

**CENTER FOR DRUG EVALUATION AND
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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS.....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES.....	4
1.3 STATISTICAL ISSUES AND FINDINGS.....	5
2. INTRODUCTION	6
2.1 INDICATION.....	6
2.2 HISTORY OF DRUG DEVELOPMENT	6
2.3 SPECIFIC STUDIES REVIEWED AND MAJOR STATISTICAL ISSUES.....	6
2.4 DATA SOURCES.....	6
3. STATISTICAL EVALUATION	7
3.1 EVALUATION OF EFFICACY (STUDY 031).....	7
3.1.1 STUDY DESIGN AND ENDPOINTS	7
3.1.2 SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS	8
3.1.2.1 SUBJECT DISPOSITION	8
3.1.2.2 BASELINE CHARACTERISTICS	10
3.1.3 STATISTICAL METHODOLOGY	12
3.1.4 RESULTS AND CONCLUSIONS	15
3.2 EVALUATION OF SAFETY	22
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	22
5. SUMMARY AND CONCLUSIONS	27
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	27
5.2 CONCLUSIONS AND RECOMMENDATIONS.....	28

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA submission the sponsor seeks approval of bimatoprost ophthalmic solution 0.01% once daily in evenings for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

This submission included data from one pivotal trial (Study 031). Study 031 was a multi-center, double masked, randomized, active-controlled, and non-inferiority study. The study objective was to evaluate the safety and efficacy of bimatoprost 0.01% and bimatoprost 0.0125% once-daily compared with LUMIGAN[®] (bimatoprost ophthalmic solution 0.03%) administered for three months (plus 9-month, masked extension) in patients with glaucoma or ocular hypertension. The IOP measurements were collected at nine post baseline time points: 0 hour, 4 hour, and 8 hours at the visits of Day 0, Week 2, Week 6, and Month 3.

According to the study protocol, there were two sets of primary efficacy endpoints: the mean IOP changes from baseline at all the post baseline time points were considered as the primary efficacy endpoints by the sponsor; and the mean IOP at all the post baseline time points were considered as the primary efficacy endpoints by the FDA clinical review team.

For the primary efficacy endpoints of mean IOP changes from baseline at all the post baseline time points (used by the sponsor), a non-inferiority test was performed. The non-inferiority criteria were defined as follows: if the upper limit of the 2-sided 95% confidence interval (CI) of the between-group difference in the mean IOP change from baseline (tested dose of bimatoprost minus LUMIGAN[®]) was less than 1.5 mm Hg at all the post baseline time points, the tested dose of bimatoprost would be declared non-inferior to LUMIGAN[®].

For the primary efficacy endpoints of mean IOP at all the post baseline time points (used by the FDA clinical review team), an equivalency test was performed. The equivalency criteria were defined as follows: if the 2-sided 95% CI of the between-group difference in the mean IOP (tested dose of bimatoprost minus LUMIGAN[®]) was within ± 1.5 mm Hg at all the post baseline time points and was within ± 1.0 mm Hg at a majority of the time points, the tested dose of bimatoprost would be declared equivalent to LUMIGAN[®].

Results based on the Primary Efficacy Endpoints of Mean IOP Changes from Baseline at All the Post Baseline Time Points (used by the Sponsor)

For the comparison between bimatoprost 0.01% and LUMIGAN[®] (Table 3), at 8/9 time points, the upper limit of the 95% CI of the between-treatment difference was within the 1.50 mm Hg margin. For one time point (Hour 4 at Week 2 visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.5 mm Hg. At three time points (Hours 4 and 8 at Week 2 Visit, and Hour 4 at Month 3 Visit), the lower limit of the 2-sided 95% CI for the group difference was

above zero. At all the post baseline time points, the average IOP reduction in the bimatoprost 0.01% group was smaller than the one in the LUMIGAN[®] group.

For the comparison between bimatoprost 0.0125% and LUMIGAN[®] (Table 3), at 8/9 time points, the upper limit of the 95% CI of the between-treatment difference was within the 1.50 mm Hg margin. For one point (Hour 4 at Week 2 visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.5 mm Hg. At 2/9 time points (Hour 4 at Week 2 Visit, and Hour 4 at Month 3 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP reduction in the bimatoprost 0.0125% group was smaller than the one in the LUMIGAN[®] group.

In conclusion, using the non-inferiority margin of 1.5 mg Hg, study 031 failed to demonstrate non-inferiority of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to LUMIGAN[®] in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Results based on the Primary Efficacy Endpoints of Mean IOP at All the Post Baseline Time Points (used by the FDA clinical review team)

For the comparison between bimatoprost 0.01% and LUMIGAN[®] (Table 5), at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 5/9 time points (Hours 0, 4 and 8 at Week 2 Visit, and Hour 0 at Week 6 Visit, and Hour 4 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was at or above 1.0 mm Hg. At 2/9 time (Hours 4 and 8 at Week 2 Visit) points, the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP in the bimatoprost 0.01% group was higher than the one in the LUMIGAN[®] group.

For the comparison between bimatoprost 0.0125% and LUMIGAN[®] (Table 5), at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 7/9 time points (Hours 0, 4, and 8 at Week 2 Visit, Hour 0 at Week 6 Visit, Hours 0, 4, and 8 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.0 mm Hg. At 2/9 time points (Hours 4 and 8 at Week 2 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP in the bimatoprost 0.0125% group was higher than the one in the LUMIGAN[®] group.

In conclusion, using the equivalency margin of 1.0 mg Hg, study 031 failed to demonstrate equivalency of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to LUMIGAN[®] in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension at a majority of the post baseline time points.

1.2 Brief Overview of Clinical Studies

Study 031 was a multi-center, double masked, randomized, active-controlled, and non-inferiority study. The study duration was one year. However, only the first 3-month data were available and included in this submission. A total of 561 study subjects were randomized with a 1:1:1 ratio to

receive one of three treatment arms: bimatoprost 0.01% (186 subjects), or bimatoprost 0.0125% (188 subjects), or LUMIGAN[®] (187 subjects) once-daily in evenings. The NDA submission included IOP data measured at 0 hour, 4 hour, and 8 hours at the visits of Day 0, Week 2, Week 6, and Month 3.

1.3 Statistical Issues and Findings

There were two statistical issues identified in this review.

The first issue is that the Hochberg's procedure was applied at the level of the measurement time points (performed at each post baseline time point). This might lead to difficulty in the interpretation of the testing results when one dose concentration is tested to be effective at one time point and not effective at another time point. Since an effective dose concentration needs to be demonstrated effectiveness at all post baseline time points, the Hochberg's procedure should be applied at the level of the study drug dose concentrations.

The second issue is related to the testing procedure for the hypothesis "the difference in mean IOP between treatment groups is within 1.0 mm Hg at a majority of the post baseline time points." The sponsor's testing procedure for this hypothesis was that if the 2-sided 95% confidence interval was contained within 1.0 mm Hg at a majority of the post baseline time points, this hypothesis would be accepted. This testing procedure is not appropriate since it doesn't control overall familywise error rate.

Justification of Non-inferiority Margins of 1.0 mm Hg and 1.5 mm Hg

For the non-inferiority test, 1.5 mm Hg was used as the non-inferiority margin. For the equivalency test, 1.0 mm Hg and 1.5 mm Hg were used as the equivalency margins. Justification of these margins was not provided in this NDA submission. These margins were recommended to the sponsor by the FDA clinical review team during the design stage of the study protocol.

Secondary and Sensitivity Efficacy Analyses

Various secondary and sensitivity efficacy analyses were performed by the sponsor. The results of these analyses were consistent with the results of the primary efficacy analyses.

