

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science

Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 20-2667  
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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

In this submission, the applicant is seeking approval of preservative-free (PF) 2.0% dorzolamide/0.5% timolol combination for the treatment for lowering elevated Intra-ocular pressure (IOP). The applicant compared the efficacy and tolerability of preservative-free and preservative-containing (PC) formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated IOP. Note that the Agency approved PC COSOPT Sterile Ophthalmic solution (under NDA 20869), a fixed dose combination product of 2% dorzolamide hydrochloride and 0.5% timolol maleate containing the preservative benzalkonium chloride (BAK), for the treatment for lowering elevated intra-ocular pressure on April 7<sup>th</sup>, 1998.

Based on the evaluation of the efficacy and safety data in this submission, this reviewer has made the following conclusions:

In an active-treatment-controlled, parallel, double-masked study in 261 patients with elevated Intraocular pressure  $\geq 22$  mmHg in one or both eyes, COSOPT Preservative-Free treatment is non-inferior to COSOPT Preservative-Containing in lowering IOP (using non-inferiority margin of 1.5 mmHg). The safety profile of COSOPT Preservative-Free was similar to COSOPT Preservative-Containing.

### **1.2 Brief Overview of Clinical Studies**

The current submission contained the efficacy and safety data of study protocol P081. The submission also contains the efficacy results for the studies submitted in NDA 20869 for PC COSOPT™ (approved on April 7, 1998). Note that the agency recommended that the NDA supporting the PF dorzolamide/timolol combination should cross reference the studies submitted in NDA 20869 for PC COSOPT™ (approved on April 7, 1998). See Appendix-1 for Comparisons of efficacy results of study P081/studies submitted in the Original NDA 20,869.

Study 081 was a double masked, parallel, active treatment controlled study of preservative free (PF) 2% dorzolamide hydrochloride /0.5% Timolol Maleate combination and containing preservative (PC) 2% dorzolamide hydrochloride /0.5% Timolol Maleate combination. The study was conducted in one center (Eye Research Associates, Austin, TX, USA) during the Period: May 1997 to December 1997. This study was designed to compare the efficacy and safety of PF 2.0% dorzolamide/0.5% timolol combination with PC 2.0% dorzolamide/0.5% timolol combination in patients with elevated intraocular pressure. Men and women (of childbearing potential using adequate means of contraception) over 21 years of age with open-angle glaucoma or ocular hypertension were admitted. Following a 3-week run-in on 0.5% timolol b.i.d., Day -1 intraocular pressure (IOP) was required to be  $\geq 22$  mm Hg in one or both eyes at 0830 hours in order to enter the study. 131 subjects received PF combination whereas 130 subjects received PC combination drug. Both drugs were administered twice as a combination drug (Drug administered twice a day: 9am and bedtime). Four subjects discontinued the study in PF 2.0%

dorzolamide/0.5% timolol combination treated group and 3 subjects discontinued the study in PC dorzolamide/0.5% timolol combination treated group.

The aim of this study was to compare the efficacy and tolerability of PF and PC formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated intraocular pressure (IOP).

The primary endpoint was the difference between the 0830 (morning trough) IOP obtained at the Week 12 clinical visit and the 0830 (morning trough) IOP obtained on Day -1. IOP measurements taken at approximately 0830 hours (prior to morning dose; trough) and at approximately 1100 hours (2 hours after morning dose; peak) on Day -1 (baseline), Weeks 2, 6, and 12 were used for the efficacy evaluation.

### 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 margin using preservative-containing (PC) formulations of the dorzolamide/timolol fixed combination (COSOPT™) as the active comparator for study P081 was agreed in a Type B Pre-NDA meeting with the Agency held on April 28, 2010. The Agency further agreed that Protocol 081 would support review of an NDA for preservative-free dorzolamide/timolol. The agency recommended that the NDA supporting the PF dorzolamide/timolol combination should cross reference the studies submitted in NDA 20869 for PC COSOPT™ (approved on April 7, 1998).

The reviewer has examined the study results submitted in NDA 20869 for the justification of the 1.5 mmHg margin used in study P018 in the current submission (see Appendix-2 for details). It is difficult for the reviewer to reliably estimate the IOP lowering effect of PC COSOPT™ over placebo and thus to justify the chosen margin of 1.5 mmHG in the setting of study P018 due to following observations:

- There was no placebo arm in the studies in NDA20869.
- Study P081 had lower baseline IOP measurements compared with the studies in NDA20869.
- The PC dorzolamide/timolol treatment (the active control) in study P018 had a smaller average IOP lowering effect (approximately 3.0 mmHg) at 2 hour (peak) compared with those observed in studies from NDA20869 (approximately 4.0 mmHg).

Some preliminary results of an ongoing research project at FDA found that the placebo effect could be in the range of 1.0 mmHg to 2.5 mmHg. Based on this finding and subtracting the placebo effect from the upper bounds of the 95% confidence intervals presented in Table A.2.1 of the Appendix-2, a margin of 1.0 mmHg could be justified if the placebo effect does not exceed 2.0 mmHg, and a margin of 1.5 mmHg could be justified when the placebo effect does not exceed 1.5 mmHg in the setting of study P081.

It should be noted that the results of study P081 show that the upper limits of the 95% confidence intervals at both hours and all the visits are less than 1.0 mmHg in magnitude. Thus, using the margin of 1.0 mmHg, one could conclude that the PF dorzolamide/timolol treatment would be non-inferior to the PC dorzolamide/timolol treatment in lowering IOP.

## **Findings:**

### *Efficacy:*

In patients with elevated IOP, the ocular hypotensive effect of preservative-free 2.0% dorzolamide/0.5% timolol combination administered b.i.d. was found to be non-inferior (using non-inferiority margin of 1.5 mmHg to Preservative-Containing 2.0% dorzolamide/0.5% timolol combination with preservative administered b.i.d. at morning trough (just prior to morning dose). At Week 12, the mean week 12 (trough) IOP change (from baseline) was: -2.9 mm Hg for patients receiving PF dorzolamide/timolol and -2.6 mm Hg for patients receiving PC dorzolamide/timolol. The 95% confidence interval for the estimated treatment difference in mean change from baseline to Week 12 trough IOP was -0.86 to 0.23 mm Hg.

### *Safety:*

There were no statistically significant differences between the treatment groups in the proportion of patients with one or more adverse experiences or of patients with drug-related adverse experiences, serious adverse experiences, discontinuations due to adverse experiences, or discontinuations due to drug related adverse experiences. No patients died during the study. *See clinical review for further details.*

## **2. INTRODUCTION**

### **2.1 Overview**

The Agency approved (on April 7<sup>th</sup>, 1998) PC COSOPT Sterile Ophthalmic solution, a fixed dose combination product of 2% dorzolamide hydrochloride and 0.5% timolol maleate, containing the preservative benzalkonium chloride (BAK or BAC) under NDA 20869. In this NDA, the sponsor proposes to remove 0.0075% benzalkonium chloride from the formulation and develop COSOPT-Preservative-Free Ophthalmic Solution (COSOPT PF) for the same indication as PC COSOPT.

The applicant has been developing the preservative free Sterile Ophthalmic Solution of 2% Dorzolamide Hydrochloride and 0.5% Timolol Maleate under IND 52080 since November 25<sup>th</sup>, 1996. In a Type B Pre-NDA meeting held on April 28, 2010 the Food and Drug Administration (FDA) agreed that Protocol 081 would support review of an NDA for preservative-free dorzolamide/timolol. The agency also agreed that the NDA supporting the PF dorzolamide/timolol combination should cross reference the studies submitted in support of PC COSOPT, and that both ANCOVA (adjusting for baseline) and ANOVA (unadjusted for baseline) results be presented. In addition, the agency requested presentation of these analyses for two endpoints, change from baseline in IOP and raw IOP, at every efficacy visit (Weeks 2, 6,

and 12) and time point (peak and trough). The applicant agreed to submit this additional information.

Note that the preservative free formulation was approved in Europe in 2006. It was approved in many countries around the world based on the clinical equivalence of the preservative-free formulation to the preservative-containing formulation.

## 2.2 Data Sources

The application was electronic (dated February 16, 2011) and can be found in FDA internal network drive of [\\Cdsesub1\n202667\000](#). A summary of the study reviewed in this submission is presented in Table 1.

**Table 1: Summary of the Study (P081) Reviewed**

| STUDY # and protocol title  | Treatment arms  | Primary endpoints/criterion for equivalency)  |
|---|---|---|
| P081: <i>A Multiple-Dose, Double-Masked, Parallel, Active Treatment Controlled Study of Preservative-Free (PF) 2.0% Dorzolamide/0.5% Timolol Combination and PC 2.0% Dorzolamide/0.5% Timolol Combination With Preservative in Patients With Elevated IOP</i> | 1) Arm 1 (n=131): Preservative-free 2.0% dorzolamide/0.5% timolol combination b.i.d. for 12 weeks;<br><br>2) Arm 2(n=130): 2.0% dorzolamide/0.5% timolol combination with preservative b.i.d. for 12 weeks. | Primary endpoint:<br><i>The primary endpoint is the difference between the 0830 (morning trough) IOP obtained at the Week 12 clinical visit and the 0830 (morning trough) IOP obtained on Day -1.</i><br><br>Criterion for equivalency:<br><i>The sponsor's criterion for establishing equivalency was defined as follows: confidence must be 95% or better that the true difference between the 2 treatments in mean IOP changes from Baseline (Day -1) to Week 12 (at morning trough-just prior to morning dose) falls within the Interval (-1.5, 1.5) mm Hg.</i> |

### 3. Statistical Evaluation

#### 3.1 Evaluation of Efficacy

##### 3.1.1 Study Design and Efficacy Endpoints (Study P081)

###### *Study Design*

This was a double-masked, single-center, multiple-dose, parallel, randomized active treatment controlled study of preservative free 2% dorzolamide hydrochloride /0.5% Timolol Maleate combination and 2% dorzolamide hydrochloride /0.5% Timolol Maleate combination. This study was conducted in one center: Eye Research Associates, Austin, TX, USA. Period: May 1997 to December 1997. Men and women over 21 years of age with open-angle glaucoma or ocular Hypertension were included in the study. The study had a run-in-period/screening for 3 weeks (Day -21 to day -2). At the start of the run-in period, patients discontinued their ocular hypotensive therapy and began taking 0.5% timolol ophthalmic solution b.i.d. at 0900 hours and bedtime. During the 3-week run-in period, patients completed a pre-study screening evaluation to determine if they fulfilled the admission/exclusion criteria. The pre-study evaluation included visual acuity, external ocular examination, slit lamp examination, IOP measurement, dilated ophthalmoscopy, pregnancy test (of childbearing potential) and a visual field examination.

The following are the visit schedules:

- Baseline (day -1):

On study Day -1, patients returned to the clinic prior to instillation of the 0.5% timolol ophthalmic solution run-in treatment for an examination at 0830 hours which included an evaluation of visual acuity, slit lamp and external ocular examination and IOP. If the IOP was  $\geq 22$  mm Hg in at least one eye at 0830 hours, patients were eligible to continue with the Day -1 examinations. 131 subjects received preservative free combination and 130 subjects received Preservative containing combination drug. Both drugs were administered twice a combination drug (Drug administered twice a day: 9am and bedtime).

- Day 1: 8:30am (trough) and 11 am (peak):

On Day 1, patients returned to the clinic at 0830 hours. Each patient was assigned to one treatment sequence according to a randomized allocation schedule. To control for confounding of extraneous factors, patients were randomized into each treatment group using a computer generated random allocation schedule. To ensure in-house blinding, the randomization schedule was generated by a statistician who will not be involved in the analysis of this study. The randomization did not involve any stratification variable.

- Week 2 (+/- 2 days): 8:30am (trough) 11am (peak)

- Week 6 (+/- 2 days): 8:30am (trough) 11am (peak)

- Week 12 (+/- 2 days): 8:30am (trough) 11am (peak)

- Last dose + 14 days: follow up phone interview (to report AEs).

Statistical analyses were performed on worse eye (eye with higher IOP at baseline at 8:30am, if eyes tie at that time, choose the eye with highest IOP at baseline at 11am; if eyes tie at that time as well, choose the right eye).

*Sample Size Estimation:*

Power analyses were performed during the planning phase of this study. These analyses indicated that for morning trough (Hour 0), a sample size of 240 patients (120 in each treatment group) provided a 97% probability of concluding equivalency based on the above criterion if the response to the 2 treatments was indeed equal. This computation assumed that the between-patient standard deviation (SD) for changes in IOP was equal to 3.0 mm Hg.

*Patient Disposition:*

Two hundred sixty-one patients from a single U.S. clinical site included in the study. Table 2 below presents the number (%) of patients, who entered, completed, or discontinued the study.

**Table 2: Patient Disposition**

| Demographic/baseline characteristics | Treatment groups             |                              |
|--------------------------------------|------------------------------|------------------------------|
|                                      | PF Dorzolamide /Timolol(131) | PC Dorzolamide /Timolol(130) |
| Randomized                           | 131                          | 130                          |
| Completed                            | 127 (96.9%)                  | 127(97.7%)                   |
| Discontinued:                        | 4                            | 3                            |
| Clinical adverse experience          | 4                            | 3                            |

It can be seen from the above table that the patients were equally distributed to treatment with preserved or preservative-free combination therapy. The number of patients completed/discontinued the study were also equally distributed to treatment with preserved or preservative-free combination therapy.

