drop QPM OU 1 drop QPM OU	12 weeks	158 subjects
5 Japanese studies  (b) (4)   	Retinal blood flow study, Dose-finding study, Latanoprost non-inferiority study, Normal					6 subjects 83 subjects 55 subjects 49 subjects

(b) (4)	tension glaucoma study Long-term safety study					351 subjects
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Reviewer’s Comments:

Adverse event rates were derived from adverse events pooled from the five studies identified in the table above. These studies were pooled for safety evaluation because each study evaluated the 0.0015% concentration of tafluprost, the proposed to-be-marketed dose strength.

7.1.2 Categorization of Adverse Events

Routine clinical testing was used to establish the safety of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.). This was adequately addressed in the design and conduct of the clinical trials. All adverse events were coded using a MedDRA dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Due to the size of the data base, pooled data across five trials (Studies 15-002, 74457, 15-003, 74458, and 001) was the primary data used to evaluate safety and in the analysis of common adverse events. Each of the five trials evaluated the 0.0015% concentration of tafluprost utilizing an active controlled, double-masked study design.

7.2 Adequacy of Safety Assessments

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

A total of 905 patients were exposed to tafluprost 0.0015% in the five pooled studies.

Overview of Exposure to Study Drug by Protocol

Protocol #	Safety N	PC or PF tafluprost 0.0015%	PC or PF Timolol 0.05%	Latanoprost 0.005%
15-002	144	30	29	28
74457	38	19		19
15-003	450	267	191	
74458	533	269		264
001	643	320	323	
Total	1808	905	543	311

Distribution of Subjects by Study and Duration of Treatment for Tafluprost 0.0015%

Duration of Treatment (weeks)	Study Number: Number of Subjects
0 to ≤1	74458: 3 15-003: 2 74460: 1 001: 3 Total: 9
>1 to ≤2	74457: 1 74460: 2 001: 2 Total: 5
>2 to ≤4	15-002: 5 74458: 3 15-003: 1 74460: 1 001: 2 Total: 12
>4 to ≤12	15-002: 25 74457: 18 74458: 5 15-003: 3 74460: 50 77550: 4377552: 119 001: 198 Total: 464
>12 to ≤26	74458: 9 15-003: 6 74460: 42 77552: 39 001: 115 Total: 211
>26 to ≤52	74458: 34 15-003: 180 Total: 214
>52 to ≤78	74458: 27 15-003: 72 Total: 99
>78 to ≤104	74458: 66 Total: 66
>104	74458: 122 Total: 122
	TOTAL: 1202

7.2.2 Explorations for Dose Response

Two dose-response studies (15-001 and 15-002) were performed. Five concentrations of tafluprost (0.005%, 0.003%, 0.0025%, 0.015% and 0.001%) were evaluated. Neither study

demonstrated a definitive dose-response. The numerically largest mean change from baseline IOP was observed with tafluprost 0.0015%, the concentration selected for marketing.

See Section 5.3 for more details of the two dose-response studies.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with tafluprost.

7.2.4 Routine Clinical Testing

The routine clinical testing used to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable. This data was not collected.

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

The adverse events reported during the development of tafluprost are consistent with other topical prostaglandin analogs. The assessments of these adverse events in the clinical trials were adequate.

7.3 Major Safety Results

7.3.1 Deaths

Eight deaths were reported during the clinical development of tafluprost. One subject in study 74460 died of stroke and arterial hypertension 11 days after completion of a 12-week course of tafluprost.

Deaths in the Safety Population

Study #	Patient #	Age (yrs)	Treatment	Time on treatment	Cause of death/Event
74460	2203	77	tafluprost	3 months	Cerebrovascular accident
74458	3101	46	tafluprost	10 months	Bronchial carcinoma
74458	4103	77	tafluprost	12 months	Circulatory system insufficiency
74458	4153	51	tafluprost	11 months	Pulmonary embolus
74458	0351	82	latanoprost	18 months	Myocardial infarction
74458	7153	64	latanoprost	5 months	Unknown
74458	9153	76	latanoprost	24 months	Flu and multi-organ Insufficiencies
(b) (4)	L-032-08	71	latanoprost	12 months	Hepatic tumor

Clinical Review
 Lucious Lim, M.D., M.P.H.
 NDA 202514
 Zioptan (tafluprost ophthalmic solution) 0.0015%

(Japan study)					
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Reviewer's comments:

The number of deaths is consistent with the population being studied and the studies' time frame. Narrative summaries of the deaths were submitted and are consistent with the causes of death listed.

