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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

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 non-inferiority (1.5 mmHg) versus latanoprost.

Using the non-inferiority margin of 1.5 mmHg, both studies 15-003 and 001 demonstrated non-inferiority 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.

1.2 Brief Overview of Clinical Studies

The Phase III program consisted of three pivotal non-inferiority efficacy studies (two timolol non-inferiority studies [15-003 and 001] and one Latanoprost Non-Inferiority Study [74458]), an adjunctive therapy to timolol study (74460) examining the additive effect of tafluprost to timolol,

and a study comparing the PC formulation and PF formulation (Study 77550). In addition, an open-label Phase IIIb clinical trial (Study 77552) investigated changes in ocular signs and symptoms when patients were switched from preservative-containing latanoprost to preservative-free tafluprost.

The focus of this review will be the three pivotal non-inferiority efficacy studies and the bridging study that compared the PC formulation with the PF formulation.

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.

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.

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.

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.

1.3 Statistical Issues and Findings

There are no major statistical issues for this submission. The choice of 1.5 mmHg as the non-inferiority (NI) margin using timolol as the active comparator for studies 15-003, 001, and 74458 was recommended to the Applicant by the FDA clinical review team during the design stage of the study protocol; the statistical reviewer considered this margin reasonable (for a detailed discussion, please see Appendix A).

The pre-defined primary analyses were slightly different for the three non-inferiority studies. In order to present the studies' results in a uniform format, the statistical reviewer analyzed the IOP change from baseline by visit and time point for each study using an ANCOVA model. The ANCOVA model includes the treatment and baseline IOP as independent variables. The following table lists the statistical reviewer's analyses results of IOP change from baseline at each time point at each visit through month 6 for all the three non-inferiority studies and the bridging study; these results were consistent with the Applicant's analyses results.

Table 1: IOP Change from Baseline Analysis Results (FAS, LOCF, ANCOVA)

Study 15-003			
Visit / Time	PC Tafluprost 0.0015% (N=265) LS Mean ¹ (mmHg)	PC Timolol 0.5% (N=187) LSMean ¹ (mmHg)	Difference (95% CI) ¹ (mmHg)
Week 2			
8:00	-6.97	-6.48	-0.49 (-1.06, 0.09)
10:00	-6.13	-5.92	-0.21 (-1.17, 0.75)
16:00	-5.41	-5.07	-0.34 (-1.24, 0.56)
Week 6			
8:00	-7.07	-6.91	-0.01 (-0.70, 0.68)
10:00	-5.82	-5.81	-0.02 (-0.71, 0.69)
16:00	-5.26	-4.79	-0.47 (-1.17, 0.23)
Month 3			
8:00	-6.62	-6.13	-0.49 (-1.10, 0.12)
10:00	-5.79	-5.76	-0.03 (-0.58, 0.53)
16:00	-5.21	-4.83	-0.38 (-0.92, 0.16)
Month 6			
8:00	-6.52	-6.32	-0.20 (-0.81, 0.41)
10:00	-5.56	-5.67	0.11 (-0.49, 0.72)
16:00	-5.23	-4.44	-0.79 (-1.32, -0.25)
Month 9			
8:00	-7.07	-6.32	-0.76 (-1.36, -0.16)
10:00	-5.78	-5.48	-0.30 (-0.89, 0.30)
Month 12			
8:00	-6.53	-6.57	-0.05 (-0.67, 0.58)
10:00	-5.43	-5.62	-0.19 (-0.84, 0.46)
16:00	-4.84	-4.21	-0.62 (-1.19, -0.05)

Study 001			
Visit / Time	PF Tafluprost 0.0015% (N=316) LSMean¹ (mmHg)	PF Timolol 0.5% (N=321) LSMean¹ (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-7.21	-6.81	-0.41 (-0.85, 0.04)
10:00	-6.81	-6.10	-0.73 (-1.16, -0.29)
16:00	-6.17	-5.34	-0.83 (-1.26, -0.40)
Week 6			
8:00	-7.24	-7.36	0.12 (-0.32, 0.56)
10:00	-6.95	-6.60	-0.36 (-0.80, 0.08)
16:00	-6.33	-5.52	-0.81 (-1.26, -0.36)
Month 3			
8:00	-7.48	-7.50	0.02 (-0.42, 0.47)
10:00	-7.08	-6.69	-0.39 (-0.84, 0.05)
16:00	-6.28	-5.73	-0.55 (-0.98, -0.11)
Study 74458			
Visit / Time	PC Tafluprost 0.0015% (N=264) LSMean¹ (mmHg)	PC Latanoprost 0.5% (N=264) LSMean¹ (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)

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

For the crossover study 77550 comparing the preserved and unpreserved formulation of tafluprost 0.0015%, the Applicant used a repeated measurements analysis of covariance (RM ANCOVA) model to analyze the changes from baseline in the diurnal IOP at 4 weeks. The model included fixed effects for baseline IOP, sequence, period, treatment, time, sequence by time, period by time, and treatment by time. The difference (unpreserved vs. preserved tafluprost) at 4 weeks and a 95% confidence interval for the difference was estimated from the RM ANCOVA model using a contrast (over all four time points). The following table lists the Applicant's analysis results for the bridging study 77550 comparing the preserved and unpreserved formulation of tafluprost 0.0015%.

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.

2. INTRODUCTION

2.1 Overview

Tafluprost (AFP-168) is an analogue of prostaglandin F₂α (PGF₂ α) that is hydrolyzed by corneal esterases to become the biologically active metabolite, AFP-172. Preclinical ocular pharmacology studies in ocular normotensive and ocular hypertensive monkeys have demonstrated that topical ocular administration of tafluprost lowers IOP in a dose-dependent manner (SR2750, SR2557). In addition, an in vitro investigation has showed that the active metabolite of tafluprost, AFP-172, has greater affinity for the human prostanoid FP receptor (receptors of PGF₂α) than latanoprost, PGF₂α, or unoprostone (SR2710).

In several phase I and phase II studies, Tafluprost concentrations of up to 0.005% have been generally well tolerated, with the most frequently reported adverse events for the 0.0015% concentration being ocular hyperemia, eye irritation, abnormal eye sensation, and eye pruritis. Based on the overall efficacy and safety results from these trials, the 0.0015% concentration has been selected for further clinical investigation.

Tafluprost is available both as a preserved formulation and an unpreserved formulation. The preservative, benzalkonium chloride (BAK) may adversely affect the tolerability of prostaglandin analogues and contribute to the risk for developing symptoms of dry eyes. In addition, a subset of patients exhibit a delayed hypersensitivity reaction (allergy) to BAK. As no other prostaglandin analogues are available as unpreserved eye drops, preservative-free tafluprost has the potential to provide a currently unavailable treatment option for patients with glaucoma as an alternative to preservative containing formulations.

To date, Tafluprost 0.0015% preservative free (PF) has been approved for reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension in 18 European countries. Preservative containing (PC) tafluprost has also been approved in Germany, Finland, Japan, Korea, and Georgia.

In this submission, the Applicant is seeking the approval of the preservative free formulation.

2.2 Application History

Tafluprost was developed under the Sponsorship of Santen, Inc. since 2001. The referenced IND for this NDA is 62690. By November 2009, Merck acquired the product from Santen, Inc. and assumed Sponsorship for the product. Therefore, for the submitted clinical studies, other than study 001 was conducted under Merck's Sponsorship, all the other studies were conducted by Santen, Inc.

The choice of 1.5 mmHg as the non-inferiority margin using timolol as the active comparator for studies 15-003, 001, and 74458 was recommended to the Applicant by the FDA clinical review team during the design stage of the study protocol. During an internal meeting discussion for study 001 protocol, the statistical review team recommended that the Applicant should provide

justification for the chosen NI margin. However, the director of the medical team didn't want to convey this recommendation to the Applicant and indicated that all the information needed for justifying the NI margin of 1.5 mmHG was available in FDA's own database.

2.3 Data Sources

The Applicant's study reports and datasets are available on the EDR at [\\CDSESUBI\EVSPROD\NDA202514](#).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Designs and Endpoints

Dose was explored in 2 dose-ranging studies (Studies 15-001 [Dose Finding I] and 15-002 [Dose Finding II]). The Applicant selected 0.0015% concentration for further development based on these two dose ranging studies. (For a detailed review of these two Phase II studies, please see Appendix B.)

The Phase III program had three pivotal non-inferiority efficacy studies (two timolol non-inferiority studies [15-003 and 001] and one Latanoprost Non-Inferiority Study [74458]).

These three Phase III non-inferiority studies were all double-masked, randomized, parallel group studies that included patients aged 18 years or older with open glaucoma or ocular hypertension. Patients were randomized to: PC Tafluprost 0.0015% once daily (q.d) or latanoprost 0.005% q.d. (1:1) for study 74458; PC Tafluprost 0.0015% q.d. or timolol 0.5% twice daily (b.i.d.) (3:2) for study 15-003; and PF tafluprost 0.0015% q.d. or timolol PF 0.5% b.i.d. (1:1) for Study 001. Study 001 had a 3-month double-masked treatment period and Studies 15-003 and 74458 had 6-month double-masked treatment periods; Studies 15-003 and 74458 were extended to 12 and 24 months (double-masked treatment period), respectively to provide additional long term safety and tolerability data as well as supportive efficacy data.

There were different primary outcome measures between the three pivotal trials. For Studies 15-003 and 74458, the protocol-specified primary outcome measure was the difference in diurnal IOP reduction at Month 6 from baseline. The protocol-specified primary outcome measure for Study 001 was mean IOP change from baseline at all 9 time points during the study (0800 hrs, 1000 hrs, and 1600 hrs at Weeks 2, 6, and 12). The non-inferiority limit for all 3 studies was 1.5 mmHg based on the upper limit of the 95% CI for the difference between groups (tafluprost - control).

However, based on a recommendation communicated by FDA to Santen, efficacy analyses (ANOVA including term for treatment group) examining the two-sided 95% CI for the difference in IOP between treatments at each time point and visit up to Month 6 were performed for Studies 15-003, and 74458. These analyses were included in a protocol amendment prior to

unmasking of the data from each of the two studies mentioned above. 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.

The following table summarizes the key design elements and primary endpoints for the three Phase III non-inferiority studies.

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.

The Phase III program also included a study comparing the preservative-containing (PC) formulation and preservative-free (PF) formulation (Study 77550), and an adjunctive therapy to timolol study (74460) examining the additive effect of tafluprost to timolol. In addition, an open-label Phase IIIb clinical trial (Study 77552) investigated changes in ocular signs and symptoms when patients were switched from PC latanoprost to PF tafluprost.

Study 77550 (PF/PC Formulation Comparison Study) was a single-masked, randomized, crossover study that included patients aged 18 years or older who were randomized (1:1) to tafluprost 0.0015% PF or tafluprost 0.0015% PC for 4 weeks per treatment period. The primary endpoint was difference in diurnal IOP reduction at week 4. 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.

Study 74460 (Adjunctive Treatment to Timolol) was a double-masked, randomized, parallel group study that included patients aged 18 years or older who were randomized (1:1) to

tafluprost 0.0015% or vehicle q.d. as adjunctive therapy to 0.5% timolol b.i.d. for 6 weeks. The primary endpoint in the CSR was diurnal IOP reduction at week 6 from baseline. Superiority over vehicle was determined if upper limit of 95% CI for the difference between groups (tafluprost - vehicle) <0 mmHg. There was 6-week open-label extension period that included a timolol + tafluprost arm, and patients who had been in the vehicle arm during the first 6 weeks of treatment were switched to tafluprost.

Study 77552 (PF Tafluprost/Latanoprost Switch Study) was an open-label study that included patients aged 18 years or older who were switched from latanoprost 0.005% (after at least 6 months of treatment) to PF tafluprost 0.0015% for 12 weeks. The primary outcome was changes in ocular signs, symptoms and conjunctival inflammatory markers that occur when patients are switched from latanoprost to PF tafluprost.

The following table summarizes the key design elements and the primary endpoints for these three other Phase III studies.

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.

For a more detailed review of studies 74460, and 77552, please see Appendix C.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Study 15-003

A total of 458 patients were randomized to the study: 267 patients received tafluprost (tafluprost group) and 191 patients received timolol (timolol group). Disposition of all randomized patients is shown in Table 5.