Seven patients (2.7%) discontinued the study early; 4 (3.1%) patients in the PF dorzolamide/timolol treatment group and 3 (2.3%) patients in the PC dorzolamide/timolol treatment group. All 7 patients discontinued the study due to a clinical adverse experience. Of the 4 patients who discontinued while receiving PF dorzolamide/timolol treatment, 2 discontinued during Week 2, and 2 discontinued during Week 6. Three patients discontinued while receiving PC dorzolamide/timolol, 2 patients discontinued during Week 2, and 1 discontinued during Week 6.

*Demographic and baseline characteristics:*

The demographic and baseline characteristics for the patient population of the study are summarized in the following table:

**Table 3: Demographic and Baseline Characteristics for the Patient Population**

| Demographic/baseline characteristics | Treatment groups             |                              | Total      |
|--------------------------------------|------------------------------|------------------------------|------------|
|                                      | PF Dorzolamide /Timolol(131) | PC Dorzolamide /Timolol(130) |            |
|                                      |                              |                              | 261        |
| Gender:                              |                              |                              |            |
| Male                                 | 64(48.9%)                    | 43(33.1%)                    | 107(41%)   |
| Female                               | 67(51.1%)                    | 87(66.9%)                    | 154 (59%)  |
| Race:                                |                              |                              |            |
| White                                | 96(73.3%)                    | 88(67.7%)                    | 184(70.5%) |
| Non-white                            | 35(26.7%)                    | 42(32.3%)                    | 77(29.5%)  |
| Age-group:                           |                              |                              |            |
| <65                                  | 94(71.8%)                    | 99(76%)                      | 193(74%)   |
| ≥65                                  | 37 (28.2%)                   | 31(24%)                      | 68(26%)    |
| Mean                                 | 56                           | 54.8                         | 55.4       |
| Mean Baseline IOP(hour 0)            | 23.7                         | 23.7                         | 23.7       |
| Iris color category:                 |                              |                              |            |
| Dark                                 | 76(58.0%)                    | 75(57.7%)                    | 151(57.9%) |
| Light                                | 55(42.0%)                    | 55(42.3%)                    | 110(42.1%) |

*Source: Extracted from table 7, page 36, clinical study report*

It can be seen from the above table that the percentages of males and females randomized to PF dorzolamide/timolol were 48.9% and 51.1%, respectively. In contrast, the percentages of males and females randomized to PC dorzolamide/timolol were 33.1% and 66.9%, respectively. This difference in the randomization of males and females between the 2 groups was statistically significant (p-value: 0.012 by Fisher's exact test). No significant differences were found between treatment groups for age-group, race, iris category and baseline IOP. Nominal variables were compared by the Fisher's exact test and continuous variables were compared by t-test.

*Efficacy assessments:*

IOP measurements (by Goldmann applanation) used in the efficacy evaluation were performed at Day -1 (baseline), Week 2, 6, and 12. IOP measured at trough at approximately 0830 hours (prior to morning dose; Hour 0) and peak at approximately 1100 hours (2 hours after morning dose; Hour 2) were analyzed. Ocular hypotensive effects were assessed using changes in IOP measurements from Day -1 (baseline) to those obtained at Weeks 2, 6, and 12. See *Table A.3.1 in the Appendix-3* for the Schedule of Clinical Observations.

*Primary efficacy variable:*

The change in trough IOP from Day -1 (baseline) to Week 12 was defined as the primary efficacy variable. The primary hypothesis was based on the change in IOP from baseline at Week 12. The analysis was performed on the measurements from the patient's worse eye.

*Secondary efficacy variable:*

The change in peak IOP from Day -1 to Week 12 and from Day -1 to Week 2 and Day -1 to Week 6 were defined as secondary efficacy variables.

*Safety:*

Visual acuity, external ocular examination, slit-lamp evaluation, Goldmann applanation IOP (measured on Day 1), ophthalmoscopy, and visual field evaluation, as well as monitoring of adverse experiences were safety parameters in this study. Day 1 assessments of IOP were only used for safety comparisons. Other safety parameters included measures visual acuity, external ocular and slit lamp evaluations, ophthalmoscopy, visual field evaluations, and changes in the cup to disk ratio. Incidence rates for ocular signs and symptoms and for clinical adverse experiences were compared using Fisher's exact tests (two-sided).

### **3.1.2 Statistical Methodologies**

*Patient Population and Approaches to the Analysis:*

Study inclusion criteria dictated that only patients with an IOP of  $\geq 22$  mm Hg in one or both eyes at 0830 hours on Day -1 after the 3-week run-in period were randomized to study therapy. All efficacy analyses were performed using the patient's worse eye. The worse eye was defined as follows:

- The eye with the higher intraocular pressure at 0830 hours on Day -1. If both eyes were equal then the eye with the higher intraocular pressure 1100 hours on Day -1;
- If both eyes were equal then the right eye will be selected.

Two approaches to data analysis were undertaken. The primary analysis was done with an All-Patients-Treated (Intention-to-Treat), Last Observation Carried Forward approach. This approach will be referred to as APT-LOCF. A Per-Protocol, Observed

Cases (PP-OC) approach was used in secondary analyses.

These approaches differ with respect to: 1) inclusion criteria and 2) estimation of missing values as detailed below. Serious protocol violators were identified prior to unblinding of the database based on pre-determined criteria.

*All-Patients-Treated, Last Observation Carried Forward (APT-LOCF)*

The aim of the APT-LOCF approach was to include all randomized patients in the primary treatment efficacy comparison and so the APT-LOCF was based on the Intent-to-Treat principle. Thus, the APT-LOCF analyses were carried out by imputing missing Week 12 IOP values using LOCF with respect to the worse eye. The total number of patients contributing data in patient characteristics, efficacy, and safety Populations are summarized in the following table:

**Table 4: Number of Patients Contributing Data in Patient Characteristics, Efficacy, and Safety Populations**

| Treatment groups/<br>Number of patients                | PF<br>Dorzolamide<br>/Timolol<br>(131) |        | PC<br>Dorzolamide<br>/Timolol<br>(130) |           | Total<br>(261) |        |
|--|--|--------|--|-----------|----------------|--------|
|  | Hour<br>0                              | Hour 2 | Hour 0                                 | Hour<br>2 | Hour<br>0      | Hour 2 |
| Efficacy:  |  |        |  |           |                |        |
| Number of patients<br>with data<br>available(APT-LOCF) | 130<br>130                             |        | 128<br>128                             |           | 258<br>258     |        |
| Safety:  |  |        |  |           |                |        |
| Number of patients                                     | 131<br>131                             |        | 130<br>130                             |           | 261<br>261     |        |

*Source: Extracted from table 4, page 33, clinical study report*

Note that the Day 1 value was not used in the imputation algorithm because it was only a safety measurement. Thus, patients included in the APT-LOCF primary analysis for trough IOP if their worse eye trough IOP was available for any follow-up beyond Day 1. Similarly, patients included in the APT-LOCF secondary analysis for peak IOP if the worse eye peak IOP was available for any follow-up beyond Day 1.

The following table summarizes the number (%) of patients in the primary and secondary Week 12 efficacy analyses at trough (Hour 0):

**Table 5: Number (%) of Patients in Primary and Secondary Week 12 Analysis - Trough (Hour 0)**

|  | PF Dorzolamide /Timolol<br>n (%) | PC Dorzolamide /Timolol<br>n (%) | Total<br>n (%) |
|--|----------------------------------|----------------------------------|----------------|
| Total number entered                       | 131(100%)                        | 130 (100%)                       | 261 (100%)     |
| Week 12 trough IOP observed                | 127 (96.9)                       | 127(97.7)                        | 254(97.3)      |
| Week 12 carried forward from week 6        | 2                                | 1                                | 3              |
| Week 12 carried forward from week 2        | 1                                | 0                                | 1              |
| Total with LOCF                            | 3(2.3%)                          | 1(0.8%)                          | 4(1.5%)        |
| Total with all patients treated (APT-LOCF) | 130(99.2)                        | 128 (98.5)                       | 258(98.9)      |

*Source: Extracted from table 13, page 47, clinical study report*

Two hundred sixty-one patients were randomly assigned to 1 of the 2 treatment groups. Of these, three patients were not included in the primary efficacy evaluation (APT-LOCF) of change in trough IOP from baseline Day -1 to Week 12. All 3 patients were missing trough IOP data for Weeks 2, 6, and 12 and so there were no values available to be carried forward. All discontinued from the study due to clinical adverse events. One (suffered dermatitis/pruritus) of the 3 patients was randomized to the PF dorzolamide/timolol treatment group and 2 (one suffered form suffered dermatitis/pruritus and the other suffered from burning/stinging eye) were randomized to the dorzolamide/timolol group. The APT-LOCF values were imputed according to the algorithm specified in the Statistical Planning and Analysis section of this report.

All 261 patients who entered the study were included in the evaluation of clinical adverse experiences, ocular and non-ocular symptoms, changes in visual acuity, optic nerve cup-to-disc ratios, and emergent or worsening ocular signs of the external and anterior chamber exams, and lens and ophthalmoscopy evaluations. One patient did not use a computerized perimeter for the visual field examination and therefore was missing data for the visual field Global Indices evaluation. Thus, 260 patients are included in this evaluation.

*Per-Protocol, Observed Cases (PP-OC)*

Efficacy was also examined with respect to the per-protocol, observed cases (PP-OC) approach. The Per-Protocol, Observed Cases (PP-OC) analyses were performed after excluding serious protocol violators and without imputing missing data. Serious

protocol violations were assessed on a per visit basis and so a serious protocol violation at one visit will not necessarily imply that all follow-up data were excluded. Two hundred fifty-four patients were included in this analysis. Note that 7 patients were excluded from this evaluation. These included the 3 patients excluded from the APT-LOCF analysis due to lack of any measurements beyond Day 1. In addition, 4 patients (3 patients from PC dorzolamide/timolol treatment group and 1 patient from dorzolamide/timolol treatment group) were excluded from the PP-OC evaluation due to study discontinuation for a clinical adverse event during or after Week 2 and so there were no Week 12. Note that the three patients in PF dorzolamide/timolol treatment group suffered from blurred vision/burning/stinging eye dermatitis/pruritus burning/stinging eye, burning/stinging eye and sinus disorder/headache/dermatitis/pruritus, respectively. One patient in dorzolamide/timolol treatment group suffered from nausea/anorexia.

#### *Hypotheses tested:*

##### *Efficacy:*

The primary efficacy hypothesis tested in study 081 was that the preservative-free formulation would be non-inferior to the preserved formulation with regard to trough ocular hypotensive effect. The two ocular hypotensive therapies would be equivalent if their Day -1 to Week 12 mean changes were within 1.5 mm Hg of each other. Thus, results were presented in terms of a confidence level that the true between-group difference in mean change lies between -1.5 and 1.5 mm Hg. A confidence level  $\geq 95\%$  was the criterion used to conclude non-inferiority. Analogous Day -1 to Week 12 changes in peak IOP as well as changes in trough and peak IOP at Weeks 2 and 6 were similarly analyzed as secondary efficacy endpoints. See Appendix-3 concerning the construction of the confidence interval.

##### *Safety:*

The safety profiles of preservative-free dorzolamide/timolol combination and dorzolamide/timolol containing preservative would be similar. Incidence rates for dichotomous outcomes was compared using Fisher's Exact tests employing two-sided Type I error rates of  $\alpha = 0.05$  with regard to dichotomous safety outcome variables. Mean Day 1 IOP values would be compared between treatments using a Student's t-test.

##### *Efficacy Comparisons*

Two-way analyses of variance (ANOVA) were performed on the IOP (change from baseline) data. Factors examined included main effects of treatment group, patient characteristic group and treatment group by patient characteristic group interaction. Statistical significance for covariate-by-treatment-group interactions was assessed at  $\alpha = 0.100$  because of low statistical power inherent in tests concerning interaction. Each ANOVA model will include a treatment group factor, a covariate factor, and a factor representing covariate by treatment group interaction. If the covariate by treatment group interaction is not significant using an F-test with  $\alpha = 0.10$ , it will be removed from the model prior to testing for covariate main effects. If the covariate interaction is significant with  $p\text{-value} < 0.10$ , then IOP comparisons will be also made within level of the covariate. Significance of covariate main effects was assessed using  $\alpha = 0.05$ .

### 3.1.3 Efficacy Analyses

*Efficacy analyses:* In the following IOP summary statistics and efficacy results by treatment groups are discussed. This reviewer verified the summary statistics and efficacy results provided by the applicant.

*IOP (mm Hg) Summary Statistics by Treatment (Primary and secondary endpoints):*

Table below presents summary statistics for the APT-LOCF approach by treatment for the primary efficacy endpoint of trough IOP and the secondary endpoint of peak IOP.