Additional sensitivity efficacy analysis was also performed based on the audit report by the review team from the FDA division of scientific investigations. Two domestic study sites from this study were audited by the review team from the division of scientific investigations. The adverse event reporting from one study site (investigator number 3761) was considered unreliable in the audit report. To examine whether the key efficacy results of the primary endpoints are biased by the data from this study site, the statistical reviewer repeated the primary efficacy analysis for two subgroups: (1) including all the ITT subjects except for those from this site; (2) including all the ITT subjects from this site only. The analysis results were consistent with those observed based on the whole ITT population.

2. INTRODUCTION

2.1 Indication

The sponsor submitted this NDA, under the provisions specified in the Federal Food, Drug and Cosmetic Act, Section 505(b)(1), for bimatoprost ophthalmic solution 0.01%, applied topically once daily in evenings to the eye for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Bimatoprost is the active ingredient in the marketed product LUMIGAN[®] (bimatoprost ophthalmic solution 0.03%, NDA 21275). LUMIGAN[®] has been marketed in the US since March 2001. The indication for LUMIGAN[®] is for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed indication for bimatoprost ophthalmic solution 0.01% is the same as that for LUMIGAN[®].

The sponsor developed the new product in an effort to maintain effective IOP reduction while enhancing safety and tolerability. Compared with LUMIGAN[®], which contains 0.03% bimatoprost and 50 ppm benzalkonium chloride (BAK), this new product contains a third of the concentration of bimatoprost (0.01%) and 200 ppm BAK. The sponsor claimed that the higher concentration of BAK increased the ocular absorption of bimatoprost thus allowing for a lower concentration of bimatoprost to be administered.

2.2 History of Drug Development

The initial IND bimatoprost ophthalmic solution 0.01%, IND 48929, was submitted to the FDA in 1995. The sponsor had an End-of-Phase 2 meeting with the FDA on August 18 of 2005. In this meeting, it was agreed that the sponsor could obtain approval for a lower strength bimatoprost ophthalmic solution based on a single Phase 3 clinical study (study 031).

2.3 Specific Studies Reviewed and Major Statistical Issues

The pivotal study 031 was reviewed to evaluate the efficacy of bimatoprost ophthalmic solution 0.01% for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. There were two statistical issues identified in this review (see section 3.1.3).

2.4 Data Sources

The NDA submission, including the sponsor's study report and data sets for study 031 are available on the EDR at "Cdsub1\evsprod\NDA022184".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy (Study 031)

3.1.1 Study Design and Endpoints

Study 031 was a randomized, double-masked, parallel, multi-center, and active-controlled study in subjects with glaucoma or ocular hypertension. The study subjects were randomized with a 1:1:1 ratio to receive either bimatoprost 0.01%, bimatoprost 0.0125%, or LUMIGAN[®] (bimatoprost ophthalmic solution 0.03%) once-daily in evenings for 3 months (plus 9-month masked extension). The study visits were: prestudy with washout up to 6 weeks, Baseline (Day 0), Weeks 2, 6, Months 3, 6, 9, and 12.

According to the study protocol, there were two sets of primary efficacy endpoints: the mean IOP changes from baseline at all the post baseline time points were considered as the efficacy primary endpoints by the sponsor; and the mean IOP at all the post baseline time points were considered as the primary efficacy endpoints by the FDA clinical review team.

Non-inferiority testing was performed for the primary efficacy endpoints of mean IOP changes from baseline at all the post baseline time points. The non-inferiority criteria were defined as follows: if the upper limit of the 2-sided 95% confidence interval (CI) of the between-group difference in the mean change from baseline in IOP (test dose minus LUMIGAN[®]) was less than 1.5 mm Hg at all the post baseline time points, the test dose would be declared non-inferior to LUMIGAN[®].

Equivalency testing was performed for the primary efficacy endpoints of mean IOP at all the post baseline time points. The equivalency criteria were defined as follows: if the 2-sided 95% CI of the between-group difference in the mean IOP (test dose minus LUMIGAN[®]) was within ± 1.5 mm Hg at all the post baseline time points and was within ± 1.0 mm Hg at a majority of the time points, the test dose would be declared equivalent to LUMIGAN[®].

The key inclusion criteria were: male or female, at least 18 years of age, baseline best-corrected visual acuity score approximately equivalent to a Snellen acuity of 20/100 or better in each eye using a logarithmic visual acuity chart, washout of all IOP-lowering medications, baseline IOP ≥ 22 and ≤ 34 mm Hg in each eye, asymmetry of IOP 5 mm Hg between eyes, required bilateral treatment, IOP likely to be controlled monotherapy.

The key exclusion criteria were: uncontrolled systemic disease; female patients who were pregnant, nursing, or planning a pregnancy, or who were of childbearing potential and not using a reliable means of contraception; recurrent history of ocular seasonal allergies, active ocular disease, history of severe ocular trauma, laser or intraocular eye surgery, filtering or refractive surgery, recent or anticipated alteration of existing chronic systemic therapy that could effect IOP; use of other ocular medications; use of oral, injectable, or topical ophthalmic steroids; corneal abnormalities; contact lenses; significant ocular surface findings at baseline.

There were three analysis populations: safety population, intent-to-treated (ITT) population, and per protocol (PP) population. The safety population consisted of all randomized and treated patients. It was based on the actual treatment received and used in the safety analyses. The ITT population consisted of all randomized patients. It was based on the treatment to which the patient was randomized and used in the primary efficacy analyses. The PP population consisted of ITT patients who had no major protocol deviations. It was used in the efficacy analysis.

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

3.1.2.1 Subject Disposition

The summaries of subject disposition are presented in Table 1.

A total of 561 patients were randomized: 186 patients received bimatoprost 0.01% (Bim 0.01%), 188 patients received bimatoprost 0.0125% (Bim 0.0125%), and 187 patients received LUMIGAN[®]. Twenty-five patients discontinued the study: 3.8% (7/186) in the Bim 0.01% group, 3.7% (7/188) in the Bim 0.0125% group and 5.9% (11/187) in the LUMIGAN[®] group. The main reasons for discontinuation were ocular adverse events: 1.6% (3/186) in the Bim 0.01% group, 0.5% (1/188) in the Bim 0.0125% group and 3.7% (7/187) in the LUMIGAN[®] group.

Table 1: Subject Disposition and Exit Status

	0.01% Bim	0.0125% Bim	Lumigan	Total
Included in Intent-to-Treat Population[a]				
Enrolled	186	188	187	561
Completed	179 (96.2%)	181 (96.3%)	176 (94.1%)	536 (95.5%)
Discontinued	7 (3.8%)	7 (3.7%)	11 (5.9%)	25 (4.5%)
Adverse Events[b]	3 (1.6%)	2 (1.1%)	7 (3.7%)	12 (2.1%)
Ocular	3 (1.6%)	1 (0.5%)	7 (3.7%)	11 (2.0%)
Non-Ocular	1 (0.5%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow Up	1 (0.5%)	2 (1.1%)	0 (0.0%)	3 (0.5%)
Personal Reasons	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Violation	0 (0.0%)	1 (0.5%)	3 (1.6%)	4 (0.7%)
Other	3 (1.6%)	2 (1.1%)	1 (0.5%)	6 (1.1%)
Included in Per Protocol Population[c]				
Enrolled	185	186	187	558
Completed	179 (96.8%)	179 (96.2%)	176 (94.1%)	534 (95.7%)
Discontinued	6 (3.2%)	7 (3.8%)	11 (5.9%)	24 (4.3%)
Adverse Events[b]	3 (1.6%)	2 (1.1%)	7 (3.7%)	12 (2.2%)
Ocular	3 (1.6%)	1 (0.5%)	7 (3.7%)	11 (2.0%)
Non-Ocular	1 (0.5%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow Up	1 (0.5%)	2 (1.1%)	0 (0.0%)	3 (0.5%)
Personal Reasons	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Violation	0 (0.0%)	1 (0.5%)	3 (1.6%)	4 (0.7%)
Other	2 (1.1%)	2 (1.1%)	1 (0.5%)	5 (0.9%)

[a] Including all randomized subjects.