Table 5: Study 15-003 Disposition of All Randomized Subjects

	Tafluprost	Timolol	Total
All randomized patients	267	191	458
Completed	250 (93.6%)	168 (88.0%)	418 (91.3%)
Discontinued	17 (6.4%)	23 (12.0%)	40 (8.7%)
Adverse events	6	9	15
Lack of efficacy	4	7	11
Lost to follow-up	2	1	3
Improper entry	0	2	2
Other	0	2	2

Source: Table 14.1.1 of Study 15-003 Report

A total of 458 patients were randomized in this study and all randomized patients received study medication. All these patients were included in the Safety dataset. Two tafluprost patients and 4 timolol patients had no efficacy measurements after the baseline visit and consequently they were excluded from the Full Analysis Set (FAS, defined as all randomized patients who received at least 1 dose of study drug and who had at least one post-baseline efficacy measurement) for efficacy. Thus, the FAS dataset for efficacy (FAS Efficacy) includes 452 patients (Table 6).

Table 6: Study 15-003 Summary of Each Analysis Set

Analysis Set	Tafluprost	Timolol
Randomized and treated	267	191
Safety	267	191
FAS Efficacy	265	187
PP Efficacy	264	186

Source: Table 6 of Study 15-003 Report.

The summaries of baseline demographic characteristics are presented in Table 7. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 7: Study 15-003 Demographic Characteristics

		Tafluprost (N=267)		Timolol (N=191)		Total (N=458)	
		n	(%)	n	(%)	n	(%)
Gender	Male	104	39.0%	83	43.5%	187	40.8%
	Female	163	61.0%	108	56.5%	271	59.2%
Age	MEAN		61.3		61.5		61.3
	SD		12.1		11.4		11.8

MEDIAN RANGE			61 21-88		62 21-84		61 21-88
Race	White	167	62.5%	123	64.4%	290	63.3%
	Black or African American	64	24.0%	47	24.6%	111	24.2%
	Asian	0	0	1	0.5%	1	0.2%
	Hispanic or Latino	36	13.5%	19	9.9%	55	12.0%
	Other	0	0	1	0.5%	1	0.2%
Iris Color	Brown	155	58.1%	109	57.1%	264	57.6%
	Blue	58	21.7%	48	25.1%	106	23.1%
	Blue-brown	19	7.1%	14	7.3%	33	7.2%
	Green-brown	14	5.2%	3	1.6%	17	3.7%
	Green	9	3.4%	6	3.1%	15	3.3%
	Gray-brown	1	0.4%	2	1.0%	3	0.7%
	Gray	1	0.4%	0	0.0%	1	0.2%
	Yellow-brown	0	0.0%	1	0.5%	1	0.2%
	Other	10	3.7%	8	4.2%	18	3.9%
		Right	Left	Right	Left	Right	Left
Central Corneal Thickness	MEAN	563.6	566.0	563.9	563.6	563.7	565.0
	SD	40.6	39.6	39.9	38.9	40.3	39.3
	MEDIAN	565	568	564	565	565	565
	RANGE	447-675	457-675	440-790	454-713	440-790	454-713

Source: Table 14.1.2, and Table 14.1.4 of Study 15-003 Report.

The mean baseline IOPs for each time point are presented in Table 8. The mean IOPs were comparable between the treatment groups.

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

The ocular diagnosis for the 458 patients and 916 eyes are presented in Table 9. In both treatment groups, most of the patients had either primary open-angle glaucoma or ocular hypertension. The distribution of ocular diagnoses was comparable between the treatment groups, although there were slightly more glaucoma patients in the timolol group.

Table 9: Study 15-003 Ocular Diagnosis

	Tafluprost		Timolol	
	Right	Left	Right	Left
Diagnosis	N (%)	N (%)	N (%)	N (%)
Primary open-angle glaucoma	143 (53.6%)	145 (54.3%)	107 (56.0%)	108 (56.5%)
Ocular hypertension	121 (45.3%)	118 (44.2%)	78 (40.8%)	78 (40.8%)

Pigmentary glaucoma	1 (0.4%)	1 (0.4%)	8 (4.2%)	8 (4.2%)
Pseudoexfoliative glaucoma	2 (0.7%)	2 (0.7%)	2 (1.0%)	1 (0.5%)
Other	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Normal	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)

Source: Table 10 of Study 15-003 Report.

Study 001

The overall disposition of patients screened and randomized in the study is shown in the following table. Of the 643 patients randomized, 618 (96.1%) patients completed the study. Reasons for discontinuation were generally similar between treatment groups.

Table 10: Study 001 Disposition of All Randomized Subjects

	Tafluprost	Timolol	Total
All randomized patients	320	323	643
Completed	306 (95.6%)	312 (96.6%)	618 (96.1%)
Discontinued	14 (4.4%)	11 (3.4%)	25 (3.9%)
Adverse events	4	3	7
Lost to follow-up	2	0	2
Physician Decision	1	1	2
Protocol Violation	0	2	2
Withdrawal by Subject	7	5	12

Source: Table 10-2 of Study 001 Report

Of the 643 randomized patients, 5 (0.8%) patients were excluded from the FAS set for the primary endpoint. The Per-Protocol approach (primary approach) excluded all patients with important protocol violations and was performed for the efficacy endpoints. The Per-Protocol population excluded patients due to important deviations from the protocol that may have substantially affected the results of the primary endpoints. See Table 11 for detailed listing of each analysis set.

Table 11: Study 001 Summary of Each Analysis Set

Analysis Set	Tafluprost	Timolol
Randomized and treated	320	323
Safety	320	323
FAS Efficacy	317	321
PP Efficacy	299	313

Source: Table 10-3 and 10-4 of Study 001 Report.

The summaries of baseline demographic characteristics are presented in Table 12. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 12: Study 001 Demographic Characteristics

	Tafluprost (N=320)		Timolol (N=323)		Total (N=643)	
	n	(%)	n	(%)	n	(%)

Gender	Male	137	42.8%	83	43.5%	187	40.8%
	Female	183	57.2%	108	56.5%	271	59.2%
Age	MEAN		63.3		63.3		
	SD		11.7		11.6		
	MEDIAN		64.0		64.0		
	RANGE		25 to 91		21 to 94		
Race	White	236	73.8%	244	75.5%	480	74.7%
	Black or African American	75	23.4%	71	22%	146	22.7%
	Asian	6	1.9%	5	1.5%	11	1.7%
	Hispanic or Latino	25	7.8%	26	8.0%	51	7.9%
	Other	3	0.9%	3	0.9%	6	0.9%
Ocular Diagnosis	Open-Angle Glaucoma	193	60.3%	194	60.1%	387	60.2%
	Ocular Hypertension	127	39.7%	129	39.9%	256	39.8%
Baseline IOP	< 25 mmHg	126	39.4%	127	39.3%	253	39.3%
	>= 25 mmHg	194	60.6%	196	60.7%	390	60.7%
Ocular Diagnosis	Open-Angle Glaucoma	193	60.3%	194	60.1%	387	60.2%
	Ocular Hypertension	127	39.7%	129	39.9%	256	39.8%

Source: Table 10-5 of Study 001 Report.

The mean baseline IOPs for each time point are presented in Table 13. The mean IOPs were comparable between the treatment groups.

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 74458

A total of 533 patients were randomized to the study: 269 patients received tafluprost (tafluprost group) and 264 latanoprost (latanoprost group). A total of 35 patients discontinued the study: 23 for tafluprost and 12 for latanoprost. The reasons for discontinuations are given in the following table.

Table 14: Study 74458 Disposition of All Randomized Subjects

	Tafluprost	Latanoprost	Total
All randomized patients	269	264	533
Completed	246 (91.4%)	252 (95.5%)	498 (93.4%)
Discontinued	23 (8.6%)	12 (4.5%)	35 (6.6%)
Adverse events	3	2	5
Lack of efficacy	7	3	10
Lost to follow-up	0	2	2

Patient request	8	3	11
Compliance	1	0	1
Other	1	1	2

Source: Figure 1 and Table 4 of Study 74458 Report

A total of 533 patients were randomized in this study and all randomized patients received study medication. Five tafluprost patients (1153, 9154, 9155, 9353 and 9402) had no efficacy or safety measurements after the baseline visit and consequently they were excluded from the FAS dataset for efficacy and the Safety dataset. Thus, the FAS dataset for efficacy (FAS Efficacy) and the Safety dataset include 528 patients. The Per Protocol dataset for efficacy (PP Efficacy) excludes additional 11 patients with improper entry, too short wash-out or incorrectly chosen worse eye, and thus includes 517 patients.

Table 15: Study 74458 Summary of Each Analysis Set

Analysis Set	Tafluprost	Latanoprost
Randomized and treated	269	264
Safety	264	264
FAS Efficacy	264	264
PP Efficacy	259	258

Source: Table 6 of Study 74458 Report.

The summaries of baseline demographic characteristics of Study 74458 are presented in Table 16. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 16: Study 77548 Demographic Characteristics

		Tafluprost (N=269)		Latanoprost (N=264)		Total (N=533)	
		n	(%)	n	(%)	n	(%)
Gender	Male	109	40.5%	160	59.5%	221	41.5%
	Female	160	59.5%	152	57.6%	312	58.5%
Age	MEAN		62.5		62.4		62.4
	SD		11.3		12.3		11.8
	MEDIAN		64		64		64
	RANGE		23-86		18-88		18-88
Race	White	268	99.6%	262	99.2%	530	99.4%
	Black or African American	0	0%	2	0.8%	2	0.4%
	Asian	1	0.4%	0	0%	1	0.2%
	Hispanic or Latino	36	13.5%	19	9.9%	55	12.0%
Iris Color	Blue/gray	204	37.9%	210	39.8%	414	38.8%
	Brown	158	29.4%	140	26.5%	298	28.0%
	Blue/gray-brown	88	16.4%	94	17.8%	182	17.1%
	Green-brown	56	10.4%	48	9.1%	104	9.8%
	Green	14	2.6%	16	3.0%	30	2.8%
	Yellow-brown	4	0.7%	8	1.5%	12	1.1%
	Other	14	2.6%	12	2.3%	26	2.4%
		Right	Left	Right	Left	Right	Left
Central	MEAN	555.4	554.4	558.6	558.3	557.0	556.3

Corneal Thickness	SD MEDIAN RANGE	37.2 555 428-684	36.3 552 422-681	35.9 560 432-669	35.3 560 436-672	36.6 557 428-684	35.8 558 422-681
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Source: Table 14.1.4 of Study 74458 Report.

The mean (SD) baseline IOPs for each time point are presented in Table 17. The mean IOPs were comparable between the two groups.

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.

Table 18 summarizes the distribution of ocular diagnoses that was comparable between the treatment groups. In both treatment groups, most of the patients had either primary open-angle glaucoma or ocular hypertension.

Table 18: Study 77548 Ocular Diagnosis

	Tafluprost		Latanoprost	
	Right	Left	Right	Left
Diagnosis	N (%)	N (%)	N (%)	N (%)
Primary open-angle glaucoma	151 (56.1%)	149 (55.4%)	146 (55.3%)	152 (57.8%)
Ocular hypertension	100 (37.2%)	103 (38.3%)	94 (35.6%)	91 (34.6%)
Capsular glaucoma	9 (3.3%)	7 (2.6%)	13 (4.9%)	15 (5.7%)
Pigmentary glaucoma	4 (1.5%)	3 (1.1%)	3 (1.1%)	3 (1.1%)
Normal	5 (1.9%)	7 (2.6%)	8 (3.0%)	2 (0.8%)

Source: Table 10 of Study 74458 Report.

Study 77550

A total of 43 patients were randomized in the study, and all randomized patients received study treatment and had an efficacy measurement after randomization. Thus, the Intention-to-Treat (ITT) dataset for efficacy (ITT Efficacy) includes all 43 randomized patients. The Per Protocol dataset for efficacy (PP Efficacy) excludes patient no. 108 with a major protocol violation and patient no. 105 who discontinued the study, and thus includes 41 patients with complete data on both treatment periods.

For the 43 randomized and treated patients, the mean age of the patients was 65.3 years (range 35-85). There were 16 (37.2%) males and 27 (62.8%) females in this study. Only 1 (3.7%)

female was of childbearing potential, and she used chemical contraception and had a negative pregnancy test result. All patients were Caucasian.

The ocular diagnosis for the 43 patients and 86 eyes are presented in the following table. Slightly over 60% of the patients were diagnosed with primary open-angle glaucoma and slightly over 30% of the patients with ocular hypertension.

Table 19: Study 77550 Ocular Diagnosis

	Tafluprost	
	Right	Left
Diagnosis	N (%)	N (%)
Primary open-angle glaucoma	26 (60.5%)	28 (65.1%)
Ocular hypertension	14 (32.6%)	13 (30.2%)
Capsular glaucoma	3 (7.0%)	1 (2.3%)
Normal	0	1 (2.3%)

Source: Table 14.1.3 of Study 77550 Report.