**Table 6: IOP (mm Hg) Summary Statistics by Treatment of Study P081 (All-patients-treated, last observations carried forward-worse eye)**

| Time             | Wk | Treatment   | N   | Baseline <sup>†</sup> |     |      | Study Value |     |      | Change |     |      | Percent Change |      |       |
|------------------|----|-------------|-----|-----------------------|-----|------|-------------|-----|------|--------|-----|------|----------------|------|-------|
|                  |    |             |     | Mean                  | SD  | Med  | Mean        | SD  | Med  | Mean   | SD  | Med  | Mean           | SD   | Med   |
| Trough<br>(Hr 0) | 2  | PF Dorz/Tim | 130 | 23.7                  | 1.5 | 23.0 | 21.3        | 2.9 | 21.0 | -2.4   | 2.6 | -2.0 | -10.2          | 11.0 | -9.1  |
|                  |    | Dorz/Tim    | 128 | 23.7                  | 1.5 | 23.0 | 21.1        | 2.8 | 21.0 | -2.6   | 2.7 | -2.0 | -10.9          | 11.5 | -9.1  |
|                  | 6  | PF Dorz/Tim | 130 | 23.7                  | 1.5 | 23.0 | 21.0        | 2.7 | 21.0 | -2.7   | 2.4 | -3.0 | -11.4          | 10.2 | -12.0 |
|                  |    | Dorz/Tim    | 128 | 23.7                  | 1.5 | 23.0 | 21.2        | 2.8 | 21.0 | -2.4   | 2.7 | -2.0 | -10.2          | 11.2 | -9.1  |
|                  | 12 | PF Dorz/Tim | 130 | 23.7                  | 1.5 | 23.0 | 20.8        | 2.6 | 21.0 | -2.9   | 2.3 | -3.0 | -12.3          | 9.4  | -12.5 |
|                  |    | Dorz/Tim    | 128 | 23.7                  | 1.5 | 23.0 | 21.1        | 2.5 | 21.0 | -2.6   | 2.2 | -3.0 | -11.0          | 9.3  | -11.1 |
| Peak<br>(Hr 2)   | 2  | PF Dorz/Tim | 130 | 21.2                  | 2.5 | 21.0 | 18.6        | 2.5 | 19.0 | -2.5   | 2.3 | -3.0 | -11.5          | 10.4 | -12.5 |
|                  |    | Dorz/Tim    | 128 | 21.4                  | 2.7 | 21.5 | 18.6        | 2.4 | 19.0 | -2.9   | 2.7 | -3.0 | -12.7          | 11.8 | -12.8 |
|                  | 6  | PF Dorz/Tim | 130 | 21.2                  | 2.5 | 21.0 | 18.4        | 2.3 | 18.0 | -2.8   | 2.4 | -3.0 | -12.5          | 10.9 | -14.3 |
|                  |    | Dorz/Tim    | 128 | 21.4                  | 2.7 | 21.5 | 18.4        | 2.4 | 18.0 | -3.0   | 2.6 | -3.0 | -13.5          | 11.3 | -14.3 |
|                  | 12 | PF Dorz/Tim | 130 | 21.2                  | 2.5 | 21.0 | 18.1        | 2.1 | 18.0 | -3.1   | 2.0 | -3.0 | -14.0          | 8.8  | -14.3 |
|                  |    | Dorz/Tim    | 128 | 21.4                  | 2.7 | 21.5 | 18.2        | 2.3 | 18.0 | -3.2   | 2.3 | -3.0 | -14.3          | 10.4 | -15.2 |

<sup>†</sup> Baseline used in computations for changes in IOP.  
SD = Standard deviation.  
Med = median.

*Source: Extracted from Table 15, page 317, clinical study report, last-observation-carried forward-worse eye*

This table includes summary statistics for IOP at Baseline (Day -1) as well as for change from baseline and percent change from baseline in IOP at Weeks 2, 6, and 12.

**Efficacy at Trough (Hour 0):**

Mean trough IOP in the study ranged (across visits) from 20.8 to 21.3 mmHg, which corresponds to a mean IOP reduction of -2.9 to -2.4 mmHg (percent change in IOP: -12.3 to -10.2%) from the Day -1 baseline. At Week 12, the mean IOP was 20.8 mmHg for patients receiving PF dorzolamide/timolol and 21.1 mmHg for patients receiving PC dorzolamide/timolol. These values represent a mean IOP change of -2.9 mmHg (percent change in IOP: -12.3%) and -2.6 mmHg (percent change in IOP: -11.0%) from baseline for patients receiving PF dorzolamide/timolol and PC dorzolamide/timolol, respectively. Figure 1 in the Appendix-3 illustrates the mean change from baseline (and 95% confidence interval) at Weeks 2, 6, and 12 for trough IOP.

**Efficacy at Peak (Hour 2):**

At peak, the mean IOP ranged (across visits) from 18.1 to 18.6 mmHg, which corresponds to a mean IOP reduction of -3.2 to -2.5 mmHg (percent change in IOP: -14.3 to -11.5%) from baseline. At Week 12, the mean IOP was 18.1 mmHg for patients who were receiving PF dorzolamide/timolol and 18.2 mmHg for patients receiving PC dorzolamide/timolol. These values correspond to mean IOP changes of -3.1 mmHg (percent change in IOP: -14.0%) and -3.2 mmHg (percent change in IOP: -14.3%) from baseline for patients receiving PF dorzolamide/timolol and PC

dorzolamide/timolol, respectively. Figure 2 in the Appendix-2 illustrates the mean change from baseline (and 95% CI) at Weeks 2, 6, and 12 for peak IOP.

*Estimated Difference between Treatments and 95% Confidence Intervals in IOP:*

Table 7 presents the estimated difference between treatments (PF dorzolamide/timolol-dorzolamide/timolol) and the corresponding 95% confidence intervals in IOP for trough and peak at Weeks 2, 6, and 12. Note that there were no significant treatment interactions (*see Table A.3.2 in the Appendix-3*) with regard to age, gender or race for changes in trough or peak IOP from Baseline Day-1 and Week 12.

**Table 7: Estimated Difference between Treatments and 95% Confidence Intervals in IOP (mm Hg): All-Patients-Treated, Last Observation-carried- Forward-worst eye**

| Week          | Sample size             |                         | Mean Change: Difference Between Treatments | Standard Error of Difference | 95% Confidence Interval for Difference Between Mean Changes |
|---------------|-------------------------|-------------------------|--|------------------------------|---|
|               | PF Dorzolamide /Timolol | PC Dorzolamide /Timolol |  |                              |   |
| Trough (Hr 0) |                         |                         |  |                              |   |
| Week 2        | 130                     | 128                     | 0.18                                       | 0.33                         | (-0.47, 0.83)   |
| Week 6        | 130                     | 128                     | -0.29                                      | 0.32                         | (-0.91, 0.34)   |
| Week 12       | 130                     | 128                     | -0.31                                      | 0.28                         | (-0.86, 0.23)   |
| Peak (Hr 2)   |                         |                         |  |                              |   |
| Week 2        | 130                     | 128                     | 0.34                                       | 0.31                         | (-0.27, 0.96)   |
| Week 6        | 130                     | 128                     | 0.25                                       | 0.31                         | (-0.36, 0.87)   |
| Week 12       | 130                     | 128                     | 0.14                                       | 0.27                         | (-0.39, 0.07)   |

*Source: Extracted from table 16, page 46, clinical study report*

It can be seen from the above table that at all trough and peak time points during the study (Weeks 2, 6, and 12), the estimated difference between treatments was less than 0.5 mm Hg. The confidence intervals for all time points include zero. Thus, the 2 treatments were found to be clinically equivalent at the *primary* and *all secondary* efficacy time points.

At Week 12, the mean week 12 (trough) IOP change (from baseline) was: -2.9 mm Hg for patients receiving PF dorzolamide/timolol and -2.6 mm Hg for patients receiving PC dorzolamide/timolol. The 95% confidence interval for the estimated treatment difference in mean change from baseline to Week 12 trough IOP was -0.86 to 0.23 mm Hg. In patients with elevated IOP, the ocular hypotensive effect of preservative-free 2.0% dorzolamide/0.5% timolol combination administered b.i.d. was found to be equivalent (i.e., within 1.5 mm Hg) to that of 2.0% dorzolamide/0.5% timolol combination with preservative administered b.i.d. at morning trough (just prior to morning dose).

Figure 3 and figure 4 (in the Appendix-3) illustrate the estimated treatment differences in mean change, with 95% confidence intervals, at Weeks 2, 6, and 12, for trough and

peak, respectively. It can be seen from figure 3 and figure 4 that both upper and lower limits of the 95% confidence intervals for differences in mean change from baseline are within -1.5 and 1.5. Although the pre-specified primary endpoint in Protocol 081 included change from baseline IOP at trough at week 12, the 95% CIs for the estimated differences in mean change from baseline between the treatments (PF dorzolamide/timolol minus PC dorzolamide/timolol) were contained within the interval from -1 to 1 mmHg at each of the 6 time points in the study.

*PP Analysis:*

Efficacy was also examined with respect to the per-protocol, observed cases (PP-OC) approach. Efficacy results at both trough and peak time are provided in the following table:

**Table 8: Estimated Difference Between Treatments and 95% Confidence Intervals in IOP (mm Hg):Per-protocol, Observed-Cases- Worst Eye**

| Week          | Sample size             |                         | Mean Change: Difference between Treatments | Standard Error of Difference | 95% Confidence Interval for Difference between Mean Changes |
|---------------|-------------------------|-------------------------|--|------------------------------|---|
|               | PF Dorzolamide /Timolol | PC Dorzolamide /Timolol |  |                              |   |
| Trough (Hr 0) |                         |                         |  |                              |   |
| Week 2        | 130                     | 128                     | 0.18                                       | 0.33                         | (0.47, 0.83)  |
| Week 6        | 129                     | 128                     | -0.28                                      | 0.32                         | (-0.90, 0.35)   |
| Week 12       | 127                     | 127                     | -0.32                                      | 0.28                         | (-0.88, 0.23)   |
| Peak (Hr 2)   |                         |                         |  |                              |   |
| Week 2        | 130                     | 128                     | 0.34                                       | 0.31                         | (-0.27, 0.96)   |
| Week 6        | 129                     | 128                     | 0.24                                       | 0.31                         | (-0.37, 0.86)   |
| Week 12       | 127                     | 127                     | 0.17                                       | 0.27                         | (-0.37, 0.70)   |

*Source: Extracted from Appendix 4.19, page 327, clinical study report*

The estimated differences in IOP (mm Hg) between treatments with 95% confidence intervals for trough and peak are provided in the above table. Figures 5 and 6 displaying these confidence intervals are provided in the Appendix-3 for trough (Hour 0) and in for peak (Hour 2). These results were consistent with the primary analysis (APT-LOCF).

*Additional efficacy analyses:*

The FDA requested additional analyses at a pre-NDA meeting held with the Sponsor. The primary results of this study were based upon a pre-specified primary analysis strategy that used change from baseline as the response variable, ANOVA (i.e., unadjusted for baseline IOP) as the statistical method, and APT-LOCF as the analysis approach. A secondary, pre-specified analysis used the same strategy as defined above, but using the PP-OC approach. To assess robustness of the results, the FDA requested additional analyses at a pre-NDA meeting held with the applicant. These included evaluation of the raw IOP (in addition to the change from baseline in IOP) using both ANOVA and analysis of covariance (ANCOVA; i.e., adjusted for baseline IOP) methods for both the APT-LOCF and PP-OC approaches. The applicant reported that these analyses provided similar results to those from the pre-specified analysis strategy and support the overall conclusion that clinical non-inferiority was demonstrated between PF and PC dorzolamide/timolol.

**Reviewer's conclusions:**

*In an active-treatment-controlled, parallel, double-masked study in 261 patients with elevated Intraocular pressure  $\geq 22$  mmHg in one or both eyes, COSOPT Preservative-Free had an IOP-lowering effect which was non-inferior to that of COSOPT (preserved formulation).*

**3.1.4 Safety analyses:**

The applicant presented the summary of the numbers (%) of patients within each treatment group who experienced clinical adverse experiences, drug-related adverse experiences, serious adverse experiences, or discontinued due to adverse experiences during the study. The Clinical Adverse Experience Summary are noted in the following table.

**Table 9: Clinical Adverse Experience Summary**

| Clinical adverse experiences (AEs)            | PF Dorz/Tim<br>(N=131) | PC Dorz/Tim<br>(N=130) |
|---|------------------------|------------------------|
|   | n (%)                  | n (%)                  |
| Number (%) of patients:                       |                        |                        |
| with one or more AEs                          | 35 (26.7)              | 44 (33.8)              |
| with no AE                                    | 96 (73.3)              | 86 (66.2)              |
| with drug-related AEs                         | 27 (20.6)              | 35 (26.9)              |
| with serious AEs                              | 2 (1.5)                | 0 (0.0)                |
| with serious drug-related AEs                 | 0 (0.0)                | 0 (0.0)                |
| who died                                      | 4 (3.1)                | 3 (2.3)                |
| discontinued due to an AE                     | 4(3.1)                 | 2(1.5)                 |
| discontinued due to a drug-related AE         | 0 (0.0)                | 0 (0.0)                |
| discontinued due to a serious AE              | 0 (0.0)                | 0 (0.0)                |
| discontinued due to a serious drug-related AE |                        |                        |

*Source: Extracted from page 4, clinical study report*

It can be seen from the above table that the proportions of patients with any adverse experience while receiving PF dorzolamide/timolol and PC dorzolamide/timolol therapy were 26.7% and 33.8%, respectively. There were no statistically significant differences between the treatment groups in the proportion of patients with one or more adverse experiences (p-value=0.227). Furthermore, there were no statistically significant differences between the 2 treatment groups in the proportions of patients with drug-related adverse experiences (p-value=0.247), serious adverse experiences (p-value=0.498), discontinuations due to adverse experiences (p-value=1.000), or discontinuations due to drug-related adverse experiences (p-value=0.684). No patients died during the study. *See clinical review for further details.*

**Reviewer’s conclusions:** The safety profile of COSOPT Preservative-Free was similar to COSOPT PC (preserved formulation).