[b] Patients who discontinued due to an AE may be counted as having both an Ocular and Non-ocular AE.

[c] Including all randomized patients with no major protocol deviations.

[d] Including all randomized subjects receiving at least one dose of medication.

Data source: Sponsor's CSR Table 14.1-1.

3.1.2.2 Baseline Characteristics

The summaries of subject disposition are presented in Table 2. There was no marked difference in the baseline demographic characteristics among the three treatment groups.

Table 2: Demographics and Baseline Characteristics

Characteristic		0.01% Bim (N=186)	0.0125% Bim (N=188)	Lumigan (N=187)	Total (N=561)
Age (years)	N	186	188	187	561
	Mean	61.6	64.7	64.2	63.5
	SD	11.73	10.94	11.60	11.49
	Median	62.0	65.0	64.0	64.0
	Min	25	40	23	23
	Max	86	93	94	94
	<45	11 (5.9%)	5 (2.7%)	10 (5.3%)	26 (4.6%)
	45-65	98 (52.7%)	91 (48.4%)	91 (48.7%)	280 (49.9%)
	>65	77 (41.4%)	92 (48.9%)	86 (46.0%)	255 (45.5%)
Sex	N	186	188	187	561
	Male	79 (42.5%)	72 (38.3%)	89 (47.6%)	240 (42.8%)
	Female	107 (57.5%)	116 (61.7%)	98 (52.4%)	321 (57.2%)
Race	N	186	188	187	561
	Caucasian	130 (69.9%)	141 (75.0%)	138 (73.8%)	409 (72.9%)
	Black	28 (15.1%)	25 (13.3%)	23 (12.3%)	76 (13.5%)
	Asian	2 (1.1%)	3 (1.6%)	2 (1.1%)	7 (1.2%)
	Hispanic	25 (13.4%)	17 (9.0%)	23 (12.3%)	65 (11.6%)
	Other	1 (0.5%)	2 (1.1%)	1 (0.5%)	4 (0.7%)
	Black	28 (15.1%)	25 (13.3%)	23 (12.3%)	76 (13.5%)
	Non-Black	158 (84.9%)	163 (86.7%)	164 (87.7%)	485 (86.5%)
Height (cm)	N	186	188	187	561
	Mean	167.37	166.91	168.37	167.55
	SD	9.859	10.300	10.166	10.111
	Median	167.60	165.10	167.60	167.60
	Min	142.2	134.6	146.1	134.6
	Max	188.0	193.0	193.0	193.0
Weight (kg)	N	186	188	187	561
	Mean	87.14	84.99	88.32	86.82
	SD	21.157	20.484	22.545	21.418
	Median	85.05	81.60	84.80	83.90
	Min	44.9	51.7	49.9	44.9
	Max	168.7	157.4	172.4	172.4

Data source: Sponsor's CSR Table 14.1-2.1.

Table 2: Demographics and Baseline Characteristics (continued)

Characteristic			0.01% Bim (N=186)	0.0125% Bim (N=188)	Lumigan (N=187)	Total (N=561)
Iris Color [a]	Blue		40 (21.5%)	49 (26.1%)	56 (29.9%)	145 (25.8%)
	Green		6 (3.2%)	4 (2.1%)	5 (2.7%)	15 (2.7%)
	Brown		77 (41.4%)	69 (36.7%)	77 (41.2%)	223 (39.8%)
	Dark Brown		19 (10.2%)	23 (12.2%)	12 (6.4%)	54 (9.6%)
	Blue/gray		5 (2.7%)	11 (5.9%)	8 (4.3%)	24 (4.3%)
	Blue/gray-brown		4 (2.2%)	7 (3.7%)	2 (1.1%)	13 (2.3%)
	Gray		3 (1.6%)	3 (1.6%)	0 (0.0%)	6 (1.1%)
	Green-brown		4 (2.2%)	1 (0.5%)	3 (1.6%)	8 (1.4%)
	Hazel		27 (14.5%)	20 (10.6%)	23 (12.3%)	70 (12.5%)
	Other		1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (0.5%)
	Dark		96 (51.6%)	92 (48.9%)	89 (47.6%)	277 (49.4%)
	Light		90 (48.4%)	96 (51.1%)	98 (52.4%)	284 (50.6%)
IOP						
Hour 0	N		186	188	187	
	Mean		25.1	25.1	25.0	
	SD		2.91	2.95	2.55	
	Median		24.3	24.0	24.3	
	Min		22.0	22.0	22.0	
	Max		33.3	34.0	34.0	
Hour 4	N		186	188	187	
	Mean		23.0	23.0	23.2	
	SD		3.23	3.27	3.26	
	Median		22.5	22.5	22.5	
	Min		16.0	15.8	16.8	
	Max		34.0	32.8	39.5	
Hour 8	N		185	188	187	
	Mean		22.3	22.4	22.3	
	SD		3.60	3.80	3.16	
	Median		22.0	22.0	22.0	
	Min		13.3	14.3	15.0	
	Max		35.5	43.0	35.5	

[a]Iris Color: Other=Light brown, Gray-brown; Dark=Brown, Dark Brown; Light=Blue, Blue-gray, Blue/gray-brown, Gray, Green, Green-brown, Hazel, and other.

Data source: Sponsor's CSR Table 14.1-2.1 and Table 14.2.-1.1.

3.1.3 Statistical Methodology

Primary Efficacy Endpoints

The mean IOP changes from the baseline at all the post baseline time points were considered as the primary efficacy endpoints by the sponsor. For the FDA clinical review team, the mean IOP measurements at all the post baseline time points were considered as the primary endpoints.

Statistical Reviewer's Comments: For a non-inferiority or equivalency study to demonstrate the effectiveness of a test drug in lowering IOP, the statistical reviewer believes that the mean IOP changes from baseline at the post baseline time points are more clinically meaningful efficacy endpoints than the mean IOP measurements. The rationale is that without comparing to the baseline values, the equivalency of two drugs in terms of the mean IOP measurements at the post baseline time points will not indicate whether the test drug reduces IOP or not.

Statistical Hypotheses

The non-inferiority test was performed for the mean IOP changes at all the post baseline time points. The equivalence test was performed for the mean IOP at all the post baseline time points. Since the issue identified for the non-inferiority analysis method was part of the issues identified for the equivalency analysis method, only the equivalency analysis method is presented in this section.

According to the sponsor's statistical analysis plan, the equivalence of efficacy would be attained if the difference in mean IOP between treatment groups was within ± 1.5 mm Hg at all the post baseline time points; and within ± 1.0 mm Hg at a majority of the post-baseline time points.

Note: the notations used below are from the sponsor's statistical analysis plan.

Let $\Delta_{0.01\%}$ denote the difference in mean IOP of bimatoprost 0.01% minus mean IOP of LUMIGAN[®]. Similarly, let $\Delta_{0.0125\%}$ denote the difference in mean IOP of bimatoprost 0.0125% minus mean IOP of LUMIGAN[®].