The mean (SD) baseline IOPs for each time point are presented in Table 20. Overall, the mean IOPs were comparable between the formulations at baseline.

Table 20: Study 77550 Baseline IOPs (in worst eye)

	Timepoint	N	Mean ± SD mmHg
Preserved Formulation	8:00	42	22.57 ± 3.04
	12:00	42	20.86 ± 2.79
	16:00	42	21.73 ± 3.19
	20:00	42	21.77 ± 3.02
Unpreserved Formulation	8:00	43	22.98 ± 3.18
	12:00	43	21.78 ± 2.68
	16:00	43	21.51 ± 2.49
	20:00	43	21.81 ± 2.61

Source: Table 14.2.1.1 of Study 77550 Report

3.1.3 Statistical Methodologies

3.1.3.1 Studies 15-003, 001, and 74458

Primary Efficacy Endpoints and Analysis Methods

For studies 15-003 and 74458, the Applicant received FDA clinical review team’s guidance on the appropriate endpoint for one of their ongoing Phase III studies (74458; Latanoprost Non-inferiority Study). Subsequent to the guidance, the primary efficacy endpoints for U.S. regulatory purpose were IOP in the study eye at each time point at each visit through Month 6; and statistical plans for studies 15-003 (PC Tafluprost and PC Timolol Non-Inferiority Study), 74458 (Latanoprost Non-Inferiority Study) were amended accordingly prior to unmasking.

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. Efficacy analysis (ANOVA including term for treatment group) of IOP by visit and time point was performed per FDA's recommendation using an FAS population and a last-observation-carried-forward (LOCF) approach to handle missing data. 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.

For study 001, the primary endpoint used to evaluate efficacy was the mean IOP change from baseline at all 9 time points during the study (0800 hrs, 1000 hrs and 1600 hrs at Weeks 2, 6 and 12). For the analysis of the primary efficacy endpoint, IOP change from baseline, an analysis of covariance (ANCOVA) model was used to estimate the treatment difference at each of the 9 time points using the per-protocol (PP) population and a last-observation-carried-forward (LOCF) approach to handle missing data. 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).

For all the three NI studies, the primary analysis of efficacy was based on IOP of the study eye (worse eye).

Furthermore, per FDA statistical review team's request, and as discussed at the pre-NDA teleconference, the following analyses were performed for the three non-inferiority studies as well: mean IOP change from baseline at each visit and time point with and without adjusting for the baseline IOP and ocular diagnosis and in both per-protocol and the full analysis sets. These analyses were performed for study eye, non-study eye, and average of both eyes.

Efficacy Analysis Datasets

The definitions of the efficacy analysis datasets were consistent across all three NI studies.

The safety dataset included all randomized patients who had received at least one dose of study treatment and had a subsequent safety measurement. The Full Analysis Set (FAS) dataset included all randomized patients who had received at least one dose of study treatment and had at least one efficacy measurement available. The per-protocol (PP) dataset was a subset of the FAS dataset excluding those patients or measures for a given patient with a major protocol violation expected to alter the outcome to treatment. All data excluded from the PP dataset was identified before unmasking the study.

Determination of Sample Size

Study 15-003

The sample size calculation assumed a two-sided type I error rate of 5%, a power of 90% and a non-inferiority limit of 1.5 mmHg (defined by regulatory criteria). Based on the results from two previous Phase II studies, the standard deviation for the change in IOP is assumed to be 4.5 mmHg. In addition, it is assumed that the change in IOP in the tafluprost group will be larger than in the timolol group. Therefore, the difference used in the sample size calculation is set as 1.5 mmHg + 0.1 mmHg = 1.6 mmHg. When using a normal approximation, this results in a sample size of 170 eligible subjects (at least 216 randomized subjects) per treatment group.

To increase the number of subjects exposed to tafluprost, an unequal allocation between the treatment groups was used (3:2). To achieve the power justified, above (two groups with 216 randomized subjects in each group), 270 subjects will be randomized to the tafluprost group and 180 subjects to the timolol group.

Study 001

The study was designed to enroll 620 patients (310 per treatment group) to yield 576 evaluable patients (288 per treatment group) in the Per-Protocol population. The probability that the upper bound of the two-sided 95% confidence interval for the between-treatment difference in mean IOP change from baseline (PF tafluprost minus PF timolol maleate) is ≤ 1.5 mmHg was 0.999 at each of the 9 time points during the study (0800 hrs, 1000 hrs and 1600 hrs at Weeks 2, 6 and 12), resulting in approximately 99% power ($0.999^9 = 0.991$) to establish that PF tafluprost (0.0015%) is non-inferior to PF timolol maleate (0.5%) with respect to the IOP change from baseline over 12 weeks of therapy in patients with open-angle glaucoma and ocular hypertension.

The power and sample size were based on the following assumptions at each of the 9 time points during the study, which were based on the study results from Protocol 15-003 (Phase III non-inferiority study vs. timolol conducted by Santen, Inc.):

- $\alpha = 0.025$ (1-sided)
- Non-inferiority margin = 1.5 mmHg
- True treatment difference = 0 mmHg
- Standard deviation = 3.5 mmHg

Study 74458

A non-inferiority limit of 1.5 mmHg was assumed in the sample size calculations. In addition, the following assumptions were made:

- A standard deviation of 4.5 mmHg for the change in IOP
- A two-sided type I error rate of 5 %
- A power of 90 %

A normal approximation was used in the sample size calculations. This resulted in a sample size of 190 evaluable patients (at least 240 randomized patients) per treatment group.

3.1.3.2 Study 77550

Efficacy Analysis Sets

The safety dataset included all randomized patients who receive at least one dose of study treatment and have any subsequent safety measurement. The Full Analysis Set (FAS) dataset will include all randomized patients who receive at least one dose of study treatment and have at least one pharmacodynamic (IOP) measurement available. The per protocol (PP) dataset will be a subset of the ITT dataset excluding patients or measurements for a given patient with major protocol violation(s) expected to alter the outcome of the treatment. Patient classification (analysis exclusions) for the PP dataset will be completed before unmasking the study.

Primary Analysis Methods

A repeated measurements analysis of covariance (RM ANCOVA) model was used to analyze the changes from baseline in the diurnal IOP at 4 weeks (Wallenstein and Fisher, 1977). The model included fixed effects for baseline IOP, sequence, period, treatment, time, sequence by time, period by time, and treatment by time. The difference (unpreserved vs. preserved tafluprost) at 4 weeks and a 95% confidence interval for the difference was estimated from the RM ANCOVA model using a contrast (over all four time points). A similar analysis without the baseline IOP as a covariate (RM ANOVA) was done for sensitivity purposes.

Determination of Sample Size

The sample size calculation assumes a two-sided type I error rate of 5%, a power of 80% and an equivalence limit of 1.5 mmHg (defined by regulatory guidance). Based on previous studies, the standard deviation for the change in IOP is assumed to be 3.0 mmHg. In addition, an intraclass correlation coefficient of 0.60 is assumed (between preserved and unpreserved tafluprost). When using a normal approximation (Fleiss, 1986), this results in a planned sample size of 17 eligible patients (at least 20 randomized patients) per treatment sequence.

3.1.4 Results and Conclusions

The pre-defined primary analyses were slightly different for the three non-inferiority studies. In order to present the studies' results in a uniform format, the statistical reviewer analyzed the IOP change from baseline using the ANNOVA model by visit and time point for each of the non-inferiority study. The model had terms for the treatment and baseline IOP. The analyses populations for the statistical reviewer's ANCOVA model were the full analysis set (FAS) for all three studies; and the missing data was imputed using the last observation carried forward (LOCF) approach.

Table 21 lists the statistical reviewer's analyses results for all the three non-inferiority studies; these results were consistent with the Applicant's analyses results.

Table 21: IOP Change from Baseline Analysis Results by Statistical Reviewer (FAS, LOCF, ANOCVA)

Study 15-003			
Visit / Time	PC Tafluprost 0.0015% (N=265) LS Mean¹ (mmHg)	PC Timolol 0.5% (N=187) LSMean¹ (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-6.97	-6.48	-0.49 (-1.06, 0.09)
10:00	-6.13	-5.92	-0.21 (-1.17, 0.75)
16:00	-5.41	-5.07	-0.34 (-1.24, 0.56)
Week 6			
8:00	-7.07	-6.91	-0.01 (-0.70, 0.68)
10:00	-5.82	-5.81	-0.02 (-0.71, 0.69)
16:00	-5.26	-4.79	-0.47 (-1.17, 0.23)
Month 3			
8:00	-6.62	-6.13	-0.49 (-1.10, 0.12)
10:00	-5.79	-5.76	-0.03 (-0.58, 0.53)
16:00	-5.21	-4.83	-0.38 (-0.92, 0.16)
Month 6			
8:00	-6.52	-6.32	-0.20 (-0.81, 0.41)
10:00	-5.56	-5.67	0.11 (-0.49, 0.72)
16:00	-5.23	-4.44	-0.79 (-1.32, -0.25)
Month 9			
8:00	-7.07	-6.32	-0.76 (-1.36, -0.16)
10:00	-5.78	-5.48	-0.30 (-0.89, 0.30)
Month 12			
8:00	-6.53	-6.57	-0.05 (-0.67, 0.58)
10:00	-5.43	-5.62	-0.19 (-0.84, 0.46)
16:00	-4.84	-4.21	-0.62 (-1.19, -0.05)
Study 001			
Visit / Time	PF Tafluprost 0.0015% (N=316) LSMean¹ (mmHg)	PF Timolol 0.5% (N=321) LSMean¹ (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-7.21	-6.81	-0.41 (-0.85, 0.04)
10:00	-6.81	-6.10	-0.73 (-1.16, -0.29)
16:00	-6.17	-5.34	-0.83 (-1.26, -0.40)
Week 6			
8:00	-7.24	-7.36	0.12 (-0.32, 0.56)
10:00	-6.95	-6.60	-0.36 (-0.80, 0.08)
16:00	-6.33	-5.52	-0.81 (-1.26, -0.36)

Month 3			
8:00	-7.48	-7.50	0.02 (-0.42, 0.47)
10:00	-7.08	-6.69	-0.39 (-0.84, 0.05)
16:00	-6.28	-5.73	-0.55 (-0.98, -0.11)
Study 74458			
Visit / Time	PC Tafluprost 0.0015% (N=264) LSMean ¹ (mmHg)	PC Latanoprost 0.5% (N=264) LSMean ¹ (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)

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

For the crossover study 77550 comparing the preserved and unpreserved formulation of tafluprost 0.0015%, the Applicant used a repeated measurements analysis of covariance (RM

ANCOVA) model to analyze the changes from baseline in the diurnal IOP at 4 weeks. The following table lists the Applicant's analysis results for the bridging study 77550 comparing the preserved and unpreserved formulation of tafluprost 0.0015%.

Table 22: 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.

From the results of study 15-003 and 001, 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 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. It is also noted that at all the post baseline time points, the average IOP reduction in the tafluprost group was slightly higher than the one in the timolol group. Both studies demonstrated that tafluprost was non-inferior to timolol using 1.50 mmHg as the NI margin in both preservative-containing and preservative-free formulation.

From the results of study 77550, for both the preserved and unpreserved formulation, a similar IOP lowering effect was seen clearly at Week 1 and it was sustained at Week 4. These results showed that the removal of preservative from the tafluprost 0.0015% ophthalmic formulation has no effect on the drug's effectiveness.

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. Therefore, study 74458 failed to demonstrate non-inferiority of efficacy of tafluprost compared with latanoprost using the pre-defined 1.50 mmHg non-inferiority margin.

The statistical reviewer also performed additional sensitivity analysis by using multiple imputation methods for imputing the missing values. Since the missing pattern is not monotone, the statistical reviewer used MCMC method to impute the missing IOP values for each treatment group separately. The missing data are filled in 10 times to generate 10 complete datasets and corresponding IOP change from baseline was calculated for these datasets; then the 10 complete datasets are analyzed by using ANCOVA with terms for treatment and baseline IOP values by visit and time point; finally the results from the 10 complete datasets are combined for the inference. The statistical reviewer's sensitivity analysis results using multiple imputation method for missing values were consistent with the results of the primary analysis (see Table 23). In addition, the Applicant also performed sensitivity analyses using baseline value carried forward, worst value carried forward, and multiple imputation method (slightly different from statistical reviewer's method) for missing IOP values, all these analyses results were consistent with the results of the primary analysis.