#### 4. Subgroup Analysis

##### 4.1.1 Subgroup Analysis by Age, Gender and Race

Summary statistics are provided in the following subsections for the IOP response to treatment for the APT-LOCF approach stratified by each of the following baseline covariates:

- Age (<65, ≥65)
- Sex
- Race (white, other).

The applicant reported that there were no significant treatment interactions (*see Table A.3.2 in the Appendix-3*) with regard to age, gender or race for changes in trough or peak IOP from Baseline Day-1 and Week 12.

##### 4.1.1.1 Subgroup Analysis by Age

The age was dichotomized into <65 and ≥65 years. The 95% confidence interval (produced by this reviewer) of difference between mean changes in IOP are summarized by race in the following table:

**Table 10: Changes in IOP (Worse eye: APT-LOCF) by Age-group at Week 12(0 hr):**

| Age-group | Sample size   |              | PF Dorzo /Tim |               |               | PC Dorz/Tim   |               |               | 95% Confidence Interval         |
|-----------|---------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------------------------|
|           | PF Dorz / Tim | PC Dorz/ Tim | Baseline IOP  | 12-week IOP   | Change in IOP | Baseline IOP  | 12-week IOP   | Change in IOP | Difference Between Mean Changes |
| <65       | 91            | 94           | 23.6<br>(1.4) | 20.9<br>(2.2) | -2.7<br>(2.0) | 23.6<br>(1.3) | 21.1<br>(2.3) | -2.5<br>(2.2) | (-0.72, 0.46)                   |
| ≥65       | 39            | 34           | 24.1<br>(1.7) | 20.6<br>(3.2) | -3.5<br>(2.7) | 23.9<br>(2.0) | 21.1<br>(3.1) | -2.8<br>(2.3) | (-2.25, 0.51)                   |

*Source: Extracted from Appendix 4.1.3, page 315, clinical study report*

The efficacy results for this subgroup analysis showed that for both age-group PF Dorzolamide /Timolol treated group was non-inferior to PC Dorzolamide /Timolol treated group.

#### 4.1.1.2 Subgroup Analysis by Gender

The 95% confidence interval (produced by the reviewer) of difference between mean changes in IOP are summarized by gender in the following table:

**Table 11: Changes in IOP (Worse eye: APT-LOCF) by Gender at Week 12(0 hr):**

| Gender | Sample size   |                | PF Dorz / Tim |               |                | PC Dorz / Tim |               |               | 95% Confidence Interval         |
|--------|---------------|----------------|---------------|---------------|----------------|---------------|---------------|---------------|---------------------------------|
|        | PF Dorz / Tim | PC Dorz / Timo | Baseline IOP  | 12-week IOP   | Change in IOP  | Baseline IOP  | 12-week IOP   | Change in IOP | Difference Between Mean Changes |
| Female | 67            | 86             | 23.8<br>(1.5) | 21.1<br>(2.4) | - 2.6<br>(2.1) | 23.7<br>(1.5) | 21.1<br>(2.5) | -2.6<br>(2.3) | (-0.77, 0.63)                   |
| Male   | 63            | 42             | 23.7<br>(1.6) | 20.4<br>(2.6) | -3.2<br>(2.4)  | 23.7<br>(1.5) | 21.0<br>(2.6) | -2.7<br>(2.1) | (-1.43, 0.38)                   |

Source: Extracted from Appendix 4.1.5, page 319, clinical study report

The efficacy results for this subgroup analysis showed that for either gender PF Dorzolamide /Timolol treated group was non-inferior to PC Dorzolamide /Timolol treated group.

#### 4.1.1.3 Subgroup Analysis by Race

Race was categorized into two groups: White and other. The 95% confidence interval (produced by this reviewer) of difference between mean changes in IOP are summarized by gender in the following table:

**Table 12: Changes in IOP (Worse eye: APT-LOCF) by Race at Week 12(0 hr)**

| Race  | Sample size    |                | PF Dorzolamide /Timolol |               |               | PC Dorzolamide /Timolol |               |               | 95% Confidence Interval         |
|-------|----------------|----------------|-------------------------|---------------|---------------|-------------------------|---------------|---------------|---------------------------------|
|       | PF Dorz / Timl | PC Dorz / Timl | Baseline IOP            | 12-week IOP   | Change in IOP | Baseline IOP            | 12-week IOP   | Change in IOP | Difference Between Mean Changes |
| White | 95             | 86             | 23.8<br>(1.5)           | 20.9<br>(2.7) | -2.9<br>(2.3) | 23.6<br>(1.5)           | 20.9<br>(2.7) | -2.7<br>(2.4) | (-0.83, 0.54)                   |
| Other | 35             | 42             | 23.6<br>(1.5)           | 20.5<br>(2.3) | -3.1<br>(2.2) | 23.8<br>(1.5)           | 21.4<br>(2.1) | -2.4<br>(1.8) | (-1.61, 0.19)                   |

Source: Extracted from Appendix 4.1.4, page 317, clinical study report

The efficacy results for this subgroup analysis showed that for either race PF Dorzolamide /Timolol treated group was non-inferior to PC Dorzolamide /Timolol treated group.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

#### *Statistical Issues:*

There are no major statistical issues for this submission. The choice of 1.5 mmHg as the non-inferiority margin using preservative-containing (PC) formulations of the dorzolamide/timolol fixed combination (COSOPT™) as the active comparator for study P081 was agreed in a Type B Pre-NDA meeting with the Agency held on April 28, 2010. The Agency further agreed that Protocol 081 would support review of an NDA for preservative-free dorzolamide/timolol. The agency recommended that the NDA supporting the PF dorzolamide/timolol combination should cross reference the studies submitted in NDA 20869 for PC COSOPT™ (approved on April 7, 1998).

The reviewer has examined the study results submitted in NDA 20869 for the justification of the 1.5 mmHg margin used in study P018 in the current submission (see Appendix-2 for details). It is difficult for the reviewer to reliably estimate the IOP lowering effect of PC COSOPT™ over placebo and thus to justify the chosen margin of 1.5 mmHg in the setting of study P018 due to following observations:

- There was no placebo arm in the studies in NDA20869.
- Study P018 had lower baseline IOP measurements compared with the studies in NDA20869.
- The PC dorzolamide/timolol treatment (the active control) in study P018 had a smaller average IOP lowering effect (approximately 3.0 mmHg) at 2 hour (peak) compared with those observed in studies from NDA20869 (approximately 4.0 mmHg).

Some preliminary results of an ongoing research project at FDA found that the placebo effect could be in the range of 1.0 mmHg to 2.5 mmHg. Based on this finding and subtracting the placebo effect from the upper bounds of the 95% confidence intervals presented in Table A.2.1 of the Appendix -1, a margin of 1.0 mmHg could be justified if the placebo effect does not exceed 2.0 mmHg, and a margin of 1.5 mmHg could be justified when the placebo effect does not exceed 1.5 mmHg in the setting of study P081.

It should be noted that the results of study P081 show that the upper limits of the 95% confidence intervals at both hours and all the visits are less than 1.0 mmHg in magnitude. Thus, using the margin of 1.0 mmHg, one could conclude that the PF dorzolamide/timolol treatment would be non-inferior to the PC dorzolamide/timolol treatment in lowering IOP.

#### *Collective Evidence:*

The study reviewed was designed to compare the efficacy and safety of preservative-free 2.0% dorzolamide/0.5% timolol combination with 2.0% dorzolamide/0.5% timolol combination containing preservative in patients with elevated intraocular pressure. Patients received either the preserved or preservative-free formulation for 12 weeks following a 3-week open-label 0.5% timolol solution run-in period. The patients were equally distributed to treatment with preserved or preservative-free combination therapy by use of a random allocation schedule. The masked study treatments were considered equivalent if the IOP lowering effect in patients receiving the preservative free formulation was within 1.5 mm Hg of that observed in patients receiving the preserved formulation.

The efficacy data submitted in this application showed that the 95% CIs for the estimated differences in mean change from baseline between the treatments (PF dorzolamide/timolol minus PC dorzolamide/timolol) were contained within the interval from -1 to 1 mmHg at each of the 6 time points in the study. These results support the hypothesis that the ocular hypotensive effect of PF dorzolamide/timolol given b.i.d. is equivalent to PC dorzolamide/timolol given b.i.d.

## **5.2 Conclusions and Recommendation**

The efficacy data in this submission demonstrated that COSOPT Preservative-Free had an IOP-lowering effect which was non-inferior to that of PC COSOPT (preserved formulation). The safety profile of COSOPT Preservative-Free was similar to COSOPT PC(preserved formulation).

## 6. APPENDICES: *Appendix -1, Appendix -2 and Appendix -3*

These appendices contain 1) Comparisons of study P081 and studies submitted in the Original NDA 20,869, 2) Justification of the Non-inferiority Margin, and 3) Table of the schedule of clinical observations, Computation of confidence interval and Figures for Study P081.

### ***Appendix-1: Comparisons of study P081/studies submitted in the Original NDA 20,869***

In this section, this reviewer:

- Compares the studies submitted in NDA 20,869 and study P081 (current submission) with respect to designs, inclusion criteria and efficacy results;

Note that in the pre-NDA meeting (under IND 52080) dated April 28, 2010, the Agency specified the following:

- Protocol 081 (current submission) together with cross reference to the studies submitted in support of COSOPT PC is sufficient to enable a review of a new drug application for the revised formulation of Cosopt;
- Equivalence of Dorzolamide Hydrochloride/Timolol Maleate Preservative-Free Ophthalmic Solution between the two formulations is recommended to be defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over the three month period and being less than 1.0 mmHg for the majority of direct group comparisons; the time points should include both the peak and trough efficacy times for both the test and control agents.

### *Comparisons of study P081 (current submission) and the studies submitted NDA 20,869:*

Table below presents an overview of the Phase 3 studies that were conducted to evaluate the efficacy and safety of dorzolamide/timolol in patients with open angle glaucoma or ocular hypertension and included in the original NDA for COSOPT™ PC.

Table 2.7.3-elevatediop: 2

Overview of Phase 3 Studies  
Patients With Open Angle Glaucoma or Ocular Hypertension

| Protocol Number | Patients Randomized (n) | IOP Inclusion Requirement at Both 0830 and 1030 hours | Screening Period Prior to Baseline Visit | Open-Label Run-In                            | Methodology  |
|-----------------|-------------------------|---|--|--|--|
| 043             | 242                     | ≥22 mmHg in at least 1 eye                            | 2 weeks                                  | 0.5% timolol b.i.d. (all pts.) 0830, bedtime | Parallel, randomized, double-masked, active-controlled, multicenter study following by an open-label extension / 3 months of double-masked therapy followed by a 9 month open label extension  |
| 044             | 350                     | ≥24 mmHg in at least 1 eye                            | 3 weeks                                  | None (washout period)                        | Parallel, randomized, double-masked, active-controlled, multicenter study following by an open-label extension / 3 months of double-masked therapy followed by a 12 month open label extension |
| 047             | 335                     | ≥24 mmHg in at least 1 eye                            | 3 weeks                                  | None (washout period)                        | Parallel, randomized, double-masked, active-controlled, multicenter study / 3 months of double-masked therapy  |
| 058             | 299                     | ≥22 mmHg in at least 1 eye                            | 2 weeks                                  | 0.5% timolol b.i.d. (all pts.) 0830, bedtime | Parallel, randomized, double-masked, active-controlled, multicenter study / 3 months of double-masked therapy  |
| 063             | 253                     | ≥22 mmHg in at least 1 eye                            | 3 weeks                                  | 0.5% timolol b.i.d. (all pts.) 0900, bedtime | Parallel, randomized, double-masked, active-controlled, 3 month multicenter study / 3 months of double-masked therapy  |

Overview of Phase 3 Studies  
Patients With Open Angle Glaucoma or Ocular Hypertension (Cont.)

| Protocol Number | Patients Randomized (n) | IOP Inclusion Requirement at Both 0830 and 1030 hours | Screening Period Prior to Baseline Visit | Open-Label Run-In                            | Methodology  |
|-----------------|-------------------------|---|--|--|--|
| 064             | 247                     | ≥22 mmHg in at least 1 eye                            | 3 weeks                                  | 0.5% timolol b.i.d. (all pts.) 0900, bedtime | Parallel, randomized, double-masked, active-controlled, multicenter study / 3 months of double-masked therapy  |
| 081             | 261                     | ≥22 mmHg in at least 1 eye                            | 3 weeks                                  | 0.5% timolol b.i.d. (all pts.) 0900, bedtime | Parallel, randomized, double-masked, active-treatment controlled, multiple-dose, randomized, single-center study / 3 months of double-masked therapy |

[Ref. 5.3.5.1: P081] and NDA 20,869, COSOPT™, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998)

*Note: Extracted from Applicant's Clinical Summary Report submitted in Module 2, Pages 7-8-*

It can be seen from the above table that four studies comparing PC dorzolamide/timolol to each of its components were included in NDA 20,869, COSOPT™ PC, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998). Protocol 044 and Protocol 047 were conducted in patients who had bilateral open-angle glaucoma or ocular hypotension and whose IOP was ≥ 24 mmHg after washout of any previous ocular hypotensive therapy. These studies did not have an open label run-in period. Protocol 063 and Protocol 064 were conducted in patients whose IOP was ≥ 22 mmHg after at least 3 weeks of treatment with 0.5% timolol b.i.d. Two studies comparing PC dorzolamide/timolol to the concomitant administration of 2.0% dorzolamide and 0.5% timolol b.i.d. were included in NDA 20,869, COSOPT™ PC, Dorzolamide Hydrochloride/Timolol Maleate combination (Approval date: April 7, 1998). Protocol 043 and Protocol 058 were conducted in patients who had bilateral open angle glaucoma or ocular hypotension and whose IOP was ≥ 22 mmHg after at least 2 weeks of treatment with 0.5% timolol b.i.d. Dorzolamide Hydrochloride/Timolol Maleate Preservative-Free Ophthalmic Solution.