7.3.2 Other Serious Adverse Events

There were a total of 110 serious adverse events, inclusive of deaths, across all treatment groups in all masked phase 2 and phase 3 studies (Studies 15-002, 74457, 74458, 15-002 and 001) during the clinical development of tafluprost; 62 of these patients were treated with tafluprost.

**Serious Adverse Events
 Studies 15-002, 74457, 74458, 15-003 and 001
 Incidence >0% in at Least One Treatment Group**

Adverse Event	Tafluprost 0.0015% (N=905) n (%)	Timolol Maleate 0.5% (N=543) n (%)	Latanoprost 0.0005% (N=311) n (%)
OCULAR			
Eye Disorders	4 (0.4)	4 (0.7)	2 (0.6)
Cataract	1 (0.1)	0 (0.0)	0 (0.0)
Cataract aggravated	0 (0.0)	0 (0.0)	1 (0.3)
Conjunctival bleb	0 (0.0)	0 (0.0)	1 (0.3)
Intraocular pressure increased	1 (0.1)	0 (0.0)	0 (0.0)
Macular edema	0 (0.0)	1 (0.2)	0 (0.0)
Retinal detachment	1 (0.1)	1 (0.2)	0 (0.0)
Retinal vein branch occlusion	1 (0.1)	0 (0.0)	0 (0.0)
Retinal vein occlusion	0 (0.0)	2 (0.4)	0 (0.0)
NONOCULAR			
Cardiac Disorders	8 (0.9)	4 (0.7)	2 (0.6)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.3)
Angina unstable	1 (0.1)	0 (0.0)	0 (0.0)
Asystole	0 (0.0)	1 (0.2)	0 (0.0)
Atrial fibrillation	1 (0.1)	1 (0.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac failure congestive	1 (0.1)	0 (0.0)	0 (0.0)
Coronary artery disease	4 (0.4)	0 (0.0)	0 (0.0)
Inferior myocardial infarction	0 (0.0)	1 (0.2)	0 (0.0)
Long QT syndrome	0 (0.0)	1 (0.2)	0 (0.0)
Myocardial infarction	1 (0.1)	0 (0.0)	0 (0.0)
Ear and Labyrinth Disorders	1 (0.1)	0 (0.0)	0 (0.0)