For the 1.5 mm Hg margin, the following set of hypotheses was tested for the comparison between bimatoprost 0.01% and LUMIGAN[®] at each time point:

$$\begin{aligned} H_{05}: \Delta_{0.01\%} &\leq -1.5 \text{ mm Hg or } \Delta_{0.01\%} \geq 1.5 \text{ mm Hg} \\ H_{a5}: -1.5 \text{ mm Hg} &< \Delta_{0.01\%} < 1.5 \text{ mm Hg} \end{aligned}$$

Analogous set of hypotheses (denoted as H_{06} and H_{a6} , respectively) was applied to the comparison of bimatoprost 0.0125% versus LUMIGAN[®].

Similarly, analogous hypotheses were applied to the comparisons when the equivalence margin is ± 1.0 mm Hg. The sets of hypotheses are denoted as

$H_{07}: \Delta_{0.01\%} \leq -1.0 \text{ mm Hg or } \Delta_{0.01\%} \geq 1.0 \text{ mm Hg}$

$H_{a7}: -1.0 \text{ mm Hg} < \Delta_{0.01\%} < 1.0 \text{ mm Hg}$

and

$H_{08}: \Delta_{0.0125\%} \leq -1.0 \text{ mm Hg or } \Delta_{0.0125\%} \geq 1.0 \text{ mm Hg}$

$H_{a8}: -1.0 \text{ mm Hg} < \Delta_{0.0125\%} < 1.0 \text{ mm Hg}$

for bimatoprost 0.01% versus LUMIGAN[®] and bimatoprost 0.0125% versus LUMIGAN[®], respectively.

Methods of Analysis

Each set of hypotheses (e.g., H_{05} and H_{a5}) was tested by using the Two One-Sided Tests (TOST) (Schuirmann, 1987). It has been established that a size- α TOST consists of two size- α one-sided tests and is operationally identical to the procedure of declaring equivalence if the ordinary 2-sided $(1-2\alpha)$ 100% confidence interval is contained within the equivalence range. In this study, α was set at 0.025 for TOST.

The tests of equivalence described above were performed at each scheduled post baseline time point. The between-group comparisons were analyzed using the contrasts from a 1-way ANOVA model with a fixed effect of treatment. The two between-treatment differences (i.e., $\Delta_{0.01\%}$ and $\Delta_{0.0125\%}$, respectively) in mean IOP were estimated based on the least squares means from the ANOVA model. Two-sided confidence intervals for $\Delta_{0.01\%}$ and $\Delta_{0.0125\%}$ were generated by using the t-test statistic from the ANOVA model. At each scheduled post-baseline time point, a bimatoprost formulation was considered equivalent to LUMIGAN[®] if its 2-sided null hypothesis was rejected by the TOST at $\alpha = 0.025$.

Multiplicity Assessment

Overall, three types of multiplicity in this procedure were considered for controlling the Type-I error.

(1) Multiplicity due to the two primary comparisons (i.e., bimatoprost 0.01% versus LUMIGAN[®] and bimatoprost 0.0125% versus LUMIGAN[®] at each time point using the margin of $\pm 1.5 \text{ mm Hg}$). Since the requirement is to establish the equivalence of either or both concentrations of bimatoprost and LUMIGAN[®], the significance level is adjusted by applying Hochberg's procedure. Specifically,

Step 1: if both null hypotheses H_{05} and H_{06} are rejected by the TOST at the 0.025 level each, then, both concentrations of bimatoprost will be declared as equivalent to LUMIGAN[®]. Otherwise,

Step 2: if either H_{05} or H_{06} (but not both) is rejected by the TOST at the 0.0125 level, then the bimatoprost concentration whose null hypothesis is rejected will be declared as equivalent to LUMIGAN[®]. Otherwise,

Step 3: neither bimatoprost concentration will be declared as equivalent to LUMIGAN[®].

The above 3-step procedure of hypothesis testing concludes the same as the following confidence interval procedure:

Step 1: if both 2-sided 95% CIs are within ± 1.5 mm Hg, then both bimatoprost concentrations will be considered equivalent to LUMIGAN[®] at the 1.5 mm Hg margin. Otherwise,

Step 2: if only one of the 2-sided 97.5% CI is within ± 1.5 mm Hg, then the associated bimatoprost concentration will be considered equivalent to LUMIGAN[®] at the 1.5 mm Hg margin. Otherwise,

Step 3: neither bimatoprost concentration will be declared equivalent to LUMIGAN[®].

(2) Multiplicity due to the two criteria of comparisons for each concentration at each time point (i.e., at ± 1.5 mm Hg first and, if successful at ± 1.0 mm Hg subsequently). The test for equivalence at ± 1.0 mm Hg is performed only if the bimatoprost concentration is proven to be equivalent to LUMIGAN[®] at 1.5 mm Hg. Both bimatoprost concentrations, or just one, may be declared equivalent to LUMIGAN[®] as permitted by Hochberg's procedure described above. Regardless, once a concentration of bimatoprost is considered equivalent to LUMIGAN[®] at ± 1.5 mm Hg, it will be further declared equivalent to LUMIGAN[®] at ± 1.0 mm Hg if the 2-sided 95% confidence interval is contained within ± 1.0 mm Hg. It is noted that $H_{05} \cap H_{07} = H_{05}$ and since H_{07} can only be rejected if H_{05} is, this fixed sequence test procedure preserves the Type-I error under the closed testing principle. Therefore, no further adjustment of the significance level is required due to 2 criteria of comparisons.

(3) Multiplicity across multiple time points for each concentration. Since the requirement is to establish the equivalence at all time points, there is no need to adjust the significance level in order to control the Type-I error.

Statistical Reviewer's Comments: There were two issues regarding the analysis methods mentioned above and stated in the sponsor's statistical analysis plan.

The first issue is that the Hochberg's procedure was applied at the level of the measurement time points (performed at each time point). This might lead to difficulty in the interpretation of the testing results when one dose concentration is tested to be effective at one time point and not effective at another time point. Since an effective dose concentration needs to be demonstrated effectiveness at all post baseline time points, the Hochberg's procedure should be applied at the level of the study drug dose concentrations.

The second issue is related to the testing procedure for the hypothesis "the difference in mean IOP between treatment groups is within ± 1.0 mm Hg at a majority of the post baseline time points." The sponsor's testing procedure for this hypothesis was that if the 2-sided 95% confidence interval was contained within ± 1.0 mm Hg at a majority of the post baseline time

points, this hypothesis would be accepted. This testing procedure is not appropriate since it doesn't control overall familywise error rate.

Justification of Equivalency Margin

For the non-inferiority test, 1.5 mm Hg was used as the non-inferiority margin. For the equivalency test, 1.0 mm Hg and 1.5 mm Hg were used as the equivalency margins. Justification of these margins was not provided in this NDA submission. These margins were recommended to the sponsor by the FDA clinical review team during the design stage of the study protocol.

3.1.4 Results and Conclusions

Primary Efficacy Endpoints: Mean IOP Changes from Baseline at All Post-baseline Time Points (used by the sponsor)

The analysis results for the mean IOP changes from baseline at all the post-baseline time points are presented in Table 3 for the ITT population (using the LOCF method to impute missing data). The analysis results for the per protocol population (no imputation was made for missing data) are presented in Table 4.

Based on the ITT analysis with LOCF method, the average IOP was reduced at all the post baseline time point in the three treatment groups. The mean IOP changes from baseline ranged from -7.8 to -5.4 mm Hg in the bimatoprost 0.01% group, -7.5 to -5.5 mm Hg in the bimatoprost 0.0125% group, and -8.0 to -5.8 mm Hg in the LUMIGAN[®] group.