Tables below present summary statistics for the APT-LOCF approach by treatment for the primary efficacy endpoint of trough IOP and the secondary endpoint of peak IOP for PF dorzolamide/timolol, PC dorzolamide/timolol, and dorzolamide/timolol.

**Appendix 2.7.3-elevatediop:8 (sponsor's)**  
**IOP (mmHG) Summary Statistics by Treatment All-Patients-Treated Last-Observation –Carried –Forward-Worse Eye-Trough(Hour 0) and Peak (hour 2)**  
**Protocol 081 and 6 Cosopt Approved NDA Phase 3 Studies**

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| Time             | Wk/Mo | Treatment                 | N                         | Baseline <sup>1</sup> |      |      | Study Value |      |      | Change |      |      | Percent Change |       |       |       |
|------------------|-------|---------------------------|---------------------------|-----------------------|------|------|-------------|------|------|--------|------|------|----------------|-------|-------|-------|
|                  |       |                           |                           | Mean                  | SD   | Med  | Mean        | SD   | Med  | Mean   | SD   | Med  | Mean           | SD    | Med   |       |
| Trough<br>(Hr 0) | Wk 2  | P081 PF Dorz/Tim          | 130                       | 23.7                  | 1.5  | 23.0 | 21.3        | 2.9  | 21.0 | -2.4   | 2.6  | -2.0 | -10.2          | 11.0  | -9.1  |       |
|                  |       | P081 Dorz/Tim             | 128                       | 23.7                  | 1.5  | 23.0 | 21.1        | 2.8  | 21.0 | -2.6   | 2.7  | -2.0 | -10.9          | 11.5  | -9.1  |       |
|                  |       | P043 Dorz/Tim             | 115                       | 26.0                  | 3.0  | 25.0 | 22.9        | 4.2  | 22.0 | -3.1   | 3.1  | -3.0 | -12.0          | 11.8  | -12.5 |       |
|                  |       | P044 Dorz/Tim             | 113                       | 27.2                  | 3.4  | 26.0 | 20.1        | 3.6  | 20.0 | -7.1   | 3.3  | -7.0 | -25.9          | 11.1  | -26.7 |       |
|                  |       | P058 Dorz/Tim             | 150                       | 25.6                  | 3.1  | 25.0 | 21.8        | 4.0  | 21.2 | -3.8   | 3.2  | -4.0 | -14.6          | 11.9  | -14.8 |       |
|                  |       | P047 Dorz/Tim             | 113                       | 27.9                  | 5.0  | 26.0 | 19.7        | 4.1  | 20.0 | -8.1   | 4.6  | -7.0 | -28.5          | 13.3  | -28.0 |       |
|                  | Wk 6  | P063 Dorz/Tim             | 99                        | 25.5                  | 3.4  | 24.0 | 22.6        | 3.4  | 22.0 | -2.9   | 3.3  | -3.0 | -10.9          | 11.7  | -10.0 |       |
|                  |       | P064 Dorz/Tim             | 99                        | 25.7                  | 3.0  | 25.0 | 22.9        | 3.4  | 23.0 | -2.9   | 3.7  | -3.0 | -10.6          | 13.2  | -9.1  |       |
|                  |       | P081 PF Dorz/Tim          | 130                       | 23.7                  | 1.5  | 23.0 | 21.0        | 2.7  | 21.0 | -2.7   | 2.4  | -3.0 | -11.4          | 10.2  | -12.0 |       |
|                  |       | P081 Dorz/Tim             | 128                       | 23.7                  | 1.5  | 23.0 | 21.2        | 2.8  | 21.0 | -2.4   | 2.7  | -2.0 | -10.2          | 11.2  | -9.1  |       |
|                  |       | Wk 12                     | P081 PF Dorz/Tim          | 130                   | 23.7 | 1.5  | 23.0        | 20.8 | 2.6  | 21.0   | -2.9 | 2.3  | -3.0           | -12.3 | 9.4   | -12.5 |
|                  |       |                           | P081 Dorz/Tim             | 128                   | 23.7 | 1.5  | 23.0        | 21.1 | 2.5  | 21.0   | -2.6 | 2.2  | -3.0           | -11.0 | 9.3   | -11.1 |
|                  | Mo 6  | P043 Dorz/Tim*            | 107                       | 25.9                  | 2.9  | 25.0 | 22.1        | 3.8  | 22.0 | -3.8   | 2.8  | -4.0 | -14.6          | 10.7  | -15.4 |       |
|                  |       | P044 Dorz/Tim*            | 110                       | 27.3                  | 3.5  | 26.0 | 19.6        | 3.1  | 19.5 | -7.7   | 3.6  | -7.0 | -27.7          | 10.9  | -26.9 |       |
|                  |       | P058 Dorz/Tim             | 151                       | 25.6                  | 3.1  | 25.0 | 21.4        | 4.1  | 21.0 | -4.2   | 3.3  | -4.0 | -16.3          | 12.5  | -16.7 |       |
|                  |       | P047 Dorz/Tim             | 114                       | 27.8                  | 5.0  | 26.0 | 20.1        | 4.5  | 19.5 | -7.7   | 4.2  | -8.0 | -27.4          | 13.1  | -29.4 |       |
|                  |       | P063 Dorz/Tim             | 102                       | 25.5                  | 3.4  | 24.0 | 22.7        | 3.9  | 22.0 | -2.8   | 3.4  | -2.8 | -10.6          | 12.5  | -10.4 |       |
|                  |       | P064 Dorz/Tim             | 100                       | 25.7                  | 3.0  | 25.0 | 22.6        | 4.0  | 22.0 | -3.2   | 3.3  | -3.0 | -12.1          | 12.4  | -12.0 |       |
|                  |       | P043 Dorz/Tim-Open label* | 105                       | 26.0                  | 2.9  | 25.0 | 22.2        | 4.3  | 22.0 | -3.8   | 3.2  | -4.0 | -14.8          | 12.6  | -16.7 |       |
|                  |       | P044 Dorz/Tim-Open label* | 108                       | 27.4                  | 3.5  | 26.0 | 20.1        | 3.8  | 19.0 | -7.3   | 3.9  | -7.0 | -26.3          | 12.5  | -26.9 |       |
|                  |       | Mo 9                      | P043 Dorz/Tim-Open label* | 105                   | 26.0 | 2.9  | 25.0        | 22.3 | 3.9  | 22.0   | -3.6 | 3.1  | -4.0           | -13.9 | 11.6  | -14.3 |
|                  |       |                           | P044 Dorz/Tim-Open label* | 108                   | 27.4 | 3.5  | 26.0        | 19.6 | 3.6  | 19.0   | -7.7 | 3.8  | -8.0           | -27.9 | 11.7  | -28.9 |

**IOP (mmHG) Summary Statistics by Treatment All-Patients-Treated Last-Observation –Carried –Forward-Worse Eye-Trough(Hour 0) and Peak (hour 2) Protocol 081 and 6 Cosopt Approved NDA Phase 3 Studies (continued)**

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| Time  | Wk/Mo | Treatment                 | N   | Baseline <sup>†</sup> |     |      | Study Value |     |      | Change |     |      | Percent Change |      |       |
|---|-------|---------------------------|-----|-----------------------|-----|------|-------------|-----|------|--------|-----|------|----------------|------|-------|
|   |       |                           |     | Mean                  | SD  | Med  | Mean        | SD  | Med  | Mean   | SD  | Med  | Mean           | SD   | Med   |
| Trough  | Mo 12 | P043 Dorz/Tim-Open label* | 105 | 26.0                  | 2.9 | 25.0 | 22.4        | 5.1 | 22.0 | -3.5   | 4.3 | -4.0 | -13.7          | 15.5 | -14.3 |
|   |       | P044 Dorz/Tim-Open label* | 108 | 27.4                  | 3.5 | 26.0 | 19.8        | 4.2 | 20.0 | -7.6   | 3.9 | -8.0 | -27.5          | 12.8 | -28.6 |
|   | Mo 15 | P044 Dorz/Tim-Open label* | 108 | 27.4                  | 3.5 | 26.0 | 19.7        | 4.1 | 19.0 | -7.6   | 4.2 | -7.5 | -27.6          | 12.9 | -28.6 |
| <sup>†</sup> Baseline used in when computing changes in IOP<br>* Week 12 was the final visit of the double-masked phase for patients who continued into the open-label phase.<br>SD= Standard deviation<br>Med=Median |       |                           |     |                       |     |      |             |     |      |        |     |      |                |      |       |

*Note: Extracted from Applicant’s Clinical Summary Report(submitted in Module 2), Pages 38-39*

**IOP (mmHG) Summary Statistics by Treatment All-Patients-Treated Last-Observation –Carried –Forward-Worse Eye-Trough(Hour 0) and Peak (hour 2) Protocol 081 and 6 Cosopt Approved NDA Phase 3 Studies(continued)**

| Time           | Wk/Mo | Treatment                 | N   | Baseline <sup>†</sup> |     |      | Study Value |     |      | Change |     |      | Percent Change |      |       |
|----------------|-------|---------------------------|-----|-----------------------|-----|------|-------------|-----|------|--------|-----|------|----------------|------|-------|
|                |       |                           |     | Mean                  | SD  | Med  | Mean        | SD  | Med  | Mean   | SD  | Med  | Mean           | SD   | Med   |
| Peak<br>(Hr 2) | Wk 2  | P081 PF Dorz/Tim          | 130 | 21.2                  | 2.5 | 21.0 | 18.6        | 2.5 | 19.0 | -2.5   | 2.3 | -3.0 | -11.5          | 10.4 | -12.5 |
|                |       | P081 Dorz/Tim             | 128 | 21.4                  | 2.7 | 21.5 | 18.6        | 2.4 | 19.0 | -2.9   | 2.7 | -3.0 | -12.7          | 11.8 | -12.8 |
|                |       | P043 Dorz/Tim             | 114 | 25.1                  | 3.3 | 24.0 | 20.5        | 3.9 | 20.0 | -4.6   | 3.2 | -4.0 | -18.1          | 12.2 | -17.6 |
|                |       | P044 Dorz/Tim             | 113 | 26.8                  | 3.6 | 26.0 | 18.0        | 3.3 | 18.0 | -8.8   | 3.4 | -9.0 | -32.6          | 10.7 | -33.3 |
|                |       | P058 Dorz/Tim             | 151 | 24.7                  | 3.2 | 24.0 | 19.5        | 3.6 | 19.0 | -5.2   | 2.9 | -5.0 | -20.9          | 11.1 | -22.2 |
|                |       | P047 Dorz/Tim             | 111 | 27.1                  | 4.4 | 26.0 | 18.0        | 3.5 | 18.0 | -9.1   | 3.9 | -8.0 | -33.1          | 11.2 | -32.0 |
|                |       | P063 Dorz/Tim             | 100 | 25.0                  | 4.0 | 24.0 | 21.0        | 4.0 | 21.0 | -4.0   | 3.1 | -4.0 | -15.8          | 11.4 | -16.7 |
|                |       | P064 Dorz/Tim             | 99  | 24.2                  | 2.6 | 23.5 | 20.1        | 3.0 | 20.0 | -4.1   | 2.7 | -4.0 | -16.7          | 10.6 | -17.4 |
|                |       | P081 PF Dorz/Tim          | 130 | 21.2                  | 2.5 | 21.0 | 18.4        | 2.3 | 18.0 | -2.8   | 2.4 | -3.0 | -12.5          | 10.9 | -14.3 |
|                | Wk 6  | P081 Dorz/Tim             | 128 | 21.4                  | 2.7 | 21.5 | 18.4        | 2.4 | 18.0 | -3.0   | 2.6 | -3.0 | -13.5          | 11.3 | -14.3 |
|                |       | P081 PF Dorz/Tim          | 130 | 21.2                  | 2.5 | 21.0 | 18.1        | 2.1 | 18.0 | -3.1   | 2.0 | -3.0 | -14.0          | 8.8  | -14.3 |
|                |       | P081 Dorz/Tim             | 128 | 21.4                  | 2.7 | 21.5 | 18.2        | 2.3 | 18.0 | -3.2   | 2.3 | -3.0 | -14.3          | 10.4 | -15.2 |
|                |       | P043 Dorz/Tim*            | 107 | 24.8                  | 2.9 | 24.0 | 19.7        | 3.5 | 19.0 | -5.1   | 3.4 | -5.0 | -20.3          | 12.8 | -21.7 |
|                |       | P044 Dorz/Tim*            | 110 | 26.9                  | 3.6 | 26.0 | 17.8        | 2.8 | 17.0 | -9.1   | 3.5 | -9.0 | -33.3          | 10.0 | -34.3 |
|                |       | P058 Dorz/Tim             | 151 | 24.7                  | 3.2 | 24.0 | 19.4        | 3.7 | 19.0 | -5.4   | 3.1 | -5.0 | -21.6          | 12.3 | -22.2 |
|                |       | P047 Dorz/Tim             | 112 | 27.1                  | 4.3 | 26.0 | 18.1        | 3.8 | 18.0 | -9.0   | 4.3 | -9.0 | -32.7          | 12.9 | -33.3 |
|                |       | P063 Dorz/Tim             | 103 | 25.0                  | 3.9 | 24.0 | 20.7        | 4.5 | 20.0 | -4.4   | 3.3 | -4.5 | -17.3          | 12.9 | -18.2 |
|                |       | P064 Dorz/Tim             | 100 | 24.2                  | 2.6 | 23.5 | 20.1        | 3.9 | 20.0 | -4.0   | 3.0 | -4.0 | -16.8          | 12.8 | -16.7 |
|                | Mo 6  | P043 Dorz/Tim-Open label* | 105 | 24.9                  | 2.9 | 24.0 | 19.5        | 3.4 | 20.0 | -5.4   | 3.4 | -5.0 | -21.4          | 12.5 | -21.7 |
|                |       | P044 Dorz/Tim-Open label* | 108 | 26.9                  | 3.7 | 26.0 | 18.1        | 3.5 | 18.0 | -8.9   | 3.5 | -9.0 | -32.6          | 10.7 | -34.5 |
|                |       | P043 Dorz/Tim-Open label* | 105 | 24.9                  | 2.9 | 24.0 | 19.9        | 3.3 | 20.0 | -5.0   | 3.3 | -5.0 | -19.7          | 12.7 | -20.8 |
|                | Mo 9  | P044 Dorz/Tim-Open label* | 108 | 26.9                  | 3.7 | 26.0 | 17.9        | 3.4 | 17.5 | -9.0   | 3.8 | -9.0 | -33.0          | 11.1 | -34.3 |