Table 23: IOP Change from Baseline Sensitivity Analysis Results by Statistical Reviewer (FAS, Multiple Imputation, ANOCVA)

Study 15-003			
Visit / Time	PC Tafluprost 0.0015% (N=265) Mean (mmHg)	PC Timolol 0.5% (N=187) Mean (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-6.96	-6.49	-0.49 (-1.06, 0.09)
10:00	-5.63	-6.08	0.24 (-0.64, 1.12)
16:00	-5.90	-6.11	0.00 (-0.92, 0.92)
Week 6			
8:00	-7.06	-6.94	-0.14 (-0.71, 0.43)
10:00	-5.91	-5.94	-0.12 (-0.73, 0.50)
16:00	-5.99	-5.99	-0.15 (-0.73, 0.44)
Month 3			
8:00	-6.60	-6.19	-0.42 (-1.03, 0.19)
10:00	-5.74	-5.87	-0.02 (-0.57, 0.53)
16:00	-5.75	-5.87	-0.40 (-0.93, 0.13)
Month 6			
8:00	-6.53	-6.43	-0.11 (-0.71, 0.50)
10:00	-5.55	-5.81	0.10 (-0.51, 0.70)
16:00	-5.55	-5.79	0.08 (-0.52, 0.67)
Month 9			
8:00	-7.13	-6.44	-0.70 (-1.29, -0.11)
10:00	-5.81	-5.61	-0.37 (-0.95, 0.22)
Month 12			
8:00	-6.62	-6.73	0.10 (-0.54, 0.74)
10:00	-5.62	-5.64	-0.15 (-0.75, 0.46)
16:00	-5.64	-5.72	-0.09 (-0.70, 0.53)

Study 001			
Visit / Time	PF Tafluprost 0.0015% (N=316) Mean (mmHg)	PF Timolol 0.5% (N=321) Mean (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-7.23	-6.79	-0.41 (-0.85, 0.03)
10:00	-6.89	-6.00	-0.73 (-1.16, -0.29)
16:00	-6.26	-5.27	-0.83 (-1.26, -0.41)
Week 6			
8:00	-7.29	-7.41	0.18 (-0.28, 0.63)
10:00	-7.06	-6.58	-0.32 (-0.78, 0.13)
16:00	-6.42	-5.46	-0.81 (-1.27, -0.34)
Month 3			
8:00	-7.50	-7.50	0.06 (-0.40, 0.51)
10:00	-7.15	-6.62	-0.36 (-0.81, 0.09)
16:00	-6.33	-5.65	-0.52 (-0.96, -0.08)
Study 74458			
Visit / Time	PC Tafluprost 0.0015% (N=264) Mean (mmHg)	PC Latanoprost 0.5% (N=264) Mean (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-8.12	-8.56	0.70 (0.21, 1.19)
Week 6			
8:00	-8.01	-8.65	0.96 (0.45, 1.48)
Month 3			
8:00	-8.18	-8.99	1.13 (0.62, 1.64)
12:00	-7.38	-8.37	1.18 (0.70, 1.66)
16:00	-6.87	-7.25	0.70 (0.23, 1.18)
20:00	-6.30	-6.98	0.88 (0.45, 1.32)
Month 6			
8:00	-7.97	-9.03	1.37 (0.82, 1.92)
12:00	-7.15	-8.48	1.54 (1.02, 2.07)
16:00	-6.62	-7.51	1.22 (0.73, 1.72)
20:00	-6.28	-7.04	0.98 (0.52, 1.45)
Month 9			
8:00	-7.68	-8.77	1.41 (0.84, 1.98)
Month 12			
8:00	-7.50	-8.80	1.63 (1.05, 2.21)
12:00	-7.01	-8.21	1.39 (0.85, 1.94)
16:00	-6.26	-7.30	1.37 (0.81, 1.93)
20:00	-5.77	-6.78	1.21 (0.65, 1.78)
Month 15			
8:00	-7.88	-9.22	1.69 (1.08, 2.30)
Month 18			

8:00	-8.06	-9.16	1.44 (0.85, 2.04)
12:00	-7.39	-8.11	0.92 (0.36, 1.47)
16:00	-6.74	-7.41	1.00 (0.42, 1.58)
20:00	-6.21	-6.91	0.91 (0.34, 1.47)
Month 24			
8:00	-7.48	-8.90	1.71 (1.02, 2.39)
12:00	-7.12	-8.20	1.27 (0.66, 1.88)
16:00	-6.45	-7.06	0.94 (0.37, 1.52)
20:00	-6.04	-6.79	0.95 (0.31, 1.59)

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

3.2 Evaluation of Safety

The following tables summarized adverse events (AEs) for studies 15-003, 011, 74458, and 77550 respectively.

For study 15-003, the most prevalent ocular adverse event was ocular hyperaemia, which was reported by 44 out of the 458 patients (9.6%). The largest difference was seen in ocular hyperaemia: 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 hyperaemia, 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 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 hyperaemia and conjunctival hyperaemia), eye irritation, growth of eyelashes and eye pain. The largest difference was seen in related eye pain (13 for tafluprost and 4 for latanoprost).

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.

Table 24: Ocular AEs Reported for More Than 5 subjects in either group for study 15-003 (Safety Population)

Adverse Event	PC Tafluprost (n = 267)	PC Timolol (n = 191)
Ocular hyperaemia	34 (12.7%)	10 (5.2%)
Eye irritation	20 (7.5%)	15 (7.9%)
Eye pain	17 (6.4%)	17 (8.9%)
Eye pruritus	19 (7.1%)	5 (2.6%)
Conjunctival hyperaemia	11 (4.1%)	1 (0.5%)
Punctate keratitis	5 (1.9%)	4 (2.1%)
Vision blurred	8 (3.0%)	8 (4.2%)
Foreign body sensation in eyes	9 (3.4%)	4 (2.1%)
Photophobia	5 (1.9%)	4 (2.1%)
Lacrimation increase	5 (1.9%)	3 (1.6%)
Visual acuity reduced	12 (4.5%)	6 (3.1%)
Visual field defect	1 (0.4%)	5 (2.6%)

Source: Table 23 of Study 15-003 Report.

Table 25: Ocular AEs Reported for ≥ 4 subjects in either group for study 001 (Safety Population)

Adverse Event	PF Tafluprost 0.0015% (N = 320)	PF Timolol 0.5% (N = 323)
Conjunctival hyperaemia	9 (2.8%)	0 (0.0%)
Dry eye	3 (0.9%)	4 (1.2%)
Eye irritation	3 (0.9%)	4 (1.2%)
Eye pruritus	6 (1.9%)	3 (0.9%)
Ocular hyperaemia	5 (1.6%)	2 (0.6%)
Photophobia	4 (1.3%)	0 (0.0%)
Punctate keratitis	4 (1.3%)	5 (1.5%)
Vision blurred	2 (0.6%)	6 (1.9%)

Source: Table 12-3 of Study 001 Report

Table 26: Ocular AEs Reported for More Than 5 subjects in either group for study 74458 (Safety Population)

Adverse Event	PC Tafluprost (n = 264)	PC Latanoprost (n = 264)
Eye irritation	10 (3.8%)	10 (3.8%)
Growth of eyelashes	9 (3.4%)	7 (2.7%)
Eye pain	13 (4.9%)	4 (1.5%)
Ocular hyperaemia	10 (3.8%)	6 (2.3%)
Eyelash discoloration	5 (1.9%)	7 (2.7%)
Conjunctival hyperaemia	7 (2.7%)	3 (1.1%)
Eye pruritus	7 (2.7%)	3 (1.1%)
Eyelid oedema	4 (1.5%)	3 (1.1%)
Eyelash thickening	3 (1.1%)	3 (1.1%)
Dry eye	3 (1.1%)	4 (1.5%)
Visual field defect	3 (1.1%)	3 (1.1%)

Source: Table 22 of Study 74458 report.

Table 27: Ocular AEs in Either Group for Study 77550 (Safety Population)

Adverse Event	Preserved Tafluprost	Unpreserved Latanoprost
	(n = 42)	(n = 43)
Conjunctival hyperaemia	2 (4.8%)	6 (14.0%)
Erythema of eyelid	1 (2.4%)	1 (2.3%)
Eye pruritus	1 (2.4%)	1 (2.3%)
Foreign body sensation in eyes	1 (2.4%)	1 (2.3%)
Ocular hyperaemia	0	2 (4.7%)
Anterior chamber cell	0	1 (2.3%)
Blepharitis	0	1 (2.3%)
Eye pain	0	1 (2.3%)
Lacrimation increased	0	1 (2.3%)
Punctate keratitis	0	1 (2.3%)
Vision blurred	1 (2.4%)	0
Asthenopia	0	1 (2.3%)
Conjunctival haemorrhage	0	1 (2.3%)
Dry eye	0	1 (2.3%)
Superficial injury of eye	1 (2.4%)	0

Source: Table 22 of Study 74458 report.

Please see the review of the medical officer for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study 15-003

Summary statistics for IOP change from baseline by previous use of prostaglandin and ocular diagnosis for study 15-003 are presented in the following table. Overall the results for these subgroups resembled those of the primary analysis results.

Table 28: Study 15-003 Summary Statistics for IOP (mmHg) by Previous Use of Prostaglandin and Ocular Diagnosis

Prostaglandin Use - Prior Prostaglandin User					
		PC Tafluprost		PC Timolol	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	189	-6.94 (3.71)	135	-6.67 (3.61)
	10:00	48	-6.00 (4.08)	39	-6.37 (4.79)
	16:00	48	-5.40 (4.36)	39	-5.82 (3.89)
Week 6	8:00	185	-7.04 (3.48)	133	-7.00 (3.69)
	10:00	93	-5.60 (3.29)	73	-6.08 (3.76)
	16:00	93	-5.30 (4.27)	73	-5.24 (3.21)
Month 3	8:00	184	-6.54 (3.45)	129	-6.26 (3.72)
	10:00	184	-5.55 (3.62)	129	-6.25 (3.68)
	16:00	184	-5.27 (3.85)	129	-4.97 (3.77)
Month 6	8:00	179	-6.38 (3.35)	122	-6.40 (3.30)
	10:00	179	-5.41 (3.57)	122	-5.74 (3.84)
	16:00	177	-5.16 (3.36)	122	-4.56 (3.66)

Prostaglandin Use - Prostaglandin Naïve Patients					
	PC Tafluprost			PC Timolol	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	76	-7.03 (3.23)	52	-6.02 (2.80)
	10:00	29	-6.31 (3.82)	23	-5.20 (2.91)
	16:00	29	-5.50 (3.34)	23	-3.70 (3.18)
Week 6	8:00	75	-7.15 (3.13)	52	-6.78 (3.33)
	10:00	48	-5.99 (3.92)	32	-5.64 (2.64)
	16:00	47	-4.78 (3.37)	32	-4.44 (3.54)
Month 3	8:00	73	-7.01 (3.33)	51	-6.33 (2.99)
	10:00	73	-6.23 (3.39)	50	-4.88 (2.56)
	16:00	73	-5.06 (3.30)	51	-4.50 (3.47)
Month 6	8:00	72	-7.09 (3.41)	49	-6.57 (3.17)
	10:00	72	-5.84 (3.64)	50	-5.39 (3.40)
	16:00	72	-5.54 (3.70)	49	-3.94 (3.62)
Ocular Diagnosis - Glaucoma Patients					
	PC Tafluprost			PC Timolol	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	147	-6.84 (3.64)	115	-6.63 (3.50)
	10:00	43	-5.92 (4.30)	37	-6.18 (4.59)
	16:00	43	-5.20 (4.22)	37	-5.42 (4.15)
Week 6	8:00	145	-7.17 (3.69)	113	-7.08 (3.74)
	10:00	70	-5.92 (3.84)	63	-6.23 (3.73)
	16:00	69	-5.37 (4.18)	63	-5.43 (3.63)
Month 3	8:00	145	-6.84 (3.59)	110	-6.64 (3.60)
	10:00	145	-6.03 (3.74)	110	-6.28 (3.78)
	16:00	145	-5.69 (3.95)	110	-5.32 (4.06)
Month 6	8:00	141	-6.82 (3.65)	103	-6.64 (3.32)
	10:00	141	-5.69 (3.66)	103	-5.69 (3.99)
	16:00	140	-5.75 (3.63)	103	-4.67 (3.94)
Ocular Diagnosis – Ocular Hypertension Patients					
	PC Tafluprost			PC Timolol	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	118	-7.11 (3.51)	72	-6.26 (3.28)
	10:00	34	-6.37 (3.54)	25	-5.58 (3.62)
	16:00	34	-5.74 (3.71)	25	-4.46 (3.08)
Week 6	8:00	115	-6.95 (2.95)	72	-6.72 (3.35)
	10:00	71	-5.55 (3.16)	42	-5.52 (2.98)
	16:00	71	-4.89 (3.81)	42	-4.35 (2.69)
Month 3	8:00	112	-6.46 (3.17)	70	-5.71 (3.33)
	10:00	112	-5.36 (3.31)	69	-5.21 (2.77)
	16:00	112	-4.59 (3.25)	70	-4.07 (2.87)
Month 6	8:00	110	-6.28 (2.99)	68	-6.15 (3.15)
	10:00	110	-5.34 (3.50)	69	-5.57 (3.29)
	16:00	109	-4.66 (3.13)	68	-3.94 (3.14)

Source: Tables 14.2.4.1 to 14.2.4.8 of Study 15-033 Report.