The differences in the mean IOP changes from baseline between each of the test drugs and LUMIGAN[®] were all positive, ranging from 0.19 to 1.07 mm Hg, indicating that the IOP reductions in the test drug groups were smaller than the ones in the LUMIGAN[®] group.

For the comparison between bimatoprost 0.01% and LUMIGAN[®] (Table 3), at 8/9 time points, the upper limit of the 95% CI of the between-treatment difference was within the 1.50 mm Hg margin. For one time point (Hour 4 at Week 2 visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.5 mm Hg. At three time points (Hours 4 and 8 at Week 2 Visit, and Hour 4 at Month 3 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP reduction in the bimatoprost 0.01% group was smaller than the one in the LUMIGAN[®] group.

For the comparison between bimatoprost 0.0125% and LUMIGAN[®] (Table 3), at 8/9 time points, the upper limit of the 95% CI of the between-treatment difference was within the 1.50 mm Hg margin. For one point (Hour 4 at Week 2 visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.5 mm Hg. At 2/9 time points (Hour 4 at Week 2 Visit, and Hour 4 at Month 3 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP reduction in the bimatoprost 0.0125% group was smaller than the one in the LUMIGAN[®] group.

The results based on the per protocol population were similar to those based on the ITT population using LOCF method for imputing missing data.

In conclusion, study 031 failed to demonstrate non-inferiority of bimatoprost 0.01% or bimatoprost 0.0125% to LUMIGAN[®] using the non-inferiority criteria defined in the study protocol as follows: if the upper limit of the 2-sided 95% confidence interval (CI) of the between-group difference in the mean change from baseline in IOP (test dose minus LUMIGAN[®]) was less than 1.5 mm Hg at all the post baseline time points, the test dose would be declared non-inferior to LUMIGAN[®].

Primary Efficacy Endpoint (used by the FDA clinical review team): Mean IOP at All Post-baseline Time Points

The analysis results for the mean IOP at all post-baseline time points are presented in Table 5 for the ITT population (using the LOCF method to impute missing data). The summary results for the difference in the mean IOP between each of the test drugs and LUMIGAN[®] are also presented in this Table. The analysis results for the per protocol population (no imputation was made for missing data) are presented in Table 6.

The differences in the mean IOP between each of the test drug does and LUMIGAN[®] were all positive, ranging from 0.23 to 0.86 mm Hg, indicating that the mean IOP in the two test drug groups were higher than the ones in the LUMIGAN[®] group.

For the comparison between bimatoprost 0.01% and LUMIGAN[®] (Table 5), at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 5/9 time points (Hours 0, 4 and 8 at Week 2 Visit, and Hour 0 at Week 6 Visit, and Hour 4 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was at or above 1.0 mm Hg. At 2/9 time (Hours 4 and 8 at Week 2 Visit) points, the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP in the bimatoprost 0.01% group was higher than the one in the LUMIGAN[®] group.

For the comparison between bimatoprost 0.0125% and LUMIGAN[®] (Table 5), at all the time points, the 2-sided 95% CI for the group difference was within 1.5 mm Hg. At 7/9 time points (Hours 0, 4, and 8 at Week 2 Visit, Hour 0 at Week 6 Visit, Hours 0, 4, and 8 at Month 3 Visit), the upper limit of the 2-sided 95% CI for the group difference was above 1.0 mm Hg. At 2/9 time points (Hours 4 and 8 at Week 2 Visit), the lower limit of the 2-sided 95% CI for the group difference was above zero. At all the post baseline time points, the average IOP in the bimatoprost 0.0125% group was higher than the one in the LUMIGAN[®] group.

The efficacy results based on the per protocol population were similar to those based on the ITT population using LOCF method for imputing missing data.

In conclusion, study 031 failed to demonstrate equivalency of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% compared with LUMIGAN[®] using the equivalency criteria defined in the study protocol as follows: if the 2-sided 95% CI of the between-group difference in the mean

IOP (test dose minus LUMIGAN[®] was within ± 1.5 mm Hg at all the post baseline time points and was within ± 1.0 mm Hg at a majority of the time points, the test dose would be declared equivalent to LUMIGAN[®].

Secondary and Sensitivity Efficacy Analyses

Various secondary and sensitivity efficacy analyses were performed by the sponsor. The results of these analyses are consistent with the results of the primary efficacy analyses. The responder analysis results (see Table 14.5-8 in sponsor's clinical study report) showed that the proportions of patients with IOP < 18 mm Hg at every post baseline scheduled time point are 26.3% for Bimatoprost 0.01%, 28.2% for bimatoprost 0.0125%, and 34.8% for LUMIGAN[®] groups, respectively.

Addition sensitivity efficacy analysis was also performed by the statistical reviewer based on the audit report by the review team from the FDA division of scientific investigations. Two domestic study sites from this study were audited by the review team from the division of scientific investigations. The adverse event reporting from one study site (investigator number 3761) was considered unreliable in the audit report. To examine whether the key efficacy results of the primary endpoints are biased by the data from this site, the statistical reviewer repeated the primary efficacy analysis for two subgroups: (1) including all the ITT subjects except for those from this site; (2) including all the ITT subjects from this site only. The analysis results were consistent with those observed based on the whole ITT population.

**Table 3: Mean Change from Baseline Intraocular Pressure (mm Hg) (ITT with LOCF)
Comparison with LUMIGAN® Test of Non-inferiority at 1.5 mm Hg Margin**

Visit	Timepoint	Mean Change from Baseline Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 186/187	Bim 0.0125% / LUMIGAN® N = 188/187
Week 2	Hour 0 Difference ^a (95% CI ^b)	-7.3 / -7.7 0.42 (-0.22 to 1.07)	-7.3 / -7.7 0.35 (-0.29 to 1.00)
	Hour 4 Difference ^a (95% CI ^b)	-5.9 / -7.0 1.07 (0.44 to 1.70)	-5.9 / -7.0 1.04 (0.42 to 1.67)
	Hour 8 Difference ^a (95% CI ^b)	-5.4 / -6.1 0.68 (0.05 to 1.32)	-5.5 / -6.1 0.58 (-0.06 to 1.21)
Week 6	Hour 0 Difference ^a (95% CI ^b)	-7.5 / -7.7 0.24 (-0.40 to 0.87)	-7.3 / -7.7 0.45 (-0.18 to 1.09)
	Hour 4 Difference ^a (95% CI ^b)	-6.2 / -6.8 0.52 (-0.15 to 1.20)	-6.2 / -6.8 0.55 (-0.13 to 1.23)
	Hour 8 Difference ^a (95% CI ^b)	-5.6 / -5.8 0.19 (-0.48 to 0.85)	-5.6 / -5.8 0.22 (-0.44 to 0.89)
Month 3	Hour 0 Difference ^a (95% CI ^b)	-7.8 / -8.0 0.19 (-0.45 to 0.83)	-7.5 / -8.0 0.46 (-0.18 to 1.10)
	Hour 4 Difference ^a (95% CI ^b)	-6.3 / -7.1 0.78 (0.09 to 1.48)	-6.4 / -7.1 0.71 (0.01 to 1.40)
	Hour 8 Difference ^a (95% CI ^b)	-5.9 / -6.1 0.24 (-0.44 to 0.92)	-5.8 / -6.1 0.33 (-0.35 to 1.01)

^a Calculated as test formulation minus LUMIGAN®; a negative value favored the test formulation.

^b 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment.

Data source: Sponsor's CSR Table 11.4-1.