**IOP (mmHG) Summary Statistics by Treatment All-Patients-Treated Last-Observation –Carried –Forward-Worse Eye-Trough(Hour 0) and Peak (hour 2) Protocol 081 and 6 Cosopt Approved NDA Phase 3 Studies(continued)**

| Time | Wk/Mo | Treatment                 | N   | Baseline <sup>†</sup> |     |      | Study Value |     |      | Change |     |      | Percent Change |      |       |
|------|-------|---------------------------|-----|-----------------------|-----|------|-------------|-----|------|--------|-----|------|----------------|------|-------|
|      |       |                           |     | Mean                  | SD  | Med  | Mean        | SD  | Med  | Mean   | SD  | Med  | Mean           | SD   | Med   |
| Peak | Mo 12 | P043 Dorz/Tim-Open label* | 105 | 24.9                  | 2.9 | 24.0 | 19.8        | 5.1 | 19.0 | -5.1   | 4.5 | -6.0 | -20.5          | 16.4 | -21.7 |
|      |       | P044 Dorz/Tim-Open label* | 108 | 26.9                  | 3.7 | 26.0 | 17.6        | 3.9 | 17.0 | -9.3   | 4.0 | -9.0 | -34.3          | 12.1 | -35.6 |
|      |       | P044 Dorz/Tim-Open label* | 108 | 26.9                  | 3.7 | 26.0 | 18.1        | 3.7 | 18.0 | -8.8   | 3.9 | -9.0 | -32.4          | 11.9 | -33.3 |

<sup>†</sup> Baseline used in when computing changes in IOP  
\* Week 12 was the final visit of the double-masked phase for patients who continued into the open-label phase.  
SD= Standard deviation.  
Med=Median

Note: Extracted from Applicant’s Clinical Summary Report(submitted in Module 2), Pages 40-41

It can be seen from the above two tables that the IOP lowering effects of PF dorzolamide/timolol (e.g., -2.9 at hour 0 and -3.1 at hour 2) and PC dorzolamide/timolol (e.g.,-2.6 at hour 0 and -3.2 at hour 2) at week 12 in study P081 (current submission) were somewhat less than the average IOP lowering activity that has been previously reported for PC dorzolamide/timolol at trough and peak ( -3.71 and -5.71, respectively at week 12). However, mean IOP values observed at Week 12 in study P081, 20.8 mmHg and 21.1 mmHg at trough and 18.1 mmHg and 18.2 mmHg at peak for PF dorzolamide/timolol and PC dorzolamide/timolol respectively, were similar to the Week 12 mean IOP values reported in previous studies with PC Dorzolamide Hydrochloride/Timolol Maleate Preservative-Free Ophthalmic Solution dorzolamide/timolol. In study P081, the baseline values were lower, 23.7 mmHg at trough and 21.2 mmHg at peak for PF dorzolamide/timolol and PC dorzolamide/timolol respectively, than the values generally observed in studies of dorzolamide hydrochloride/timolol maleate that include a timolol run-in (25 to 26 mmHg at trough and 24 mmHg at peak). The lower baseline values may account for the lesser percent change in IOP observed in this study compared to previous studies, while the mean IOP values were similar.

***APPENDIX-2: Justification of the use of margin (1.5 mmHg) in the current submission based on two studies (Studies 063 and 064) submitted in NDA 20,869***

In this section this reviewer justifies the use of margin (1.5 mmHg) in the current submission based on two studies (Studies 063 and 064) submitted in NDA 20,869. Note that in the pre-NDA meeting (under IND 52080) dated April 28, 2010, the Agency specified the following:

- Equivalence of Dorzolamide Hydrochloride/Timolol Maleate Preservative-Free Ophthalmic Solution between the two formulations is recommended to be defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over the three month period and being less than 1.0 mmHg for the majority of direct group comparisons; the time points should include both the peak and trough efficacy times for both the test and control agents.

In assessing the non-inferiority margin of 1.5 mmHg recommended to the applicant by the Agency (in the pre-NDA meeting under IND 52080 dated April 28, 2010), this statistical reviewer conducted additional analyses to estimate the IOP lowering effect of PC dorzolamide/timolol treated Group based on the data from study 063 and study 064 submitted in NDA 20,869 (submitted in Module of the current submission). Among all the submitted studies for NDA 20869, the inclusion criteria (patients whose IOP was  $\geq 22$  mmHg after at least 3 weeks of treatment with 0.5% timolol b.i.d.) of study 063 and study 064 satisfy the inclusion criteria of study P081.

Therefore, this reviewer has used the efficacy data (PC dorzolamide/timolol treated Group) from study 063 and study 064. As there is no placebo arm in these two studies, the IOP change from baseline for placebo arm was not available. As a result, this reviewer has computed the 95% confidence interval based on the mean change from baseline for PC dorzolamide/timolol treated Group. Table (reviewer's) below contains the efficacy results (along with 95% confidence interval) of PC dorzolamide/timolol treated group for studies 063 and 064 by visit and hour.

**Table A.2.1: Efficacy Results of Studies 063 and 064 of PC dorzolamide/timolol treated Group**

| Study | Visit (n)     | Hour | Baseline Mean | Mean Change from Baseline (sd) | 95% Confidence Interval |
|-------|---------------|------|---------------|--------------------------------|-------------------------|
| 063   | Week 2 (99)   | 0    | 25.5          | -2.9 (3.3)                     | (-3.55, -2.25)          |
| 063   | Month 1 (102) | 0    | 25.5          | -3.0 (3.4)                     | (-3.66, -2.34)          |
| 063   | Month 2 (102) | 0    | 25.5          | -2.9 (3.1)                     | (-3.50, -2.30)          |
| 063   | Month 3 (102) | 0    | 25.5          | -2.8 (3.4)                     | (-3.46, -2.14)          |
| 063   | Week 2 (100)  | 2    | 25.0          | -4.0 (3.1)                     | (-4.61, -3.39)          |
| 063   | Month 1 (103) | 2    | 25.0          | -4.4 (3.0)                     | (-4.98, -3.82)          |
| 063   | Month 2 (103) | 2    | 25.5          | -4.4 (3.3)                     | (-5.04, -3.76)          |
| 063   | Month 3 (103) | 2    | 25.0          | -4.4 (3.3)                     | (-5.04, -3.76)          |
| 064   | Week 2 (99)   | 0    | 25.7          | -2.9 (3.7)                     | (-3.63, -2.17)          |
| 064   | Month 1 (100) | 0    | 25.7          | -3.2 (3.7)                     | (-3.93, -2.47)          |
| 064   | Month 2 (100) | 0    | 25.7          | -3.2 (3.8)                     | (-3.94, -2.46)          |
| 064   | Month 3 (100) | 0    | 25.7          | -3.2 (3.3)                     | (-3.85, -2.55)          |
| 064   | Week 2 (99)   | 2    | 24.2          | -4.1 (2.7)                     | (-4.63, -3.56)          |
| 064   | Month 1 (100) | 2    | 24.2          | -4.2 (2.6)                     | (-4.71, -3.69)          |
| 064   | Month 2 (100) | 2    | 24.2          | -4.2 (2.7)                     | (-4.73, -3.67)          |
| 064   | Month 3 (100) | 2    | 24.2          | -4.0 (3.0)                     | (-4.59, -3.41)          |

It can be seen from the above table that in general the upper limit of the 95% confidence interval in all cases is less than -2. Therefore, if we assume that placebo effect to be of magnitude 0.5, the margin of 1.5 mmHg may be feasible. However, in half of the cases, the upper limit of the 95% confidence interval is of magnitude of over 3. Therefore, if assume that placebo effect to be of magnitude 1.5, the non-inferiority margin of 1.5 mmHg may be feasible. However, in one case, the upper limit of the 95% confidence interval is of magnitude of about 2.5. Therefore, if assume that placebo effect to be of magnitude 1, the non-inferiority margin of 1.5 mmHg can be justified.

In particular, for study 063 at month 3 and hour 0, if we assume the placebo effect to be of magnitude 0.5, the non-inferiority margin of 1.5 mmHg may be feasible. However in study 064 at month 3 and hour 0, if we assume placebo effect to be of magnitude 1, non-inferiority margin of 1.5 mmHg may be feasible.

Note that in the absence of placebo effect in study 063 and study 064 it is difficult for the reviewer to reliably estimate the IOP lowering effect of the active control (PC dorzolamide/timolol) used in study P081 and thus to justify the chosen non-inferiority margin of 1.5 mmHG.

The reviewer has examined the study results submitted in NDA 20869 for the justification of the 1.5 mmHg margin used in study P018 in the current submission (see Appendix-1 for details). It is difficult for the reviewer to reliably estimate the IOP lowering effect of COSOPT™ PC over placebo and thus to justify the chosen margin of 1.5 mmHG in the setting of study P081 due to following observations:

- There was no placebo arm in the studies in NDA20869.
- Study P018 had lower baseline IOP measurements compared with the studies in NDA20869.
- The PC dorzolamide/timolol treatment (the active control) in study P018 had a smaller average IOP lowering effect (approximately 3.0 mmHg) at 2 hour (peak) compared with those observed in studies from NDA20869 (approximately 4.0 mmHg).

Some preliminary results of an ongoing research project at FDA found that the placebo effect could be in the range of 1.0 mmHg to 2.5 mmHg. Based on this finding and subtracting the placebo effect from the upper bounds of the 95% confidence intervals presented in Table A.1.2 of Appendix-2, a margin of 1.0 mmHg could be justified if the placebo effect does not exceed 2.0 mmHg, and a margin of 1.5 mmHg could be justified when the placebo effect does not exceed 1.5 mmHg in the setting of study P081.

It should be noted that the results of study P081 show that the upper limits of the 95% confidence intervals at both hours and all the visits are less than 1.0 mmHg in magnitude. Thus, using the margin of 1.0 mmHg, one could conclude that the PF dorzolamide/timolol treatment would be non-inferior to the PC dorzolamide/timolol treatment in lowering IOP.

It should be noted that the results of study P081 show that the upper limits of the 95% confidence intervals at both hours and all the visits are less than 1.0 mmHg in magnitude. Thus, using the margin of 1.0 mmHg, one could conclude that the PF and PC dorzolamide/timolol treated Groups would be equivalent in lowering IOP.

It should be noted here that the baseline IOP in study P081 and studies 063 and 064 were not similar. For example, in study P081 (see Table 6), the baseline IOP values were lower, 23.7 mmHg at trough and 21.2 mmHg at peak for PF dorzolamide/timolol and PC dorzolamide/timolol respectively, than the IOP values (25 to 26 mmHg at trough and 24 to 26 mmHg at peak) generally observed (see Table A.1) in dorzolamide hydrochloride/timolol maleate treated group of studies 063 and 064 that included a timolol run-in.