Vertigo	1 (0.1)	0 (0.0)	0 (0.0)
Endocrine Disorders	1 (0.1)	0 (0.0)	0 (0.0)
Goiter	1 (0.1)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	5 (0.6)	1 (0.2)	3 (1.0)
Abdominal pain	1 (0.1)	0 (0.0)	1 (0.3)
Colitis	0 (0.0)	1 (0.2)	0 (0.0)
Diverticulosis	1 (0.1)	0 (0.0)	0 (0.0)
Gastritis	1 (0.1)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.1)	0 (0.0)	0 (0.0)
Esophageal stricture	0 (0.0)	0 (0.0)	1 (0.3)
Pancreatitis chronic	1 (0.1)	0 (0.0)	0 (0.0)
Rectal polyp	0 (0.0)	0 (0.0)	1 (0.3)
General Disorders and Administration Site Conditions	7 (0.8)	2 (0.4)	5 (1.6)
Adverse drug reaction	0 (0.0)	1 (0.2)	0 (0.0)
Chest pain	2 (0.2)	0 (0.0)	2 (0.6)
Death	3 (0.3)	0 (0.0)	3 (1.0)
Fever	1 (0.1)	0 (0.0)	0 (0.0)
Hernia	0 (0.0)	1 (0.2)	0 (0.0)
Nonspecific chest pain	1 (0.1)	0 (0.0)	0 (0.0)
Hepatobiliary Disorders	3 (0.3)	1 (0.2)	0 (0.0)
Bile duct stone	1 (0.1)	0 (0.0)	0 (0.0)
Cholecystitis	1 (0.1)	1 (0.2)	0 (0.0)
Gallbladder disorder	1 (0.1)	0 (0.0)	0 (0.0)
Infections and Infestations	3 (0.3)	0 (0.0)	4 (1.3)
Chronic Sinusitis	0 (0.0)	0 (0.0)	1 (0.3)
Gastroenteritis	1 (0.1)	0 (0.0)	0 (0.0)
Gastrointestinal fungal infection	1 (0.1)	0 (0.0)	0 (0.0)
Maxillary sinusitis	0 (0.0)	0 (0.0)	1 (0.3)
Shigella infection	1 (0.1)	0 (0.0)	0 (0.0)
Urospepsis	0 (0.0)	0 (0.0)	1 (0.3)
Viral infection	0 (0.0)	0 (0.0)	1 (0.3)
Injury, Poisoning and Procedural Complications	5 (0.6)	3 (0.6)	5 (1.6)
Compression fracture	0 (0.0)	0 (0.0)	1 (0.3)
Fracture	0 (0.0)	1 (0.2)	0 (0.0)
Fracture bone	1 (0.1)	0 (0.0)	0 (0.0)
Heat exhaustion	1 (0.1)	0 (0.0)	0 (0.0)
Injury to shoulder NOS	0 (0.0)	0 (0.0)	1 (0.3)
Joint dislocation	0 (0.0)	1 (0.2)	0 (0.0)
Knee injury	1 (0.1)	0 (0.0)	0 (0.0)
Lumbar vertebral fracture	1 (0.1)	0 (0.0)	0 (0.0)
Meniscus lesion	0 (0.0)	0 (0.0)	1 (0.3)
Pelvic fracture	1 (0.1)	0 (0.0)	0 (0.0)
Scapula fracture	0 (0.0)	0 (0.0)	1 (0.3)
Tendon rupture	0 (0.0)	1 (0.2)	1 (0.3)
Investigations	1 (0.1)	0 (0.0)	0 (0.0)
Catheterisation cardiac	1 (0.1)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders	0 (0.0)	1 (0.2)	1 (0.3)
Hypoglycemia	0 (0.0)	0 (0.0)	1 (0.3)
Morbid obesity	0 (0.0)	1 (0.2)	0 (0.0)