4.2 Study 001

The treatment effects on IOP reduction across different subgroups defined by age, race, gender, baseline IOP, and ocular diagnosis were analyzed and summarized based on the study eye in the PP population at each time point during the day at Week 12. Summary statistics for the IOP change from baseline at Week 12 are displayed by treatment group and subgroup; additionally, the estimated mean difference (and 95% CI) between treatment groups is provided within each subgroup based upon the ANCOVA model.

Table 29: Study 15-003 Summary Statistics for IOP (mmHg) by Time Point and Subgroup at Week 12 (PP, Study Eye)

		PF Tafluprost		PF Timolol	
		N	Mean (SD)	N	Mean (SD)
Age					
≤ 65 Years	8:00	163	18.8 (3.1)	175	18.3 (2.9)
	10:00	165	17.8 (2.9)	179	17.6 (2.8)
	16:00	165	17.5 (2.8)	179	17.7 (3.0)
> 65 Years	8:00	133	18.3 (3.0)	133	18.8 (3.4)
	10:00	133	17.5 (2.9)	133	18.4 (3.6)
	16:00	133	17.4 (3.0)	132	18.2 (3.4)
Gender					
Female	8:00	168	18.5 (2.8)	182	18.7 (3.2)
	10:00	169	17.5 (2.8)	186	18.1 (3.2)
	16:00	169	17.2 (2.7)	185	17.9 (3.2)
Male	8:00	128	18.7 (3.4)	126	18.2 (3.1)
	10:00	129	17.9 (3.0)	126	17.8 (3.2)
	16:00	129	17.8 (3.0)	126	17.9 (3.2)
Race					
White	8:00	217	18.6 (3.0)	233	18.5 (3.1)
	10:00	217	17.7 (2.8)	235	17.9 (3.2)
	16:00	217	17.5 (2.9)	234	17.9 (3.2)
Non-white	8:00	79	18.7 (3.2)	75	18.6 (3.4)
	10:00	81	17.5 (3.1)	77	18.1 (3.4)
	16:00	81	17.2 (2.9)	77	18.0 (3.1)
Baseline IOP					
<25 mmHg	8:00	115	17.3 (2.3)	120	17.2 (2.6)
	10:00	116	16.8 (2.5)	120	17.1 (2.9)
	16:00	116	16.8 (2.5)	120	17.2 (3.0)
≥25 mmHg	8:00	181	19.4 (3.2)	188	19.3 (3.2)
	10:00	182	18.3 (3.0)	192	18.5 (3.3)
	16:00	182	17.9 (3.0)	191	18.4 (3.2)
Ocular Diagnosis					
Open-Angle Glaucoma	8:00	178	18.5 (3.3)	183	18.4 (3.2)
	10:00	180	17.6 (3.0)	187	17.7 (3.3)
	16:00	180	17.3 (3.0)	186	17.8 (3.2)
Ocular Hypertension	8:00	118	18.7 (2.8)	125	18.7 (3.1)
	10:00	118	17.8 (2.7)	125	18.3 (3.1)

	16:00	118	17.6 (2.7)	125	18.1 (3.1)
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Source: Table 11-10 of Study 001 Report.

4.3 Study 74458

Summary statistics for IOP change from baseline by previous use of prostaglandin and ocular diagnosis for study 74458 are presented in the following table. Overall the results for these subgroups resembled those of the primary analysis results.

Table 30: Study 74458 Summary Statistics for IOP (mmHg) by Previous Use of Prostaglandin and Ocular Diagnosis (PP, Study Eye)

Prostaglandin Use - Prior Prostaglandin User					
	PC Tafluprost			PC Latanoprost	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	122	-7.66 (3.22)	126	-8.71 (3.35)
Week 6	8:00	122	-7.40 (3.49)	125	-8.55 (3.61)
Month 3	8:00	116	-7.87 (3.36)	122	-8.98 (3.43)
	12:00	115	-6.99 (6.46)	122	-8.16 (3.35)
	16:00	114	-6.46 (3.81)	120	-6.88 (3.28)
	20:00	114	-5.52 (3.57)	121	-6.73 (3.34)
Month 6	8:00	110	-7.85 (3.64)	118	-9.26 (3.67)
	12:00	108	-7.00 (3.55)	118	-8.52 (4.44)
	16:00	110	-6.14 (3.65)	117	-7.20 (3.83)
	20:00	110	-5.75 (3.49)	117	-6.76 (3.55)
Prostaglandin Use - Prostaglandin Naïve Patients					
	PC Tafluprost			PC Latanoprost	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	142	-8.52 (2.70)	138	-8.43 (3.18)
Week 6	8:00	141	-8.54 (3.12)	135	-8.82 (3.23)
Month 3	8:00	138	-8.63 (3.30)	134	-9.21 (3.16)
	12:00	137	-7.63 (3.60)	134	-8.60 (3.25)
	16:00	136	-7.32 (3.80)	134	-7.44 (3.24)
	20:00	138	-6.92 (3.19)	134	-7.14 (3.06)
Month 6	8:00	134	-8.21 (3.26)	133	-9.08 (3.20)
	12:00	134	-7.16 (3.29)	133	-8.45 (3.37)
	16:00	133	-7.19 (3.72)	131	-7.78 (3.35)
	20:00	133	-6.75 (3.28)	131	-7.31 (3.43)
Ocular Diagnosis - Glaucoma Patients					
	PC Tafluprost			PC Latanoprost	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	164	-8.28 (2.84)	166	-8.76 (3.19)
Week 6	8:00	164	-8.49 (2.99)	164	-8.73 (3.39)
Month 3	8:00	159	-8.55 (3.35)	161	-9.29 (3.29)
	12:00	157	-7.72 (3.63)	161	-8.49 (3.17)
	16:00	156	-7.28 (3.94)	160	-7.33 (3.22)
	20:00	158	-6.84 (3.33)	161	-7.13 (3.22)

Month 6	8:00	153	-8.29 (3.36)	157	-9.41 (3.31)
	12:00	151	-7.40 (3.57)	157	-8.69 (3.82)
	16:00	151	-6.96 (3.77)	155	-7.71 (3.45)
	20:00	152	-6.68 (3.35)	155	-7.22 (3.44)
Ocular Diagnosis – Ocular Hypertension Patients					
		Tafluprost		Latanoprost	
		N	Mean (SD)	N	Mean (SD)
Week 2	8:00	100	-7.86 (3.19)	98	-8.22 (3.36)
Week 6	8:00	99	-7.23 (3.72)	96	-8.61 (3.47)
Month 3	8:00	95	-7.85 (3.29)	95	-8.78 (3.28)
	12:00	95	-6.71 (3.29)	95	-8.22 (3.52)
	16:00	94	-6.34 (3.57)	94	-6.91 (3.33)
	20:00	94	-5.36 (3.43)	94	-6.64 (3.14)
Month 6	8:00	91	-7.64 (3.54)	94	-8.76 (3.59)
	12:00	91	-6.57 (3.04)	94	-8.12 (4.03)
	16:00	92	-6.32 (3.61)	93	-7.16 (3.81)
	20:00	91	-5.67 (3.43)	93	-6.78 (3.56)

Source: Table 14.2.4.1 to 14.2.4.8 of Study 74458 Report.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are no major statistical issues for this submission. The choice of 1.5 mmHg as the non-inferiority margin using timolol as the active comparator for studies 15-003, 001, and 74458 was recommended to the Applicant by the FDA clinical review team during the design stage of the study protocol; the statistical reviewer considered this margin reasonable (for a detailed discussion of the margin, please see Appendix A).

The following table lists the statistical reviewer's analyses results for all the three non-inferiority studies; these results were consistent with the Applicant's analyses results.

Table 31: IOP Change from Baseline Analysis Results by Statistical Reviewer (FAS, LOCF, ANOCVA)

Study 15-003			
Visit / Time	PC Tafluprost 0.0015% (N=265) LS Mean ¹ (mmHg)	PC Timolol 0.5% (N=187) LSMean ¹ (mmHg)	Difference (95% CI) ¹ (mmHg)
Week 2			
8:00	-6.97	-6.48	-0.49 (-1.06, 0.09)
10:00	-6.13	-5.92	-0.21 (-1.17, 0.75)
16:00	-5.41	-5.07	-0.34 (-1.24, 0.56)
Week 6			
8:00	-7.07	-6.91	-0.01 (-0.70, 0.68)
10:00	-5.82	-5.81	-0.02 (-0.71, 0.69)

16:00	-5.26	-4.79	-0.47 (-1.17, 0.23)
Month 3			
8:00	-6.62	-6.13	-0.49 (-1.10, 0.12)
10:00	-5.79	-5.76	-0.03 (-0.58, 0.53)
16:00	-5.21	-4.83	-0.38 (-0.92, 0.16)
Month 6			
8:00	-6.52	-6.32	-0.20 (-0.81, 0.41)
10:00	-5.56	-5.67	0.11 (-0.49, 0.72)
16:00	-5.23	-4.44	-0.79 (-1.32, -0.25)
Month 9			
8:00	-7.07	-6.32	-0.76 (-1.36, -0.16)
10:00	-5.78	-5.48	-0.30 (-0.89, 0.30)
Month 12			
8:00	-6.53	-6.57	-0.05 (-0.67, 0.58)
10:00	-5.43	-5.62	-0.19 (-0.84, 0.46)
16:00	-4.84	-4.21	-0.62 (-1.19, -0.05)
Study 001			
Visit / Time	PF Tafluprost 0.0015% (N=316) LSMean¹ (mmHg)	PF Timolol 0.5% (N=321) LSMean¹ (mmHg)	Difference (95% CI)¹ (mmHg)
Week 2			
8:00	-7.21	-6.81	-0.41 (-0.85, 0.04)
10:00	-6.81	-6.10	-0.73 (-1.16, -0.29)
16:00	-6.17	-5.34	-0.83 (-1.26, -0.40)
Week 6			
8:00	-7.24	-7.36	0.12 (-0.32, 0.56)
10:00	-6.95	-6.60	-0.36 (-0.80, 0.08)
16:00	-6.33	-5.52	-0.81 (-1.26, -0.36)
Month 3			
8:00	-7.48	-7.50	0.02 (-0.42, 0.47)
10:00	-7.08	-6.69	-0.39 (-0.84, 0.05)
16:00	-6.28	-5.73	-0.55 (-0.98, -0.11)
Study 74458			
Visit / Time	PC Tafluprost 0.0015% (N=264) LSMean¹ (mmHg)	PC Latanoprost 0.5% (N=264) LSMean¹ (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)

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

For the crossover study 77550 comparing the preserved and unpreserved formulation of tafluprost 0.0015%, the Applicant used a repeated measurements analysis of covariance (RM ANCOVA) model to analyze the changes from baseline in the diurnal IOP at 4 weeks. The following table lists the Applicant's analysis results for the bridging study 77550 comparing the preserved and unpreserved formulation of tafluprost 0.0015%.

Table 32: 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.

5.2 Conclusions and Recommendations

From the results of study 15-003 and 001, 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 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. It is also noted that at all the post baseline time points, the average IOP reduction in the tafluprost group was slightly higher than the one in the timolol group. Both studies demonstrated that tafluprost was non-inferior to timolol using 1.50 mmHg as the NI margin in both preservative-containing and preservative-free formulation.

From the results of study 77550, for both the preserved and unpreserved formulation, a similar IOP lowering effect was seen clearly at Week 1 and it was sustained at Week 4. These results showed that the removal of preservative from the tafluprost 0.0015% ophthalmic formulation has no effect on the drug's effectiveness.