**Appendix-3: Table of the schedule of clinical observations, Computation of confidence interval and Figures for Study P081**

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**Table A.3.1: Schedule of Clinical Observations of Study P081**

| Schedule of Clinical Observations                                 |                        |                 |      |       |      |      |               |      |      |          |      |      |
|---|------------------------|-----------------|------|-------|------|------|---------------|------|------|----------|------|------|
|   | Prestudy Day -21 to -2 | Baseline Day -1 |      | Day 1 |      |      | Weeks 2 and 6 |      |      | Week 12# |      |      |
|   | Prestudy               | 0830            | 1100 | 0830  | 0900 | 1100 | 0830          | 0900 | 1100 | 0830     | 0900 | 1100 |
| Visual acuity   | X                      | X               | X    |       |      |      | X             |      | X    | X        |      | X    |
| External ocular examination (lids)                                | X                      | X               | X    | X     |      | X    | X             |      | X    | X        |      | X    |
| Slit lamp examination (conjunctiva, cornea, and anterior chamber) | X                      | X               | X    | X     |      | X    | X             |      | X    | X        |      | X    |
| Ophthalmoscopy (lens, post. retina, and optic disc)               | X                      |                 |      |       |      |      |               |      |      |          |      | X    |
| Goldmann applanation IOP†   | X                      | X‡              | X    |       |      | X    | X‡            |      | X    | X‡       |      | X    |
| Instill study drug  |                        |                 |      |       | X    |      |               |      | X    |          | X    |      |
| Visual field  | X§                     |                 |      |       |      |      |               |      |      |          |      | X¶   |

† Measurement of IOP were obtained within ± one-half hour of the 0830 hour and 1100 hour time points. IOP measurements on Days -1, and Weeks 2, 6, and 12 were efficacy measures. IOP on Day 1 was a safety measure only.  
‡ IOP measurement obtained prior to morning dose (trough: 0830 hours).  
§ If patient did not complete a computerized visual field evaluation within 1 year of the prestudy exam, a learning visual field was performed and discarded. A second visual field evaluation was conducted as the official prestudy visual field examination.  
|| Mydriatic agents were instilled after 1100 IOP measurement.  
¶ If a clinically significant change from baseline was noted in the visual field, the exam was repeated within 2 weeks.  
# Fourteen-day follow-up phone call was made to patients to inquire about whether any serious adverse experiences had occurred following final study drug instillation.  
NOTE: All examinations were to be scheduled within ±2 days of the scheduled time.

Source: Extracted from table 1, page 23, clinical study report, last-observation-carried forward-worse eye

*Computation of Confidence interval (extracted from page 248-249 (Appendix 3.3:) of the study report*

**Group Comparisons of IOP**

The hypotheses concerning efficacy are that the preservative-free formulation is equivalent to the preserved formulation with regard to trough and peak ocular hypotensive effect. The two ocular hypotensive agents will be considered to have equivalent activity if their mean changes are within 1.5 mm Hg of each other. The results from this study will be presented in terms of a confidence level that the true between-group mean difference lies between -1.5 and 1.5 mm Hg. A confidence level  $\geq 95\%$  will be the criterion used to conclude equivalence. The estimated difference between mean changes in IOP ( $D_{\bullet\Delta}$ ) will be obtained in the following manner along with its estimated standard error ( $S_{D_{\bullet\Delta}}$ ):

Let  $D_{ij} = X_{ij12} - X_{ij0}$  represent the change in trough IOP from baseline Day -1 to Week 12 for subject  $i$  under treatment  $j$ . Let  $j=1$  represent PFDorz./timolol (i.e., preservative-free Dorzolamide/timolol combination) and  $j=2$  represent Dorz./timolol (i.e., Dorzolamide/timolol combination containing preservative). Let the subscript "12" and "0" represent Week 12 and Day -1, respectively. That is,

$X_{ij12}$  = trough IOP at Week 12 for subject  $i$  on treatment  $j$   
 $X_{ij0}$  = trough IOP at Day -1 for subject  $i$  on treatment  $j$

Let  $D_{\bullet j}$  = mean change in trough IOP from Day -1 to Week 12 for treatment  $j$

The treatment effect will be estimated as:

Let  $D_{\bullet\Delta} = D_{\bullet 1} - D_{\bullet 2}$  = estimated treatment difference where  
 $D_{\bullet 1}$  = mean change for PFDorz./timolol  
 $D_{\bullet 2}$  = mean change for Dorz./timolol

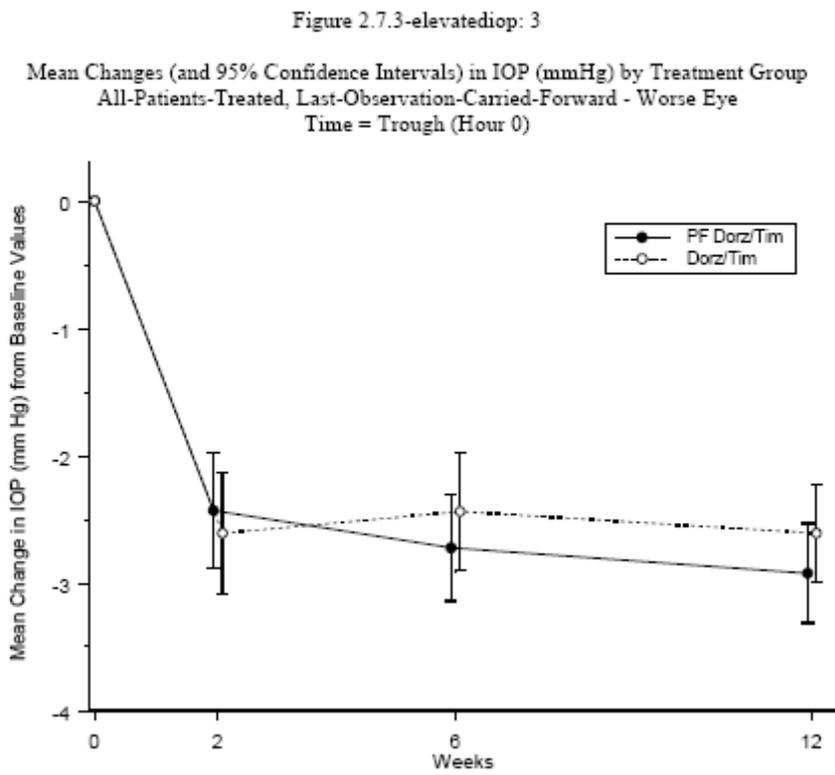
Let  $n_1$  and  $n_2$  be defined as the analysis sample sizes for PFDorz./timolol and Dorz./timolol, respectively. The variance for the estimated treatment difference is:

(b) (4)

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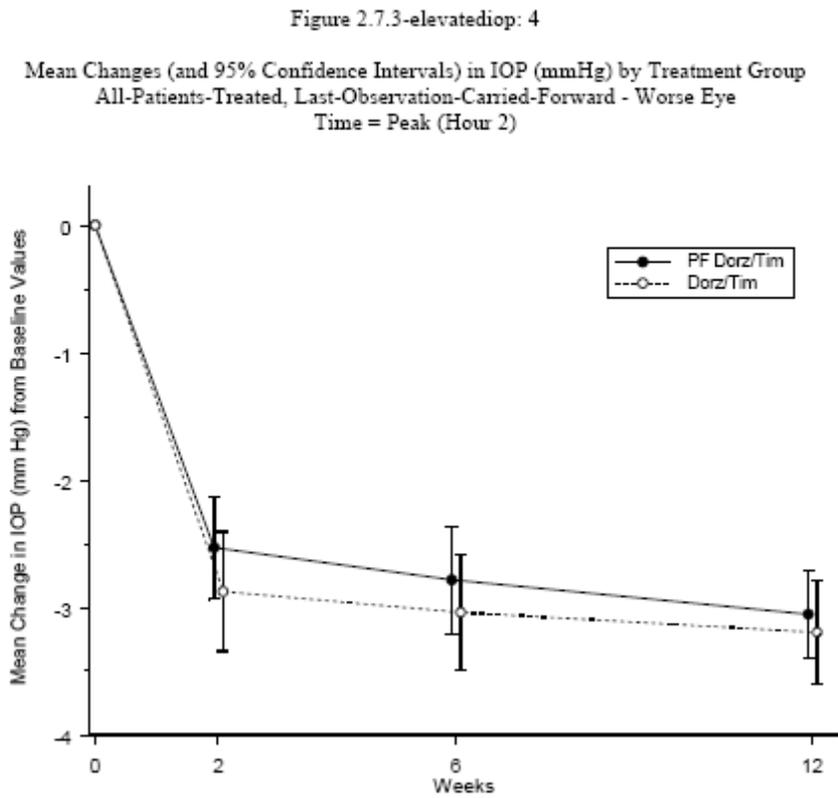
Figure 1:

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Source: Extracted from , page 20, clinical summary report, last-observation-carried forward-worse eye

Figure 2:



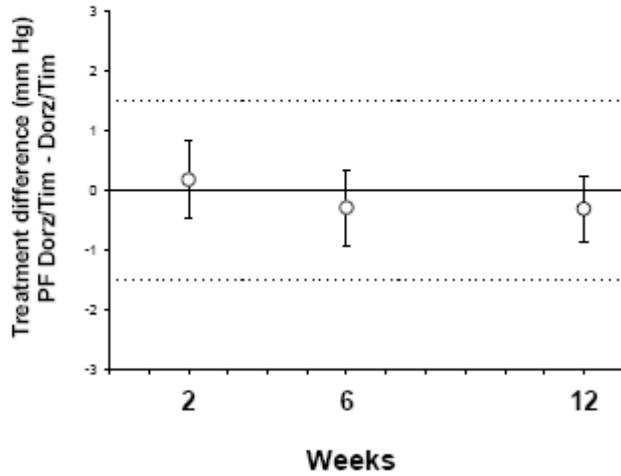
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Source: Extracted from , page 21, clinical summary report, last-observation-carried forward-worse eye

**Figure 3**

Estimated Differences Between Treatments in  
Mean Changes in IOP (mm Hg) With 95% Confidence Intervals—  
All-Patients-Treated, Last-Observation-Carried-Forward—Worse Eye,  
Time = Trough (Hour 0)

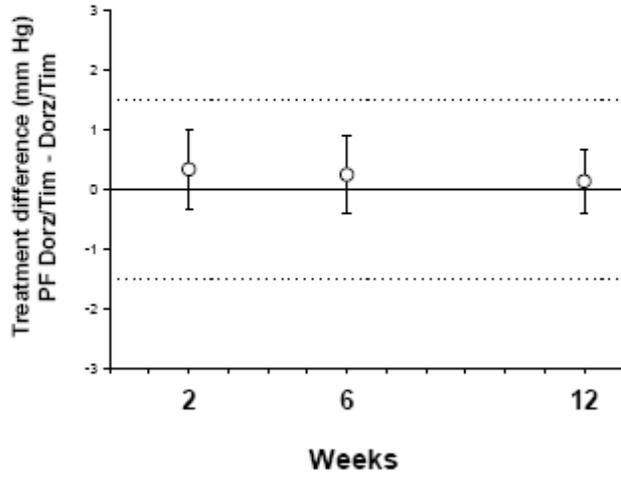
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*Source: Extracted from figure 3, page 55, clinical study report, last-observation-carried forward-worse eye (time=Trough (hour 0))*

**Figure 4**

Estimated Differences Between Treatments in  
Mean Changes in IOP (mm Hg) With 95% Confidence Intervals—  
All-Patients-Treated, Last-Observation-Carried-Forward—Worse Eye,  
Time = Peak (Hour 2)



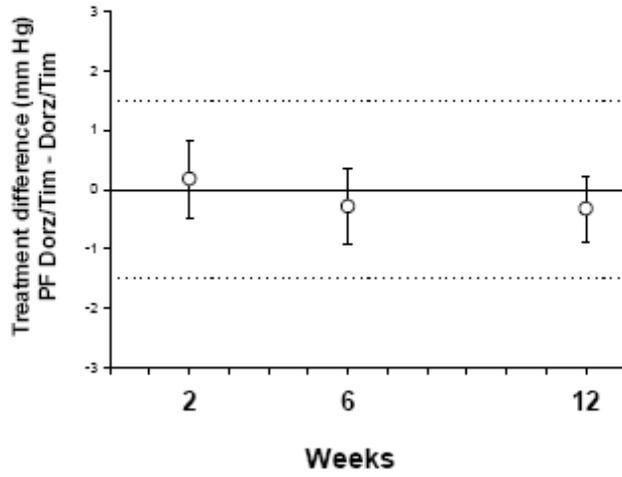
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*Source: Extracted from figure 4, page 56, clinical study report, last-observation-carried forward-worse eye (time=Trough (hour 2))*

Figure 5:

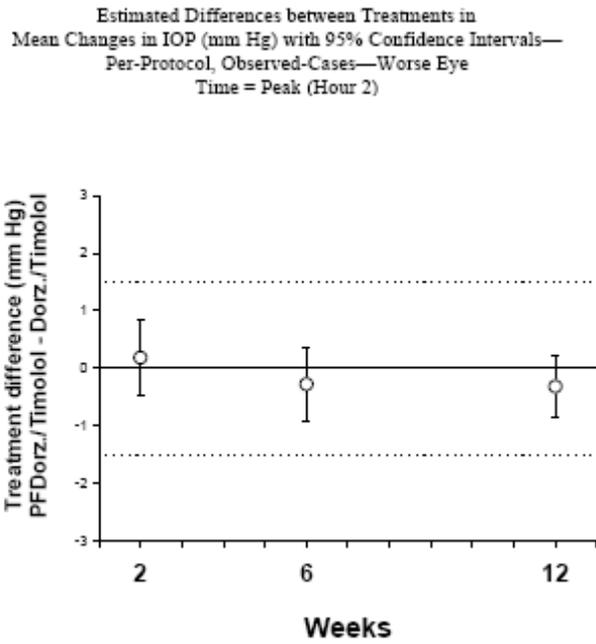
Estimated Differences between Treatments in  
Mean Changes in IOP (mm Hg) with 95% Confidence Intervals—  
Per-Protocol, Observed Cases—Worse Eye  
Time = Trough (Hour 0)

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Source: Extracted from page 328, clinical study report, last-observation-carried forward-worse eye (time=Trough (hour 2))

Figure 6:



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Source: *Extracted from page 329, clinical study report, last-observation-carried forward-worse eye (time=Trough (hour 2))*

**Table A.3.2: Summary of analyses of variances for Covariates for Study P081 (extracted from page 323 of study report)**

Appendix 4.1.7

Summary of Analyses of Variance for Covariates—  
All-Patients-Treated, Last-Observation-Carried-Forward—Worse Eye

COSOPT/MK-507 Protocol 081

CSR (IOPGMDM.SAS)

Appendix 4.1.7

IOP Concomitant Treatment by Factor Analysis

Mean Change in IOP from Baseline

Double-Masked Phase

| Time   | Exam  | Factor     | P-Value For Trt | P-Value for Factor With Interaction | P-Value for Trt*Factor Interaction | P-Value for Factor - No Interaction |
|--------|-------|------------|-----------------|-------------------------------------|------------------------------------|-------------------------------------|
| =====  | ===== | =====      | =====           | =====                               | =====                              | =====                               |
| Hour 0 | Wk 2  | Age        | 0.577           | 0.553                               | 0.772                              | 0.552                               |
|        |       | Race       | 0.607           | 0.747                               | 0.481                              | 0.747                               |
|        |       | Sex        | 0.580           | 0.875                               | 0.623                              | 0.875                               |
|        |       | Iris Color | 0.596           | 0.400                               | 0.942                              | 0.400                               |
|        | Wk 6  | Age        | 0.414           | 0.017                               | 0.925                              | 0.016**                             |
|        |       | Race       | 0.363           | 0.859                               | 0.528                              | 0.859                               |
|        |       | Sex        | 0.440           | 0.445                               | 0.097*                             | 0.447                               |
|        |       | Iris Color | 0.365           | 0.418                               | 0.442                              | 0.418                               |
|        | Wk 12 | Age        | 0.287           | 0.079                               | 0.438                              | 0.079                               |
|        |       | Race       | 0.265           | 0.908                               | 0.354                              | 0.908                               |
|        |       | Sex        | 0.372           | 0.163                               | 0.428                              | 0.163                               |
|        |       | Iris Color | 0.259           | 0.455                               | 0.692                              | 0.454                               |

\* - interaction significant at p<0.100

\*\* - main effect significant at p<0.050

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/s/  
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MUSHFIQUR M RASHID  
08/29/2011

YAN WANG  
08/29/2011

## STATISTICS FILING CHECKLIST FOR NDA 202667

**NDA Number:** 202667

**Applicant:** Merck Sharpe &  
Dohme Corp.

**Stamp Date:** February 16,  
2011

**Drug Name:** MK-0507A  
(Preservative-Free Dorzolamide  
Hydrochloride/Timolol Maleate)  
Ophthalmic Solution

**NDA/BLA Type:** NDA, Standard  
Review

**Indication:** Treatment for  
lowering elevated Intra-  
ocular pressure

### *Overview of the NDA 202667:*

|   | <b>Content Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comments</b> |
|---|---|------------|-----------|-----------|-----------------|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc.   | ✓          |           |           |                 |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)          | ✓          |           |           |                 |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.                         | ✓          |           |           |                 |
| 4 | Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets). | ✓          |           |           |                 |

### **IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes**

The NDA is fileable from the statistical perspective.

## STATISTICS FILING CHECKLIST FOR NDA 202667

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

| <b>Content Parameter (possible review concerns for 74-day letter)</b>   | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b> |
|---|------------|-----------|-----------|----------------|
| Designs utilized are appropriate for the indications requested.   | ✓          |           |           |                |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.  | ✓          |           |           |                |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. |            |           | ✓         |                |
| Appropriate references for novel statistical methodology (if present) are included.   |            |           | ✓         |                |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA.   | ✓          |           |           |                |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.   | ✓          |           |           |                |

## STATISTICS FILING CHECKLIST FOR NDA 202667

### Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

| STUDY # and protocol title   | Treatment arms   | Primary endpoints/criterion for equivalency)   | Conclusions   |
|--|--|--|---|
| <p>P081: A Multiple-Dose, Double-Masked, Parallel, Active Treatment Controlled Study of Preservative-Free (PF) 2.0% Dorzolamide/0.5% Timolol Combination and 2.0% Dorzolamide/0.5% Timolol Combination With Preservative in Patients With Elevated IOP</p> | <p>1) Arm 1 (n=131): Preservative-free 2.0% dorzolamide/0.5% timolol combination b.i.d. for 12 weeks;</p> <p>2) Arm 2(n=130): 2.0% dorzolamide/0.5% timolol combination with preservative b.i.d. for 12 weeks.</p> | <p><i>Primary endpoint</i><br/>The primary endpoint is the difference between the 0830 (morning trough) IOP obtained at the Week 12 clinical visit and the 0830 (morning trough) IOP obtained on Day -1.</p> <p><i>Criterion for equivalency</i><br/>The criterion for establishing equivalency was defined as follows: confidence must be 95% or better that the true difference between the 2 treatments in mean IOP changes from Baseline (Day -1) to Week 12 (at morning trough-just prior to morning dose) falls within the interval (-1.5, 1.5) mm Hg.</p> | <p><i>Efficacy</i><br/>In patients with elevated IOP, the ocular hypotensive effect of preservative-free 2.0% dorzolamide/0.5% timolol combination administered b.i.d. was found to be equivalent (i.e., within 1.5 mm Hg) to that of 2.0% dorzolamide/0.5% timolol combination with preservative administered b.i.d. at morning trough (just prior to morning dose).</p> <p>At Week 12, the mean week 12 (trough) IOP change (from baseline) was : -2.9 mm Hg for patients receiving PF dorzolamide/timolol and -2.6 mm Hg for patients receiving dorzolamide/timolol.</p> <p>The 95% confidence interval for the estimated treatment difference in mean change from baseline to Week 12 trough IOP was -0.86 to 0.23 mm Hg (see Table 1 below).</p> <p>IOP summary statistics are provided in Table 2 below.</p> <p><i>Safety</i> There were no statistically significant differences between the treatment groups in the proportion of patients with one or more adverse experiences, or for patients with drug-related adverse experiences, serious adverse experiences, discontinuations due to adverse experiences, or discontinuations due to drug related adverse experiences. No patients died during the study.</p> |

# STATISTICS FILING CHECKLIST FOR NDA 202667

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**Table 1:**

Estimated Difference Between Treatments and 95% Confidence Intervals in IOP (mm Hg)  
All-Patients-Treated, Last-Observation-Carried-Forward—Worse Eye

| Week  | Sample Size     |              | Mean Change <sup>†</sup><br>Difference<br>Between<br>Treatments | Standard<br>Error of<br>Difference | 95% Confidence<br>Interval for<br>Difference<br>Between Mean<br>Changes | Confidence<br>Difference Lies<br>Between -1.5 and 1.5 |
|---|-----------------|--------------|---|------------------------------------|---|---|
|   | PF Dorz<br>/Tim | Dorz<br>/Tim |   |                                    |   |   |
| <u>Trough (Hr 0)</u>  |                 |              |   |                                    |   |   |
| Week 2  | 130             | 128          | 0.18  | 0.33                               | (-0.47, 0.83)   | >0.999*   |
| Week 6  | 130             | 128          | -0.29   | 0.32                               | (-0.91, 0.34)   | >0.999*   |
| Week 12   | 130             | 128          | -0.31   | 0.28                               | (-0.86, 0.23)   | >0.999*   |
| <u>Peak (Hr 2)</u>  |                 |              |   |                                    |   |   |
| Week 2  | 130             | 128          | 0.34  | 0.31                               | (-0.27, 0.96)   | >0.999*   |
| Week 6  | 130             | 128          | 0.25  | 0.31                               | (-0.36, 0.87)   | >0.999*   |
| Week 12   | 130             | 128          | 0.14  | 0.27                               | (-0.39, 0.67)   | >0.999*   |
| <sup>†</sup> Mean change difference in IOP (mm Hg) between treatments is based on Day -1 baseline and computed as PF dorzolamide/timolol-dorzolamide/timolol.<br>* The confidence is 0.950 or more that the difference between treatment means lies between -1.5 and 1.5 mm Hg. |                 |              |   |                                    |   |   |

Source: Sponsor's Table 16, page 46 (study report)

**STATISTICS FILING CHECKLIST FOR NDA 202667**

**Table 2:**

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IOP (mm Hg) Summary Statistics by Treatment  
All-Patients-Treated, Last-Observation-Carried-Forward—Worse Eye

| Time             | Wk | Treatment   | N   | Baseline <sup>1</sup> |     |      | Study Value |     |      | Change |     |      | Percent Change |      |       |
|------------------|----|-------------|-----|-----------------------|-----|------|-------------|-----|------|--------|-----|------|----------------|------|-------|
|                  |    |             |     | Mean                  | SD  | Med  | Mean        | SD  | Med  | Mean   | SD  | Med  | Mean           | SD   | Med   |
| Trough<br>(Hr 0) | 2  | PF Dorz/Tim | 130 | 23.7                  | 1.5 | 23.0 | 21.3        | 2.9 | 21.0 | -2.4   | 2.6 | -2.0 | -10.2          | 11.0 | -9.1  |
|                  |    | Dorz/Tim    | 128 | 23.7                  | 1.5 | 23.0 | 21.1        | 2.8 | 21.0 | -2.6   | 2.7 | -2.0 | -10.9          | 11.5 | -9.1  |
|                  | 6  | PF Dorz/Tim | 130 | 23.7                  | 1.5 | 23.0 | 21.0        | 2.7 | 21.0 | -2.7   | 2.4 | -3.0 | -11.4          | 10.2 | -12.0 |
|                  |    | Dorz/Tim    | 128 | 23.7                  | 1.5 | 23.0 | 21.2        | 2.8 | 21.0 | -2.4   | 2.7 | -2.0 | -10.2          | 11.2 | -9.1  |
|                  | 12 | PF Dorz/Tim | 130 | 23.7                  | 1.5 | 23.0 | 20.8        | 2.6 | 21.0 | -2.9   | 2.3 | -3.0 | -12.3          | 9.4  | -12.5 |
|                  |    | Dorz/Tim    | 128 | 23.7                  | 1.5 | 23.0 | 21.1        | 2.5 | 21.0 | -2.6   | 2.2 | -3.0 | -11.0          | 9.3  | -11.1 |
| Peak<br>(Hr 2)   | 2  | PF Dorz/Tim | 130 | 21.2                  | 2.5 | 21.0 | 18.6        | 2.5 | 19.0 | -2.5   | 2.3 | -3.0 | -11.5          | 10.4 | -12.5 |
|                  |    | Dorz/Tim    | 128 | 21.4                  | 2.7 | 21.5 | 18.6        | 2.4 | 19.0 | -2.9   | 2.7 | -3.0 | -12.7          | 11.8 | -12.8 |
|                  | 6  | PF Dorz/Tim | 130 | 21.2                  | 2.5 | 21.0 | 18.4        | 2.3 | 18.0 | -2.8   | 2.4 | -3.0 | -12.5          | 10.9 | -14.3 |
|                  |    | Dorz/Tim    | 128 | 21.4                  | 2.7 | 21.5 | 18.4        | 2.4 | 18.0 | -3.0   | 2.6 | -3.0 | -13.3          | 11.3 | -14.3 |
|                  | 12 | PF Dorz/Tim | 130 | 21.2                  | 2.5 | 21.0 | 18.1        | 2.1 | 18.0 | -3.1   | 2.0 | -3.0 | -14.0          | 8.8  | -14.3 |
|                  |    | Dorz/Tim    | 128 | 21.4                  | 2.7 | 21.5 | 18.2        | 2.3 | 18.0 | -3.2   | 2.3 | -3.0 | -14.3          | 10.4 | -15.2 |

<sup>1</sup> Baseline used in computations for changes in IOP.  
SD = Standard deviation.  
Med = median.

Source: Sponsor's Table 15, page 42 (study report)

Mushfigur Rashid

Reviewing Statistician

Date

Yan Wang

Supervisor/Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MUSHFIQUR M RASHID  
04/25/2011