Musculoskeletal and Connective Tissue Disorders	7 (0.8)	1 (0.2)	2 (0.6)
Arthrosis	1 (0.1)	0 (0.0)	0 (0.0)
Back pain	2 (0.2)	0 (0.0)	0 (0.0)
Back pain aggravated	0 (0.0)	0 (0.0)	1 (0.3)
Cervical spine degeneration	1 (0.1)	0 (0.0)	0 (0.0)
Chronic back pain	0 (0.0)	1 (0.2)	0 (0.0)
Hips osteoarthritis	1 (0.1)	0 (0.0)	0 (0.0)
Intervertebral disc proplapse	1 (0.1)	0 (0.0)	0 (0.0)
Knee osteoarthritis	1 (0.1)	0 (0.0)	0 (0.0)
Spondylosis deformans	0 (0.0)	0 (0.0)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	6 (0.7)	0 (0.0)	5 (1.6)
Breast carcinoma	0 (0.0)	0 (0.0)	1 (0.3)
Cancer	1 (0.1)	0 (0.0)	0 (0.0)
Carcinoma bronchiogenic	1 (0.1)	0 (0.0)	0 (0.0)
Colorectal cancer	0 (0.0)	0 (0.0)	1 (0.3)
Metastases to liver	1 (0.1)	0 (0.0)	1 (0.3)
Ovarian cystadenoma	1 (0.1)	0 (0.0)	0 (0.0)
Ovarian low malignant potential tumor	0 (0.0)	0 (0.0)	1 (0.3)
Prostate cancer	1 (0.1)	0 (0.0)	0 (0.0)
Rectal adenoma	0 (0.0)	0 (0.0)	1 (0.3)
Renal cell carcinoma	1 (0.1)	0 (0.0)	0 (0.0)
Nervous System Disorders	3 (0.3)	4 (0.7)	2 (0.6)
Depressed level of consciousness	0 (0.0)	0 (0.0)	1 (0.3)
Headache	1 (0.1)	0 (0.0)	0 (0.0)
Loss of consciousness	0 (0.0)	0 (0.0)	1 (0.3)
Stroke	1 (0.1)	1 (0.2)	0 (0.0)
Syncope	1 (0.1)	2 (0.4)	0 (0.0)
Unconsciousness	0 (0.0)	1 (0.1)	0 (0.0)
Pregnancy, Puerperium and Prenatal Conditions	1 (0.1)	0 (0.0)	0 (0.0)
Pregnancy	1 (0.1)	0 (0.0)	0 (0.0)
Psychiatric Disorders	0 (0.0)	0 (0.0)	1 (0.3)
Schizophrenia, residual type	0 (0.0)	0 (0.0)	1 (0.3)
Renal and Urinary Disorders	5 (0.6)	0 (0.0)	0 (0.0)
Bleeding urogenital	1 (0.1)	0 (0.0)	0 (0.0)
Hematuria	1 (0.1)	0 (0.0)	0 (0.0)
Incontinence	1 (0.1)	0 (0.0)	0 (0.0)
Renal failure acute	1 (0.1)	0 (0.0)	0 (0.0)
Ureteric stenosis	1 (0.1)	0 (0.0)	0 (0.0)
Reproductive System and Breast Disorders	3 (0.3)	0 (0.0)	1 (0.3)
Endometrial hypertrophy	1 (0.1)	0 (0.0)	0 (0.0)
Genital cyst	1 (0.1)	0 (0.0)	0 (0.0)
Gynecomastia	0 (0.0)	0 (0.0)	1 (0.3)
Vaginal prolapse	1 (0.1)	0 (0.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	6 (0.7)	2 (0.4)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	1 (0.2)	0 (0.0)
Dyspnea	2 (0.2)	0 (0.0)	0 (0.0)
Epistaxis	1 (0.1)	0 (0.0)	0 (0.0)

Pharyngeal hemorrhage	1 (0.1)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.1)	1 (0.2)	0 (0.0)
Pulmonary fibrosis	1 (0.1)	0 (0.0)	0 (0.0)
Skin and Medical Procedures	1 (0.1)	0 (0.0)	1 (0.3)
Skin cancer	1 (0.1)	0 (0.0)	0 (0.0)
Skin lesion	0 (0.0)	0 (0.0)	1 (0.3)
Surgical and Medical Procedures	6 (0.7)	2 (0.4)	2 (0.6)
Basal cell carcinoma excision	0 (0.0)	0 (0.0)	1 (0.3)
Benign tumor excision	0 (0.0)	1 (0.2)	0 (0.0)
Breast reduction	0 (0.0)	0 (0.0)	1 (0.3)
Chemotherapy	1 (0.1)	0 (0.0)	0 (0.0)
Cholecystectomy	1 (0.1)	0 (0.0)	0 (0.0)
Colectomy partial	0 (0.0)	1 (0.2)	0 (0.0)
Coronary stent placement	1 (0.1)	0 (0.0)	0 (0.0)
Gallbladder operation	1 (0.1)	0 (0.0)	0 (0.0)
Gastric bypass	0 (0.0)	1 (0.2)	0 (0.0)
Knee operation	1 (0.1)	0 (0.0)	0 (0.0)
Penile operation	0 (0.0)	1 (0.2)	0 (0.0)
Renal transplant	1 (0.1)	0 (0.0)	0 (0.0)
Vascular Disorders	2 (0.2)	2 (0.4)	1 (0.3)
Carotid artery stenosis	0 (0.0)	1 (0.2)	0 (0.0)
Hypertension aggravated	2 (0.2)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (0.3)
Varicose veins of lower extremities	0 (0.0)	1 (0.2)	0 (0.0)