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. Therefore, study 74458 failed to demonstrate non-inferiority of efficacy of tafluprost compared with latanoprost using the pre-defined 1.50 mmHg non-inferiority margin.

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.

Appendix A: Discussion Regarding the Choice of 1.5 mmHg Non-Inferiority Margin Using Timolol (0.5% twice daily) as the Active Comparator

In assessing the non-inferiority margin of 1.5 mmHg recommended to the Applicant by the clinical review team, the statistical reviewer conducted additional analyses to estimate the IOP lowering effect of Timolol over placebo based on the data submitted in this NDA. As shown in Table 36, PC Timolol and PF Timolol had similar IOP lowering effect; thus in our assessment of the NI margin for Timolol, we assume that there is no difference between PC Timolol and PF Timolol treatments. As supported by the results of Study 77550, we also assume that there is no difference between PC tafluprost and PF tafluprost treatments.

Among all the submitted studies for this NDA application, only one study (Study 15-001) had a placebo arm; therefore, the IOP change from baseline for placebo arm was derived solely from this Phase II study. Study 15-001 was a randomized, double-masked, parallel-group, multi-center, dose-response trial of tafluprost ophthalmic solution to investigate the dose-response relationship of tafluprost in patients with open-angle glaucoma or ocular hypertension and to compare the safety and efficacy of three concentrations of tafluprost ophthalmic solution (0.001%, 0.0025%, 0.005%) with placebo and 0.005% latanoprost. The IOP mean change from baseline for each treatment group at each post-baseline time point are shown in Table 33 with the results of the placebo arm highlighted.

From these results in Table 33, the mean IOP change from baseline for placebo range from -2.36 to 1.00. It also seems that the IOP change from baseline estimates were similar in all the three tafluprost treatment groups, with the 0.005% tafluprost group had slightly lower treatment effect compared with the other two tafluprost groups (0.001% and 0.0025%).

Table 34 lists the difference of mean change from baseline between each treatment group compared with the placebo group. From Table 34, it is clear that the treatment differences between the three tafluprost groups and the placebo group were similar.

Table 33: Mean Change ± SD from Baseline in IOP (mmHg) in Study 15-001

Time Point	Placebo	0.001% Tafluprost	0.0025% Tafluprost	0.005% Tafluprost	Latanoprost
Day 7	N=29	N=30	N=31	N=28	N=28
08:00	-1.62 ± 2.72	-6.10 ± 3.42	-6.06 ± 3.25	-5.71 ± 2.92	-6.85 ± 2.85
12:00	-0.69 ± 3.22	-5.50 ± 3.64	-5.23 ± 3.74	-4.07 ± 2.87	-5.78 ± 3.24
16:00	-0.62 ± 2.65	-5.17 ± 3.47	-4.68 ± 3.51	-4.85 ± 2.76	-5.22 ± 2.58
20:00	-0.86 ± 3.09	-4.57 ± 3.50	-4.77 ± 3.57	-4.81 ± 3.50	-4.07 ± 2.77
Day 14	N=29	N=30	N=31	N=27	N=27
08:00	-1.41 ± 4.02	-6.33 ± 3.21	-6.35 ± 3.55	-5.78 ± 3.07	-7.78 ± 3.11
12:00	1.00 ± 4.84	-6.30 ± 3.30	-5.81 ± 3.58	-4.48 ± 2.86	-5.11 ± 3.29
16:00	-0.48 ± 4.12	-5.53 ± 2.66	-5.39 ± 3.51	-4.59 ± 2.48	-5.30 ± 3.38
20:00	-1.34 ± 4.14	-5.17 ± 4.13	-5.13 ± 3.36	-4.74 ± 4.19	-4.00 ± 3.65
Day 28	N=28	N=29	N=30	N=27	N=27
08:00	-2.36 ± 3.58	-5.93 ± 3.66	-6.57 ± 2.90	-5.37 ± 2.63	-7.81 ± 3.58

12:00	-0.43 ± 3.55	-5.00 ± 3.86	-5.30 ± 3.95	-3.89 ± 3.37	-6.04 ± 3.78
16:00	-0.46 ± 3.54	-5.24 ± 3.77	-4.77 ± 4.39	-4.44 ± 3.22	-5.56 ± 4.02
20:00	-1.25 ± 2.59	-3.93 ± 3.40	-4.72 ± 3.40	-4.04 ± 4.16	-3.04 ± 3.61

Table 34: Treatment Difference with 95% CI for Mean Change from Baseline in IOP (mmHg) for Study 15-001

Time Point	Placebo vs. 0.001% Tafluprost	Placebo vs. 0.0025% Tafluprost	Placebo vs. 0.005% Tafluprost	Placebo vs. Latanoprost
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Day 7				
08:00	-4.48 (-6.09, -2.87)	-4.44 (-6.00, -2.89)	-4.09 (-5.59, -2.60)	-5.24 (-6.71, -3.76)
12:00	-4.81 (-6.60, -3.02)	-4.54 (-6.35, -2.73)	-3.38 (-5.02, -1.75)	-5.10 (-6.81, -3.38)
16:00	-4.55 (-6.16, -2.93)	-4.06 (-5.67, -2.44)	-4.23 (-5.68, -2.78)	-4.60 (-3.20, -6.00)
20:00	-3.71 (-5.43, -1.98)	-3.91 (-5.64, -2.18)	-3.95 (-5.72, -2.19)	-3.21 (-4.79, -1.63)
Day 14				
08:00	-4.92 (-6.81, -3.03)	-4.94 (-6.90, -2.99)	-4.36 (-6.29, -2.44)	-6.36 (-8.30, -4.43)
12:00	-7.3 (-9.45, -5.15)	-6.81 (-9.00, -4.62)	-5.48 (-7.63, -3.33)	-6.11 (-8.34, -3.88)
16:00	-5.05 (-6.85, -3.25)	-4.90 (-6.88, -2.93)	-4.11 (-5.95, -2.27)	-4.81 (-6.84, -2.79)
20:00	-3.83 (-6.00, -1.65)	-3.78 (-5.73, -1.84)	-3.40 (-5.63, -1.16)	-2.66 (-4.75, -0.56)
Day 28				
08:00	-3.57 (-5.50, -1.65)	-4.21 (-5.92, -2.50)	-3.01 (-4.72, -1.31)	-5.46 (-7.40, -3.52)
12:00	-4.57 (-6.54, -2.60)	-4.87 (-6.85, -2.89)	-3.46 (-5.33, -1.59)	-5.61 (-7.49, -3.73)
16:00	-4.78 (-6.72, -2.83)	-4.30 (-6.41, -2.19)	-3.98 (-5.82, -2.15)	-5.09 (-7.14, -3.04)
20:00	-2.68 (-4.29, -1.07)	-3.47 (-5.08, -1.87)	-2.79 (-4.66, -0.92)	-1.79 (-3.48, -0.09)

In addition, three submitted studies for this NDA had 0.5% timolol as the active control arm; they were Phase II study 15-002, and two Phase III studies 15-003 and 001.

Study 15-002 was a randomized, double-masked, parallel-group, multi-center, dose-response trial investigating the dose-response relationship of tafluprost in patients with open-angle glaucoma or ocular hypertension and to compare the safety and efficacy of three concentrations of tafluprost ophthalmic solution (0.0003%, 0.0015%, 0.0025%) with 0.5% timolol and 0.005% latanoprost.

Table 35: Mean Change from Baseline in IOP (mmHg) in Study 15-002

Day/Time	Tafluprost 0.0015% (mmHg)	Tafluprost 0.0025% (mmHg)	Timolol 0.5% (mmHg)	Latanoprost 0.005% (mmHg)
Day 7	N=29	N=27	N=28	N=25
8 AM	-7.33 ± 3.11	-6.26 ± 3.05	-6.3 ± 2.77	-7.46 ± 3.42
Day 14	N=29	N=27	N=29	N=28
8 AM	-7.22 ± 3.26	-6.74 ± 3.00	-6.74 ± 2.70	-8.13 ± 2.79
10 AM	-6.71 ± 3.43	-5.71 ± 3.77	-5.19 ± 2.54	-6.73 ± 3.46
4 PM	-6.10 ± 3.69	-6.96 ± 2.83	-4.38 ± 3.61	-6.41 ± 3.17
8 PM	-5.00 ± 3.52	-5.94 ± 3.93	-3.96 ± 3.88	-5.48 ± 3.68
Day 28	N=29	N=25	N=28	N=28
8 AM	-7.28 ± 3.12	-7.14 ± 2.99	-7.09 ± 1.96	-7.96 ± 3.16
10 AM	-6.09 ± 3.33	-4.84 ± 2.88	-5.48 ± 3.09	-7.25 ± 3.84
4 PM	-5.86 ± 2.95	-5.70 ± 2.95	-4.55 ± 3.04	-6.13 ± 3.53
8 PM	-4.75 ± 3.94	-4.46 ± 4.75	-4.23 ± 3.84	-5.23 ± 4.11

Both Study 15-003 and Study 001 were double-masked, randomized, active-controlled, parallel group non-inferiority studies that included patients aged 18 years or older who were randomized to: PC Tafluprost 0.0015% q.d. or timolol 0.5% b.i.d. (3:2) for study 15-003; and PF tafluprost 0.0015% q.d. or timolol PF 0.5% b.i.d. (1:1) for Study 001. Study 001 had a 3-month double-masked treatment period and Studies 15-003 had 6-month double-masked treatment periods; Studies 15-003 was extended to 12 months (double-masked treatment period) to provide additional long term safety and tolerability data as well as supportive efficacy data.

Table 36: Mean IOP Change from Baseline for Studies 15-003 and 001

Study 15-003				
Visit / Time	PC Tafluprost 0.0015%		PC Timolol 0.5%	
	N	Mean ± SD (mmHg)	N	Mean ± SD (mmHg)
Week 2				
8:00	265	-6.96 ± 3.58	187	-6.49 ± 3.41
10:00	77	-6.11 ± 3.96	62	-5.94 ± 4.20
16:00	77	-5.44 ± 3.98	62	-5.03 ± 3.76
Week 6				
8:00	260	-7.07 ± 3.37	186	-6.94 ± 3.58
10:00	141	-5.73 ± 3.51	105	-5.95 ± 3.46
16:00	140	-5.13 ± 3.99	105	-5.00 ± 3.32
Month 3				
8:00	257	-6.67 ± 3.42	181	-6.28 ± 3.51
10:00	257	-5.74 ± 3.57	180	-5.86 ± 3.45
16:00	257	-5.21 ± 3.69	180	-4.84 ± 3.69
Month 6				
8:00	251	-6.58 ± 3.38	173	-6.45 ± 3.23
10:00	251	-5.54 ± 3.59	172	-5.64 ± 3.71
16:00	249	-5.27 ± 3.46	172	-4.38 ± 3.64
Month 9				

8:00	265	-7.07 ± 3.56	187	-6.32 ± 3.51
10:00	259	-5.74 ± 3.73	185	-5.55 ± 3.78
Month 12				
8:00	265	-6.57 ± 3.77	187	-6.53 ± 3.42
10:00	259	-5.57 ± 3.93	185	-5.49 ± 4.11
16:00	259	-4.85 ± 3.99	185	-4.20 ± 3.59
Study 001				
Visit / Time	PF Tafluprost 0.0015%		PF Timolol 0.5%	
	N	Mean ± SD (mmHg)	N	Mean ± SD (mmHg)
Week 2				
8:00	315	-7.23 ± 3.01	318	-6.78 ± 3.12
10:00	315	-6.89 ± 3.22	318	-6.01 ± 3.32
16:00	310	-6.25 ± 3.43	315	-5.26 ± 3.25
Week 6				
8:00	316	-7.27 ± 2.93	321	-7.33 ± 3.17
10:00	316	-7.04 ± 3.45	321	-6.52 ± 3.21
16:00	312	-6.42 ± 3.70	319	-5.44 ± 3.13
Month 3				
8:00	316	-7.51 ± 3.18	321	-7.47 ± 3.13
10:00	316	-7.18 ± 3.54	321	-6.60 ± 3.34
16:00	312	-6.37 ± 3.55	319	-5.64 ± 3.36

From the above results, it is obvious that the IOP lowering effect of timolol is consistent across different studies. In addition, treatment effect is also consistent from treatment Day 7 for up to 12-month and do not diminish over the treatment course. Moreover, the treatment effect at the same time point (8:00, 10:00, etc) is similar no matter the time point is on Day 7 or on Month 3.