**Table 4: Mean Change from Baseline Intraocular Pressure (mm Hg) (Per Protocol)
Comparison with LUMIGAN® Test of Non-inferiority at 1.5 mm Hg Margin**

Visit	Timepoint	Mean Change from Baseline Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 186/187	Bim 0.0125% / LUMIGAN® N = 188/187
Week 2	Hour 0 Difference ^a (95% CI ^b)	-7.3 / -7.7 0.43 (-0.21 to 1.08)	-7.4 / -7.7 0.30 (-0.34 to 0.95)
	Hour 4 Difference ^a (95% CI ^b)	-6.0 / -7.0 0.92 (0.28 to 1.55)	-6.0 / -7.0 0.96 (0.33 to 1.59)
	Hour 8 Difference ^a (95% CI ^b)	-5.6 / -6.0 0.45 (-0.19 to 1.09)	-5.6 / -6.0 0.47 (-0.17 to 1.10)
Week 6	Hour 0 Difference ^a (95% CI ^b)	-7.5 / -7.8 0.23 (-0.43 to 0.89)	-7.4 / -7.8 0.39 (-0.26 to 1.05)
	Hour 4 Difference ^a (95% CI ^b)	-6.3 / -6.9 0.54 (-0.16 to 1.25)	-6.3 / -6.9 0.55 (-0.15 to 1.25)
	Hour 8 Difference ^a (95% CI ^b)	-5.7 / -5.9 0.25 (-0.45 to 0.94)	-5.6 / -5.9 0.30 (-0.39 to 0.99)
Month 3	Hour 0 Difference ^a (95% CI ^b)	-7.9 / -8.1 0.17 (-0.50 to 0.84)	-7.7 / -8.1 0.41 (-0.27 to 1.08)
	Hour 4 Difference ^a (95% CI ^b)	-6.5 / -7.2 0.66 (-0.04 to 1.36)	-6.5 / -7.2 0.64 (-0.07 to 1.35)
	Hour 8 Difference ^a (95% CI ^b)	-6.0 / -6.3 0.24 (-0.46 to 0.95)	-5.8 / -6.3 0.45 (-0.27 to 1.16)

^a Calculated as test formulation minus LUMIGAN®; a negative value favored the test formulation.

^b 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment.

Data source: Sponsor's CSR Table 11.4.2-1.

**Table 5: Mean Intraocular Pressure (mm Hg) (ITT with LOCF)
Comparison with LUMIGAN® Test of Non-inferiority at 1.5 mm Hg Margin**

Visit	Timepoint	Mean Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 185/187	Bim 0.0125% / LUMIGAN® N = 186/187
Week 2	Hour 0	17.8 / 17.3	17.7 / 17.3
	Difference ^a (95% CI ^b)	0.56 (-0.10 to 1.22)	0.44 (-0.22 to 1.10)
	Hour 4	17.1 / 16.3	17.1 / 16.3
Week 6	Difference ^a (95% CI ^b)	0.84 (0.21 to 1.46)	0.86 (0.23 to 1.48)
	Hour 8	16.9 / 16.2	16.9 / 16.2
	Difference ^a (95% CI ^b)	0.73 (0.10 to 1.35)	0.67 (0.05 to 1.29)
Month 3	Hour 0	17.6 / 17.2	17.8 / 17.2
	Difference ^a (95% CI ^b)	0.37 (-0.25 to 1.00)	0.54 (-0.09 to 1.16)
	Hour 4	16.8 / 16.5	16.8 / 16.5
Month 3	Difference ^a (95% CI ^b)	0.29 (-0.31 to 0.89)	0.37 (-0.23 to 0.97)
	Hour 8	16.7 / 16.4	16.8 / 16.4
	Difference ^a (95% CI ^b)	0.23 (-0.37 to 0.82)	0.32 (-0.28 to 0.91)
Month 3	Hour 0	17.3 / 17.0	17.6 / 17.0
	Difference ^a (95% CI ^b)	0.33 (-0.31 to 0.97)	0.55 (-0.09 to 1.18)
	Hour 4	16.7 / 16.1	16.6 / 16.1
Month 3	Difference ^a (95% CI ^b)	0.55 (-0.05 to 1.16)	0.52 (-0.08 to 1.13)
	Hour 8	16.4 / 16.2	16.6 / 16.2
	Difference ^a (95% CI ^b)	0.28 (-0.31 to 0.87)	0.43 (-0.16 to 1.01)

^a Calculated as test formulation minus LUMIGAN®; a negative value favored the test formulation.

^b 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment.

Data source: Sponsor's CSR Table 11.4-4.

Table 6: Mean Intraocular Pressure (mm Hg) (Per Protocol)
Comparison with LUMIGAN® Test of Non-inferiority at 1.5 mm Hg Margin

Visit	Timepoint	Mean Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 185/187	Bim 0.0125% / LUMIGAN® N = 186/187
Week 2	Hour 0	17.7 / 17.2	17.5 / 17.2
	Difference ^a (95% CI ^b)	0.55 (-0.09 to 1.19)	0.37 (-0.27 to 1.00)
	Hour 4	17.0 / 16.2	17.0 / 16.2
Week 6	Difference ^a (95% CI ^b)	0.83 (0.22 to 1.43)	0.83 (0.23 to 1.43)
	Hour 8	16.9 / 16.1	16.8 / 16.1
	Difference ^a (95% CI ^b)	0.73 (0.11 to 1.35)	0.62 (0.00 to 1.23)
Week 6	Hour 0	17.5 / 17.2	17.7 / 17.2
	Difference ^a (95% CI ^b)	0.34 (-0.29 to 0.96)	0.49 (-0.13 to 1.12)
	Hour 4	16.6 / 16.4	16.8 / 16.4
Month 3	Difference ^a (95% CI ^b)	0.26 (-0.34 to 0.86)	0.40 (-0.20 to 1.00)
	Hour 8	16.7 / 16.4	16.7 / 16.4
	Difference ^a (95% CI ^b)	0.28 (-0.33 to 0.89)	0.33 (-0.28 to 0.94)
Month 3	Hour 0	17.1 / 16.7	17.4 / 16.7
	Difference ^a (95% CI ^b)	0.39 (-0.23 to 1.01)	0.70 (0.08 to 1.33)
	Hour 4	16.5 / 15.8	16.5 / 15.8
Month 3	Difference ^a (95% CI ^b)	0.67 (0.07 to 1.27)	0.73 (0.12 to 1.34)
	Hour 8	16.3 / 15.9	16.4 / 15.9
	Difference ^a (95% CI ^b)	0.45 (-0.14 to 1.04)	0.59 (0.00 to 1.19)

^a Calculated as test formulation minus LUMIGAN®; a negative value favored the test formulation.

^b 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment.

Data source: Sponsor's CSR Table 11.4-4.

3.2 Evaluation of Safety

See clinical team's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The primary efficacy endpoints were analyzed by subgroups based on age, sex, race, and iris color. In general, there were no marked differences in the efficacy results among the various subpopulations (see Tables 7-10).