7.3.3 Dropouts and/or Discontinuations

Patient Dropouts Studies 15-002, 74457, 74458, 15-003 and 001

Patients	Tafluprost 0.0015% n (%)	Timolol Maleate 0.5% n (%)	Latanoprost 0.005% n (%)
Total randomized	905 (100)	543 (100)	311 (100)
Completed Study	811 (89.6)	502 (92.4)	286 (92.0)
Discontinued Study:	94 (10.4)	41 (7.6)	25 (8.0)
Adverse event	24 (2.7)	13 (2.4)	8 (2.6)
Concomitant medication	2 (0.2)	0 (0.0)	0 (0.0)
Lack of efficacy	23 (2.5)	9 (1.7)	3 (1.0)
Non-compliance	5 (0.6)	4 (0.7)	2 (0.6)
Improper entry	1 (0.1)	2 (0.4)	1 (0.3)
Patient request	27 (3.0)	9 (1.7)	9 (2.9)
Lost to follow-up	11 (1.2)	3 (0.6)	2 (0.6)
Physician decision	1 (0.1)	1 (0.2)	0 (0.0)

Listing of Patients with Adverse Events Associated with Discontinuation – Study 15-002

Patient	Age	Sex	Treatment	Onset day	Adverse event
1009	60	M	Tafluprost 0.0003%	8	Blood pressure increased

Listing of Patients with Adverse Events Associated with Discontinuation – Study 74457

Patient	Age	Sex	Treatment	Onset day	Adverse event
207	53	F	Tafluprost 0.0015%	1	Eye irritation, abnormal sensation in eye, lacrimation increased, eye pruritus
204	55	F	Latanoprost 0.005%	1,2,7, 10	Headache, Eye irritation, abnormal sensation in eye, lacrimation increased, eye pruritus, dry eye, photophobia, conjunctival/ocular hyperemia

Listing of Patients with Adverse Events Associated with Discontinuation – Study 74458

Patient	Age	Sex	Treatment	Onset day	Adverse event
156	65	F	Tafluprost 0.0015%	5	Blepharitis
458	63	M	Tafluprost 0.0015%	421	Intraocular pressure increased
1151	83	M	Tafluprost 0.0015%	377	Pulmonary fibrosis
1157	86	F	Tafluprost 0.0015%	321	Scleritis
4951	68	F	Tafluprost 0.0015%		Dry skin, conjunctival disorder, conjunctival/ocular hyperemia
5652	65	F	Tafluprost 0.0015%	171	Headache, hypertrichosis
6155	56	F	Tafluprost 0.0015%	257	Cough
6401	62	M	Tafluprost 0.0015%	135	Metastases to liver
7152	34	F	Tafluprost 0.0015%	518	Eye pain
201	70	F	Latanoprost 0.005%	368	Intraocular pressure increased
4154	75	F	Latanoprost 0.005%	2	Headache, eye pain, conjunctival/ocular hyperemia, eyelid edema
6152	70	F	Latanoprost 0.005%	26, 40	Dyspnea, wheezing
7153	63	F	Latanoprost 0.005%	220	Death
7501	73	M	Latanoprost 0.005%	458	Myalgia

Listing of Patients with Adverse Events Associated with Discontinuation – Study 15-003

Patient	Age	Sex	Treatment	Onset day	Adverse event
01102	51	M	Tafluprost 0.0015%	2	Conjunctival/ocular hyperemia
04503	49	M	Tafluprost 0.0015%	274	Detachment of retinal pigment epithelium
04516	38	M	Tafluprost 0.0015%	64	Headache
04539	69	F	Tafluprost 0.0015%	104	Cholecystitis
14713	27	F	Tafluprost 0.0015%	265	Pregnancy
14715	48	F	Tafluprost 0.0015%	348	Vision blurred, eye irritation, eye allergy, eye pruritus

Clinical Review

Lucious Lim, M.D., M.P.H.