None of the studies submitted in this NDA have any direct comparison between timolol and placebo. In order to estimate the treatment difference between timolol and placebo and further derive the NI margin for using timolol as the active comparator, this review will focus on Study 15-001 and use the treatment effect of tafluprost to estimate the treatment effect of timolol based on the following rationale:

1. 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 is better and can beat timolol, it indicates that tafluprost can beat placebo, hence there is no need of NI study or NI margin.
2. 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.

Based on the above rationale and because the treatment effects are similar among tafluprost groups in Study 15-001, the statistical reviewer combine the observations for each time point for

tafluprost 0.001%, tafluprost 0.0025%, and tafluprost 0.005% in study 15-001 together and compare the combined tafluprost results with placebo. It should be noted that the final concentration of tafluprost the Applicant selected for registration purpose is 0.0015%, which falls in between 0.001% and 0.0025%. The combined results show as follows.

Table 37: Combined IOP Change from Baseline for Placebo and Timolol at Each Time Point

Time Point	Placebo	0.001% Tafluprost + 0.0025% Tafluprost + 0.005% Tafluprost	Difference (95% CI)
Day 7	N=29	N=89	
08:00	-1.62 ± 2.72	-5.97 ± 3.18	-4.35 (-5.65, -3.04)
12:00	-0.69 ± 3.22	-4.97 ± 3.47	-4.28 (-5.72, -2.83)
16:00	-0.62 ± 2.65	-4.90 ± 3.25	-4.28 (-5.60, -2.96)
20:00	-0.86 ± 3.09	-4.72 ± 3.48	-3.85 (-5.29, -2.42)
Day 14	N=29	N=88	
08:00	-1.41 ± 4.02	-6.17 ± 3.26	-4.76 (-6.23, -3.29)
12:00	1.00 ± 4.84	-5.57 ± 3.33	-6.57 (-8.16, -4.98)
16:00	-0.48 ± 4.12	-5.19 ± 2.94	-4.71 (-6.10, -3.33)
20:00	-1.34 ± 4.14	-5.02 ± 3.85	-3.68 (-5.35, -2.01)
Day 28	N=28	N=86	
08:00	-2.36 ± 3.58	-5.98 ± 3.11	-3.62 (-5.01, -2.23)
12:00	-0.43 ± 3.55	-4.76 ± 3.75	-4.33 (-5.92, -2.73)
16:00	-0.46 ± 3.54	-4.83 ± 3.81	-4.36 (-5.98, -2.74)
20:00	-1.25 ± 2.59	-4.24 ± 3.63	-2.99 (-4.46, -1.51)

The point estimates of the treatment difference between tafluprost 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.

In conclusion, we derive the NI margin using timolol as the active comparator based on the following observations:

1. 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 12-month and do not diminish over the treatment course. Moreover, the treatment effect at the same time point (8:00, 10:00, etc) is similar no matter it is on treatment Day 7 or on Month 12.
2. Study 15-001 showed that the IOP lowering effect of placebo is consistent from treatment Day 7 for up to Day 28 and do 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.
3. Study 15-001 showed that the mean IOP change from baseline were similar in all the three tafluprost treatment groups, with the 0.005% tafluprost group had slightly lower treatment effect compared with the other two tafluprost groups (0.001% and 0.0025%).

4. 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.
5. The treatment effect of tafluprost can be used to estimate the treatment effect of timolol.
6. 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.

Therefore, a 1.5 mmHg non-inferiority margin for a non-inferiority study using timolol as the active comparator seems reasonable.

Appendix B: Summary of Phase II Studies

1. Study 15-001 (Phase II Dose-Finding Study I)

Study 15-001 was a randomized, double-masked, parallel-group, multi-center, dose-response trial of tafluprost ophthalmic solution in patients with open-angle glaucoma or ocular hypertension. The study was carried out in the United States.

Study objective: To investigate the dose-response relationship of tafluprost in patients with open-angle glaucoma or ocular hypertension and to compare the safety and efficacy of three concentrations of tafluprost ophthalmic solution (0.001%, 0.0025%, 0.005%) with placebo and 0.005% latanoprost.

Study design/methodology: Randomized, double-masked, placebo-/active-controlled, parallel group, multicenter trial. In addition to the baseline visit there were visits at Day 7, 14 and 28.

Patients: Patients diagnosed with primary open-angle glaucoma, pseudoexfoliation glaucoma, pigmentary glaucoma or ocular hypertension were enrolled in the study. A total of 152 patients entered and 142 completed the study. The mean age was 60.1 years, and 61% were females. Seventy-two percent (72%) of patients were Caucasians, 15% Hispanics, 12% Black, one was Asian and one Indian.

Test products and dose regimen: Tafluprost ophthalmic solution (preservative-containing) 0.001%, 0.0025%, 0.005%, placebo (vehicle), 0.005% latanoprost once daily at 20:00.

Criteria for efficacy evaluation: Efficacy based on change in diurnal IOP based on measurements at 08:00, 12:00, 16:00 and 20:00 at baseline, and on Days 7, 14 and 28.

Statistical methods: Analysis of variance (ANOVA) was used to compare changes in diurnal IOP between different concentrations of tafluprost and placebo. The primary efficacy analysis was based on the change from baseline in diurnal IOP on Day 28. Pairwise comparisons between the latanoprost group and all other treatment groups were performed with t-tests.

Efficacy results: All three concentrations of tafluprost statistically significantly reduced the diurnal IOP compared to placebo. There were no statistically significant differences among the three concentrations of tafluprost or latanoprost in the reduction of mean diurnal IOP (average of 4 daily time points) during the study. At the 0800 and 1200 time points on Day 28, the latanoprost group had significantly greater IOP reduction than the 0.005% tafluprost group. The results are displayed in below.

Conclusions: All three concentrations of tafluprost and latanoprost reduced diurnal IOP significantly from Day 7 through Day 28. The differences in diurnal IOP reduction between groups were not clinically significant. Hence, a definitive dose-response for tafluprost was not demonstrated.

Table 38: Mean Diurnal IOP during the Treatment Period (mmHg) in Study 15-001 (ANOVA, PP Population, Observed)

Visit	Placebo	0.001% Tafluprost	0.0025% Tafluprost	0.005% Tafluprost	Latanoprost
Day 0	23.23	24.70	22.79	22.52	23.65
Day 7	22.43	19.37	17.63	17.74	18.04
Day 14	22.59	18.87	17.15	17.79	18.19
Day 28	22.21	19.72	17.60	18.25	18.14

Source: Table 2.7.3-elevatediop:5 of Clinical Summary

Table 39: Mean Change from Baseline in Diurnal IOP (mmHg) in Study 15-001 (ANOVA, PP Population, Observed)

Visit	Placebo	0.001% Tafluprost	0.0025% Tafluprost	0.005% Tafluprost	Latanoprost
Day 7	-0.95	-5.33	-5.19	-4.88	-5.51
Day 14	-0.56	-5.83	-5.67	-4.90	-5.55
Day 28	-1.13	-5.03	-5.29	-4.44	-5.61

Source: Table 2.7.3-elevatediop:6 of Clinical Summary

Table 40: Mean Change from Baseline in IOP (mmHg) on Day 28 in Study 15-001 (ANOVA, PP Population, Observed)

Time Point	Placebo	0.001% Tafluprost	0.0025% Tafluprost	0.005% Tafluprost	Latanoprost
08:00	-2.36	-5.93	-6.57	-5.37	-7.81
12:00	-0.43	-5.00	-5.30	-3.89	-6.04
16:00	-0.46	-5.24	-4.77	-4.44	-5.56
20:00	-1.25	-3.93	-4.72	-4.04	-3.04

Source: Table 2.7.3-elevatediop:7 of Clinical Summary

2. Study 15-002 (Phase II Dose-Finding Study II)

Study 15-002 was a randomized, double-masked, parallel-group, multi-center, 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. The study was carried out in the United States.

Study objective: To investigate the dose-response relationship of tafluprost in patients with open-angle glaucoma or ocular hypertension and to compare the safety and efficacy of three concentrations of tafluprost ophthalmic solution (0.0003%, 0.0015%, 0.0025%) with 0.5% timolol and 0.005% latanoprost.

Study design/methodology: Randomized, double-masked, active-controlled, parallel group, multicenter, 4-week trial comparing the safety and efficacy of three concentrations of tafluprost with timolol and latanoprost. In addition to the baseline visit there were visits at Day 7, 14 and 28 at which the efficacy and safety were evaluated. IOP was measured at 08:00, 10:00, 16:00 and 20:00 on Days 0, 14 and 28 and in addition at 08:00 on Day 7.

Patients: Patients diagnosed with primary open-angle glaucoma, pseudoexfoliation glaucoma, pigmentary glaucoma or ocular hypertension were enrolled in the study. A total of 144 patients entered and 139 completed the study. The mean age was 61.1 years, 60% were females. Sixty percent (60%) were Caucasians, 29% Blacks, and 10% Hispanics.

Test products and dose regimen: Tafluprost ophthalmic solution 0.0003%, 0.0015%, 0.0025%, timolol 0.5%, and latanoprost ophthalmic solution 0.005%. Patients randomized to the timolol group applied timolol twice daily, 08:00 and 20:00. Patients were randomized to receive either tafluprost or latanoprost applied vehicle in the morning (08:00) and active substance in the evening (20:00).

Criteria for efficacy evaluation: In the original CSR: Efficacy was based on change in IOP at 08:00, 10:00, 16:00 and 20:00 on Day 28 from baseline. Per FDA request (Pre NDA meeting): the efficacy analysis was based on IOP values at 08:00, 10:00, 16:00 and 20:00 on Days 7, 14, and 28.

Statistical methods: In the original CSR: Analysis of variance (ANOVA) was used to compare changes in IOP between different concentrations of tafluprost and timolol/latanoprost. The primary efficacy analysis was the change from baseline at each time point (not diurnal IOP) on Day 28 compared to timolol using the per protocol dataset. A repeated measures analysis of covariance (RM-ANCOVA) was also performed for change from baseline in diurnal IOP using baseline as covariate. Per FDA request (Pre-NDA meeting): the following post-hoc analyses were performed: mean change from baseline at each time point with and without adjusting for the baseline IOP and in both per-protocol and the full analysis sets. In addition, the data was analyzed for study eye, non-study eye, and the average of both eyes.

Efficacy results: In the original CSR: As shown in Table 41 the IOP-reducing effect of 0.0015% tafluprost in these studies was similar to that of 0.5% timolol and 0.005% latanoprost. The IOP

reduction was maintained at a relatively stable level during treatment with tafluprost. All three concentrations of tafluprost reduced IOP to about the same extent as timolol and latanoprost. The 0.0015% tafluprost produced the greatest mean numerical IOP-lowering effect across all diurnal time points with the relative order of effectiveness being 0.0015% > 0.0025% > 0.0003%.

Conclusions: Among the three concentrations of tafluprost the 0.0015% solution exhibited the numerically largest mean IOP-reducing effect.

Table 41: IOP Values of Patients Treated with 0.0015% Tafluprost, 0.5% Timolol and 0.005% Latanoprost in Phase II Clinical Trial 15-002 (ANOVA, PP, Observed)

Day/Time	Tafluprost 0.0015% (mmHg)	Timolol 0.5% (mmHg)	Latanoprost 0.005% (mmHg)
Day 0 (Baseline)			
8 AM	26.37 ± 3.30	26.50 ± 3.33	26.48 ± 3.35
10 AM	24.32 ± 4.26	24.50 ± 3.38	24.96 ± 3.87
4 PM	23.42 ± 4.02	22.79 ± 3.49	24.11 ± 3.63
8 PM	21.57 ± 4.08	22.19 ± 2.97	22.77 ± 3.73
Day 7			
8 AM	19.03 ± 3.72	20.14 ± 3.16	19.07 ± 3.49
Day 14			
8 AM	19.00 ± 3.94	19.76 ± 3.63	18.36 ± 3.19
10 AM	17.76 ± 3.26	19.31 ± 3.08	18.23 ± 2.68
4 PM	17.52 ± 3.37	18.41 ± 2.83	17.70 ± 2.90
8 PM	16.78 ± 3.24	18.22 ± 3.06	17.29 ± 3.40
Day 28			
8 AM	18.95 ± 3.91	19.41 ± 3.20	18.52 ± 2.64
10 AM	18.38 ± 3.37	19.00 ± 2.87	17.71 ± 2.79
4 PM	17.76 ± 3.10	18.29 ± 2.27	17.98 ± 3.48
8 PM	17.02 ± 3.42	18.10 ± 3.22	17.54 ± 3.95

Source: Table 2.7.3-elevatediop:8 of Clinical Summary.