Table 7: Subgroup Analysis for Age: Mean Intraocular Pressure (mm Hg) for Patients aged < 65 and ≥ 65 years (ITT with LOCF)

Visit/ Timepoint	Overall Population			Age < 65 years			Age ≥ 65 years		
	Mean IOP (Differencea)								
	Bim 0.01% N = 186	Bim 0.0125% N = 188	LUM N = 187	Bim 0.01% N = 105	Bim 0.0125% N = 88	LUM N = 94	Bim 0.01% N = 81	Bim 0.0125% N = 100	LUM N = 93
Baseline									
Hour 0	25.1 (0.14)	25.1 (0.09)	25.0	25.2 (0.16)	25.1 (0.07)	25.0	25.0 (0.10)	25.0 (0.11)	24.9
Hour 4	23.0 (-0.23)	23.0 (-0.18)	23.2	23.0 (-0.13)	23.0 (-0.10)	23.1	23.0 (-0.32)	23.1 (-0.28)	23.3
Hour 8	22.3 (0.04)	22.4 (0.09)	22.3	22.1 (-0.32)	22.0 (-0.32)	22.4	22.6 (0.48)	22.6 (0.47)	22.2
Week 2									
Hour 0	17.8 (0.56)	17.7 (0.44)	17.3	18.1 (1.08)	17.6 (0.63)	17.0	17.5 (-0.03)	17.8 (0.23)	17.6
Hour 4	17.1 (0.84)	17.1 (0.86)	16.3	17.0 (0.73)	17.1 (0.88)	16.3	17.3 (0.98)	17.1 (0.84)	16.3
Hour 8	16.9 (0.73)	16.9 (0.67)	16.2	16.9 (0.77)	16.6 (0.50)	16.1	17.0 (0.70)	17.1 (0.81)	16.3
Week 6									
Hour 0	17.6 (0.37)	17.8 (0.54)	17.2	17.9 (0.93)	17.4 (0.46)	17.0	17.3 (-0.26)	18.1 (0.57)	17.5
Hour 4	16.8 (0.29)	16.8 (0.37)	16.5	16.9 (0.39)	16.6 (0.07)	16.5	16.6 (0.16)	17.1 (0.63)	16.5
Hour 8	16.7 (0.23)	16.8 (0.32)	16.4	16.6 (0.34)	16.3 (0.10)	16.2	16.8 (0.14)	17.1 (0.48)	16.6
Month 3									
Hour 0	17.3 (0.33)	17.6 (0.55)	17.0	17.5 (0.52)	17.3 (0.24)	17.0	17.1 (0.08)	17.8 (0.81)	17.0
Hour 4	16.7 (0.55)	16.6 (0.52)	16.1	16.8 (0.79)	16.3 (0.31)	16.0	16.5 (0.27)	16.9 (0.70)	16.2
Hour 8	16.4 (0.28)	16.6 (0.43)	16.2	16.4 (0.28)	16.1 (0.04)	16.1	16.5 (0.29)	17.0 (0.75)	16.2

Data source: Table 2.7.3.3.3-1 in NDA submission 2.7.3 summary of clinical efficacy.

Table 8: Subgroup Analysis for Sex: Mean Intraocular Pressure (mm Hg) for Male and Female Patients (ITT with LOCF)

Visit/ Timepoint	Overall Population			Male			Female		
	Mean IOP (Differencea)								
	Bim 0.01% N = 186	Bim 0.0125% N = 188	LUM N = 187	Bim 0.01% N = 79	Bim 0.0125% N = 72	LUM N = 89	Bim 0.01% N = 107	Bim 0.0125% N = 116	LUM N = 98
Baseline									
Hour 0	25.1 (0.14)	25.1 (0.09)	25.0	25.3 (-0.08)	25.5 (0.18)	25.4	25.0 (0.37)	24.8 (0.14)	24.6
Hour 4	23.0 (-0.23)	23.0 (-0.18)	23.2	23.1 (-0.81)	23.1 (-0.77)	23.9	23.0 (0.31)	23.0 (0.36)	22.7
Hour 8	22.3 (0.04)	22.4 (0.09)	22.3	22.2 (-0.47)	22.8 (0.19)	22.6	22.4 (0.48)	22.1 (0.14)	21.9
Week 2									
Hour 0	17.8 (0.56)	17.7 (0.44)	17.3	17.2 (-0.04)	18.0 (0.76)	17.3	18.3 (1.00)	17.5 (0.24)	17.3
Hour 4	17.1 (0.84)	17.1 (0.86)	16.3	16.8 (0.72)	17.4 (1.25)	16.1	17.3 (0.90)	17.0 (0.57)	16.4
Hour 8	16.9 (0.73)	16.9 (0.67)	16.2	16.3 (0.24)	17.2 (1.12)	16.1	17.4 (1.06)	16.7 (0.35)	16.3
Week 6									
Hour 0	17.6 (0.37)	17.8 (0.54)	17.2	17.4 (0.23)	17.5 (0.29)	17.2	17.8 (0.47)	18.0 (0.67)	17.3
Hour 4	16.8 (0.29)	16.8 (0.37)	16.5	16.5 (0.03)	16.6 (0.08)	16.5	17.0 (0.49)	17.0 (0.55)	16.5
Hour 8	16.7 (0.23)	16.8 (0.32)	16.4	16.6 (0.23)	16.8 (0.44)	16.3	16.7 (0.20)	16.7 (0.21)	16.5
Month 3									
Hour 0	17.3 (0.33)	17.6 (0.55)	17.0	16.9 (0.10)	17.5 (0.74)	16.8	17.7 (0.46)	17.6 (0.36)	17.2
Hour 4	16.7 (0.55)	16.6 (0.52)	16.1	16.5 (0.57)	16.4 (0.42)	16.0	16.8 (0.51)	16.8 (0.54)	16.3
Hour 8	16.4 (0.28)	16.6 (0.43)	16.2	16.2 (0.32)	16.5 (0.61)	15.9	16.6 (0.21)	16.6 (0.24)	16.4

Data source: Table 2.7.3.3.3-2 in NDA submission 2.7.3 summary of clinical efficacy.

Table 9: Subgroup Analysis for Race: Mean Intraocular Pressure (mm Hg) for Black and Non-Black Patients (ITT with LOCF)

Visit/ Timepoint	Overall Population			Black			Non-Black		
	Mean IOP (Differencea)								
	Bim 0.01% N = 186	Bim 0.0125% N = 188	LUM N = 187	Bim 0.01% N = 28	Bim 0.0125% N = 25	LUM N = 23	Bim 0.01% N = 158	Bim 0.0125% N = 163	LUM N = 164
Baseline									
Hour 0	25.1 (0.14)	25.1 (0.09)	25.0	25.1 (0.56)	24.5 (-0.08)	24.5	25.1 (0.08)	25.1 (0.12)	25.0
Hour 4	23.0 (-0.23)	23.0 (-0.18)	23.2	22.2 (-0.30)	21.6 (-0.98)	22.5	23.1 (-0.19)	23.3 (-0.05)	23.3
Hour 8	22.3 (0.04)	22.4 (0.09)	22.3	22.4 (1.02)	21.0 (-0.35)	21.3	22.3 (-0.10)	22.6 (0.17)	22.4
Week 2									
Hour 0	17.8 (0.56)	17.7 (0.44)	17.3	17.8 (1.72)	17.0 (0.90)	16.1	17.9 (0.40)	17.8 (0.39)	17.5
Hour 4	17.1 (0.84)	17.1 (0.86)	16.3	17.1 (2.00)	15.5 (0.37)	15.1	17.1 (0.67)	17.4 (0.95)	16.4
Hour 8	16.9 (0.73)	16.9 (0.67)	16.2	17.2 (2.60)	16.1 (1.46)	14.6	16.9 (0.45)	17.0 (0.57)	16.4
Week 6									
Hour 0	17.6 (0.37)	17.8 (0.54)	17.2	17.4 (0.96)	16.9 (0.53)	16.4	17.7 (0.30)	17.9 (0.55)	17.4
Hour 4	16.8 (0.29)	16.8 (0.37)	16.5	16.5 (0.41)	15.9 (-0.21)	16.1	16.8 (0.29)	17.0 (0.46)	16.5
Hour 8	16.7 (0.23)	16.8 (0.32)	16.4	16.4 (0.43)	15.5 (-0.52)	16.0	16.7 (0.21)	17.0 (0.45)	16.5
Month 3									
Hour 0	17.3 (0.33)	17.6 (0.55)	17.0	17.4 (2.05)	17.0 (1.73)	15.3	17.3 (0.09)	17.6 (0.39)	17.2
Hour 4	16.7 (0.55)	16.6 (0.52)	16.1	16.8 (2.09)	15.5 (0.78)	14.7	16.7 (0.33)	16.8 (0.50)	16.3
Hour 8	16.4 (0.28)	16.6 (0.43)	16.2	16.5 (1.58)	15.9 (0.92)	14.9	16.4 (0.09)	16.7 (0.37)	16.3

Data source: Table 2.7.3.3.3-3 in NDA submission 2.7.3 summary of clinical efficacy.