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Zioptan (tafluprost ophthalmic solution) 0.0015%

15221	72	F	Tafluprost 0.0015%	297	Intestinal obstruction
15619	64	F	Tafluprost 0.0015%	1	Conjunctival/ocular hyperemia, eye irritation, eye pain
16009	54	M	Tafluprost 0.0015%	17	Eye irritation
01114	77	M	Timolol 0.5%	72	Hypertension
01702	79	M	Timolol 0.5%	120	Retinal vein occlusion
02307	75	F	Timolol 0.5%	260	Cerebral infraction
09417	74	F	Timolol 0.5%	2	Eye irritation
11723	62	F	Timolol 0.5%	144	Long QT syndrome
12930	56	F	Timolol 0.5%	64	Visual acuity reduced
12930	56	F	Timolol 0.5%	71	Retinal vein occlusion, macula edema
16029	57	M	Timolol 0.5%	142	COPD
16406	54	M	Timolol 0.5%	195	Optic nerve cupping, visual field defect
16412	40	M	Timolol 0.5%	15	Erythema of eyelid, eyelid edema

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable. No specific safety issues were identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Number (%) of Patients with Adverse Events Reported by ≥ 2 % of Patients
Studies 15-002, 74457, 74458, 15-003, and 001 Pooled**

Adverse Event	Tafluprost 0.0015% N=905 n (%)	Timolol Maleate 0.5% N=543 n (%)	Latanoprost 0.005% N=311 n (%)
OCULAR			
Eye Disorders	349 (38.6)	118 (21.7)	115 (40.0)
Blepharitis	9 (1.0)	3 (0.6)	7 (2.3)
Cataract aggravated	9 (1.0)	0 (0.0)	13 (4.2)
Conjunctival hyperemia	97 (10.7)	23 (4.2)	22 (7.1)
Dry eye	27 (3.0)	11 (2.0)	9 (2.9)
Eyelash darkening	15 (1.7)	0 (0.0)	9 (2.9)
Growth of eyelashes	21 (2.3)	0 (0.0)	11 (3.5)
Ocular pain	31 (3.4)	15 (2.8)	6 (1.9)
Ocular stinging/irritation	65 (7.2)	38 (7.0)	22 (7.1)
Ocular pruritus	44 (4.9)	11 (2.0)	5 (1.6)
Vision blurred	19 (2.1)	15 (2.8)	2 (0.6)

Visual filed constriction	12 (1.3)	2 (0.4)	9 (2.9)
NONOCULAR			
Cardiac Disorders	21 (2.3)	7 (1.3)	14 (4.5)
Gastrointestinal Disorders	65 (7.2)	24 (4.4)	14 (4.5)
General Disorders and Administration Site Conditions	49 (5.4)	27 (5.0)	8 (2.6)
Infections and Infestations	136 (15.0)	79 (14.5)	48 (15.4)
Common cold	36 (4.0)	13 (2.4)	8 (2.6)
Flu	16 (1.8)	5 (0.9)	12 (3.9)
Sinusitis	9 (1.0)	3 (0.6)	8 (2.6)
Urinary tract infection	18 (2.0)	6 (1.1)	2 (0.6)
Injury, Poisoning and Procedural Complications	40 (4.4)	18 (3.3)	9 (2.9)
Investigations	35 (3.9)	9 (1.7)	28 (9.0)
Low density lipoprotein cholesterol abnormal NOS	4 (0.4)	0 (0.0)	7 (2.3)
Metabolism and Nutrition Disorders	29 (3.2)	17 (3.1)	7 (2.3)
Musculoskeletal and Connective Tissue Disorders	81 (9.0)	28 (5.2)	32 (10.3)
Nervous System Disorders	86 (9.5)	45 (8.3)	26 (8.4)
Headache	51 (5.6)	15 (2.8)	15 (4.8)
Respiratory, Thoracic and Mediastinal Disorders	60 (6.6)	22 (4.1)	15 (4.8)
Cough	27 (3.0)	9 (1.7)	7 (2.3)
Skin and Subcutaneous Tissue Disorders	36 (4.0)	10 (1.8)	13 (4.2)
Surgical and Medical Procedures	23 (2.5)	7 (1.3)	10 (3.2)
Vascular Disorders	38 (4.2)	19 (3.5)	7 (2.3)
Hypertension arterial	7 (0.8)	0 (0.0)	7 (2.3)

Reviewer's Comments:

The most common ocular adverse events (pooled) were conjunctival hyperemia (10.7%) and ocular stinging/irritation (7.2%). The most common nonocular adverse event was headache (5.6%).