Table 42: Mean Change from Baseline in IOP on Day 28 (mmHg) in Study 15-002 (ANOVA, PP, Observed Data)

Time Point	0.0003% Tafluprost	0.0015% Tafluprost	0.0025% Tafluprost	Timolol	Latanoprost
8:00	-6.22	-7.28	-7.14	-7.09	-7.96
10:00	-5.35	-6.09	-4.84	-5.48	-7.25
16:00	-4.22	-5.86	-5.70	-4.55	-6.13
20:00	-3.72	-4.76	-4.46	-4.23	-5.23

Source: Table 2.7.3-elevatediop:9 of Clinical Summary.

3. Study 74457 (Phase II Study; A Pilot Latanoprost Comparison Study)

Study 74457 is a pilot Phase II study on the duration and stability of the IOP-lowering effect of tafluprost ophthalmic solution as compared to latanoprost. The study was carried out in Finland and Italy.

Study objective: To investigate the IOP-lowering effect and tolerability of tafluprost 0.0015% eye drops in comparison to latanoprost 0.005% eye drops in patients with elevated IOP. The primary aim was to investigate the extent and duration of action up to 48 hours after the last dose and the stability of the diurnal IOP curve.

Study Design/Methodology: Randomized, double-masked, active-controlled, parallel-group and multicenter Phase IIb study in patients aged 18 years or more with primary open-angle glaucoma, capsular glaucoma or ocular hypertension (with or without pseudoexfoliation).

Patients: A total of 38 patients diagnosed with open-angle glaucoma or ocular hypertension were enrolled, and 36 patients completed the study.

Test products and mode of administration: Tafluprost 0.0015% eye drops and latanoprost 0.005% eye drops; one drop in the evening at 20:00 for 6 weeks.

Criteria for efficacy evaluation: The primary efficacy variables comprised extent and duration of action at the end of the 6-week treatment period using the IOP measurements at Days 42 and 43, and stability of the diurnal IOP curve based on the individual fluctuations at Days 42 and 43. The secondary efficacy variables comprised the IOP values at 08:00 on Days 7, 21 and 42 and proportion of responders at Day 42.

Statistical methods: A repeated measurements analysis of variance (RM-ANOVA) model, a RM-ANCOVA model (baseline IOP as a covariate) and a random coefficients regression model (Days 42 and 43). A 95% confidence interval was used from the RM models to estimate the difference in treatment effects (tafluprost-latanoprost).

Efficacy results: The summary of IOP by visit and time point for 0.0015% tafluprost and 0.005% latanoprost is shown in Table 43 for the PP population, study eye. IOP at baseline, Week 1, Week 3, and Week 6, IOP was generally similar among treatment groups. As shown in Table 44, the IOP-reducing effect of 0.0015% tafluprost was similar to that of 0.005% latanoprost for PP population, study eye using ANCOVA.

Table 43: Study 74457 Summary of IOP Change from Baseline (mmHg) by Visit, and Time Point (PP, LOCF)

Visit	Time Point	Tafluprost + Timolol		Vehicle + Timolol	
		N	Mean ± SD (mmHg)	N	Mean ± SD (mmHg)
Week 1	08:00	19	-9.55 ± 3.26	19	-8.82 ± 4.22
Week 3	08:00	18	-9.33 ± 3.39	18	-8.67 ± 3.90
Week 6	08:00	18	-9.69 ± 3.25	18	-8.83 ± 4.31

	12:00	18	-9.31 ± 2.77	18	-9.78 ± 2.37
	16:00	18	-8.36 ± 2.86	18	-8.14 ± 3.56
	20:00	18	-7.53 ± 3.65	18	-7.78 ± 3.54

Source: Table 14.2.1.2 of Study 74457 Report.

Table 44: Study 74457 Analysis of IOP Change from Baseline (mmHg) by Visit, and Time Point (PP, ANCOVA, LOCF)

Visit	Time Point	Tafluprost 0.0015%			Latanoprost 0.005%			Difference	
		N	LS Mean (mmHg)	(95% CI)	N	LS Mean (mmHg)	(95% CI)	LS Mean (mmHg)	(95% CI)
Week 1	08:00	18	-9.3	(-10.5, -8.1)	18	-9.4	(-10.6, -8.2)	0.1	(-1.7, 1.8)
Week 3	08:00	18	-9.0	(-10.1, -7.9)	18	-9.0	(-10.1, -7.9)	0.1	(-1.5, 1.6)
Week 6	08:00	18	-9.4	(-10.7, -8.0)	18	-9.2	(-10.5, -7.8)	-0.2	(-2.1, 1.7)
	12:00	18	-9.1	(-10.1, -8.2)	18	-9.9	(-10.9, -9.0)	0.8	(-0.5, 2.1)
	16:00	18	-8.1	(-9.3, -7.0)	18	-8.4	(-9.5, -7.2)	0.3	(-1.3, 1.9)
	20:00	18	-7.7	(-9.0, -6.5)	18	-7.6	(-8.8, -6.4)	-0.2	(-1.9, 1.5)

Source: Table 2.7.3-elevatediop:12 of Clinical Summary.

Appendix C: Summary of Other Phase III Studies

1. Study 74460

Study 74460 was a randomized, placebo-controlled, Phase III study in patients with open-angle glaucoma or ocular hypertension to investigate the efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy to timolol 0.5% eye drops.

Objectives: 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. The primary hypothesis for efficacy was to show that the IOP-lowering effect of tafluprost 0.0015% was superior to that of the vehicle when used adjunctively to timolol 0.5%, at the end of the 6-week randomized treatment period.

Study Design/Methodology: Randomized, double-masked, placebo-controlled, parallelgroup, multinational, multicenter Phase III trial. The efficacy measurement(s) comprised IOP.

Patients: A total of 185 patients were randomized; 96 to tafluprost and 89 to vehicle treatment.

Diagnosis and criteria for inclusion: 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, 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.

Test products and mode of administration: Tafluprost 0.0015% or vehicle eye drops, one drop once daily at 20:00 in the designated eye(s) as adjunctive therapy to 0.5% Timolol which was applied twice daily at 08:00 and 20:00 in the designated eye(s).

Duration of treatment: 12 weeks: A 6-week randomized treatment period (timolol + tafluprost/vehicle) followed by a 6-week extension period (timolol + tafluprost; vehicle switched to tafluprost).

Criteria for efficacy evaluation: 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, the change from baseline in time-wise IOP (08:00, 10:00 and 16:00) at 12 weeks and the proportion of responders at 12 weeks.

Statistical methods: Mean IOP at all time points during the study (8:00, 10:00, and 16:00 at Weeks 2, 4, and 6) on both the Intention-to-Treat (ITT) and Per-Protocol (PP) populations using ANOVA (including a term for treatment group). Tafluprost was considered superior, if the upper limit of the 95% confidence interval for the difference between groups (tafluprost – vehicle) did not exceed 0 mmHg at all of the time points (or the corresponding p-values were less than or equal to 0.05).

Efficacy results: In the randomized treatment period, an IOP-lowering effect was seen in both treatment groups. 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 (see Table 45).

Table 45: Study 74460 Summary of IOP Change from Baseline (mmHg) by Visit, and Time Point (PP, LOCF)

Visit	Time Point	Tafluprost + Timolol		Vehicle + Timolol	
		N	Mean ± SD (mmHg)	N	Mean ± SD (mmHg)
Week 1	08:00	93	-3.94 ± 3.14	88	-2.63 ± 3.02
	10:00	93	-4.44 ± 3.15	88	-2.16 ± 3.37
	16:00	93	-3.93 ± 3.55	88	-2.32 ± 2.90
Week 3	08:00	91	-5.25 ± 3.28	87	-3.43 ± 3.40
	10:00	91	-5.61 ± 3.11	87	-3.12 ± 3.55
	16:00	91	-5.13 ± 3.74	87	-2.80 ± 3.09
Week 6	08:00	90	-5.49 ± 3.18	85	-4.01 ± 3.63
	10:00	90	-5.82 ± 3.39	85	-3.99 ± 3.78
	16:00	90	-5.53 ± 3.52	85	-4.15 ± 3.54

Source: Table 14.2.1.2 of Study 74460 Report.

2. Study 77552

Study 77552 was a 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. The study was carried out in Finland, Germany, and Sweden.

Objectives: To investigate whether 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.

Study Design/Methodology: Open-label, multinational and multicenter Phase IIIb study. The outcome and safety measures were evaluated both at 6 and 12 weeks (primary analysis).

Patients: Approximately 150 were planned to be enrolled in the study. A total of 158 patients were enrolled.

Diagnosis and criteria for inclusion: Patients aged 18 years or more with ocular hypertension, primary open-angle glaucoma or capsular glaucoma treated with latanoprost 0.005% for at least six months before screening were enrolled. Eligible patients were required to have at least two ocular symptoms OR one ocular symptom and one ocular sign at screening.

Test product and mode of administration: Tafluprost 0.0015 % preservative-free formulation, one drop once daily at 20:00 in the affected eye(s).

Duration of treatment: 12 weeks (followed by a post-study period of 1-3 weeks).

Efficacy criteria/Statistical methods: The change from baseline in the mean IOP (of treated eyes) was analyzed using the repeated measurements analysis of (co)variance method.

Efficacy results: IOP was well controlled at baseline, and was maintained after switching from latanoprost to tafluprost. The mean IOP values were slightly lower after the switch.

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/s/

YUNFAN DENG
07/20/2011

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07/20/2011

I concur with the primary statistical review.

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 202514

Name Of Drug: SAFLUTAN™ (Preservative-Free Tafluprost 0.0015% Ophthalmic Solution)

Applicant: Merck & Co., Inc.

Submission Date: January 07, 2011

Indication(s): Treatment of Elevated Intraocular Pressure (IOP)

Number And Type Of Controlled Clinical Studies (By Indication): 5 Phase III Studies

Statistical Reviewer: Yunfan Deng

Clinical Reviewer: Lucious Lim

Project Manager: Constantine Markos

45 Day Meeting Date: February 16, 2011

Date Draft Review Expected: September 07, 2011

User Fee Date: November 07, 2011

A. ORGANIZATION AND DATA PRESENTATION

- | | YES | NO | N/A |
|---|------------|-----------|------------|
| I. Is there a comprehensive table of contents with adequate indexing and pagination? | ✓ | | |
| II. Are the original protocols, protocol amendments and proposed label provided | ✓ | | |
| III. Are patient profile listings (for <u>all</u> enrolled patients) provided in each study report? | ✓ | | |
| IV. Are adverse event listings by center and time of occurrence relative to enrollment date included? | ✓ | | |
| V. Have the data been submitted electronically? | ✓ | | |
| a. If so, has adequate documentation of the data sets been provided? | ✓ | | |
| b. Do the electronic data appear to accurately represent the data described in the study reports? | ✓ | | |
| c. Can the data be easily merged across studies and indications? | ✓ | | |
| d. Are inclusion/exclusion and evaluability criteria adequately coded and described? | ✓ | | |

B. STATISTICAL METHODOLOGY

- | | YES | NO | N/A |
|---|------------|-----------|------------|
| I. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division? | ✓ | | |
| II. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable subgroups (age, gender, race, etc.)? | ✓ | | |

III. Based on the summary analyses of each study, do you believe:

- a. The analyses are appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives proposed labeling claims)? ✓
 - b. Intent-to-treat and evaluable patient analyses are properly performed? ✓
 - c. Missing data has been appropriately handled? ✓
 - d. Any multiplicity issues (e.g., regarding endpoints, timepoints, or multiple dose groups) have been adequately addressed? ✓
 - e. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made? ✓
- IV. Were sufficient and appropriate reference included for novel statistical approaches? ✓
- V. Are all of the pivotal studies complete? ✓
- VI. Have safety data been comprehensively and adequately summarized? ✓

C. FILEABILITY CONCLUSIONS

From a statistical perspective, is this submission or indications therein, reviewable with only minor further input from the sponsor?

Yes, the submission is filable. In order to help us with the review process, please provide the following information:

- Please provide the integrated datasets and the programs used to conduct the analyses according to the integrated SAP for the ISE and ISS reports.

Yunfan Deng
Mathematical Statistician, DB IV

Concur: Yan Wang
Statistics Team Leader, DB IV

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

/s/

YUNFAN DENG
03/22/2011

YAN WANG
03/22/2011