Table 10: Subgroup Analysis for Iris Color: Mean Intraocular Pressure (mm Hg) for Patients with Dark and Light Iris Color (ITT with LOCF)

Visit/ Timepoint	Overall Population			Dark			Light		
	Mean IOP (Difference)								
	Bim 0.01% N = 186	Bim 0.0125% N = 188	LUM N = 187	Bim 0.01% N = 96	Bim 0.0125% N = 92	LUM N = 89	Bim 0.01% N = 90	Bim 0.0125% N = 96	LUM N = 98
Baseline									
Hour 0	25.1 (0.14)	25.1 (0.09)	25.0	25.1 (0.12)	24.9 (-0.08)	25.0	25.1 (0.16)	25.2 (0.24)	25.0
Hour 4	23.0 (-0.23)	23.0 (-0.18)	23.2	22.3 (-0.73)	22.8 (-0.20)	23.0	23.7 (0.33)	23.2 (-0.16)	23.4
Hour 8	22.3 (0.04)	22.4 (0.09)	22.3	21.9 (-0.19)	22.2 (0.08)	22.1	22.7 (0.32)	22.5 (0.12)	22.4
Week 2									
Hour 0	17.8 (0.56)	17.7 (0.44)	17.3	17.9 (0.51)	17.8 (0.46)	17.4	17.8 (0.60)	17.6 (0.41)	17.2
Hour 4	17.1 (0.84)	17.1 (0.86)	16.3	17.2 (0.96)	17.0 (0.78)	16.2	17.1 (0.72)	17.3 (0.94)	16.3
Hour 8	16.9 (0.73)	16.9 (0.67)	16.2	17.1 (1.07)	17.0 (0.94)	16.1	16.7 (0.37)	16.8 (0.42)	16.3
Week 6									
Hour 0	17.6 (0.37)	17.8 (0.54)	17.2	17.7 (0.27)	17.8 (0.36)	17.4	17.5 (0.46)	17.8 (0.70)	17.1
Hour 4	16.8 (0.29)	16.8 (0.37)	16.5	17.0 (0.35)	16.9 (0.25)	16.6	16.5 (0.20)	16.8 (0.47)	16.3
Hour 8	16.7 (0.23)	16.8 (0.32)	16.4	16.9 (0.30)	16.9 (0.30)	16.6	16.4 (0.12)	16.7 (0.33)	16.3
Month 3									
Hour 0	17.3 (0.33)	17.6 (0.55)	17.0	17.6 (0.62)	17.7 (0.76)	17.0	17.1 (0.02)	17.4 (0.35)	17.1
Hour 4	16.7 (0.55)	16.6 (0.52)	16.1	17.0 (1.04)	17.0 (1.05)	16.0	16.3 (0.06)	16.3 (0.03)	16.3
Hour 8	16.4 (0.28)	16.6 (0.43)	16.2	16.7 (0.72)	16.6 (0.64)	16.0	16.1 (-0.17)	16.5 (0.23)	16.3

Data source: Table 2.7.3.3.3-4 in NDA submission 2.7.3 summary of clinical efficacy.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were two statistical issues identified in this review.

The first issue is that the Hochberg's procedure was applied at the level of the measurement time points (performed at each post baseline time point). This might lead to difficulty in the interpretation of the testing results when one dose concentration is tested to be effective at one time point and not effective at another time point. Since an effective dose concentration needs to be demonstrated effectiveness at all post baseline time points, the Hochberg's procedure should be applied at the level of the study drug dose concentrations.

The second issue is related to the testing procedure for the hypothesis "the difference in mean IOP between treatment groups is within 1.0 mm Hg at a majority of the post baseline time points." The sponsor's testing procedure for this hypothesis was that if the 2-sided 95% confidence interval was contained within 1.0 mm Hg at a majority of the post baseline time points, this hypothesis would be accepted. This testing procedure is not appropriate since it doesn't control overall familywise error rate.

Justification of Non-inferiority Margins of 1.0 mm Hg and 1.5 mm Hg

For the non-inferiority test, 1.5 mm Hg was used as the non-inferiority margin. For the equivalency test, 1.0 mm Hg and 1.5 mm Hg were used as the equivalency margins. Justification of these margins was not provided in this NDA submission. These margins were recommended to the sponsor by the FDA clinical review team during the design stage of the study protocol.

Secondary and Sensitivity Efficacy Analyses

Various secondary and sensitivity efficacy analyses were performed by the sponsor. The results of these analyses were consistent with the results of the primary efficacy analyses.

Addition sensitivity efficacy analysis was also performed by the statistical reviewer based on the audit report by the review team from the FDA division of scientific investigations. Two domestic study sites from this study were audited by the review team from the division of scientific investigations. The adverse event reporting from one study site (investigator number 3761) was considered unreliable in the audit report. To examine whether the key efficacy results of the primary endpoints are biased by the data from this study site, the statistical reviewer repeated the primary efficacy analysis for two subgroups: (1) including all the ITT subjects except for those from this site; (2) including all the ITT subjects from this site only. The analysis results were consistent with those observed based on the whole ITT population.

5.2 Conclusions and Recommendations

Results based on the Primary Efficacy Endpoints of Mean IOP Changes from Baseline at All the Post Baseline Time Points (used by the Sponsor)

Mean IOP changes from baseline at all the post baseline time points were considered as the primary efficacy endpoints by the sponsor to demonstrate non-inferiority of the test drugs to LUMIGAN[®]. The non-inferiority criteria were defined as follows: if the upper limit of the 2-sided 95% confidence interval (CI) of the between-group difference in the mean change from baseline in IOP (test dose minus LUMIGAN[®]) was less than 1.5 mm Hg at all the post baseline time points, the test dose would be declared non-inferior to LUMIGAN[®].

Using the above non-inferiority criteria, study 031 failed to demonstrate non-inferiority of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to LUMIGAN[®] in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Results based on the Primary Efficacy Endpoints of Mean IOP at All the Post Baseline Time Points (used by the FDA clinical review team)

The mean IOP at all the post baseline time points were considered as the primary efficacy endpoints by the FDA clinical review team. The equivalency criteria were defined as follows: if the 2-sided 95% CI of the between-group difference in the mean IOP (test dose minus LUMIGAN[®]) was within ± 1.5 mm Hg at all the post baseline time points and was within ± 1.0 mm Hg at a majority of the time points, the test dose would be declared equivalent to LUMIGAN[®].

Using the above equivalency criteria, study 031 failed to demonstrate equivalency of efficacy of bimatoprost 0.01% or bimatoprost 0.0125% to LUMIGAN[®] in reducing elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

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