7.4.2 Laboratory Findings

Clinical laboratory (hematology, blood chemistry and urinalysis) evaluations were analyzed in five phase 1 studies (74450, 74451, 74452, 74453, and 15-005) and two phase 3 studies (74458 and 15-003). No clinically significant observations were seen.

7.4.3 Vital Signs

Cardiovascular parameters (systolic blood pressure, diastolic blood pressure and heart rate) were measured in studies 15-002, 74457, 74458, 15-003 and 001. No clinically relevant changes in cardiovascular parameters were observed.

7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were performed on all subjects in early phase 1 studies. There were no clinically significant effects reported.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable. No special safety studies were conducted for this product.

7.4.6 Immunogenicity

Not applicable. The drug product is not expected to induce immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Multiple concentrations of tafluprost were evaluated. No clinically significant observations were seen.

7.5.2 Time Dependency for Adverse Events

Not applicable. Tafluprost does not have a delayed onset of action.

7.5.3 Drug-Demographic Interactions

Based on a review of adverse events sorted by age, gender and race, the events are consistent with the overall safety population. As seen with other prostaglandin analogues, increased iridal pigmentation based on eye color was seen. Tafluprost's effect on eye color was similar to that of latanoprost.

7.5.4 Drug-Disease Interactions

A review of adverse events revealed no untoward safety issues in each of the subpopulations categorized by concomitant diseases.

7.5.5 Drug-Drug Interactions

No investigations on potential drug-drug interactions were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted.

In both a 24-month rat carcinogenicity study and a 78-week mouse carcinogenicity where tafluprost was administered subcutaneously, no unusual tumors or significantly increased tumor incidence suggestive of tafluprost-related carcinogenicity was observed.

7.6.2 Human Reproduction and Pregnancy Data

Animal studies have shown that tafluprost is teratogenic and tafluprost/metabolites are secreted into milk and should not be used in nursing mothers.

7.6.3 Pediatrics and Assessment of Effects on Growth

Tafluprost has not been studied in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No information is available on overdosage in humans. Symptoms of overdose in humans are unknown. There are no data on drug abuse. There are no data to suggest that there is a withdrawal or rebound effect after cessation of tafluprost.

7.7 Additional Submissions / Safety Issues

The four-month safety update was received on May 6, 2011. The information contained in this safety update is comparable to the information reviewed for the original NDA.

Original conclusions regarding the safety of tafluprost ophthalmic solution are unchanged.

8 Postmarket Experience

Tafluprost is currently registered in 32 countries.

In the time period between 30 April 2008 and 01 September 2010, there were 330 spontaneous adverse events reports meeting the minimum reporting criteria associated with the use of tafluprost worldwide. Ten of the 330 reports met the regulatory definition of serious. During this period, (b) (4) units were sold in the European Union and Norway and (b) (4) units in Japan.

The spontaneous postmarketing data for tafluprost are consistent with the safety profile from the clinical studies, and provides reassurance that no new safety issues have emerged with prolonged use.

9 Appendices

9.1 Literature Review/References

N/A – An independent literature review was not conducted for this application.

9.2 Advisory Committee Meeting

No advisory committee meeting was required or convened for this drug product. There are multiple drug products in this drug class, prostaglandin analogues marketed in the United States.

9.3 Labeling Recommendations

See labeling recommendations below.

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LUCIOUS LIM
09/27/2011

WILLIAM M BOYD
09/28/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202514 **Applicant:** Merck Sharp & Dohme Corp. **Stamp Date:** 1/7/2011
Drug Name: Saflutan (tafluprost ophthalmic solution) **NDA/BLA Type:** NDA 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: 15-001 Sample Size: 152 subjects Arms: AFP-168 0.001%, 0.0025%, 0.005%, Placebo, Latanoprost 0.005% QD Location in submission: 5.3.4.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study #1: 001; Study #2: 15-003 Indication: reduction of IOP in patients with open angle glaucoma or ocular hypertension				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Endothelial Cell Counts in Study 15-003
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Lucious Lim	2/28/11
<hr/>	
Reviewing Medical Officer	Date
William Boyd	2/28/11
<hr/>	
Clinical Team Leader	Date

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

/s/

LUCIOUS LIM
02/28/2011

WILLIAM M BOYD
02/28/2011